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Emerging Trends in Human Cardiology and Physiology

First Edition

EMERGING TRENDS IN HUMAN CARDIOLOGY AND PHYSIOLOGY

Dr. R.B. Tripathi
D.E. Nirman Kanna
Jayashree R.

THANUJ INTERNATIONAL PUBLISHERS, TAMIL NADU, INDIA

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Editors

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Preface

In the rapidly evolving field of cardiology, the quest for improved understanding and treatment of cardiovascular diseases is paramount. **"Emerging Trends in Human Cardiology and Physiology"** aims to provide a comprehensive overview of the latest developments that are shaping our approach to heart health. As cardiovascular diseases remain one of the leading causes of morbidity and mortality worldwide, the insights presented in this volume are critical for healthcare professionals, researchers, and medical students.

The chapters within this book explore a diverse range of topics, from foundational concepts like coronary circulation and the impact of thyroid hormones on cardiac health, to cutting-edge advancements in cardiac xenotransplantation and stem cell therapy. Each contributor brings their expertise to the table, shedding light on innovative therapies, the significance of nutrition and lifestyle, and the integration of genomic insights into clinical practice. We delve into both the scientific and practical aspects of cardiology, examining not only new treatment modalities such as sacubitril/valsartan and robotic assistance in surgery, but also the challenges posed by conditions like cardiac amyloidosis and heart failure. The emphasis on personalized patient care and the importance of biomarkers reflects a shift towards more tailored and effective interventions. Moreover, this volume underscores the importance of interdisciplinary collaboration in tackling complex cardiovascular issues. The synergy between advancements in technology, pharmacology, and lifestyle management is crucial for revolutionizing patient outcomes.

As we present these emerging trends, we hope to inspire further research and dialogue within the cardiology community. The collective expertise encapsulated in this book serves as a valuable resource for understanding the current landscape of cardiac health and preparing for the future.

Our hearty acknowledgement to Thanuj International Publishers who readily accept and publish the subjects. We are also extending our heartful thanks to our authors Dr. A.Hareesh, Dr. J.Jayannan, Dr. Ajith.K, Dr. P. Maheshkumar, Dr.Uma Maheswari M, Dr. Arthi , Dr. Dinesh Ragav. E, Sanya, Dr. Mahesh. P.G, Theetchanya. S, Mrs. Vaheeda Rehman, Dr. P. Shanmugasundaram, Dr. C T Meyyammai, Karthick.V, Sreekar. S.G, Dr S A Jacob Raja, A. Mohamed Ansar, M. Syed Ali Fathima, Devendran.N, Giridharan.R, Jaya Suriya.S, Ayswarya.P, S.Uma Devi, Hema Priya T L, Mr. Adnan Majeed Bhat, Praveena V, Vijay. S.B, Dr. Sudha .T, Subashini S, Ms. Swetha V, Dr. Padma Priya P, Deepsaha P, Mr. Eishan Altaf Bhat, Trisha U, Srivijith. T. D, for contributing the chapters and support for this work.

We invite you to engage with these insights, as together we navigate the challenges and opportunities in the field of cardiology, striving towards a healthier tomorrow.

The Editors,

Dr.R.B.Tripathi,

D. E. Nirman Kanna,

R. Jayashree.

About Editors

Dr.R.B.Tripathi is currently working as Assistant Professor in P.G.Department of Zoology, M.L.K.P.G.College, Balrampur-271201, Uttar Pradesh, India. He has been completed his Ph.D.in Zoology from Dr. R.M.L. Avadh University, Ayodhya, Uttar Pradesh, India. He has 23 years teaching experience in U.G and 19 years teaching experience in P.G classes, published 20 book chapters, 44 research papers in international and national reputed journals, participated and presented papers in many international and national seminars, conferences and workshops. He is Indian Zoologist, published by Surya Scientist Unique Researchers Yare Association, 2015. He is Associate Editor in International Journal of Advanced Research in Biological Sciences (ISSN:2348-8069), Editorial board member in International Journal of Advanced Multidisciplinary Research (ISSN:2393-8870),09 book Editor in Recent Trends in Life Sciences Research (ISBN:978-81-947071-3-4),published by DarshanPublishers,Tamil Nadu, India, Recent Advancements and Research in Biological Sciences (ISBN:978-81-952529-1-6),Current Trends in Biological Sciences (ISBN:978-93-94638-00-6), Current Research in Life Sciences (ISBN: 978-93-94638-22-8),Recent Research in Biosciences (ISBN:978-93-94638-25-9),Current Advances in Biosciences (ISBN:978-93-94638-64-8),Advances in Pharmaceutical and Biosciences Research (ISBN:978-93-94638-87-7), Advance Research Trends in Biology (ISBN:978-93-94638-75-4) and Biological Resources for Sustainable Research (ISBN:978-93-94638-90-7) published by Thanuj International Publishers Tamil Nadu,India.

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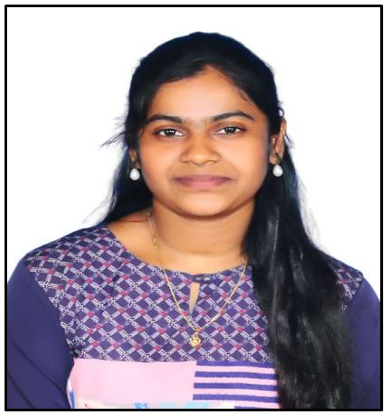

R. Jayashree is currently a Lecturer in the Department of Perfusion Technology at Vinayaka Mission's School of Allied Health Sciences, Chennai, Tamil Nadu. She has one year andsix months experience in teaching and research, she has authored three notable research articles: "A Review on Psoriasis" (ISSN 2278-4357), "Obesity Paradox in Myocardial Infarction" (ISBN: 978-93-94638-90-7), and "Pro BNP Elevation: Diagnostic and Prognostic Impact in Cardiovascular and Non-Cardiac Events" (ISSN-2349-5162). She completed her undergraduate studies in Perfusion Technology at Meenakshi Medical College Hospital and Research Institute, Kancheepuram, Tamil Nadu. During her final academic year, she interned in various departments, including Emergency Medicine, General Medicine, General Surgery, and Pediatrics. Following her graduation, she gained practical experience as a Perfusionist and PhysicianAssociate at Billroth Hospitals, Chennai, and later worked as a Perfusionist cum Physician Associate at M.S.D Hospital, Kancheepuram.

Emerging Trends in Human Cardiology and Physiology

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Coronary circulation- The oxygen and nutritional supply of heart

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Introduction

The heart supplies blood to all parts of the body. Blood is needed to survive because it carries oxygen and nutrients. Blood is carried one way. When the heart pumps, it increases the ventricle pressure and the blood rushes out of the heart. The blood is circulated to other parts of the body this is known as the "Circulatory system". The circulatory system consists of the heart, arteries and veins. The heart is a muscular organ and fist-sized. It is present between the lungs and covered by the thoracic cavity. The heart has 4 chambers. The upper two are called the atrium and the lower two are called the ventricles. The heart is covered by 3 layers, namely the pericardium, myocardium, and endocardium. The pericardium is an outer protective double membrane layer. A fluid present between the double layers is called pericardial fluid which acts as a lubricant and reduces friction. Myocardium is a thick muscular middle layer while the endocardium is a thin inner layer which protects the chambers and valves of the heart. The heart is divided into two sections by two septums called the atrial and ventricular septums. This separation is essential so that two different types of blood (oxygenated and deoxygenated blood) are not collapsed and allow effective blood pumping. The heart is a pumping organ and does not purify the blood. Blood is purified by the lungs and kidneys. The heart pumps about 5.7 litres of blood per minute. Since the heart supplies blood to all parts of the body, it requires blood to function. Here comes the role of coronary vessels.

Coronary circulation

Tofunction properly, the heart must need a reliable supply of oxygen and nutritionand also a way to remove waste. Coronary circulation does this job by carrying oxygenated blood through an arterycalled a coronary arteryand deoxygenated blood through a vein called a coronary vein. Circulation of blood throughout the vesselsthat supply the myocardium (cardiac muscle) is known

as Coronary circulation.Coronary means “crown” and circulation means “flow of blood”. Coronary vessels are wrapped around the heart. Coronary circulation is very rapid, phasic and short. When there is a block in these arteries leads to myocardial infarction (heart attack).

Coronary artery

There are major coronary arteries namely: the right and left coronary arteries. Both of them arise from the trunk of the aorta. Among the two major coronary arteries left coronary artery is the main. These two openings are present just superior to the aortic semilunar valve. When left ventricle systole (contract) blood is pumped into the aorta then left ventricle diastole (relax) the blood from the aorta falls and gets caught by aortic semilunar valves where the oxygenated blood drains out by these coronary arteries This is the reason why the coronary origin is present in the aorta. The Semilunar valve is the valve where the blood goes out from the aorta for systemic circulation. In other vessels blood feed under systole but in the case of the heart it feeds under diastole.

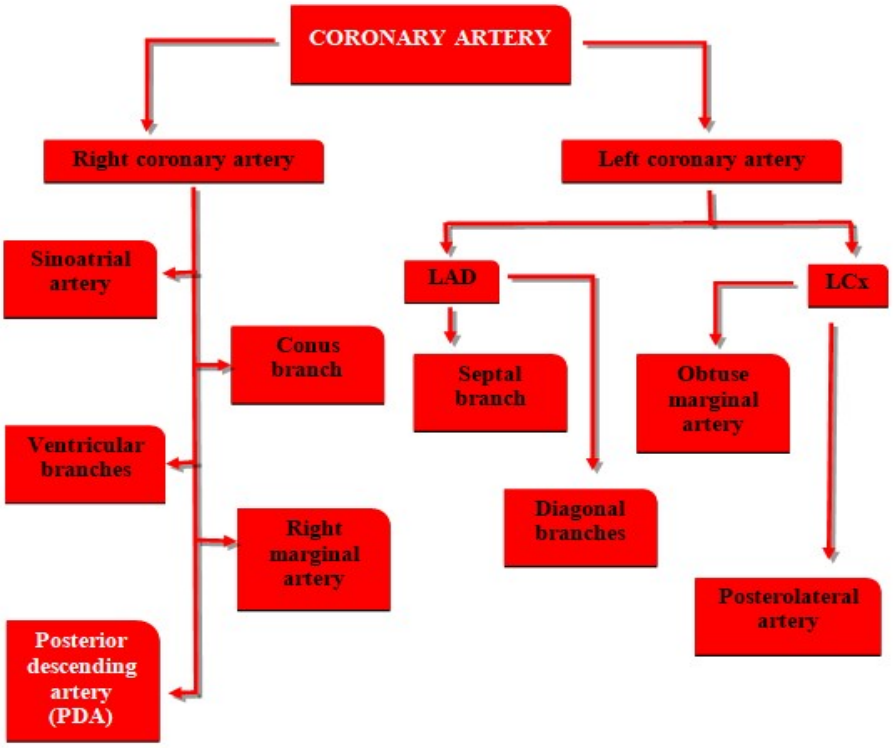

Figure 1

A. Right coronary artery

Origin

Theaortic sinus on the anterior side is known as the anterior aortic sinus whichgives rise to the right coronary artery.

Course

Itdescends in the coronary sulcus to the inferior margin and then it reaches theposterior interventricular groove.

Branches

1. Sinoatrial nodal branch of RCA:

Thefirst branch of the right coronary artery is the sinoatrial nodal branch of RCApresent between the aorta and right atrial auricle and it then winds around thesuperior vena supplying the auricle and right atrium and some parts of the leftauricle.

2. Conus branch:

A conus branch supplies the conus arteriosus (infundibulum) on the upper front part of the right ventricle.

3. Ventricular branches of the RCA:

Thereare two branches called the ventricular branches of the RCA which supply to theright ventricle.

4. Right marginal artery:

Onthe marginal side of the right side of the heart, we have the right marginalartery. It supplies blood to the lateral portion of the right ventricle.

5. Posterior descending artery (PDA):

Behindthe heart, there is a posterior interventricular branch or PAD which extends upto the apex of the heart. These are the largest branch among the other branches. It supplies blood to the inferior aspect of the myocardium.

Area of distribution

Itmoves along the coronary sulcus and is distributed to the right atrium, primarily to the right ventricle and a small portion of the left ventricle andheart conduction system (SA node, AV node).

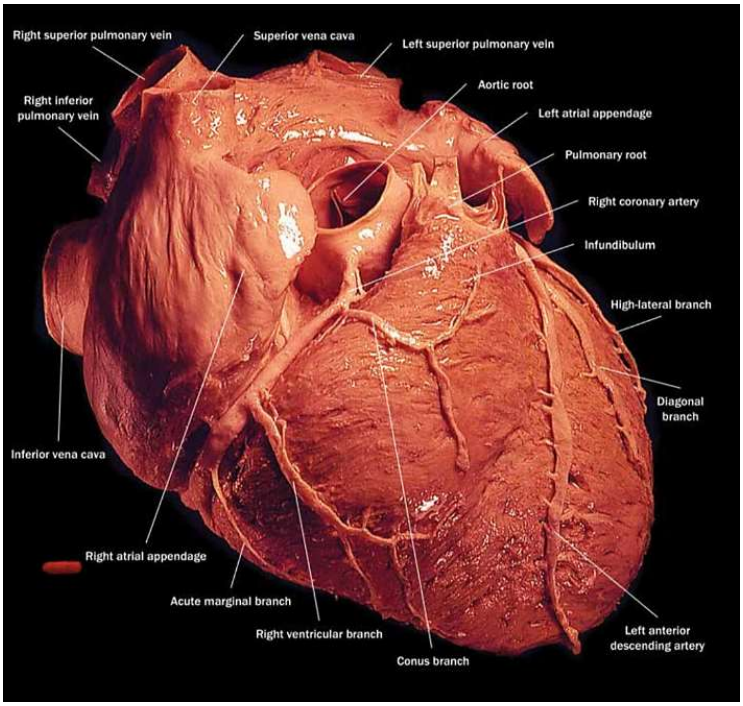

Figure 2

B. Left coronary artery

Origin

Theaortic sinus on the posterior side is known as the posterior aortic sinus whichgives rise to the left coronary artery.

Course

Theleft coronary artery passes between the pulmonary trunk and left auricle andenters the left anterior coronary sulcus where it divides into two majorbranches.

Branches

Theleft coronary artery is much more complicated than the right coronary artery.LCA usually splits into two branches.

1. Left anterior descending artery (largest coronary artery):

Thefirst is a larger major branch known as the anterior intraventricular artery orleft anterior descending artery (LAD) is the most important branch

because blockage in LAD causes myocardial infarction. This LAD has three segments: proximal, mid, and distal. LAD goes down and descends within the coronarysulcus supplying certain parts of the right, left atria, left ventricle andalso the anterior two-thirds of the interventricular septum (present betweenthe left and right ventricle). LAD is often called a "widow-maker infarction"because of the high death risk if there is a blockage in LAD.

Branches of LAD

LAD has two branches: Diagonal branches and Septal branches.

A. Septal perforated branch

A small branch perforates deep into the septum of the ventricle arising from the proximal left anterior descending artery.It supplies the anterior two-thirds of the interventricular septum. This branch is important in alcohol septal ablation proceduresfor the treatment of obstructive hypertrophic cardiomyopathy.

B. Diagonal branch

There can be many numbers of diagonal branches but ordinarily, there are at least two branches. The first diagonal branch D1arises from the mid-left anterior descending artery and the second diagonal branch D2 arises from the distal left anterior descending artery. It supplies the lateral wall of the left ventricle.

1. Left circumflex artery (LCx):

The second major branch of LCA is called the left circumflex artery it gives offtwo small branches namely: the left marginal branch or obtuse marginalartery (distributed in the left ventricle) and the posterior left ventricular branch. LCx has three segments: proximal, mid and distal.

Branches of LCx

A. Obtuse marginal artery:

There can be many marginal branches of LCx but ordinarily, there are at least two branches.The first major branch is the first obtuse marginal branch O1arises from the mid-Lcx and the second major branch is the second obtuse marginal branch O2 arises from the distal Lcx. It supplies most lateral walls of the left ventricle.

B. Posterolateral artery or posterior left ventricular branch:

The left circumflex artery curves towards the posterior surface and forms the posterolateral artery which supplies the inferior portion of the myocardium.

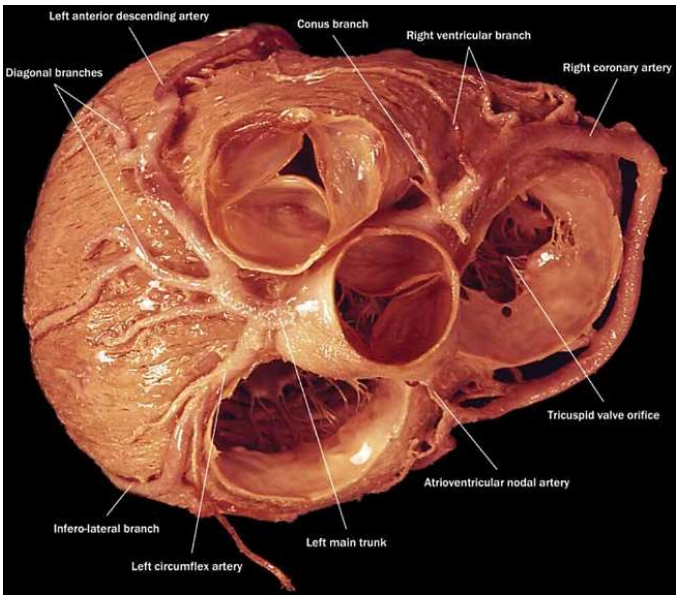

Figure 3

Area of distribution

It distributes blood to the left atrium and ventricle, and interventricular septum.

Clinical relation of coronary artery

Coronary dominance

1. Right coronary dominance - the posterior interventricular artery arising from the right coronary artery. In the interventricular septum, the anterior two-thirds are supplied by the left coronary artery and the posteroinferior aspect is supplied by the right coronary artery.

2. Left coronary dominance - the posterior interventricular artery arising from the left circumflex coronary artery. In the interventricular septum, the anterior two-thirds are supplied by the left coronary artery and the posteroinferior aspect is supplied by the left coronary artery.

3. Coronary codominance– the posterior interventricular artery arising from both the right and left coronary arteries.

Clinical significances:

- The most dangerous coronary dominance is left coronary dominance because the entire interventricular septum is supplied by the left coronary artery. If there is any blockage the entire interventricular septum will suffer.
- The safest coronary dominance is coronary codominance because two posterior interventricular are present in coronary codominance. If any one branch is blocked it can be managed by another branch.

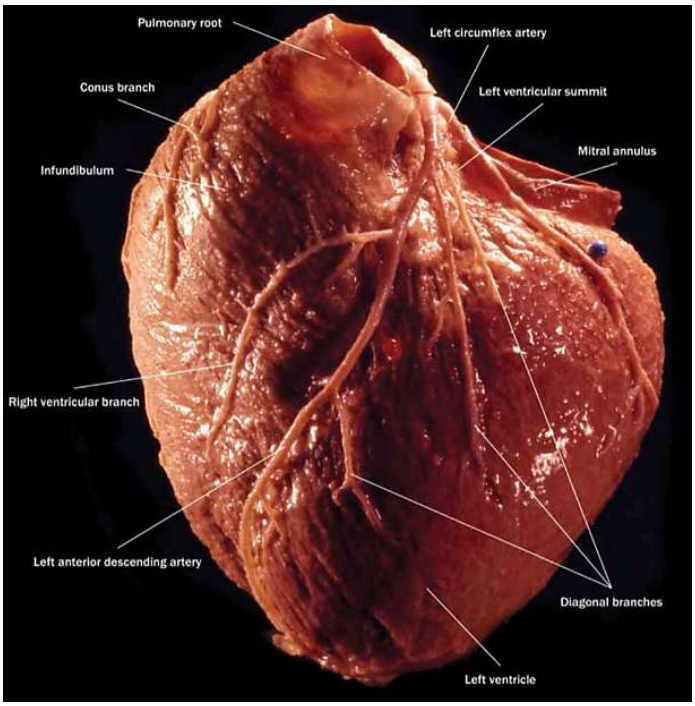

Figure 4

Coronary Artery Disease (CAD)

It occurs due to an imbalance between oxygen supply and demand in the myocardium. It is the most common disease among cardiovascular diseases. It is a chronic condition. Most commonly it occurs due to the building of plaques in the wall of the coronary artery.

Cause

Atherosclerosis of the coronary arteries causes CAD. Atherosclerosis (deposition of cholesterol and other waste products)

Risk factors

1. Age – For men around the age of 45 and women around the age of 55 have a higher risk of getting CAD. Women are at a lower risk of getting CAD before menopause because of high oestrogen levels.
2. Sedentary lifestyle – lack of exercise, not having enough sleep, sitting for a prolonged period, unhealthy diet, smoking, and stress can lead to CAD.

Symptoms

1. Angina pectoris

The term angina pectoris refers to "chest pain". This occurs due to a condition called ischemia (decreased blood supply). Angina is caused bythe narrowing of the coronary arteries.Stable angina is characterised by the pain occurring while doing some physical activitieslike walking and jogging but not during rest. Unstable angina is characterised by pain that occurs both during exercise and at rest.

2. Shortness of breath

Complications associated with CAD

1. Myocardial infarction (heart attack) – an area of myocardium that undergoes necrosis (cell death) occurs due to prolonged ischemia.
2. Cardiac arrest – sudden loss of heart function due to arrhythmia.
3. Cardiogenic shock or cardiac shock – inadequate blood supply to the other vital organs due to failure of myocardial pumping.

Diagnostic method

1. Electrocardiogram (ECG) – it is used to measure the rate and rhythm of the heartbeats by placing the electrodes in the chest, arm and left ankle. and it is a non-invasive medical procedure. It is shown in electric waves which are represented on graph paper. Resting 12 lead ECG is a standard test for measuring the heart's electric function.
2. Coronary computed tomographic angiography or coronary CTA – is a myocardial imaging test that helps to determine the plaque formation in

coronary arteries. Contrast dye is injected into the intravenous line of the arm and CT images are captured as the material flows through the heart muscles.

3. Coronary angiography – iodine-containing contrast is injected into the coronary artery and cine fluorography is recorded using X-ray equipment. A catheter is inserted in arteries. Usually, the arteries used are femoral and radial.

Treatment

1. Percutaneous coronary intervention (PCI):

A catheter is inserted into an artery and threaded to the affected artery, a thin flexible metal is then advanced through this tube and passes the site of blockage in the artery and a second smaller catheter is then inserted over the wire and threaded to the same artery. When it reaches the narrowed area, a small balloon present on its tip is inflated to reopen the artery and flatten the blockage and stretching the artery increases the blood flow. Both catheters and wire are withdrawn. About 70-90% of coronary angioplasty includes the placement of a stent (a wire mesh tube) which keeps the artery widening and prevents the narrowing of a coronary artery.

2. Coronary artery bypass surgery (CABG) or Open-heart surgery:

Blood vessels from the chest, arm or leg are used as a graft. A surgical cut is made in the middle of the sternum by using a sternal driller and then the sternum is bifurcate (divide) into two. With the help of a retractor, the thorax is expanded. The graft is attached from the aorta to a point in the coronary artery. The sternum is tied using stainless steel wires. The skin on the thorax is closed with dissolvable stitches.

Prevention

Having a healthy diet, exercising regularly and avoiding smoking, and maintaining a proper BMI may prevent CAD.

Coronary collateral circulation (Natural bypasses)

Coronary collateral is an anastomotic connection. Anastomosis (connection of blood vessels) can be between the same coronary arteries or different coronary arteries (ex. PDA to LAD collateral). When there is a proximal occlusion in the coronary artery there is a high chance of forming coronary collaterals. Coronary collateral arteries can also be present in normal persons.

Clinical importance of coronary collaterals:

In the case of acute myocardial infarction, the coronary collaterals decrease the infarct size which helps to reduce the risk of mortality by decreasing the incidence of cardiogenic shock. This can preserve the myocardial function. Blood supply by the coronary collateral circulation is sufficient for resting myocardium but it is not sufficient to prevent myocardial infarction on exertion. Coronary revascularization procedures are highly necessary for the patient with coronary collateral.

Venous drainage of the heart

Deoxygenated blood travels through the coronary veins and drains out into the right atrium. There are different coronary veins which are present in the heart.

The venous blood from the myocardium is chiefly returned through two systems namely:the superficial venous system and the deep venous system.

A. Superficial venous system (lies beneath the epicardium)

1. Coronary sinus

It is the largest coronary vein in terms of diameter and is located in the atrioventricular groove. It serves as a primary collector of deoxygenated bloodfrom the heart and then it drains the blood mostly from the left coronary artery, partly from the right coronary artery, and ends ultimately in the posterior part of the right atrium.

2. Great cardiac vein

It is present on the interventricular sulcus and it turns to the left where it enters the coronary sulcus and enters into the coronary sinus onto the posterior surface.

3. Middle cardiac vein

It presents along with the posterior interventricular artery and joins the coronary sinus

4. Small cardiac veins

It travels to the posterior surfaceand along with the right marginal veins it enters into the coronary sinus.

5. Anterior Cardiac Veins

They are generally 3 or 4 anterior cardiac veins that directly drain into the right atrium by bypassing the coronary sinus.

B. Deep venous system

There are numerous veins arising from boththe atriumand ventricle (mostly from the right). There are very small veins that are present on the surface of the heart called Thebesian veins/Venae cordis minimae (smallest cardiac veins).

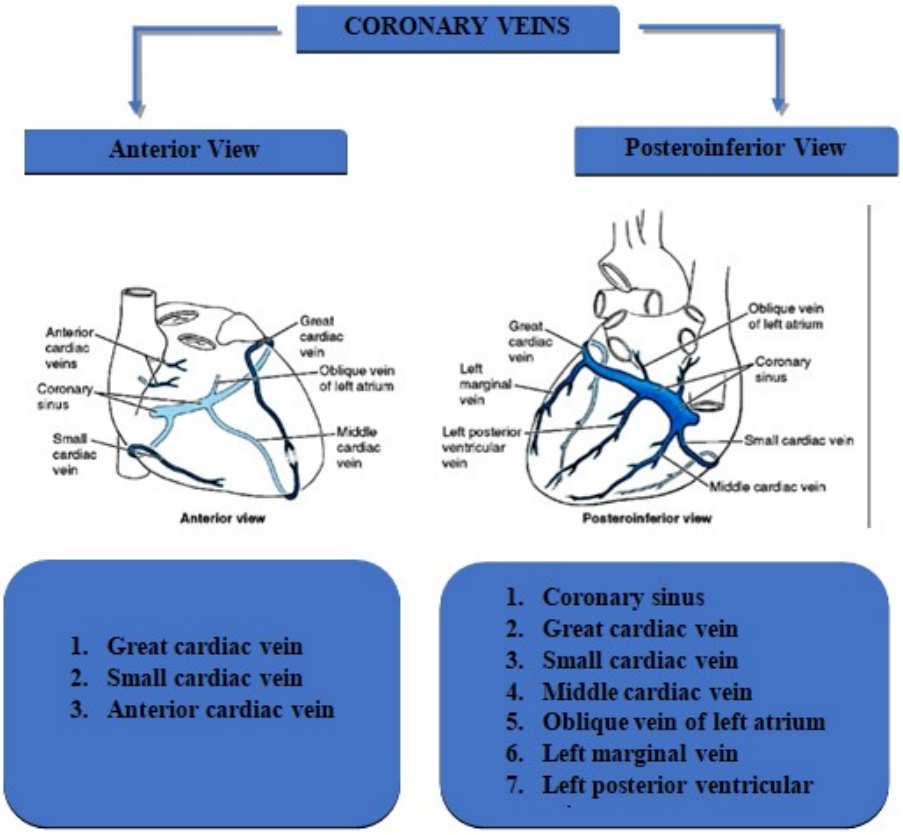

Figure 5

The majority of the coronary veins (Great cardiac vein, middle cardiac vein, posterior cardiac vein and small cardiac vein) first drain into the coronary sinus (largest vein of the heart), and from the coronary sinus the deoxygenated blood enters the right atrium. There are two to three coronary veins that

directly drain into the right atrium and they are known as anterior cardiac veins. So the right atrium receives deoxygenated blood from the coronary sinus and anterior cardiac veins. In some people, the right marginal vein merge with the small cardiac vein so that deoxygenated blood from the right marginal vein drains into a small cardiac vein and then to the coronary sinus ending up in the right atrium. For some people right marginal vein does not merge with the small cardiac vein, the deoxygenated blood from the right marginal vein directly drains into the right atrium. Thebesian veins present in the myocardium neither drain the deoxygenated blood to the right atrium nor the coronary sinus instead it drains into the cardiac chambers.

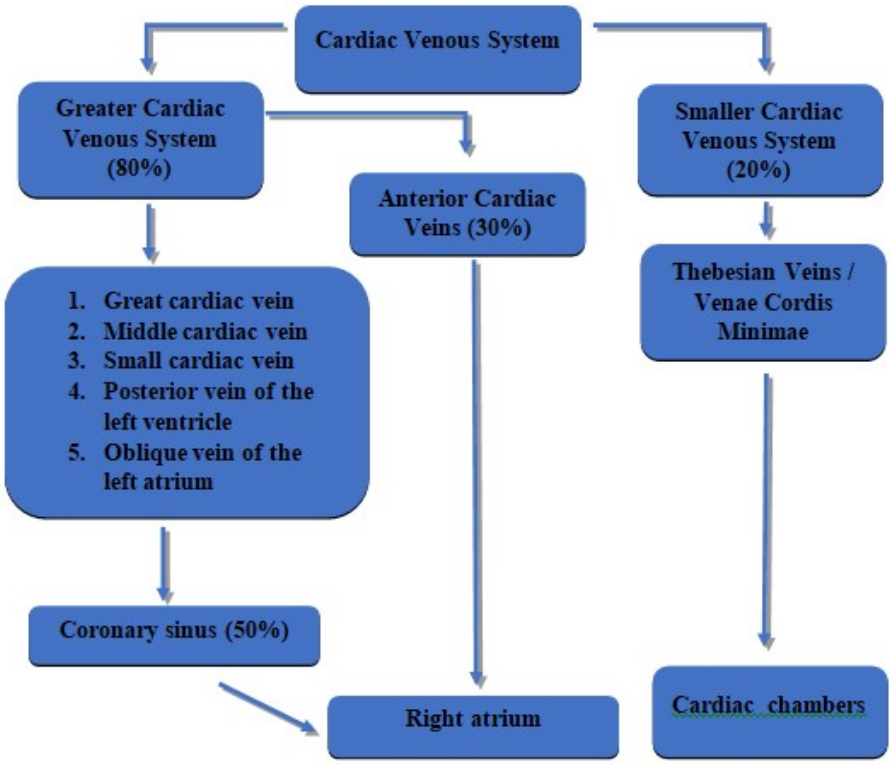

Figure 6

Venous drainage of the heart

Conclusion

Taking everything into consideration, the heart is a pumping organ that pumps blood. It supplies blood to all cells in our body by circulating it evenly throughout the body. Blood supply is essential for the heart's proper functioning, and this is where coronary vessels come into play. The origin, course, branches, and distribution of coronary vessels are discussed. If the heart does not receive an adequate blood supply, it cannot pump effectively, resulting in necrosis of the heart, which leads to death. Coronary arteries are the only arteries that supply oxygenated blood to the heart. If the coronary artery gets blocked (usually due to atherosclerosis) it leads to myocardial infarction. There are several treatments available such as PCI and CABG. Maintaining an active lifestyle prevents coronary artery disease. A coronary dominant artery is clinically related to the coronary artery. In the heart, collateral circulation acts as a natural bypass by acting as an anastomotic connection. Providing oxygenated blood does not make the task effective. There should be a way to remove unwanted materials. This is done by coronary veins by carrying deoxygenated blood and draining it out of the right atrium (which receives deoxygenated blood).

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Thyroid hormone- A new clinical parameter of cardiac failure in men

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Abstract

Heart failure (HF) represents a complex syndrome stemming from various cardiac disorders, prominently influenced by hormonal imbalances. Among these, a deficiency in growth hormone, insulin-like growth factor-1, dehydroepiandrosterone sulfate, and testosterone emerges as a pivotal aspect. Moreover, thyroid hormone (TH) alterations, notably within the non-thyroidal illness syndrome (NTIS), exhibit significant associations with HF progression, marked by diminished triiodothyronine (T3) levels and subsequent implications on left ventricular function. Notably, testosterone's role, particularly in male patients, underscores gender-specific nuances in HF pathophysiology. While the peripheral effects of testosterone demonstrate promise in mitigating HF severity, further exploration into its central effects is warranted. However, the intricate relationship between TH and HF parameters in male patients remains insufficiently explored. Therefore, this review will conclude the association between five TH markers and key HF parameters in men, while considering serum testosterone levels and other clinical variables."

Introduction

Heart failure (HF), a common final pathway of numerous cardiac disorders, is characterized by a complex pathophysiology where hormonal imbalance plays an important role. This multiple hormonal deficiency syndrome includes lower circulating levels of growth hormone, insulin-like growth factor-1, dehydroepiandrosterone sulfate, and testosterone[(1)].

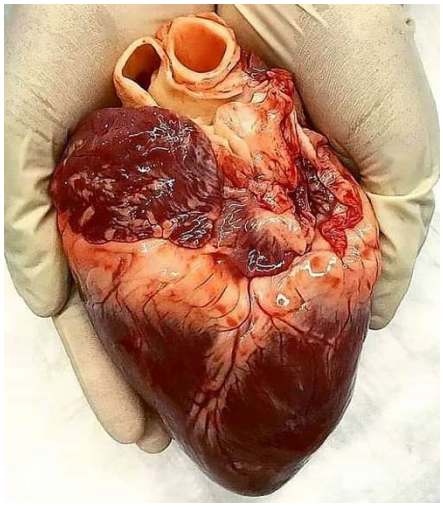

Figure 1- Healthy Human Heart

Alterations in the serum concentration of thyroid hormones (TH) have also been associated with HF. The non-thyroidal illness syndrome (NTIS) is a set of changes in the circulating concentrations of TH commonly seen in advanced HF. NTIS is represented by a decrease in serum triiodothyronine (T3) levels, which is, in more severe and prolonged cases of the syndrome, associated with a reduction in serum thyroxine (T4). These changes are not followed by an expected increase in the serum concentrations of thyroid-stimulating hormone (TSH). It has been suggested that between 18 and 30% of patients with congestive HF develop a drop in serum levels of T3. This drop has been associated with a reduced left ventricular ejection fraction (LVEF), a higher degree of diastolic dysfunction of the left ventricle (LVDD), and an increased risk of death[(2)].

All these cardiac abnormalities may be reversible with the restoration of normal thyroid hormone values. There are important differences between men and women in almost all aspects of HF due to gender-specific factors, primarily involving sex hormones[(3)].

Testosterone, the primary sex hormone in men, has been associated with LVDD and clinical parameters of HF in male patients. The peripheral effects of testosterone may explain most of its favorable effects on the pathophysiology of HF, but its central effects need further exploration. So far, the relationship between TH and the parameters of HF has not been investigated in greater detail in male patients with HF[(3) (4)].

This review will determine the association of five TH, namely free and total T3 (fT3 and TT3), free and total T4 (fT4 and TT4), and TSH, with LVEF and LVDD, and other clinical parameters of HF severity in men, while controlling for the effect of serum testosterone levels and other clinical factors.

Heart Failure

Heart failure (HF) is a chronic condition characterized by the heart's inability to effectively pump blood to meet the body's needs. It can be categorized as systolic heart failure, which involves impaired contraction of the heart, or diastolic heart failure, where the heart's ability to relax and fill with blood is compromised. Common symptoms include shortness of breath, especially during exertion or when lying down, fatigue, swelling in the legs, ankles, or abdomen (edema), persistent coughing or wheezing, and rapid or irregular heartbeat. HF can stem from various conditions that weaken or damage the heart muscle, such as coronary artery disease, hypertension, heart valve disorders, cardiomyopathy, congenital heart defects, infections, and certain medications or substances[5].

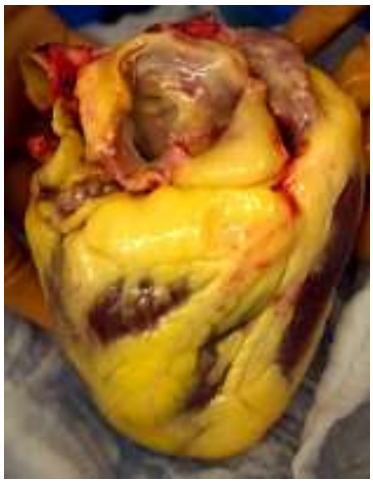

Figure 2- Human Heart with HF

Risk factors for HF development include advanced age, hypertension, diabetes, obesity, smoking, excessive alcohol consumption, family history of heart disease, and specific ethnic backgrounds. Diagnosis typically involves a comprehensive evaluation comprising medical history review, physical examination, blood tests (including BNP or NT-proBNP levels), imaging tests like echocardiogram or MRI, and sometimes cardiac catheterization or biopsy.

HF is a chronic condition with diverse outcomes, manageable with treatment but potentially leading to complications and reduced life expectancy if left untreated or if underlying causes remain unaddressed[6].

Treatment goals focus on symptom alleviation, enhancing quality of life, and slowing disease progression. Strategies may encompass lifestyle adjustments (e.g., dietary modifications, exercise, smoking cessation), medication regimens (e.g., ACE inhibitors, beta-blockers, diuretics, vasodilators), implanted devices (e.g., pacemakers, defibrillators), or surgical interventions (e.g., coronary artery bypass grafting, heart valve repair or replacement) [8].

Effect of thyroid hormone on heart failure

Thyroid hormones (TH) play crucial roles in modulating cardiac function through both cardiac and extra-cardiac mechanisms. They impact heart rate, rhythm, myocardial contraction, blood pressure, and cardiovascular risk factors, including hyperlipidemia, arterial hypertension, and thrombogenesis[9] [10]. The primary alteration of TH in heart failure (HF), known as the non-thyroidal illness syndrome (NTIS), manifests in changes in TH physiology at both the hypothalamic–pituitary–thyroid axis and organ and tissue levels. During the acute phase of critical illness, a decline in serum T3 levels may be accompanied by a transient increase in serum T4 levels. Prolonged illness can disrupt the thyroid axis, leading to decreases in serum T4 and thyroid-stimulating hormone (TSH) levels. Changes in TH levels associated with NTIS may carry prognostic significance for HF exacerbation and serve as independent predictors of cardiac and overall mortality[11].

T3 tissue availability is regulated by various factors, including TH membrane transporters, iodothyronine deiodinases, intracellular thyroid receptors, and hypothalamic thyrotropin-releasing hormone. Factors such as systemic inflammation, serum glucocorticoid elevation, or energy status can influence the expression of these regulators, potentially impacting T3 levels in NTIS[12]., Many experimental studies have demonstrated that proinflammatory cytokines (such as interleukins 6, 1, and 1β, and tumor necrosis factor α) downregulate various components of thyroid hormone (TH) synthesis and metabolism, while elevated glucocorticoid levels suppress the pituitary response to thyrotropin-releasing hormone (TRH) in men[13].

Turic et al. revealed strong predictive associations between total T3 (TT3) and three critical parameters of heart failure (HF) severity—left ventricular ejection fraction (LVEF), left ventricular diastolic dysfunction (LVDD), and N-terminal pro-brain natriuretic peptide (NT-proBNP)—during food deprivation[12] [14].

These associations remain independent of other relevant clinical variables, including testosterone levels. The study strongly supports TT3's pivotal role in modulating cardiac function and HF progression. This aligns with TT3's primary role in preserving LVEF, likely through enhancing cardiac contractility and reducing myocardial damage. Furthermore, TT3 may mitigate LVDD by reducing myocardial fibrosis through cardioprotective mechanisms, such as cytoprotection, metabolic adaptation, and neoangiogenesis[15].

Additionally, T3 has been implicated in lowering peripheral vascular resistance, which could contribute to HF amelioration by counteracting its progression's deleterious effects on the heart and circulation. These combined mechanisms likely underlie the overall beneficial effect of TT3 in HF, as evidenced by its strong inverse correlation with NT-proBNP levels in the studied patients[5] [13] [15].

Conclusion

This review concludes that among thyroid hormones, serum total triiodothyronine (TT3) levels demonstrate the strongest correlation with echocardiographic, laboratory, and clinical indicators of heart failure severity in men. This association remains significant independent of other clinical variables and factors, including circulating testosterone levels.

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The impact of ventricular assist devices in Mordern cardiology

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Abstract

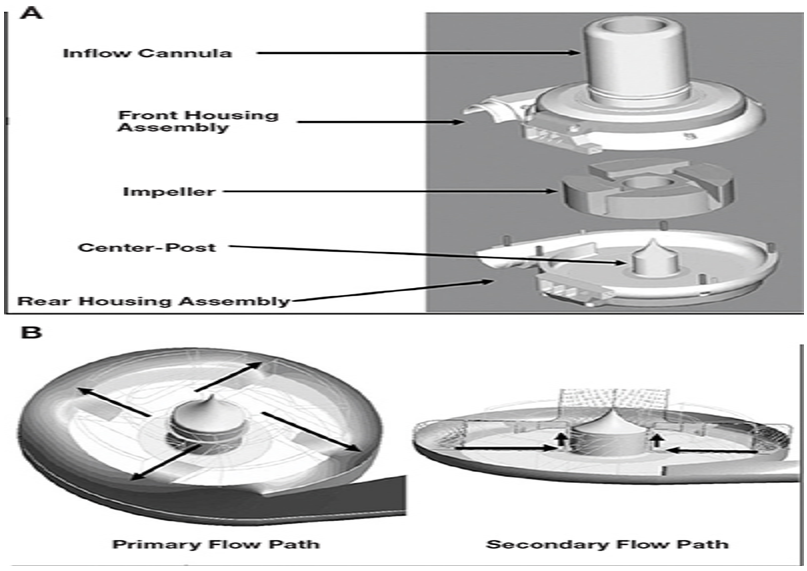
End-stage heart failure is frequently addressed utilizing ventricular assist devices. Continuous flow improvements in technology contributed to improved patient outcomes overall in addition to efficiency, size, implantability, and extended support. As a consequence, clinical relevance and application scenarios of left ventricular assist devices (LVADs) have risen. The book gives a description of the growth and current state of LVAD devices as well as forecasts for the technology's future. Ventricular Assist Devices (VADs) represent an indicator of hope for end-stage patients with cardiovascular disease in the realm of advanced cardiac therapies. These sophisticated mechanical pumps are not simply functional equipment; they are lifelines that unite the potential of survival and expanded quality of life alongside a potentially fatal root fail to function properly. A machine called a ventricular assist device (VAD) facilitates in the circulating of blood from the heart's lower chambers to the body's other vital organs. It is a therapy for heart failure or deterioration of the heart. While anticipating other therapies, such as a heart transplant, a VAD may be utilized to aid in the activity of the heart. A VAD might be used sporadically to assist the heart's blood output permanently. The left ventricle, the lower left chamber of the heart, serves as where a VAD is typically implanted. It is commonly referred to as a left ventricular assist device (LVAD) when it gets inserted into the left ventricle. The body absorbs blood from the heart consistently by virtue of LVADs. A different acronym over them is the terminus continous circulation devices.

Key words: Mechanical assistance apparatus -ventricular assist device (VAD) - right ventricular assist device (RVAD) - left ventricular assist device (LVAD) - Bi-ventricular assist device (BI-VAD) - as a bridge to a transplant.

Defintion

A Ventricular Assist Device (VAD) is a mechanical pump that is surgically implanted to help a weakened heart pump blood. It is used to support heart function and maintain blood flow in individuals with severe heart failure. VADs can serve as a bridge to heart transplantation, a bridge to recovery, or as a long-term solution for patients who are not eligible for heart transplantation.

HeartWare HVAD design and flow patterns:



(A) HVAD assembly: rotating impeller, magnetic center-post, and inflow cannula behind front housing.

(B) Represent the primary and secondary directs flow. Four centrifugally dedicated impeller flow channels receive the primary flow stream via the input cannula.

Via the outflow graft, blood leaves the housing assembly after amassing there. At the center post, the secondary flow path begins just below the impeller, generates an axial flow, and re-enters the primary flow path.

Indications:

Bridge to Transplant (BTT): Patients awaiting a heart transplant who have end-stage heart failure can receive assistance from VADs. The apparatus maintains blood flow until a suitable donor heart is found.

Destination Therapy (DT): VADs are an ongoing strategy to enhance quality of life and preserve survival for patients with chronic heart failure who are not suitable for a heart transplant because of their age, health, or other circumstances.

Bridge to Recovery (BTR): VADs can be implanted to give the heart time to rest and heal in circumstances when heart failure may be curable such as myocarditis or cardiogenic shock following a cardiotomy.

Bridge to Decision (BTD): VADs can offer bridging support until further examinations and alternatives are made when it's questionable whether a patient will make a full recovery or be a candidate for a transplant.

Short-Term Ventricular Assist Devices

While you wait for heart surgery, a VAD can gradually support your heart. If you are dealing with a severe cardiac challenge that can't be treatable with therapies, such as heart failure, ventricular arrhythmia, or cardiogenic shock, your doctor may recommend a short-term VAD. beforehand, while, with/or following surgery, a VAD can assist your heart and blood circulation while your heart rebounds. If your heart failure is catastrophic and the healthcare professionals need more analysis to figure out the most beneficial course of practice, a VAD could additionally be worthwhile.

Long-Term Ventricular Assist Devices

A healthcare provider would possibly recommend a VAD if you have heart failure and have not received a heart transplant. While you wait for a transplanted heart to become available, a VAD can prolong your life and enhance your quality of life if heart failure medications aren't working. A ventilator assist device (VAD) can be a very suitable long-term treatment option if you are not eligible for a heart transplant. It can help you live a better life and accomplish a lot of daily tasks.

When Is It Not Recommended to Use Ventricular Assist Devices?

VADs are typically not appropriate for those with certain critical health issues, like as heart failure, that could limit their long-term survival. This includes those suffering from severe infections, major brain injuries, acute kidney failure, and other potentially fatal illnesses.

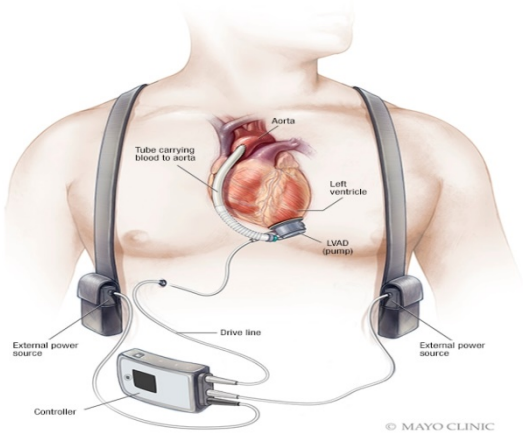
Types of Ventricular assist device (VAD):

- ❖ Left Ventricular Assist Device (LVAD)
- ❖ Right Ventricular Assist Device (RVAD)
- ❖ Bi-Ventricular Assist Device (Bi-VAD)
- ❖ Total Artificial Heart (TAH)

Pre-operative care forventricular assist device (VAD):

- o Medical Evaluation: an in-depth assessment to establish whether or not the patient is ideal for the implantation of a VAD.
- o Education: Enlightening the patient and those around them about the VAD, the process of surgery, and the recovery period.
- o Medication Management: altering or supplementing medications according to needs during preparation for surgery.
- o Nutritional Assessment: Determining that the patient has the correct nutrition to facilitate surgery and rehabilitation.
- o Psychosocial Evaluation: Analyzing the patient's emotional and mental awareness, and the quality of their networks of supporters.

Left ventricular assist device (LVAD):



Definition

A Left Ventricular Assist Device (LVAD) is a mechanical pump that is surgically implanted to assist the left ventricle of the heart in pumping blood to the rest of the body. It is used in patients with severe heart failure, specifically when the left ventricle is no longer able to pump blood effectively on its own.

Function

- **Assist the Left Ventricle:** The LVAD takes over some or all of the work of the left ventricle by pumping oxygenated blood from the left ventricle to the aorta and then to the rest of the body.
- **Improve Blood Flow:** Ensures adequate circulation of blood, thereby improving organ function and reducing symptoms of heart failure such as fatigue and shortness of breath.
- **Support Cardiac Function:** Acts as a bridge to heart transplantation, a bridge to recovery, or as a destination therapy for long-term support in patients who are not candidates for transplant.

Mechanism of action:

- **Blood Intake**: Blood flows from the heart into the VAD.
- **Pumping**: An internal pump within the device, powered by an external battery or power source, propels the blood.
- **Blood Output**: The blood is then sent back into the circulation, either to the aorta for left ventricular assist devices (LVADs) or to the pulmonary artery for right ventricular assist devices (RVADs).

Indications

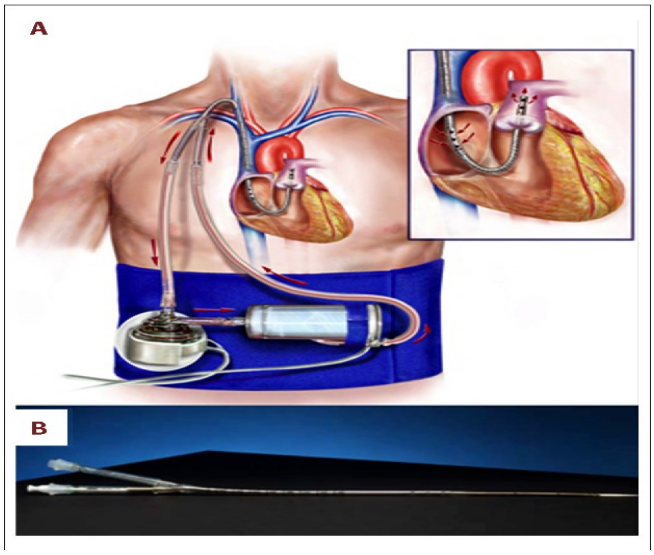
- **End-Stage Heart Failure:** Severe, advanced heart failure where other treatments have not been effective.
- **Bridge to Transplant:** Patients awaiting a heart transplant to maintain cardiac function until a donor heart becomes available.
- **Destination Therapy:** Long-term support for patients who are not candidates for heart transplantation.
- **Bridge to Recovery and Decision:** Temporary support for patients whose heart function might recover with time and rest.
- **Bridge to Decision:**Temporary support while determining the best long-term treatment option for the patient.

Contraindications

- **Severe Right Heart Failure:** Isolated right ventricular failure without left ventricular involvement, as LVADs specifically support the left ventricle.

- **Severe Pulmonary Disease:** Conditions such as severe chronic obstructive pulmonary disease (COPD) which can complicate post-surgical recovery and overall function.
- **Irreversible Renal or Hepatic Dysfunction:** Significant organ dysfunction that would not be corrected by improving cardiac output.
- **Active Infections:** Presence of active, uncontrolled infections can complicate surgical outcomes and post-implant recovery.
- **Severe Coagulopathy:** Blood clotting disorders that increase the risk of bleeding complications during and after surgery.
- **Inability to Manage Device:** Patients who cannot understand or manage the device and its external components due to cognitive or psychological conditions.

Right Ventricular Assist Device (RVAD):



A: (RVAD) B: (Catheter used for Blood flow)

Definition

A Right Ventricular Assist Device (RVAD) is a mechanical pump that is surgically implanted to assist the right ventricle of the heart in pumping blood to the lungs for oxygenation. It is used in patients with severe right-sided heart failure, where the right ventricle is unable to effectively pump blood.

Function

- **Assist the Right Ventricle:** The RVAD helps the right ventricle pump deoxygenated blood from the heart to the pulmonary arteries, which then carry the blood to the lungs for oxygenation.
- **Improve Pulmonary Circulation:** Ensures adequate blood flow to the lungs, improving oxygenation of the blood and reducing symptoms of right-sided heart failure.
- **Support Right Heart Function:** Acts as a bridge to recovery or, in some cases, as a temporary measure until other treatments or interventions can be applied.

Indications

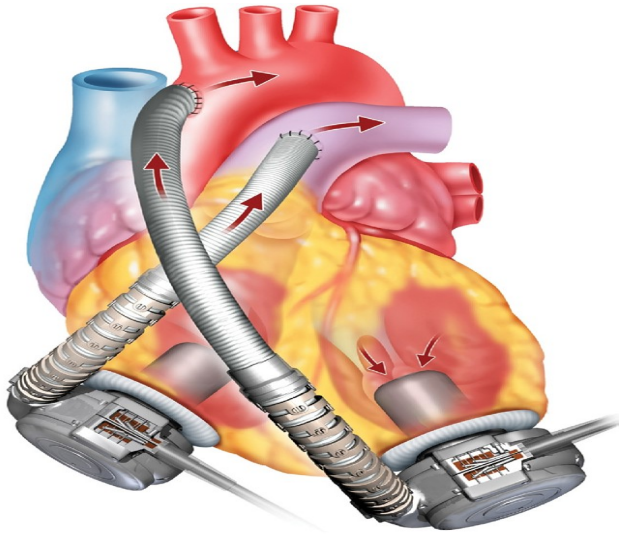
- **Right-Sided Heart Failure:** Severe right ventricular failure, often following a left ventricular assist device (LVAD) implantation if the right ventricle cannot handle the increased blood flow.
- **Post-Cardiotomy Support:** Temporary support following heart surgery, especially if the right ventricle is struggling to recover.
- **Acute Right Ventricular Failure:** Conditions such as right ventricular infarction or acute pulmonary embolism causing sudden right heart failure.
- **Bridge to Heart Transplant:** In combination with an LVAD or other device, to support patients awaiting a heart transplant.

Contraindications

- **Severe Left Heart Failure Without Right-Sided Involvement:** Isolated left ventricular failure would be better managed with an LVAD.
- **Severe Pulmonary Hypertension:** Extremely high pressures in the pulmonary arteries can render RVAD support less effective and pose additional risks.
- **Irreversible Multi-Organ Failure:** Significant organ dysfunction that would not be improved by supporting the right ventricle.
- **Active Infections:** Presence of active, uncontrolled infections can complicate surgical outcomes and post-implant recovery.
- **Severe Coagulopathy:** Blood clotting disorders that increase the risk of bleeding complications during and after surgery.

- **Inability to Manage Device:** Patients who cannot understand or manage the device and its external components due to cognitive or psychological conditions.

Biventricular Assist Device (BiVAD):



Definition

A Biventricular Assist Device (BiVAD) is a mechanical pump system that provides support to both the left and right ventricles of the heart. It is used in patients with severe biventricular heart failure, where both sides of the heart are unable to pump blood effectively.

Function

- **Assist Both Ventricles:** The BiVAD takes over the pumping function of both the left and right ventricles, ensuring that oxygenated blood is delivered to the body and deoxygenated blood is sent to the lungs for oxygenation.
- **Improve Blood Flow:** Enhances overall circulation, improving organ perfusion and reducing symptoms of heart failure.
- **Support Cardiac Function:** Acts as a bridge to heart transplantation, a bridge to recovery, or as a long-term support option for patients not eligible for transplant.

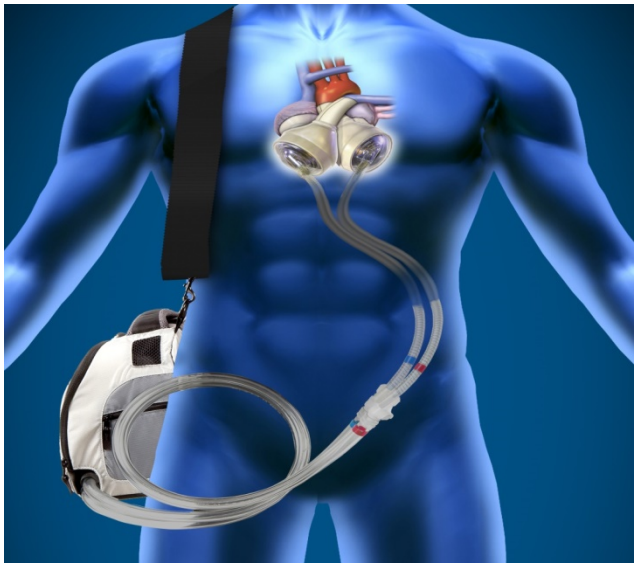
Indications

- **Severe Biventricular Heart Failure:** When both the left and right ventricles are failing, and other treatments have not been effective.
- **Bridge to Transplant:** Supporting patients awaiting a heart transplant, particularly when both ventricles are compromised.
- **Bridge to Recovery:** Temporary support for patients whose heart function might recover with time and rest, after events like acute myocarditis or severe cardiac surgery.
- **Post-Cardiotomy Support:** For patients who develop biventricular failure following cardiac surgery.
- **Bridge to Decision:** Providing time to determine the best long-term treatment plan for patients with severe heart failure affecting both sides of the heart.

Contraindications

- **Irreversible Multi-Organ Failure:** Significant dysfunction of organs that would not improve with improved cardiac output.
- **Severe Pulmonary Hypertension:** Extremely high pressures in the pulmonary arteries can make right ventricular support less effective and pose additional risks.
- **Severe Coagulopathy:** Blood clotting disorders that increase the risk of bleeding complications during and after surgery.
- **Active Infections:** Presence of active, uncontrolled infections can complicate surgical outcomes and post-implant recovery.
- **Inability to Manage Device:** Patients who cannot understand or manage the device and its external components due to cognitive or psychological conditions.
- **Significant Aortic Regurgitation:** Severe aortic valve insufficiency can complicate the function of a BiVAD.

Total Artificial Heart (TAH)



Definition

A Total Artificial Heart (TAH) is a mechanical device that replaces the function of both the left and right ventricles of the heart. Unlike ventricular assist devices (VADs) that support the existing heart, the TAH completely replaces the heart's ventricles and all four heart valves.

Function

- **Replace Heart Ventricles:** Completely take over the pumping action of the heart by replacing the left and right ventricles.
- **Maintain Blood Flow:** Ensure continuous and adequate blood flow to both the lungs and the rest of the body.
- **Provide Hemodynamic Support:** Maintain normal circulation and hemodynamics, similar to a natural heart, including maintaining appropriate blood pressures and cardiac output.

Indications

- **End-Stage Biventricular Heart Failure:** Severe heart failure affecting both ventricles where other treatments are not viable.
- **Bridge to Transplant:** Patients awaiting a heart transplant, especially when both ventricles are failing and temporary support is necessary to keep the patient alive until a donor heart is available.

- **Severe Congenital Heart Defects:** Cases where both ventricles are severely affected, and other surgical interventions are not possible.
- **Cardiomyopathy:** Severe forms of cardiomyopathy that affect both ventricles and are unresponsive to other treatments.

Contraindications

- **Irreversible Multi-Organ Failure:** Significant dysfunction of organs that would not improve with the restoration of cardiac output.
- **Severe Pulmonary Hypertension:** Extremely high pressures in the pulmonary arteries, which can complicate the effectiveness of the TAH.
- **Infection:** Presence of active, uncontrolled infections can increase the risk of complications during and after surgery.
- **Severe Coagulopathy:** Blood clotting disorders that increase the risk of bleeding complications during and after surgery.
- **Inability to Manage Device:** Patients who cannot understand or manage the device and its external components due to cognitive or psychological conditions.
- **Anatomical Limitations:** Structural or anatomical conditions that may make the implantation of the TAH technically infeasible or too risky.

Impact of VADs on Cardiac Function:

- Support Heart Function: VADs help pump blood from the lower chambers of the heart (ventricles) to the rest of the body, providing crucial support for a weakened heart or heart failure.
- Improve Organ Function: By increasing blood flow, VADs can improve the function of kidneys, liver, brain, and other organs.
- Enhance Quality of Life: They reduce symptoms such as fatigue, shortness of breath, and swelling, improving the patient's strength and ability to participate in activities.

Complication of VAD:

- Device malfunction
- Thrombosis
- Hemorrhage
- Drive-line infections

- Development of right-sided heart failure after LVAD implantation
- Air embolism
- Infection
- Aortic regurgitation
- Pump thrombosis
- Stroke
- cardiac dysrhythmia

Post-operative care:

- **Monitoring**: Close observation of vital signs, device function, and signs of infection.
- **Anticoagulation**: Management of blood thinners to prevent blood clots.
- **Wound Care**: Regular dressing changes and monitoring for signs of infection at the surgical site.
- **Rehabilitation**: Gradual physical therapy to improve strength and mobility.
- **Education**: Teaching the patient and caregivers about VAD management, battery changes, and emergency procedures.

Conclusion

Ventricular assist devices (VADs) have become a cornerstone in the management of end-stage heart failure, offering not only a bridge to transplantation but also serving as destination therapy and a bridge to recovery for many patients. The evolution of VAD technology has led to more compact, efficient, and durable systems that have significantly improved patient outcomes. As we look to the future, ongoing advancements in VAD design and patient care protocols hold the promise of further enhancing the quality of life and survival rates for individuals with advanced heart disease. The continued integration of VADs into cardiac care represents a beacon of hope and a testament to the remarkable progress in cardiovascular medicine.

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Nutrition, Physical Activity, and Lifestyle Shaping Cardiac Health Tomorrow

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Background

For Cardiovascular disease patients, the nutrition, physical activity, and lifestyle modifications play a critical role in heart disease in prevention and treatment. One of the main causes of death worldwide is still CVDS and reducing risk factors and enhancing general cardiovascular health requires living a heart healthy lifestyle. Cardiac Rehabilitation Guidelines recommend that both the illness representation model and the concept of self-efficacy can relevant frameworks for developing the effective psychological support, although undertaking regular physical activity can improve patient's prognosis and quality of life. The significance of these variables is discussed in this introduction, which also establishes the context for comprehending their vital roles in cardiac core.

Contribution of Changes in Diet

Introduction:

The relative contribution of health behaviours to cardiovascular diseases is to evaluate the additive and interactive effects of changes in health behaviours (dietary fat intake, exercise and stress management).Nutrition Guidelines for prevention of heart disease.

- Dietary modifications can play a major role in managing and preventing cardiovascular disorders.
- The following are some significant contributions: Limiting Saturated and Trans Fats: Reducing saturated and trans fats helps lower cholesterol

levels, which in turn lowers the risk of artery plaque development. Increasing Fiber Intake

- Heart disease risk is decreased by fibre's ability to balance blood sugar and lower cholesterol. Eating fish, nuts, and seeds is a good way to get omega-3 fatty acids, which can help lower triglycerides, reduce inflammation, and lower the risk of irregular heart rhythms. Reducing salt
- Cutting back on salt lowers blood pressure and lowers the risk of stroke and heart disease. A diet high in fruits and vegetables can help lower blood pressure, improve cholesterol levels, and reduce inflammation since they are a good source of vitamins, minerals, and antioxidants.

Promotion of Healthy Nutrition in Cardiac Patients

- Encouraging heart patients to eat healthily requires information, encouragement, and customized advice.
- The following are some tactics: Nutrition Education: Give thorough instruction on the significance of a heart-healthy diet, emphasizing the role of nutrients, portion control, and label reading.
- Customized Meal Plans: Assist patients in creating meal plans that are tailored to their tastes, cultural background, health history, and dietary requirements. Promote Whole Foods
- Stress the importance of eating a diet high in whole foods, such as fruits, vegetables, whole grains, lean meats, and healthy fats, and low in processed foods and sugar-filled drinks.
- Portion Control: Advise patients on how to maintain a healthy weight in order to avoid overindulging and to prevent cardiovascular disease. Promote Healthful Cooking Techniques
- Give advice on healthier cooking techniques like grilling, baking, steaming, and sautéing.

Various Risk Factors Influencing Cardiovascular Disease

Cardiovascular disease (CVD) risk factors can be broadly categorized into

- Modifiable
- Non-Modifiable factors

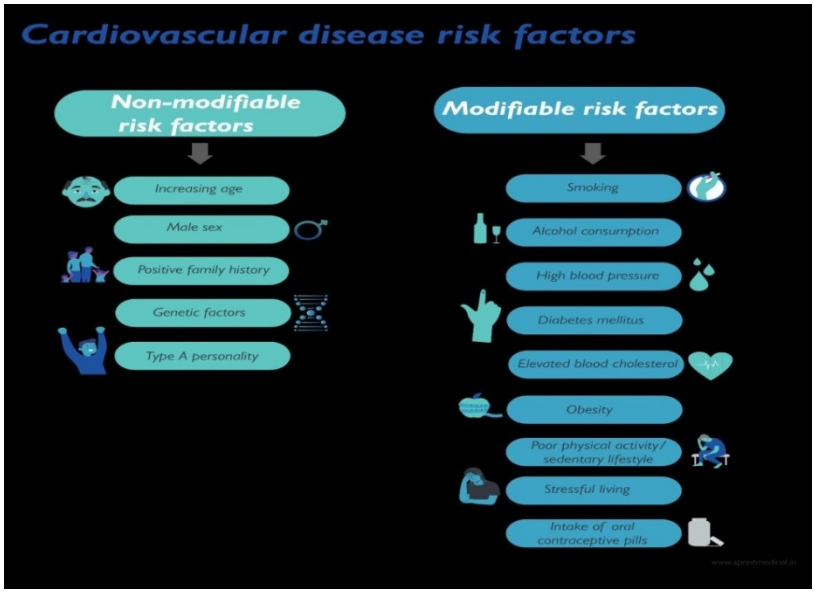
Modifiable Risk Factors:

- High Blood Pressure (Hypertension)Management
- Lifestyle changes (diet, exercise), medications. High Cholesterol Management Diet low in saturated fats, medications such as statins.
- Smoking Management: Smoking cessation programs, nicotine replacement therapy, medications.

- Diabetes Management: Blood sugar control through diet, exercise, and medications.
- Obesity Management: Healthy diet, regular physical activity, behavioural interventions, weight loss surgery if necessary.
- Physical Inactivity Management:
- Regular physical activity (150 minutes of moderate exercise per week).
- Unhealthy Diet Management: Diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats.
- Excessive Alcohol Consumption Management: Limiting alcohol intake to moderate levels. Stress Management
- Stress reduction techniques such as mindfulness, therapy, and relaxation exercises.

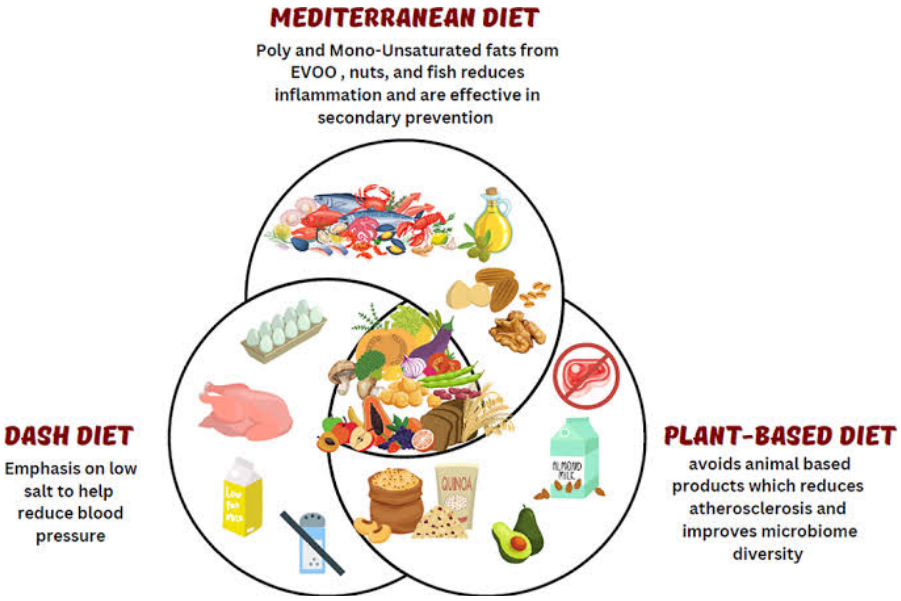
Non-Modifiable Risk Factors

- These are factors that cannot be changed, but Age Risk of CVD increases with age. Gender Men are generally at higher risk at an earlier age
- The risk for women increases and can surpass men's risk after menopause.
- Family History of CVD Genetic predisposition to heart disease. Ethnicity Certain ethnic groups have higher risks for CVD (e.g., African Americans, South Asians).
- Emerging Risk Factors These factors are currently being studied for their role in increasing CVD risk.
- Inflammation Markers like C-reactive protein (CRP) indicate inflammation and higher CVD risk.
- Sleep Apnea Obstructive sleep Apnea is associated with higher CVD risk. Chronic Kidney Disease Increases risk of hypertension and heart disease. Autoimmune Diseases Conditions like rheumatoid arthritis and lupus can increase CVD risk.
- Psychosocial Factors Depression, social isolation, and chronic stress are linked to higher CVD risk.



Heart Healthy Management

These aspects comprehensively and tailoring interventions to the individual needs of each patient, healthcare providers can effectively manage heart health in cardiac patients and improve their quality of life while reducing the risk of complications. Regular monitoring and adjustments to the treatment plan as needed are essential for long-term success.



Food Guide for a Healthy Heart:

Eat This	Limit This	Avoid This
Fresh Fruits	-	Canned Fruits in Syrup
Green Leafy Vegetables	Roots, Tubers	Fried Vegetables, Chips
Wheat, Rice, Ragi	Maida	Cakes, Pastries, Noodles
Buttermilk	Whole milk	Cheese, Butter
Egg White	-	Egg Yolk
Fish	Chicken	Shrimps
Fresh Juice	Coffee, Tea	Alcohol

Interventions to Promote Physical Activity

- For cardiac patients, physical activity is vital, but it's important to exercise caution and get medical advice before beginning.
- The following are some broad recommendations for physical activity in heart patients Consultation
- Heart patients should discuss their specific condition, risk factors, and suitability for physical activity with their healthcare physician prior to beginning any exercise program.
- Cardiac Rehabilitation by taking part in a program that usually consists of counselling, education, and supervised exercise training, cardiac patients can safely raise their levels of physical activity and enhance their general heart health.
- Begin Gradually: Start with low-intensity exercises like walking, stationary cycling, or light resistance training, and then progressively increase the intensity and duration as you feel comfortable. Keep an eye on the intensity: Apply the Borg Perceived Exertion Rating (RPE).

Exercise Recommendation:

- Exercise is essential for heart patients, but it must be done carefully.
- **Consultation:** Give priority to seeing a cardiologist or other healthcare professional to evaluate each person's cardiac health and establish any restrictions on exercise.
- **Commence Slow:** Start with low-intensity workouts to gradually raise heart rate, like comfortable walking or light stretching.

- **Duration:** Build up from shorter periods of time to at least 30 minutes of moderate-intensity activity most days of the week.
- **Exercise on a regular basis**: attempting to be consistent throughout the week. Keep your intensity at a moderate level so that you can talk without being out of breath yet still feel comfortable. Avert straining yourself to fatigue.

Overcoming Barriers to Physical Activity

Improving cardiovascular health for persons with heart disease requires removing obstacles to physical activity.

The following are some tactics:

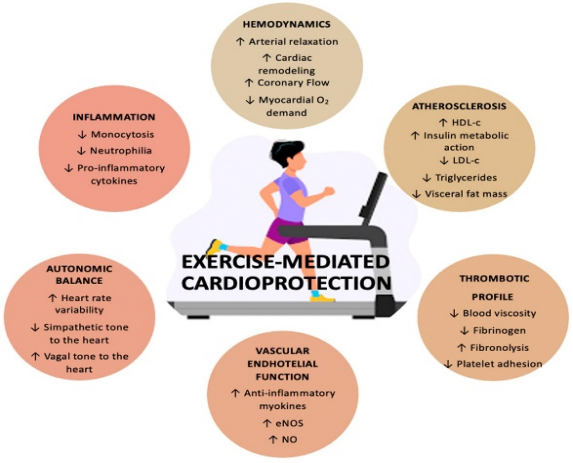
Education: Educate people on the value of exercise for heart health and debunk any rumours or false beliefs regarding physical activity after a heart attack.

Customized Exercise Programs: Create exercise regimens that are safe and efficient while taking into account each person's preferences, health issues, and physical constraints.

Support System: To offer inspiration, accountability, and encouragement for sticking to fitness regimens, encourage the engagement of friends, family, or support groups.

Monitoring Tools: To track exercise intensity and progress and to provide feedback and assurance, use wearable fitness trackers or heart rate monitors that have been prescribed by medical professionals.

Handling Anxiety: Use counselling, relaxation methods, or progressive exposure treatment to address worries or anxiety related to exercising after a cardiac incident.



Lifestyle Prevention of Cardiovascular Disease

Cardiovascular disease (CVD) risk factors can be broadly categorized into

Modifiable Management:

- High Blood Pressure (Hypertension) Management: Lifestyle changes (diet, exercise), medications.
- High Cholesterol Management: Diet low in saturated fats, medications such as statins.
- Obesity Management:Healthy diet, regular physical activity, behavioural interventions, weight loss surgery if necessary
- Increased insulin resistance.
- Increased systemic inflammation and prothrombotic effect.
- Dyslipidemia.
- Albuminuria.
- Smoking Management: Smoking cessation programs, nicotine replacement therapy, medications.
- Diabetes Management: Blood sugar control through diet, exercise, and medications
- Physical Inactivity Management: Regular physical activity (150 minutes of moderate exercise per week).
- Unhealthy Diet Management: Diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats.
- Excessive Alcohol Consumption Management: Limiting alcohol intake to moderate levels.
- Stress Management: Stress reduction techniques such as mindfulness, therapy, and relaxation exercises.

Conclusion

In conclusion, adopting a healthy diet, engaging in regular physical activity, and making positive lifestyle changes are foundational strategies for preventing and managing cardiovascular disease. These interventions work synergistically to improve overall heart health and reduce the risk of adverse cardiac events.

Remember, Small Changes Can Make A Big Difference In Your Heart Health !!!.....

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(Sacubitril/Valsartan): First-in-Class Angiotensin Receptor Neprilysin Inhibitor FDA Approved for Patients with Heart Failure

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Abstract

Heart failure affects an estimated 5.7 million patients aged ≥20 years in the United States, according to the 2009–2012 National Health and Nutrition Examination Survey.Approximately 870,000 new cases of heart failure occur annually. Heart failure is projected to affect more than 8 million individuals aged ≥18 years in the United States by 2030, representing a 46% increase from 2012. The incidence of heart failure is substantially higher in the elderly population, approaching 10 of 1000 people aged ≥65 years.

Heart failure is a life-threatening condition that occurs when the heart cannot pump enough blood and oxygen to meet the body's needs. Approximately 50% of patients with heart failure die within 5 years of diagnosis.3 In fact, heart failure was a contributing cause of death in 1 of 9 deaths in 2009.3 The common causes of heart failure include coronary artery disease, diabetes, obesity, and hypertension.

Introduction

The symptoms of heart failure include dyspnea, fatigue and weakness, edema, persistent cough, rapid or irregular heartbeat, and anginal pain.2,4 Heart failure is generally categorized into 4 classes

(class I-IV) based on symptom severity, as delineated in the New York Heart Association (NYHA) functional classification system.

NYHA Functional Classification of Heart Disease Severity

Class	Functional capacity/symptoms
I	Physical activity is not limited Typical physical activity does not result in undue fatigue, palpitation, dyspnea, or anginal pain
II	Some limitation of physical activity The patient is comfortable at rest Typical physical activity causes fatigue, palpitation, dyspnea, or anginal pain
III	Considerable physical limitation The patient is comfortable at rest Less than ordinary physicial activity results in fatigue, palpitation, dyspnea, or anginal pain
IV	Inability to conduct any physical activity without discomfort The patient has symptoms of heart failure even at rest Increased discomfort with any physical activity

NYHA indicates New York Heart Association.

Adapted from the American Heart Association. Classification of functional capacity and objective assessment. 1994. http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp. Accessed July 27, 2015.

Ejection fraction is a key measurement in assessing the heart's ability to pump out blood and in diagnosing and monitoring heart failure. A substantial number of patients with heart failure have a normal ejection fraction. A preserved ejection fraction (ie, diastolic heart failure) indicates that the heart muscle contracts normally, but the ventricles do not relax as they should; a reduced ejection fraction (ie, systolic heart failure) indicates that the heart muscle does not contract effectively and less oxygen-rich blood is pumped out to the body.

Pharmacologic treatments for heart failure typically comprise a combination of drugs depending on the symptoms. Until recently, these drugs included renin-angiotensin system inhibitors, such as angiotensin-

converting enzyme (ACE) inhibitors and angiotensin II receptor blockers, in addition to beta-blockers, diuretics, aldosterone antagonists, inotropes, and digoxin.

FDA Approves Sacubitril plus Valsartan for Chronic Heart Failure

On July 7, 2015, the US Food and Drug Administration (FDA) approved sacubitril plus valsartan (Entresto; Novartis) to reduce the risk for cardiovascular (CV) death and hospitalization in patients with chronic heart failure (NYHA Class II-IV) associated with reduced ejection fraction.Sacubitril plus valsartan oral combination is the first angiotensin receptor neprilysin inhibitor to receive FDA approval for this indication.

Valsartan (Diovan) was initially approved by the FDA in 1996 for the treatment of hypertension and in 2002 for the treatment of heart failure.In 2005, valsartan received FDA approval to reduce CV mortality in clinically stable patients with left ventricular (LV) failure or with LV dysfunction after a myocardial infarction.

The FDA granted the new oral combination a fast-track review, based on its potential to treat a serious or life-threatening condition and fill an unmet need.

“Heart failure is a leading cause of death and disability in adults,” said Norman Stockbridge, MD, PhD, Director of the Division of Cardiovascular and Renal Products at the FDA Center for Drug Evaluation and Research. “Treatment can help people with heart failure live long and enjoy more active lives.”

Mechanism of Action

Sacubitril is a neprilysin inhibitor and valsartan is an angiotensin receptor blocker.11 The combination of sacubitril plus valsartan inhibits neprilysin (neutral endopeptidase) via LBQ657, the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT1) receptor via valsartan.11 Valsartan inhibits the effects of LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT1 receptor; it also inhibits angiotensin II–dependent aldosterone release.

Via multimodal action, sacubitril plus valsartan enhances the beneficial response of the neurohormonal system of the heart while inhibiting the damaging effects of the renin-angiotensin-aldosterone system.

Dosing and Administration

The recommended starting dose of sacubitril plus valsartan is 49 mg of sacubitril/51 mg of valsartan twice daily.11 The dose is doubled after 2 to 4 weeks to the target maintenance dose of 97 mg of sacubitril/103 mg of valsartan twice daily, as tolerated by the patient.

A reduced starting dose of 24 mg of sacubitril/26 mg of valsartan twice daily should be used in patients who are not currently taking an ACE inhibitor or an angiotensin II receptor blocker, or previously taking a low dose of these agents; patients with severe renal impairment; and patients with moderate hepatic impairment. The dose is doubled every 2 to 4 weeks to the target maintenance dose of 97 mg/103 mg (sacubitril/valsartan) twice daily, as tolerated by the patient.

Sacubitril plus valsartan is available as film-coated tablets in several strengths, including 24 mg/26 mg; 49 mg/51 mg; and 97 mg/103 mg.

PARADIGM-HF: Sacubitril plus Valsartan versus Enalapril Alone

The primary objective of the PARADIGM-HF trial was to determine whether treatment with sacubitril plus valsartan was superior to enalapril, a renin-angiotensin system inhibitor, in reducing the risk for the combined end point of CV death or hospitalization for heart failure.The primary end point was the first event in the composite of CV death or hospitalization for heart failure. The median follow-up duration was 27 months, and patients received treatment for up to 4.3 years.

The patients' mean age was 64 years. At the time of randomization, 70% of patients had NYHA Class II, 24% had NYHA Class III, and 0.7% had NYHA Class IV heart failure. The mean LV ejection fraction was 29%.11 The underlying cause of heart failure was coronary artery disease in 60% of patients; 71% had a history of hypertension, 43% had a history of myocardial infarction, 37% had an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m2, and 35% had diabetes mellitus.

PARADIGM-HF Study: Effect of Sacubitril plus Valsartan versus Enalapril on the Primary Composite End Point, Its Components, and All-Cause Mortality

Outcome	Sacubitril plus valsartan, N (%) (N = 4187)	Enalapril, N (%) (N = 4213)	Hazard ratio	*P* value
Primary composite end point	914 (21.8)	1117 (26.5)	0.80 (95% CI, 0.73–0.87)	<.001
CV death as first event	377 (9.0)	459 (10.9)		
Heart failure hospitalization as first event	537 (12.8)	658 (15.6)		
Patients with events[a]				
CV death[b]	558 (13.3)	693 (16.5)	0.80 (95% CI, 0.71–0.89)	
Heart failure hospitalizations	537 (12.8)	658 (15.6)	0.79 (95% CI, 0.71–0.89)	
All-cause mortality	711 (17.0)	835 (19.8)	0.84 (95% CI, 0.76–0.93)	.009

a. Analyses of the components of the primary composite end point were not prospectively planned to be adjusted for multiplicity.
b. Includes patients who had heart failure hospitalization before death.

CV indicates cardiovascular; CI, confidence interval.

Sources: Entresto (sacubitril and valsartan) tablets prescribing information; July 2015; McMurray JJV, et al; for the PARADIGM-HF Investigators and Committees. N Engl J Med. 2014;371:993–1004.

Adverse Events

The most common adverse reactions (incidence ≥5%) with sacubitril plus valsartan included hypotension, hyperkalemia, cough, dizziness, and renal failure (Table 3).11 In the double-blind period of the PARADIGM-HF study, safety was evaluated in 4203 patients who received sacubitril plus valsartan versus 4229 patients who received enalapril. Patients used sacubitril plus valsartan for up to 4.3 years, with a median exposure of 24 months; 3271 patients received treatment for more than 1 year.11 Overall, 10.7% of patients who received sacubitril

plus valsartan discontinued treatment because of an adverse event versus 12.2% of patients who received enalapril.

Adverse Reactions Reported in ≥5% of Patients Receiving Sacubitril plus Valsartan versus Enalapril in the PARADIGM-HF Study

Adverse event	Sacubitril plus valsartan, % (N = 4203)	Enalapril, % (N = 4229)
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure or acute renal failure	5	5

Source: Entresto (sacubitrilandvalsartan) tabletsprescribinginformation; July2015.

Contraindications

The use of sacubitril plus valsartan is contraindicated in patients with hypersensitivity to any component of sacubitril plus valsartan; in patients with a history of angioedema related to previous use with an ACE inhibitor or an angiotensin II receptor blocker therapy; with concomitant use of ACE inhibitors; and with concomitant use of aliskiren in patients with diabetes.

Warnings and Precautions

Boxed warning. Sacubitril plus valsartan should be discontinued as soon as possible when pregnancy is detected. In addition, drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

Fetal toxicity. Sacubitril plus valsartan can cause fetal harm when administered to a pregnant woman. When pregnancy is detected, the use of this drug should be discontinued and alternative treatment should be considered.

Angioedema. Sacubitril plus valsartan may cause angioedema. If angioedema occurs, therapy should be discontinued immediately, appropriate therapy should be provided, and the patient should be monitored for airway compromise; sacubitril plus valsartan must not be readministered.

Hypotension. Sacubitril plus valsartan lowers blood pressure and may cause symptomatic hypotension. Patients with an activated renin-angiotensin system, including patients with volume and/or salt depletion (eg, patients receiving high doses of diuretics), are at a greater risk for developing

hypotension. If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension should be considered.

Impaired renal function. Decreases in renal function may be anticipated in susceptible individuals who receive sacubitril plus valsartan. Sacubitril plus valsartan should be down-titrated or interrupted in patients who develop a clinically significant decrease in renal function.

Hyperkalemia. Hyperkalemia may occur with sacubitril plus valsartan therapy.11 Serum potassium levels should be monitored periodically; patients with risk factors for hyperkalemia, including severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet should receive appropriate treatment. Dosage reduction or interruption of sacubitril plus valsartan may be required.

Use in Specific Populations

Pregnancy. Sacubitril plus valsartan can cause fetal harm.11 An alternative drug treatment should be considered and sacubitril plus valsartan should be discontinued when pregnancy is detected.

Lactation. Breast-feeding is not recommended during treatment with sacubitril plus valsartan, because of the potential for serious adverse reactions from the exposure to this medication.

Pediatric use. The safety and efficacy of sacubitril plus valsartan have not been established in pediatric patients.

Geriatric use. No relevant pharmacokinetic differences were observed in elderly (>65 years) or in very elderly (≥75 years) patients compared with the overall population.

Renal impairment. A starting dose of 24 mg of sacubitril/26 mg of valsartan twice daily is recommended for patients with severe renal impairment (eGFR <30 mL/min/1.73 m2).11 The dose should be doubled every 2 to 4 weeks to the target maintenance dose of 97 mg of sacubitril/103 mg of valsartan twice daily, as tolerated by the patient. No dose adjustment is required when in patients with mild or moderate renal impairment.

Hepatic impairment. A starting dose of 24 mg of sacubitril/26 mg of valsartan twice daily is recommended for patients with moderate hepatic impairment (Child-Pugh B classification). The dose should be doubled every 2 to 4 weeks to the target maintenance dose of 97 mg of sacubitril/103 mg of valsartan twice daily, as tolerated by the patient. No dose adjustment is

required in patients with mild hepatic impairment. The use of sacubitril plus valsartan is not recommended in patients with severe hepatic impairment.

Conclusion

The FDA approval of sacubitril plus valsartan made available a novel, oral treatment option for patients with heart failure. The first-in-class angiotensin receptor neprilysin inhibitor sacubitril plus valsartan demonstrated a significant mortality benefit in patients with heart failure with reduced ejection fraction in the PARADIGM-HF trial, a head-to-head study that compared sacubitril plus valsartan with enalapril.

Sacubitril plus valsartan may have an important therapeutic role in reducing the risk for CV death and hospitalizations in patients with heart failure associated with reduced ejection fraction.

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Cardiac Amyloidosis: Recent Advances 2024

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1. Introduction

Amyloidosis consists of amyloidogenic protein deposition, made of low molecular weight subunits, most of which circulate as plasma components. The amyloid deposits are formed by subunit proteins arising from soluble precursors. These proteins have undergone conformational changes that gave rise to an antiparallel beta-pleated sheet.

There are more than 30 precursor proteins which could form deposits in the extracellular space, leading to progressive organ dysfunction.

Amyloidosis are caused by 3 subtypes: the most common form, (approximately 70% of all cases) is AL amyloidosis, due to the deposition of misfolded immunoglobulin light chains. The other two forms with increased prevalence are ATTR amyloidosis caused by deposition of transthyretin either as wild-type (ATTRwt) form, or mutated/variant (ATTRv).

Cardiac Amyloidosis is a myocardial infiltrative disease due to amyloid fibril deposition in the extracellular space of the heart. The infiltrative process results in increased thickness of the left ventricular wall, diastolic dysfunction and heart failure.

In yester years amyloidosis were considered as s rare condition, managed primarily by haematologists, neurologists and nephrologists. Cardiac

Amyloidosis used to be diagnosed later stages of the disease, with negative impact on prognosis of these patients. In recent times there has been increased emphasis on early diagnosis on optimization of screening and diagnosis of CA, with the advent of targeted therapies, which showed increased efficacy in treating CA if they are applied early in the course of the disease.

Systemic forms of amyloidosis affecting the heart, are mainly AL, ATTRwt, and some forms of ATTRv amyloidosis. (ATTRwt – wild type; ATTRv-variant).

2. Pathophysiology and Epidemiology

The pathophysiology of Cardiac Amyloidosis is complex. Amyloid infiltration of the heart leads to a decrease in ventricular compliance, which in turn causes diastolic dysfunction. The decrease in ventricular compliance is associated with an elevation in ventricular filling pressures. Backward transmission of high filling pressures results in bi-atrial dilatation and stasis.

AL amyloidosis (AL-Amyloidosis Light chain or Primary Amyloidosis) is caused by a small clonal B cell or plasma cell population, with 10% of patients having multiple myeloma. From a pathophysiological standpoint there is interstitial deposition of immunoglobulin light chains, as well as direct toxicity on the myocytes caused by the free light chains. These chains can induce lysosomal dysfunction, oxidative stress, apoptosis, and dysregulation of MAP kinase signaling transduction pathways as well as autophagy. The amount of cardiac involvement independently predicts mortality.

Transthyretin (TTR), which is a transport protein for retinol and thyroid hormone synthesized by the liver, can form amyloid fibrils when it dissociates from tetramers into monomers. The destabilization tetramers with accumulation of TTR monomers can result from gene mutations in the TTR gene (ATTRv) or are the result of age-related processes (ATTRwt).

Cardiac involvement in AL amyloidosis is a major determinant of prognosis, with mean survival time is only about 6 months without treatment in cases with advanced cardiac disease and HF. The median overall survival is extended to >5 years if modern treatment strategies are used.

3.Clinical manifestations

The symptoms predominantly related with right ventricular failure and restrictive cardiomyopathy, is the common presentation in CA.

i. Pedaloedema is nonspecific, common in heart failure (HF).

ii. Elevation of jugular venous pressure
iii. Pleural effusion
iv. Ascites
v. Pain in the right hypochondriac region due to liver congestion
vi. Orthopnoea.
vii. Syncope may occur due to brady arrhythmias or high-degree/complete atrioventricular block (common in AL type); hypotension induced by autonomic neuropathy is another possibility.
viii. Palpitationsoccur in presence of atrial fibrillation (AF) due to atrial infiltration by amyloid deposits or by the dilated atrium secondary to restrictive cardiomyopathy. Ventricular tachyarrhythmias occur in advanced stages, leading to sudden cardiac death.

In advanced CA with systolic dysfunction, low cardiac output symptoms such as fatigue, dizziness, weakness, hypotension, delayed capillary refill and decreased pressure of pulse wave may occur.

Angina or myocardial infarction, rarely develop as a cause of microvascular dysfunction or amyloid deposits in the coronary arteries. However, an in vitro experiment performed by Liao R. et al. showed that amyloidogenic light chainshave a direct toxic effect on cardiac myocytesand it explains the patients with AL amyloidosis have poorer quality of life than those with ATTR amyloidosis with the same degree of cardiac involvement.

Extracardiac organ involvement leads to nephrotic syndrome, gastrointestinal symptoms, pulmonary disease, bleeding diathesis, macroglossia, purpura, musculoskeletal abnormalities, carpal tunnel syndrome, etc.

Pulmonary amyloidosis can present as diffuse alveolar septal involvement, tracheobronchial and nodular parenchymal amyloidosis in 50% of the cases. Clinical manifestations of pulmonary amyloidosis could be misinterpreted because of the nonspecific symptoms such as dyspnoea at exertion, weight loss or productive cough. Due to poor prognosis seenin pulmonary involvement of CA,detailed work-up and specific treatment is mandatory.

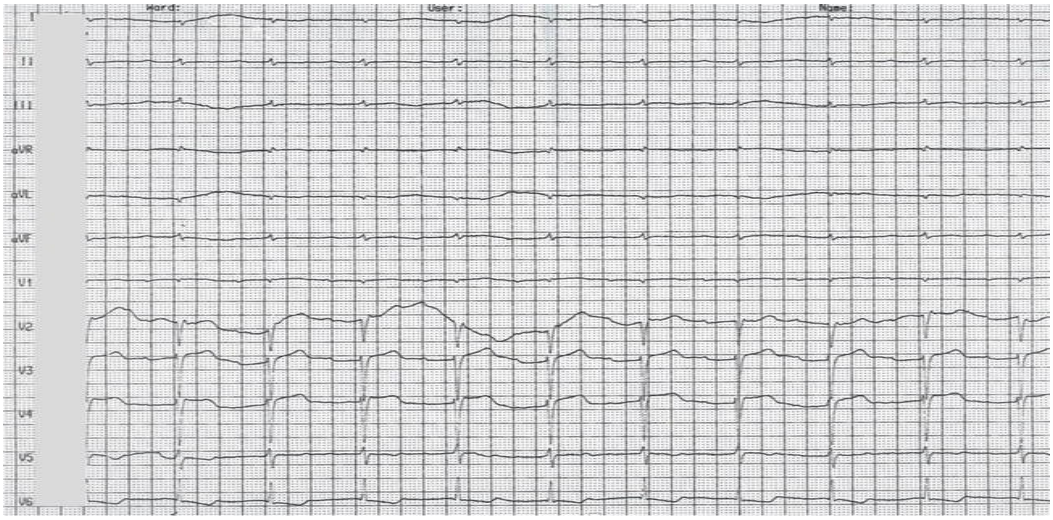
With all these clinical considerations, CA should be considered as differential diagnosis in a patient with HF, unexplained left ventricular hypertrophy and preserved ejection fraction.

4. Laboratory and electrocardiographic findings in CA

There is no specific serum biomarker for the ATTR subtype. In the case of AL amyloidosis however, blood screening tests are available such aselectrophoresis and immunofixation of serum and urine proteins, as well as quantification of immunoglobulin free light chain levels with evaluation of the kappa - lambda ratio. Due to the possible presence of a monoclonal gammopathy of undetermined significance (MGUS) in up to 5% of the general population aged >65 years, positive laboratory findings need to be carefully evaluated. In the meantime, the cardiac amyloidosis' ATTR subtype may coexist with MGUS and needs to be differentiated from the AL subtype by seeking evidence of amyloid infiltration in affected organs with identification of the precursor protein.

Amyloid fibrils deposition in the myocardium is often correlated with the onset of arrhythmias and conduction abnormalities, consequently highlighting the key role of the electrocardiogram (ECG) in the diagnostic assessment. One of the ECG findings is the presence of diffuse low voltage in the limb and/or precordial leads. Even if this ECG finding is not very sensitive and it generally occurs only in late the stages of the disease, it is common, specific and has prognostic signficance in patients with CA. In order to increase the diagnostic sensitivity, a low-voltage-to-mass ratio assessment was suggested (given the discordance between the low voltage on the ECG and the left ventricular hypertrophy on cardiac imaging) (Figure 1).

Figure 1.ECG with low voltage seen in the frontal plane leads in a patient with AL type cardiac amyloidosis.



Another important finding on the ECG, which is present in 70% of CA, is the pseudoinfarction pattern which consists of pathologic Q or QS waves in any two consecutive leads, but without any history of infarction and without wall motion abnormalities. As previously mentioned, patients with CA also tend to develop, as the disease progresses, arrhythmias which range from brady- and tachyarrhythmias or sudden cardiac death. The most common arrhythmia noted in CA is AF (up to 70% of patients), but ventricular arrhythmias such as premature ventricular beats or ventricular tachycardia can also occur. Conduction disease is also common and appears to be more frequent in the wtATTR subtype. This last condition can require implant of a pacemaker.

5. Diagnostic suspicion of CA

In olden era CA used to be underdiagnosed, given its nonspecific symptoms and thought to be a rare condition. In order to improve diagnostic specificity and sensitivity different “red flag” signs can be used to raise the clinical suspicion and allow an early diagnosis.

ATTR amyloidosis which consequentially determines cardiac amyloid infiltration is usually preceded years before onset by various clinical presentation such as: carpal tunnel syndrome, lumbar spinal stenosis, and biceps tendon rupture ;also often associated with sensory motor polyneuropathy, autonomic dysfunction as orthostatic hypotension, erectile dysfunction, gastrointestinal motility disorders or urinary retention.

Macroglossia and Periorbital purpura are specific signs of AL amyloidosis and rarely seen in ATTR subtype. Other “red flags” for AL subtype are hepatomegaly and peripheral neuropathy.Also whenever there is an undifferentiated cardiac hypertrophy and nephrotic proteinuria, AL amyloidosis should be considered as a possible diagnosis.

6. Echocardiography in CA

Transthoracic echocardiogram is the most common non-invasive imaging tool used in patients with suspected or confirmed amyloidosis. In 1975 Chew et al. described for the first time the echocardiographic appearance of CA, based on M-mode tracings. The features seen were: normal diastolic size of the left ventricle, increased systolic dimension and pericardial effusion; given these findings, the term” stiff heart” was chosen in these patients.

Later on more echocardiographic features were added to the amyloid phenotype: symmetric thickness of the left ventricular wall in patients with no history of hypertension or aortic valvular abnormalities, hypokinetic interventricular septum and posterior left ventricular wall with decreased systolic thickening, normal or small left ventricle cavity, increased thickness of the right ventricular anterior wall, dilated left atrium, a decrease of the E-F slope (given reduced ventricular compliance).

6.1 Two-dimensional echocardiography

With the advancements in 2D echocardiography few defining features of CA are detected by left ventricular hypertrophy with a normal/reduced cavity volume, increased thickness of the right ventricular wall and the valves (especially aortic and mitral valves), and bi-atrial enlargement (Figures 2 and 3).

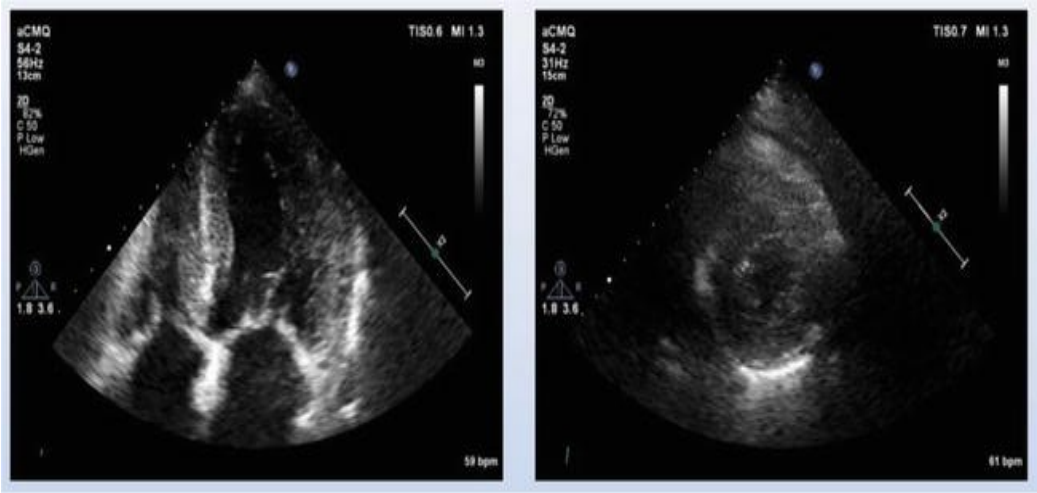


Figure 2. 2D echocardiogram (apical 4 chamber view and parasternal short axis view) in a patient with AL type cardiac amyloidosis revealing increased thickness of the left ventricular walls.

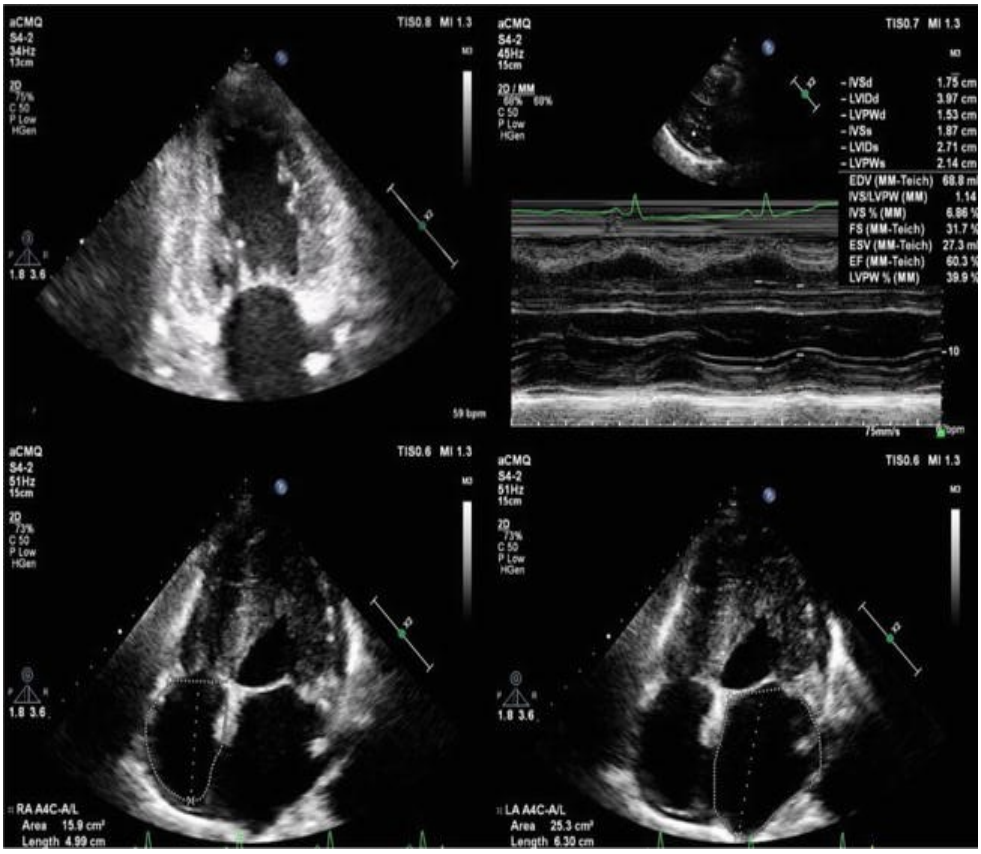


Figure 3. 2D echocardiogram (apical 2 chamber view, M-mode in parasternal long axis view and apical 4 chamber view) in a patient with AL type showing increased thickness of the left ventricular walls, biatrial dilatation and hypertrophic interatrial septum.

The left ventricular wall thicknessvarydepending on the amyloidosis type: symmetrical in AL and asymmetrical in ATTR. The presence of extracellular amyloid deposits gives the myocardium a, “granular sparkling” appearance, better visualized at the interventricular septum. A small pericardial effusion or dilated inferior vena cava are often observed as signs of a restrictive filling pattern.

6.2 Doppler

Doppler ultrasound offered better ways to characterize the heart's function and structureand the diastolic dysfunction, a main feature of CA in 1980s. First studies, performed by Klein et al. revealed that in early stages, when the parietal thickness of the left ventricle is 12-15 mm, there is an abnormal relaxation with a reduced early filling velocity, elevated late velocity, reduced early to late velocity ratio and longer isovolumic relaxation time. Contrary to this, in late-stage CA associated with significant ventricular wall thickening (parietal thickness equal to or more than 15 mm) an elevated E/A ratio was observed, suggesting a restrictive cardiomyopathy. In late-stage disease the deceleration time is markedly reduced (restrictive pattern).

The diastolic function is usually severely impaired, with a restrictive pattern defined by a decrease deceleration time on the transmitral pulsed Doppler and low tissue Doppler velocities in the left ventricular wall; E/e' is often higher than 15, which suggests elevated filling pressures (Figure 4).

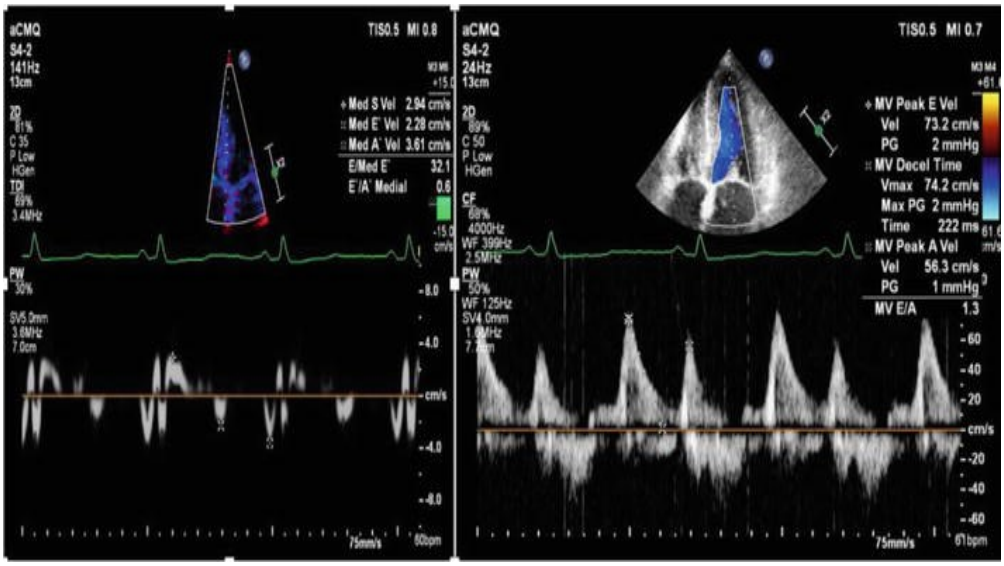


Figure 4.2D echocardiogram with tissue Doppler sample at base of the interventricular septum and pulsed-wave Doppler at mitral valve inflow in a patient with AL type cardiac amyloidosis revealing impaired relaxation, septal e' of the LV decreased and a pseudonormal pattern.

6.3 Speckle-tracking echocardiography

The speckle-tracking echocardiography (STE) plays an important role in evaluation of patients with CA, being a sensitive echocardiographic technique which detects cardiac damage due to amyloid infiltration from early stages, even when other classic parameters are still in range. In patients with CA, a reduced global longitudinal strain can be observed when the left ventricular ejection fraction is still preserved.

STE reveals reduced longitudinal shortening at the basal and mid-ventricular level with preserved longitudinal function at the apex. This pattern, described by Phelan et al. as 'relative apical sparing' is a helpful tool, both sensitive and specific, to make a diagnosis of CA. 2D STE is helpful in differentiating the thickness of myocardium caused by amyloidosis from a real left ventricular hypertrophy. (Figure 5).

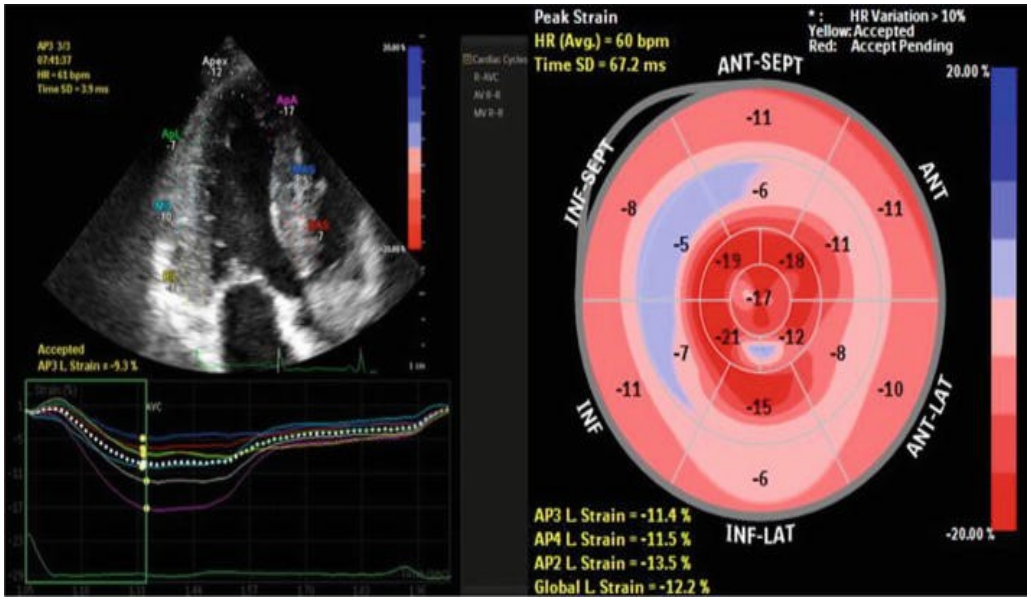


Figure 5.Left ventricular strain image with impaired longitudinal shortening at basal and mid-ventricular level with preserved longitudinal function at the apex (relative apical sparing) as seen in the bull's eye plot on the right.

7. Magnetic resonance imaging in CA

The use of cardiac magnetic resonance (CMR) in CA allows a good definition of cardiac morphology, ventricular and valvular function, and the possibility to analyze the structure of the ventricular wall.

The gadolinium contrast agents are very useful in characterizing the myocardial wall structure due to the differences in clearance of gadolinium between normal myocardium, edematous or scarred myocardium, and myocardium with amyloid deposits.

The late gadolinium enhancement (LGE) of the myocardium has different patterns in different diseases, altogether can be evaluated by MRI. The ischemic scars appear as subendocardial LGE in a coronary territory, usually associating the thinning of the myocardial wall. In contrast to this, the amyloid deposits appear as subendocardial LGE that extend beyond a coronary artery territory (the "arch" shaped LGE) and is usually associated with increased wall thickness. In more severe stages the subendocardial LGE can be diffuse (the "annular" shaped LGE) or it can even become a transmural LGE.

The extracellular space expansion due to amyloid deposition can also be measured by the T1 mapping technique allowing monitoring of the treatment response. The extracellular volume (ECV) is below 28% in normal situations and can increase significantly with edema and fibrosis, but also with amyloid deposition. An increase above 40% of ECV is a highly suggestive sign for amyloidosis in patients with high pretest probability; this sign appears early, before LGE appearance. (Figure 6).

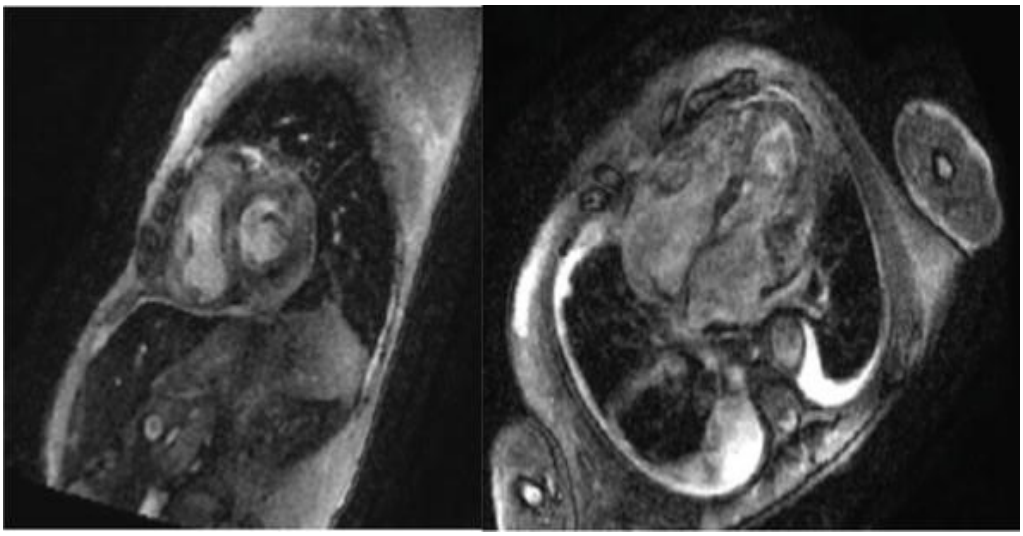


Figure 6.MRI images: short axis 2D myocardial delayed enhancement (left) and four-chamber 2D myocardial delayed enhancement (right): diffuse, inhomogeneous late gadolinium enhancement, suggestive of cardiac amyloidosis.

8. Nuclear medicine: Radionuclide scintigraphy

Bone affinity isotope scintigraphy helps in the early diagnosis of ATTR-type CA and in its differentiation from AL amyloidosis and other types of hypertrophic heart disease.

The radiotracers recommended in diagnosing ATTR amyloidosis are: 99 mTc - PYP (pyrophosphate), 99mTc - DPD (3,3-diphosphono-1,2-propanodiacarboxylic acid) and 99mTc-labeled hydroxymethylene diphosphonate (HMDP). They have an increased affinity for calcium. In ATTR-type amyloidosis, the extracellularly deposited amyloid, at the cardiac level, contains a protein that binds amyloid fibers through a calcium-dependent mechanism, this correlates the affinity of these radiotracers for this type of amyloid. There are comparative studies on endomyocardial biopsies, showing ATTR amyloidosis have frequent microcalcifications in comparison with AL amyloidosis.

Other radiotracers that are used to highlight CA and differentiate it from other hypertrophic cardiomyopathies are: 11C-Pittsburgh compound B (11C-GDP), 18F-florbetaben, and 18F-florbetapir. They have affinity for both the AL-type amyloid and ATTR.

9. Diagnostic strategy in CA

Diagnosis of CA is complex due to multi organ involvement. It is usually an exclusion diagnosis in HF with left ventricular hypertrophy and preserved ejection fraction. Two important steps in this algorithm in patients with clinical suspicion of CA are screening for monoclonal protein (for identification of kappa or lambda free light chains) and, in case this is positive, biopsy, most of the time from fat pad, which has a sensitivity and specificity of 79% and 80% respectively for diagnosing amyloidosis (Figure 7).

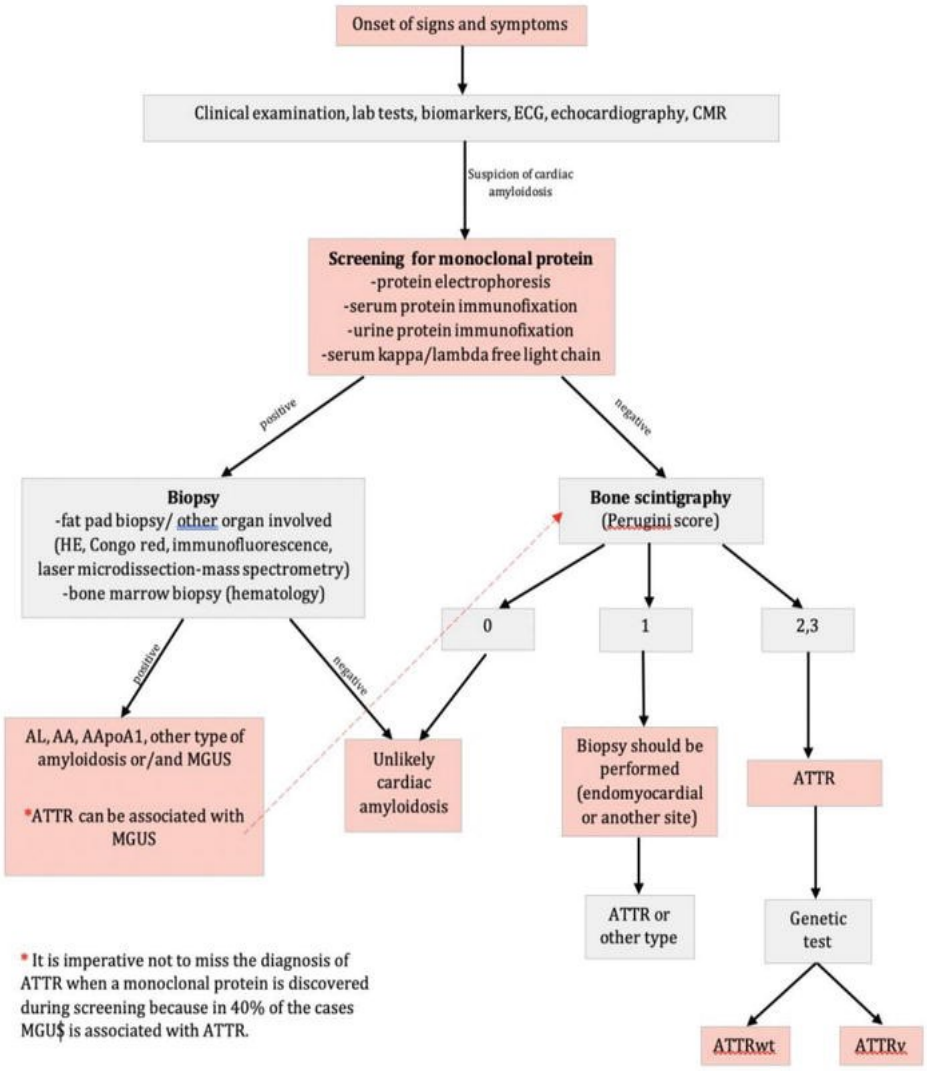


Figure 7. Diagnostic strategy in CA. (ECG, electrocardiography; CMR, cardiovascular magnetic resonance imaging; HE, hematoxylin eosin staining; AL, amyloid light-chain amyloidosis; AA, amyloid A protein amyloidosis, AApoA1, apolipoprotein AI-derived amyloidosis; MGUS, monoclonal gammopathy of undetermined significance; ATTR, transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; ATTRv, mutant transthyretin amyloidosis).

10. General treatment of heart failure in CA

Therapy of HF along with the treatment of the underlying disease stand for different sides of the same coin in CA. There are several dissimilarities regarding medications used in CA with HF, compared to those used in patients with non-CA HF with reduced ejection fraction (HFrEF). The median survival after the onset of HF is less than 6 months in untreated patients.

10.1 Medical treatment of heart failure in CA

General treatment in patients with CA and HF is challenging due to lack of randomized clinical trials on which to fundament treatment strategies. Therapy should first focus on a sodium restriction diet and daily weight monitoring in conjunction with diuretics, in order to improve congestion and relieve symptoms. Neurohormonal blockade is recommended by current HF guidelines for patients with HFrEF regardless of its etiology. Thus loop diuretics combined with a mineralocorticoid receptor antagonist, represent the cornerstone of therapeutic strategies in CA.

In amyloid cardiomyopathy, CCB and digitalis are contraindicated because they can bind to amyloid fibrils and determine severe adverse effects such as serious hypotension and syncope Moreover, BB and ACEI can cause marked hypotension due to low cardiac output and fatigue, leading to a limited tolerability among these patients. Orthostatic hypotension caused by autonomic dysfunction can be exacerbated by ACEI or angiotensin receptor blockers, and the coexistence of renal dysfunction can limit their usage. Still, these medications should be cautiously considered in selected cases of severe nephrotic syndrome with marked proteinuria.

Beta-blockers with their negative chronotropic and inotropic effects, interfere with contractility and heart rate which help maintain cardiac output, resulting in significant hypotension, extreme bradycardia and even heart block since amyloid patients are already predisposed to electrical conduction anomalies. However, in case of atrial tachyarrhythmias, BB (particularly in low doses) might present real benefits for rate control.

10.2 Heart transplantation and ventricular assist devices

Previously, overall heart transplantation in CA was thought to be contraindicated since amyloidosis represents a systemic disease and there is an increased risk of relapse. In transplanted amyloid patients compared to standard heart transplant patients, there was no difference in survival rate, and those with end stage disease continue to have an extremely poor prognosis (50% death on the waiting list).

Many authors focused their attention in the last decade on mechanical circulatory support (MCS) for end-stage CA. Left ventricular assist device (LVAD), biventricular assist device (BiVAD) and total artificial heart (TAH) nowadays represent either bridge to transplantation (BTT) or destination therapies. Some studies reveal that TAH is a feasible bridging therapy, with 82% survival, and should be preferred over LVAD therapy for durable support in selected patients. Accordingly, LVAD is not suitable for CA patients with left ventricular end-diastolic diameter under 46 mm and was even associated with higher mortality post-implantation. Other studies found no significant difference in wait-list and up-to 5-years survival after heart transplantation in subjects sustained by BiVAD or TAH as bridging therapies.

10.3 Atrial fibrillation and anticoagulation

While AF is the most frequent arrhythmia in HF patients, in amyloid patients, traditional therapies could lead to severe side effects. For rate control, beta-blockers in low doses may be tried, but their clinical benefit remains unproven in CA. Nondihydropyridine CCB and digoxin are not recommended. Options for pharmacologic rhythm control are restricted, but studies support the use of amiodarone as first choice antiarrhythmic therapy, since it tends to be well tolerated. Several studies concluded that chronic oral anticoagulation is recommended in all patients with CA and AF irrespective of CHADS-VASC score due to an increased risk of thromboembolic events.

10.4 Cardiac implantable electronic devices

Implantable electronic devices such as pacemaker and/or implantable cardioverter-defibrillator (ICD) have not been shown to prevent sudden cardiac death or improve survival in CA patients. Moreover, since overall mortality after implantation outweighs its benefits, cardiac implantable electronic devices should be used mainly for secondary prevention (hemodynamic instability due to ventricular arrhythmias) in patients with more than a year

survival rate. However, permanent pacemakers, especially biventricular pacing, were shown to improve symptoms and should be considered in patients with CA and severe conduction disease.

11. Specific treatment of AL amyloidosis cardiomyopathy

Since last decade newer treatment options are available for Cardiac Amyloidosis, among which the most notable are new chemotherapy regimens, autologous stem cell transplantation, proteasome inhibitors and monoclonal antibodies.

Treatment should be adapted according to the patient's comorbidities and severity of organ involvement in order to achieve the most efficient and safe therapeutic regimen.

Apart from patients with monoclonal gammopathies of undetermined significance (MGUS) or smoldering myeloma, in whom initiation of specific therapy could be delayed until the first sign of organ involvement, all patients diagnosed with AL amyloidosis should be initiated on specific therapy as soon as possible.

The treatment of these subjects should be decided by a multidisciplinary team, coordinated by a hematologist and with the involvement of other relevant medical specialties: nephrology, cardiology, pneumology, neurology and gastroenterology.

In addition to specific HF therapy, which has several peculiarities compared to that of the general population, patients with AL amyloidosis and cardiac involvement require treatment of the underlying disease.

The standard treatment includes high-dose chemotherapy in combination with autologous stem cell transplantation (ASCT), alkylating agents, steroids, proteasome inhibitors, and immunomodulatory drugs. An adequate response may not be obtainable in all. Because of this, treatment efficacy should be assessed at 3 months after ASCT (autologous stem cell transplantation) and 1–2 months after nontransplantation therapies. A decision to shift to other regimens depends on the hematologic response.

Risk stratification is essential when choosing the treatment strategy. Only 20% of the patients newly diagnosed with AL amyloidosis are eligible for ASCT, these being considered low risk patients. Generally, in order to be eligible for ASCT, patients should meet the following criteria: age $\leq$ 70 years, cTnT<0.06 ng/mL, NT-proBNP<5000 ng/L, systolic blood pressure $\geq$ 100

mmHg, LVEF >45%, New York Heart Association (NYHA) functional class I or II, creatinine clearance ≥50 mL/min (unless on chronic stable dialysis), Eastern Cooperative Oncology Group (ECOG) performance status ≤2, DLCO >50%, less than 3 organs significantly involved (heart, liver, kidney, or autonomic nervous system).

Treatment with bortezomib, a proteasome inhibitor, should be considered in low-risk patients prior to ASCT if there are no contraindications, in order to achieve high rates of deep and durable hematologic response. This should be followed by high dose melphalan, an alkylating agent, combined with autologous stem cell transplant rather than chemotherapy alone. ASCT allows the administration of high doses of melphalan, with myeloablative effect, thus contributing to the suppression the underlying plasma cell dyscrasia.

Daratumumab is an anti-CD38 monoclonal antibody, which has a direct on-tumor and immunomodulatory mechanism of action, with proven activity in AL amyloidosis, which is particularly attractive in case of severe cardiac involvement. High risk patients with important cardiac involvement and NYHA class III or IV and ECOG PS = 4, need a very rapidly acting and safe regimen and supportive therapy during the chemotherapy cycles in order to sustain organ function.

Low dose thalidomide in addition to cyclophosphamide and dexamethasone (CTDa) was demonstrated higher response rates, but it is not recommended as a routine maintenance therapy due to cumulative neurotoxicity. Lenalidomide in combination with low dose dexamethasone, with or without cyclophosphamide, could be taken into consideration in patients with relapsed AL amyloidosis, but with an increased risk of thrombotic complications (Figure 8).

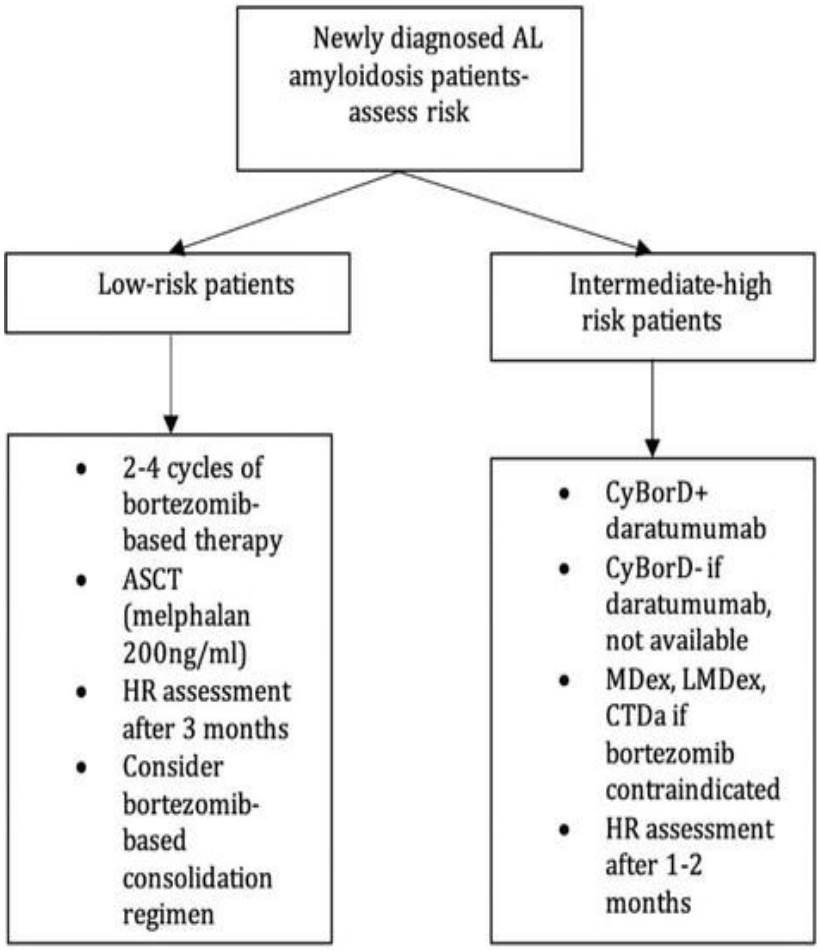


Figure 8. Treatment algorithm of AL Amyloidosis. CyBorD = cyclophosphamide and dexamethasone; ASCT = autologous stem cell transplantation; MDex = melphalan and dexamethasone; LMDex= lenalidomide, melphalan, and dexamethasone; CTDa = cyclophosphamide and dexamethasone; HR = heart rate.

12. Specific treatment of ATTR amyloid cardiomyopathy

Recent findings in the research of molecular pathogenic mechanisms revolutionized the treatment of ATTR amyloidosis. New agents have recently been developed to suppress the production of amyloid in both wild-type and hereditary CA. Current treatment strategies include management of underlying disease process in association with symptomatic relief.

12.1 Disease modifying therapies

TTR synthesis inhibitors target by inhibiting the hepatic synthesis of TTR.

Patisiran (0.3 mg/kg iv., once daily, every three weeks for 18 months) is a second-generation small interfering RNA (siRNA), which blocks the expression of TTR, leading to reduction in TTR levels.Inotersen (200 mg sc., once a week) is a second-generation antisense oligonucleotide, which lowers hepatic production of TTR by bonding to the mRNA.

Both these drugs lead to a reduction of >85% in the concentration of circulating TTR. Two recent randomized trials have demonstrated reduction in the progression of polyneuropathy in patients with ATTRv: the APOLLO trial. (The Study of an Investigational Drug, Patisiran, for the Treatment of TTR Amyloidosis) and the NEURO-TTR. trial (Efficacy and Safety of Inotersen in Familial Amyloid Polyneuropathy).

Tafamidis slows the dissociation of TTR tetramers into monomers by binding to the thyroxine-binding site of the TTR. In the ATTR-ACR randomized trial (Safety and Efficacy of Tafamidis in Patients with TTR Cardiomyopathy), which recruited both patients with ATTRv cardiomyopathy and ATTRwt cardiomyopathy, there was a significant lower all-cause mortality and cardiovascular-related hospitalization after 30 months after receiving Tafamidis when compared to placebo. Moreover, there was a lower rate of decline in the 6-minute walk test and in the quality of life under both Tafamidis doses (20 and 80 mg orally). Tafamidis was approved for the use in TTR cardiomyopathy in May 2019.

Diflunisal is a non-steroidal anti-inflammatory drug, which significantly reduced the progression of polyneuropathy by stabilizing TTR tertramers in a randomized trial. Although no controlled trials evaluated the effect of Diflunisal on TTR cardiomyopathy, two single center studies demonstratedsome benefits (250 mg orally twice daily). However, side effects are not rare (thrombocytopenia and renal dysfunction),administration should be avoided in patients with eGFR<45 mL/min/1.73m2, thrombocytopenia or signs of hemodynamic or renal instability.

AG10 is a synthetic TTR ligand, which acts by binding to the TTR tetramer and therefore prevents amyloid fibril formation and deposition.

Tolcapone is approved for the treatment of Parkinson disease and acts by inhibiting TTR aggregation. It is currently under investigation in patients with TTR amyloidosis.

TTR disruptors target the clearance of amyloid fibrils from tissue.

The combination of Doxycycline and TUDCA (tauroursodeoxycholic acid) removed amyloid deposits in preclinical studies, but there was a high incidence of side effects.

12.2 Symptomatic relief

Cardiac pacemaker implantation might be beneficial in patients with TTRv and conduction disorders. Implantable cardioverter-defibrillators (ICD) are recommended in patients with significant arrhythmias or aborted sudden cardiac death with expected survival of more than one year. Although reduction in cardiac filling pressures is also necessary, it must be performed with caution, as these patients are dependent of the cardiac output. On the same principle, many drugs used in the treatment of HF might not be beneficial in patients with CA and some agents might have an abnormal distribution by binding to amyloid fibrils (eg. digoxin).

12.3 Management of TTR amyloidosis in patients with aortic stenosis

The association between CA and aortic stenosis (AS) is more common and TTR cardiac amyloidosis is the most prevalent type to coexist with AS. Since there are no randomized trials to evaluate the best therapeutic management in patients with TTR cardiac amyloidosis and AS, the treatment of CA follows the generalised approach.

A study showed that in patients with CA and AS, trans-aortic valve replacement (TAVR) has better outcome than SAVR. Two ongoing prospective trials, ATTRact-AS (The Role of Occult Cardiac Amyloid in the Elderly With Aortic Stenosis) and Amylo-CARTESIAN (Prevalence and Post-surgical Outcomes of Cardiac Wild-type Transthyretin Amyloidosis in Elderly Patients With Aortic stenosis Referred for Valvular Replacement) might lead to better understanding of the prevalence and management of patients who present both pathologies. One recently published sub-study of the ATTRact-AS trial showed that there was no difference in mortality after TAVR between patients with CA and AS or AS alone. Thus, TAVR might be a better option for patients with intermediate to high surgical risk.

13. Summary

Amyloidosis presents as a multi-organ disease presenting with unspecific symptoms. The diagnosisis difficult and delayed, and therefore the number of unreported cases is likely quite significant.

Amyloid infiltrates all structures of the heart including ventricular and atrial walls, the conduction system, the heart valves and the coronaries. The typical clinical presentation in CA is similar to that of a restrictive cardiomyopathy.

Cardiac biomarkers, echocardiography, and other imaging techniques such as CMR or 99mTc-phosphate scintigraphy are available for the diagnosis of CA as well as determination of the extent of this disease. Endomyocardial biopsy helps in histopathological confirmation and subtyping of CA.

The main goal of the diagnostic strategy is to detect CA early, to define the extent of CA and to enable targeted therapy.

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Recent advancement of transdermal patch for hypertension: Review

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Abstract

For thousands of years, human civilizations have applied substances to the skin as cosmetic and medicinal agents. Medicines are applied topically using transdermal drug delivery methods. Transdermal patches are pharmacological preparations that come in different sizes and are designed to be placed to intact skin. The purpose of the patches is to enable the active component to penetrate the skin's barriers and reach the systemic circulation, hence preventing the first pass effect. Transdermal drug delivery system was came into existence to overcome difficulties of drug delivery especially oral route. Transdermal drug delivery refers to means of delivering drugs through the surface of the skin for local or systemic treatment. Transdermal drug delivery has several advantages over other routes of administration, for instance, it is less invasive, patient-friendly, and has the ability to bypass first pass metabolism and the destructive acidic environment of the stomach that occurs upon the oral ingestion of drugs. For decades, transdermal patches have attracted attention and were used to deliver drugs. Recently, this method is also being explored as a means of delivering biologics in various applications. Here, we review the existing literatures on the design and usage of medical patches in transdermal drug delivery, with a focus on Hypertension. In this review we revealed the skin structure, advantages, disadvantages, components, mechanisms of action, types and future decades of TDDS in Transdermal patch form for the hypertension treatment.

Key words: Transdermal drug delivery, Hypertension, Matrix, Reservoir.

Introduction

Transdermal drug delivery system:

Transdermal drug delivery systems are dosage forms designed to deliver a therapeutically effective amount of drug across the patient's skin. In order to achieve systemic effects by transmitting therapeutic substances through human skin, it is essential to consider the skin's biophysical, morphological, and physicochemical properties comprehensively. Transdermal drug delivery presents notable advantages compared to injectables and oral routes, as it improves patient compliance and circumvents the first-pass metabolism. As a result, various innovative drug delivery systems, such as Transdermal drug delivery systems, Transmucosal delivery systems, and Controlled release systems, have been developed. The benefits of transdermal drug delivery include improved therapeutic efficiency, reduced hepatic first-pass metabolism, and the maintenance of a stable drug concentration in the bloodstream. The first transdermal system was FDA-approved in 1979 for preventing nausea and vomiting. Transdermal drug delivery is an alternative way of delivering drugs via the skin layer (Chien Y.W., Liu J.C. 1986; Lasagna L., Greenblatt D.J. 1986).

The drug is carried through the skin into the bloodstream and circulates systemically in the body before reaching the target site (Chien Y.W., Liu J.C. 1986; Lasagna L., Greenblatt D.J. 1986). The transdermal drug delivery method has several advantages over other routes of administration. Examples include the ability to deliver continuous doses of drugs over an extended period of time, the ability to bypass the digestive system, and the ability to avoid first-pass metabolism in the liver (Berner B., John V.A,1984).

Specially in last twenty years, the transdermal drug delivery system has become a more focusing technology that offers significant clinical benefits over other dosage forms, because transdermal drug delivery offers controlled as well as state blood concentration (Sachan Richa, Meenakshi Bajpai, 2013).

TDDS is a suitable treatment for chronic diseases such as hypertension, target patients may reconsider due to the higher cost of antihypertensive patches compared to conventional solutions (Jamakandi VG, *et.al*., 2006)

Hypertensive is a disease characterized by persistently high blood pressure. Hypertension is one of the largest deaths causing disease for the human being. Since it is a chronic disease so it necessitates long term treatment. Hypertensive a cardiovascular disease account for a large proportional of all death and disability worldwide. Hypertensive is directly

responsible for 57% of all stroke's death and 24% of coronary heart disease in India. Transdermal system is ideally suited for disease that demand chronic treatment. In this project TDDS are mainly used for the delivery of antihypertensive drug from transdermal patches (Paneer *et. al* 2010).

Numerous classes of antihypertensive drugs reduce blood pressure by various methods; the most significant and commonly utilized antihypertensive drugs include thiazide diuretics, β-blockers, ACE inhibitors, calcium channel blockers, and angiotensin II receptor antagonists (Yadav, Pavan, 2017; Kamlesh V Warokar 2020).

The World Health Organization has recognized hypertension as one of the leading global risk factors for morbidity and mortality, accounting for over nine million deaths per year (Singh K, Singh S and Rana A, 2018).

The illness known as hypertension is defined by consistently elevated blood pressure. One heart condition that is linked to many deaths and disabilities globally is hypertension. High blood pressure is one of the leading causes of death in humans. As a chronic illness, it necessitates ongoing care (Sridhar K, *et al.* 2016).

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream (Shinde P.V. *et al.,* 2014). A benefit of a transdermal patch over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive (Dipen Patel, *et al.,* 2012).

A transdermal patch is a medicated patch that can deliver drugs directly into the bloodstream through the layers of the skin at a prescribed rate. in fact, patches are the most convenient method of administration. This review article covers brief outline advantages, disadvantages, skin pathways for transdermal drug delivery systems (TDDS), various components of transdermal patch, TDDS for the treatments of hypertension, mechanism of action of transdermal patch, types of transdermal patches, future of transdermal drug delivery system and limitation of TDDS.

Advantages of transdermal drug delivery method

- The transdermal drug delivery method has several advantages over other routes of administration.
- Examples include the ability to deliver continuous doses of drugs over an extended period of time, the ability to bypass the digestive system, and the ability to avoid first-pass metabolism in the liver (Berner B., John V.A. 1994).
- The drugs by pass the hepatic and pre systemic metabolism thereby increasing bioavailability.
- Risks and inconveniences of IV therapy are avoided. Reduced dose frequency and predictable sustained and extended duration of action.
- Easy termination of drug therapy. It gives greater patient compliance due to elimination of multiple dosing intervals.
- Enhanced therapeutic efficiency by avoiding the peaks and troughs in systemic drug levels associated with conventional delivery. Self – administration is possible.
- Topical patches are a painless, non-invasive way to deliver substances directly into the blood.
- Topical patches can bypass first-pass hepatic metabolism
- Termination of medicament can be possible by removing the patch from skin.
- Drug which is, stomach irritant can modify to topical delivery.
- Topical patches have fewer side effects than oral medications.
- Topical patches are easier to use and remember.
- Topical patches are cost-effective.
- Topical patch can release the drug at steady state over the long period of time.
- Topical patch can bypass the enzymes action on it. (Vandana Yadav, *et. aL*., 2012).

Disadvantages of transdermal patches

The major disadvantage of transdermal delivery methods is that skin is a highly efficient barrier; as a result, only medicines with tiny enough

molecules to permeate the skin may be administered this way. Also, other disadvantages of the transdermal patches are mentioned below. (Neelkanth Kote & Poornima B, 2007).

- Transdermal application may lead to allergic reactions to the skin due to drug, adhesive or other excipients.
- The use of transdermal delivery may be more expenditure.
- Skin's impermeability creates hindrance against drug entry, so only potent API can be administered via this route.
- Drug which has large molecular size gets difficulty in absorption.
- Drugs which is ionic in nature gets problems in absorption.
- Drugs which have high or very low partition coefficient fails to enter into the systemic circulation.
- Drugs which require high blood levels to be achieved cannot be used in this delivery system.
- Drug with lipophilic character is more suitable as compare to drug with hydrophilic character because of their low permeability.
- Only less quantity of lipophilic drug can be administered through the skin.

Physiology Of Skin:

The skin is the largest organ of the human body. It acts as a protective barrier against external influences such as ultraviolet radiation, chemical and physical insults, attacks by harmful microorganisms and mechanical irritation. It is one of the most readily accessible organs of the human body (Yie W,Chien, 2005 ; Eseldin Keleb & Rakesh Kumar Sharma, 2010).

Skin is considered as an important route of drug administration for both local and systemic effects. Percutaneous absorption of drugs through skin mainly occurs via the stratum corneum. Stratum corneum is made up of dead, keratinized epidermal cells having a thickness of 10 micrometers and acts as a barrier for the permeation of drugs (Figure: 1).

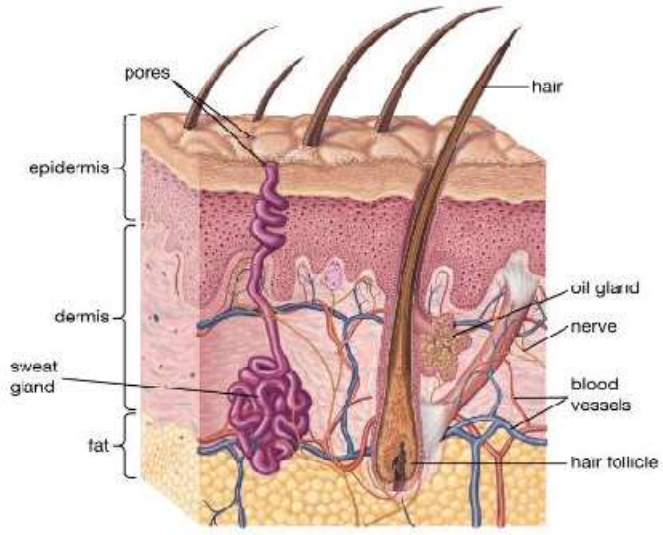

Figure: 1 Structure of skin anatomy

Skin anatomy:

Human skin consists of two layers: the epidermis and the dermis. The epidermis can be divided into four layers, with the stratum corneum being on top, followed by the stratum granulosum, stratum spinosum, and the stratum basale. The stratum corneum as the most decisive part in skin permeation.

The dermis beneath the epidermis ensures the flexibility of the skin and temperature maintenance of the body. Blood vessels, lymphatic channels, and sensory nerves run through the dermis. The dermis and subcutaneous underneath are not relevant for the penetration of substances for dermal therapy. In systemic therapy with transdermal systems, however, drugs must be able to penetrate to the blood vessels in the dermis and subcutaneous.

Sustained release drug delivery system:

Drug delivery systems that are designed to achieve **"prolonged therapeutic effect** by continuously releasing medication over an extended period of time after administration of a single dose."

Basic componenets of transdermal drug delivery systems:

Transdermal patches typically consist of several layers that are designed to deliver the medication through the skin and into the bloodstream. Figure 2 illustrates the basic component of a medicated patch. The specific

composition and structure of the patch may vary depending on the drug being delivered and the desired rate of drug release.

Figure 2: Basic components of TDDS.

The components of Transdermal device include (Jain N. K, 1997; Swarnlata Sonl and Vinod K, Dixit, 1992; Tanu Bhargava, 2011).

- Polymer matrix /Drug reservoir,
- Drug
- Drug Permeation enhancers.
- Pressure sensitive adhesive (PSA).
- Backing laminate.
- Release liner.
- Other excipients like plasticizers and solve (Vyas SP, Khar. 2002).

It is not necessary that the all components should be present in every transdermal patches. All transdermal patches have the same backing film, medication reservoir, and release liner. The usage of other components is determined by the drug's specifications.

Polymer Matrix:

Polymers are the important component of a transdermal drug delivery system. Multilayered polymeric laminations for controlled release sandwich a drug–polymer matrix or drug reservoir between two polymeric layers: an outer

impervious backing layer that prevents drug loss through the backing surface and an inner polymeric layer that serves as an adhesive and/or rate-controlling membrane. (Boretos JW, *et.al.,* 1971; Barry BW, 1988). The polymer controls the release of the drug from the device. The following criteria should be satisfied for a polymer to be used in a Transdermal system. Possible useful polymers for Transdermal devices are;

Drug:

For successfully developing a Transdermal drug delivery system, the drug should be chosen with great care. The following are some of the desirable properties of a drug for Transdermal delivery.

Drug Permeation enhancers:

Penetration enhancers, also referred to as permeation enhancers or skin penetration enhancers, are substances employed to enhance the permeability of active compounds, such as drugs, through the skin. They function by temporarily modifying the structure and properties of the stratum corneum, the skin's outermost layer. This alteration allows for better penetration of the active ingredients into the bloodstream or deeper layers of the skin, enhancing the effectiveness of topical medications.

Adhesives:

The fastening of transdermal devices to the skin has so far been done by using a pressure sensitive adhesive. The pressure sensitive adhesive can be positioned on the face of the device or in the back of the device and extending peripherally.

Both adhesive systems should fulfil the following criteria.

- Should not irritate or sensitize the skin or cause an imbalance in the normal skin flora.
- Should adhere to the skin aggressively during the dosing interval without its position being disturbed by activities such as bathing, exercise etc.
- Should not leave an unwastable residue on the skin.
- Should have excellent (intimate) contact with the skin at macroscopic and microscopic level.

Backing laminate:

It protects the patch from the environment, provides support to the patches and giving flexibility and appearance to the patch (S Banerjee P,2014). Backing membranes are flexible and they provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top, and accept printing. It is impermeable and protects the product during use on the skin e.g. metallic plastic laminate, plastic backing with absorbent pad and occlusive base plate a (aluminium foil), adhesive foam pad (flexible polyurethane) with occlusive base plate (aluminium foil disc) etc.

Release Liner:

During storage release liner prevents the loss of the drug that has migrated into the adhesive layer and contamination. It is therefore regarded as a part of the primary packaging material rather than a part of dosage form for delivering the drug. The release liner is composed of a base layer which may be non-occlusive (paper fabric) or occlusive (polyethylene, polyvinylchloride) and a release coating layer made up of silicon or Teflon. Other materials used for TDDS release liner include polyester foil and metalized laminate.

Plasticizer

Many of the polymers used in pharmaceutical formulations are brittle in nature, which requires plasticizer to reduce the brittleness into the formulation. Plasticizers are added to pharmaceutical polymers aiming to ease the thermal workability, improving the mechanical properties, modifying the drug release from polymeric systems and surface properties of the dosage form. The plasticizers used in pharmaceutical formulations present a) in coating material of solid dosage forms, and b) in transdermal therapeutic systems (Sevgi Güngör, M, 2020).

TDDS for the treatments of hypertension

Developing controlled drug delivery has become increases the importance in the pharmaceutical industry. Today about ¾th % (75%) of drug are taken orally but it is not found be as effective as desired. To improve such character transdermal drug delivery system was emerged as Novel drug delivery system. Transdermal drug delivery represents one of the most rapidly advancing areas of novel drug delivery because it overcomes the difficulties of oral antihypertensive drugs. TDDS have many advantage over conventional antihypertensive drug delivery such as non-invasive, ease of use, withdrawn (increases side effect) avoid first pass metabolism, best patient compliance, no

need of hospitalizations, avoid gastric irritation, reducing dosing frequency of drug.

Mechanism Of Action Of Transdermal Patch:

A typical transdermal patch consists of an adhesive layer which sticks on to the skin, a semi solid to liquid drug is smeared between the layers of drug releasing membranes which are exclusively semipermeable in nature. During application, the entire patch is protected by an outermost transparent backing (Figure 3). When a transdermal patch is placed to the skin, it creates a strong bond between the skin and the semipermeable membrane. Through the percutaneous drug delivery system, a gradual and steady flow of drug is delivered from the patch's drug reservoir to the skin via the drug release membrane via a simple diffusion/osmosis mechanism (Neelkanth Kote, Poornima B, 2007).

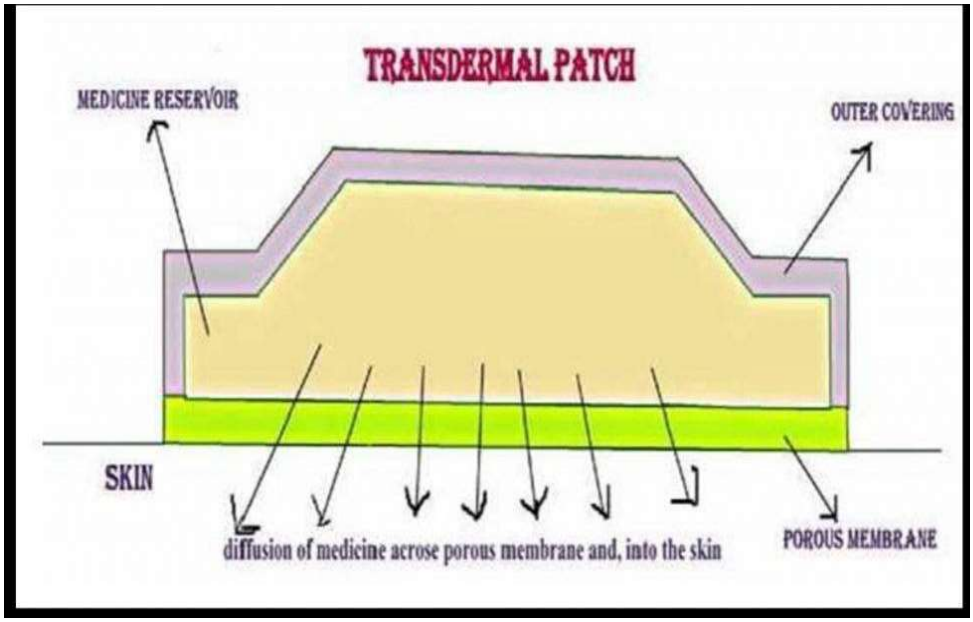

Figure 3: Diagram showing the different layers of transdermal patch with mechanism of action

Types of Transdermal Patches

In general, there are four main types of transdermal medical patches (drug-in adhesive, reservoir, matrix, and micro-reservoir systems), as shown in Figure 2. Most commercially available patches are categorized as reservoir or matrix systems (Wokovich A.M., *et. al*,2006).

Single-layer drug-in-Adhesive:

This system's sticky layer comprises both the medication and the polymer. The sticky layer serves a dual purpose in this sort of patch. The adhesive layer aids in the adhesion of the different layers, as well as the overall system, to the skin, and it is also responsible for medication release. The adhesive layer is covered by a temporary liner and a backing film30. e.g. Menostar® (estradiol transdermal system), MINIVELLE® (estradiol transdermal system), CombiPatch® (estradiol/norethindrone acetate transdermal system), DURAGESIC (fentanyl transdermal system), SANCUSO (Granisetron Transdermal System), DAYTRANA® (methylphenidate transdermal system), OXYTROL® (oxybutynin transdermal system), NEUPRO (rotigotine transdermal system), EMSAM® (selegiline transdermal system).

Multi-layer drug-in-Adhesive:

Adhesive patches with multilayer drugs are similar to single-layer systems in that both adhesive layers are responsible for medication release. Multilayer systems, on the other hand, are distinguished by the addition of a second layer of medicine in adhesive, which is generally separated by a membrane in certain situations. A temporary liner layer and a permanent backing film are also included in this patch32. e.g. EXELON® PATCH (rivastigmine transdermal system), (Montia D, 1995).

Reservoir:

The Single-layer and Multi-layer Druginadhesive systems are not the same as the Reservoir system. A distinct drug layer exists in the Reservoir transdermal system. The drug layer is in a liquid compartment that has been separated by the adhesive layer and contains drug in a solution or suspension form. The backing layer also supports this patch. By this system zero order release can be achieved. e.g ANDRODERM® (testosterone transdermal system). (Bharadwaj S, 2012).

Matrix:

The drug layer of the Matrix transdermal delivery system is a semisolid matrix containing a drug solution or suspension. This kind of transdermal patch system is partially overlaid by the adhesive layer by surrounding the drug layer. e.g BUTRANS® (buprenorphine) transdermal system (Sharma N, 2012).

Micro reservoir transdermal patches

Micro-reservoir transdermal patches integrate a drug reservoir with a matrix dispersion. The reservoir is created by suspending the drug in an aqueous solution of a hydrophilic polymer, followed by uniform dispersion of the drug suspension on a lipophilic polymer. This dispersion process involves high shear mechanical force, leading to the formation of numerous microscopic, non-leachable spheres. Drug release from these patches follows a zero-order kinetic rate, ensuring a consistent drug level in the plasma. To maintain thermodynamic stability, crosslinking polymeric agents are typically included in the drug dispersion (CL Stevenson JT & Santini R Langer, 2012).

Future Of Transdermal Drug Delivery System

Administration of medicines intended for transdermal delivery via liposomes, niosomes, and micro emulsions are among the future elements of transdermal drug delivery systems. The goal of this research is to enhance the delivery of drugs with limited intrinsic solubility in most traditional excipients. Steroids, antifungal, antibacterial, interferon, methotrexate, and local anaesthetics are only a few of the possible medicines for transdermal administration. The market for transdermal patches is expected to rise in the future, with a 25 percent annual growth rate recently discovered. This number is likely to rise in the future as new devices become available and the number of marketed transdermal drugs grows. The popularity of transdermal analgesic administration is anticipated to grow, necessitating additional design improvements. The transdermal patch may be a lesser-known treatment option for chronic and acute pain. We expect the popularity and usefulness of this mode of medication delivery to grow as delivery improves and a larger choice of analgesics becomes available. Therapeutics are being studied in order to improve their safety and efficacy. To increase patient compliance, such as the patch wearer's experience, as well as to offer more accurate medication administration with a longer duration of action. Systemic drug administration through the skin has numerous advantages, including keeping a consistent drug level in blood plasma, fewer adverse effects, improved bioavailability by avoiding hepatic first-pass metabolism, and increased patient compliance with respect to the treatment regimen. Skin is now widely regarded as the safest route for medication delivery since it allows for continuous drug release into the systemic circulation (Boolell M, 1996). The evolution of transdermal delivery methods may be divided into three generations. Many presently used medicines that may penetrate the skin at predetermined therapeutic rates are classified as first generation. Second generation representing additional

advancement in the system for small molecule delivery via skin and the Third generation allowing transdermal delivery of macromolecules (including proteins and DNA) and virus based/other vaccines through targeted permeabilization of the skin's stratum corneum.

Conclusion

The transdermal drug delivery route is considered both safe and effective when compared to other administration methods. Transdermal drug delivery is a painless, convenient, and potentially effective way to deliver regular doses of many medications. Numerous drugs, including hormonal therapies, a broad spectrum of analgesics, and medications for heart diseases, are formulated in Transdermal Drug Delivery System (TDDS) to mitigate gastrointestinal effects and first-pass metabolism. Wide range of drugs can be delivered improved drug uptake Minimal complications and side effects low cost and easy to use. Example Ten years ago, the nicotine patch had revolutionized smoking cessation; patients were being treated with nitro-glycerin for angina, clonidine for hypertension, scopolamine for motion sickness and estradiol for estrogen deficiency, all through patches used by over a million patients per year. However, the transdermal technologies have limitations due to the relatively impermeable thick of outer stratum corneum layer. Researchers are trying to overcome this hurdle of poor permeability by physical and chemical means.

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Review on Gastro retentive drug delivery system

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Abstract

Gastro Retentive Drug Delivery Systems (GRDDS), including Floating Drug Delivery Systems (FDDS), are advanced pharmaceutical technologies designed to enhance drug efficacy and reduce dosing frequency by prolonging the time a medication stays in the stomach. Unlike conventional forms that may require frequent dosing, GRDDS improve drug absorption, especially for medications with a narrow absorption window in the upper gastrointestinal tract.

GRDDS work by maintaining buoyancy in the stomach through various methods: effervescent systems generate gas to stay afloat, non-effervescent systems rely on swelling or adhesion, mucoadhesive systems stick to the gastric lining, and expandable systems increase in size after ingestion. Other approaches include high-density systems and superporous hydrogels.

Challenges include variability in gastric emptying, potential for gastric irritation, and limitations with certain drugs. Research continues to optimize GRDDS for better drug delivery and patient compliance.

Keywords: Gastro Retentive Drug Delivery Systems (GRDDS), Floating Drug Delivery Systems (FDDS), Bioavailability, Mucoadhesive Systems, Drug Retention, Gastric Residence Time, Controlled Release, Pharmaceutical Formulation.

Introduction to gastro retentive drug delivery system

Conventional dosage forms, particularly drugs having a short biological half life needs frequent daily administration resulting in wide fluctuations in peak and trough steady-state drug levels. In recent times, due to advances in the pharmaceutical formulation technologies, the pharmaceutical research is shifted towards the development of more efficacious, novel drug delivery systems using already existing molecules rather than going for new drug discovery program. These new delivery systems offer therapeutic benefits such as optimum biological response, prolonged efficacy, reduced toxicity as well as dose reduction.

GRDDS)gastro Retentive Drug Delivery System) is also known as floating drug delivery system (FDDS).GRDDS are primarily controlled release drug delivery systems, which gets retained in the stomach for longer period of time due to low density of dosage from compare to stomach density (1.004gm/cm3), thus helping in adsorption of drug for the intended duration of time.

This in term improves bioavailability, therapeutic efficacy and reduces dose frequency. It also helps in achieving local delivery of drug to the stomach and proximal small intestine. Gastro retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs.

A gastric drug delivery system (GRDDS) is particularly useful for drugs have narrow absorption window in the upper part of gastrointestinal that are primarily absorbed in the duodenum and upper jejunum segments. It retains the dosage form at the site of absorption and thus enhances the bio-availability.

Advantages of gastro retentive drug delivery system[4]

- ❖ It increases patient compliance and reducing dosing frequency.
- ❖ Buoyancy increases gastric residence time.
- ❖ Better therapeutic effect of short half-life drugs.
- ❖ Site specific drug delivery to stomach can be achieved.

- ❖ In this drug is released in a controlled manner.
- ❖ Gastric irritation can be avoided by designing sustained release.
- ❖ No risk of dose dumping by making single unit floating unit such as microspheres releases drug uniformly.

Limitations of gastro retentive drug delivery system[4]

- ❖ Aspirin and NSAID'S can cause gastric lesions and slow release of such drug in the stomach is unwanted.
- ❖ Drugs such as Isosorbidedinitrate which are equally absorbed throughout the GIT will not be benefit from incorporation into a gastric retention system.
- ❖ Bio adhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of the technique.
- ❖ Physical integrity of the system is very important and primary requirement for the success of the system.
- ❖ High variability in gastric emptying time due to variations in emptying process, unpredictable bioavailability.

Anatomy of the stomach[4]

The gastro intestinal tract can divided into three main regions

- ❖ Stomach
- ❖ Small intestine-duodenum,jejunum, and ileum
- ❖ Large intestine

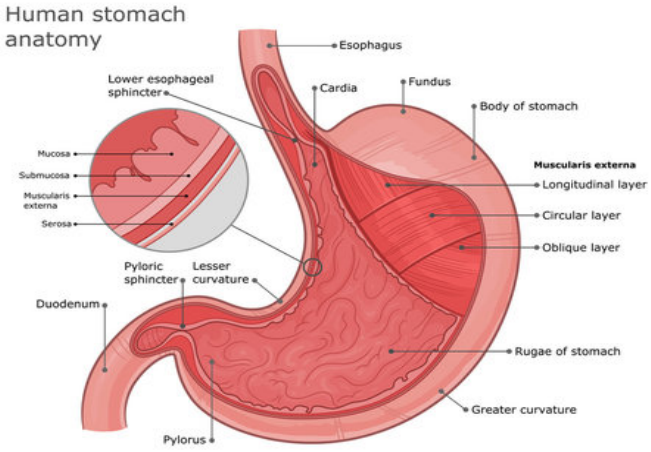


Figure 1: Phases of GI Motility

The GIT is a muscular tube of about 9m which extends from mouth to anus. Its function is to take nutrients and eliminate out waste product by physiological processes such as digestion, absorption, secretion, motility and excretion. The stomach has three muscle layers called oblique muscle and it is situated in the proximal part of the stomach, branching over the fundus and higher regions of the gastric body. The stomach is divided into fundus, body and pylorus. The stomach is a J-shaped organ located in the upper left hand portion of the abdomen. The main function of the stomach is to store the food temporarily, grind it and releases slowly in to the duodenum.

Physiology of the stomach[4]

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. In the empty state the stomach is contracted and its mucosa and sub mucosa are thrown up into folds called rugae. There are 4 major types of secretary epithelial cells that covers the stomach and extends into gastric pits and glands.

1. Mucous cells- secrete alkaline mucus
2. Parietal cells – secrete HCL
3. 3. Chief cells- secrete pepsin
4. 4. G cells- secrete hormone gastrin.

Gastric motlity and gastric empty rate[4]

Two distinct patterns of gastrointestinal motility and secretion exist to the fasted and fed state. The bioavailability of the orally administered drug depends upon the sate of feeding. In the fasted bstate, it is characterized by an inter-digestive series of electric event called inter digestive myoelectric cycle or migrating motar complex.

It is divided into 4 phases,

- ❖ Phase I (basal phase) it lasts from 40-60 min with rare contractions
- ❖ Phase II (preburst phase) last from 40-60 min with intermittent potential and contractions.
- ❖ Phase III (burst phase) last for 4-6 min. in this intense and regular contraction occur for short periods. Due to these contractions the indigestive food is swept from stomach to intestine. These are known as house keeper waves.
- ❖ Phase IV it lasts for 0-5 min and occurs between phases III and I for two consecutive cycles.

After the ingestion of the mixed meal the pattern of contraction changes from fed to that of fasted state, this is known as digestive motility pattern, these contractions reduces the size of the food particles to less than 1mm after that it is propelled to the pylorus in the suspension form. During fed state the onset of MMC is delayed which result in slow down of gastric emptying rate.

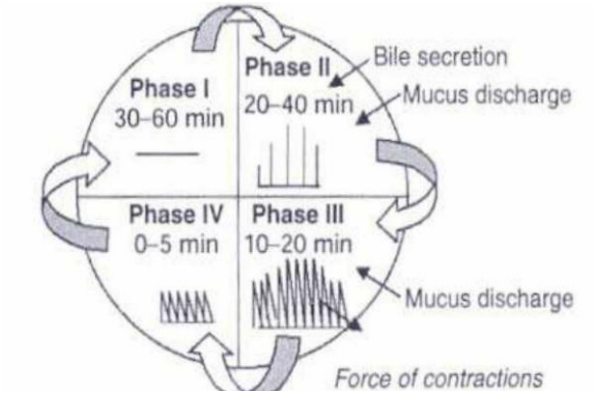


Figure: 2 Phases of GI Motility

Factors affecting effeifcacy of grdds[2]

1. Particle size

It should be in the range of 1 -2 mm to pass through the pyloric valve into the small intestine.

2. Density

Density of the dosage form affects the gastric emptying rate. A buoyant dosage form has density less than the gastric fluid to float.

3. Size

Size of the system should be in greater than 7.5 mm in diameter.

4. Shape

Ring and tetrahedron shaped system shows better gastric retention compared with the other shapes.

5. Single or multiple unit formulation

Multiple unit formulation shows more predictable release profile. It also allows co-administration of the units with different release profile or containing

incompatible substances. It also permit large margin of safety as compared to single unit formulation.

6. Nature of the meal and caloric content

Indigestible polymers, increased caloric content, fatty acid salt, increased acidity, fate and protein meal increase gastric retention time.

7. Food intake

Gastric retention time is increased in fed state.

8. Posture

Gastric retention time is different for inactive and active state of the patient.

9. Gender

Mean gastric retention time in male is less as compared to female regardless of weight, height and body surface.

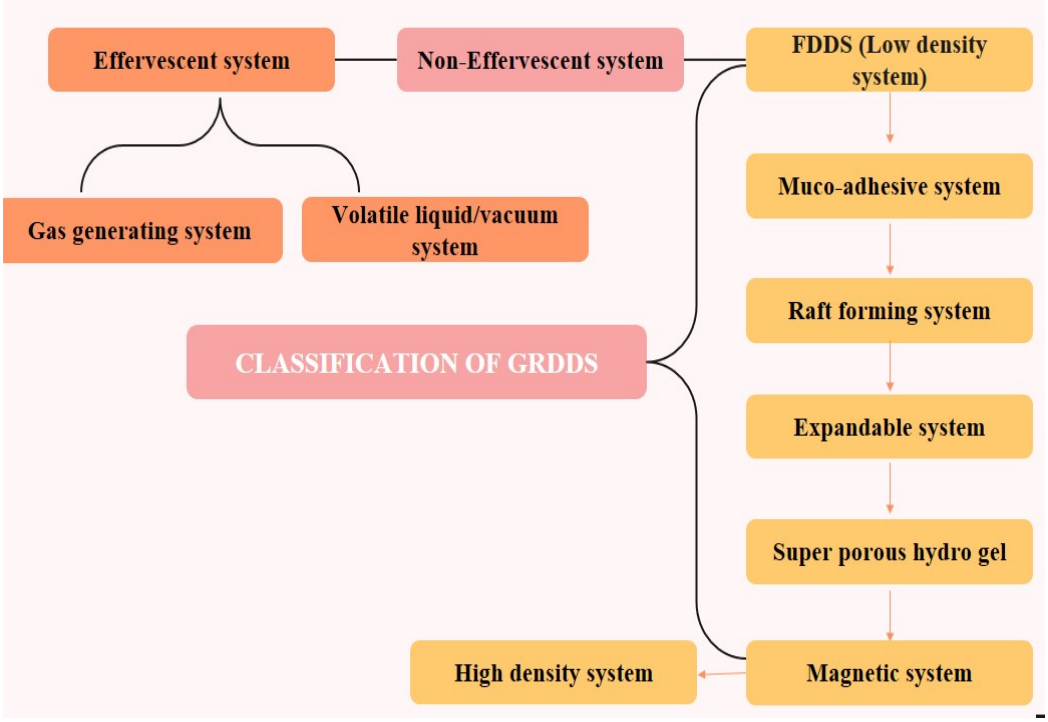
10. Age

Age greater than 70 shows longer residence time.

11. Biological factor

Disease like gastroenteritis, gastric ulcer, diabetes, hyponthyroidism retard gastric emptying rate while partial or total gastrectomy, duodenal ulcer promote gastric emptying.

Classification of GRDDS[5]



Floating drug delivery system[4][5]

By virtue of their low densities, FDDS remain afloat above the gastric contents for prolonged hperiods of time and provide continuous release of the drug. These systems in particular have been extensively studied because they do not adversely affect the motility of the GIT. Their dominance over the other types of GGDS is also evident from the large number of floating dosage forms begin commercialized and marketed world-wide.

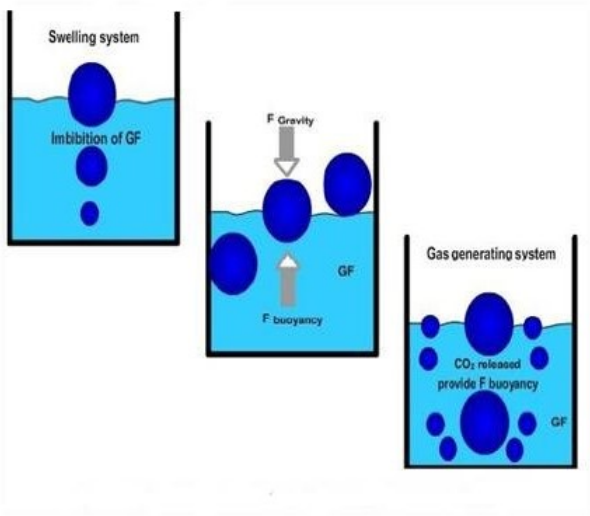


Figure 3: Floating Drug Delivery System

List of drugs explored for various floating system

Microspheres tablets/ pills: Aspirin, Griseofulvin, Acetyl salicyclic acid, Ibuprofen, Ampiclllin, Captopril, Sotalol, Isosrbidedinitrate, Terfandine.

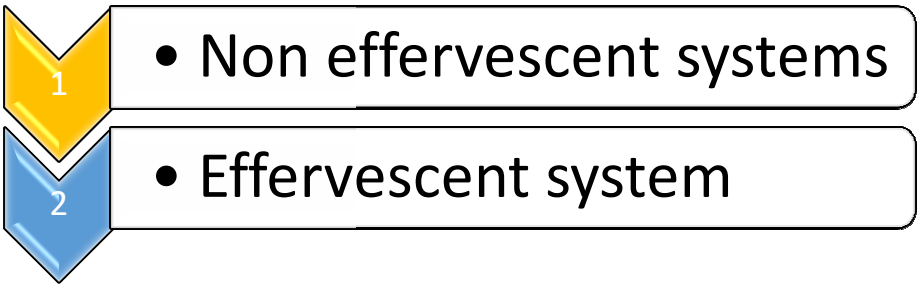
Flims: Cinnarzine, Peritanide, Quidinne, Prednisolone, P-aminobenzoic acid, Prednisolone.

Granules: Diclofenac sodium, Cinnarizine, Indomethacin, Fluorouracil, Ditiazem, Isosorbidedinitrate, Isosorbidemononitrate.

Powder: Riboflavin, Sotaol, Theophylline

Capsules: Verapamil HCL,, Diazepam, Misoprostol, Furosemide, L-dope, Nicardipin.

Classification of floating system



Non-effervescent FDDS[5]

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bio adhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bio adhesive polymers such as Chiosan.

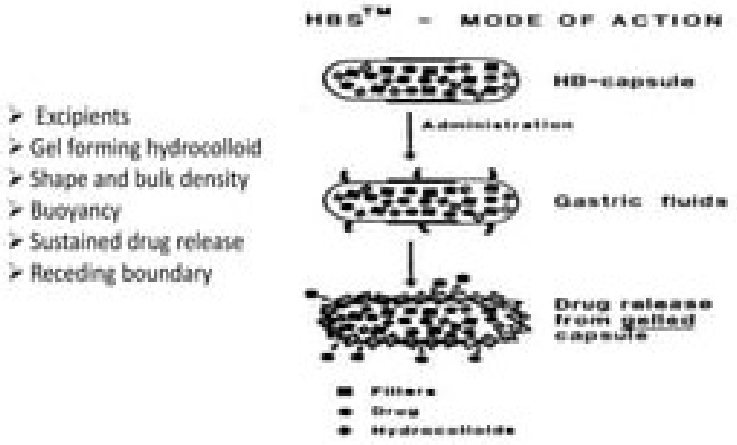


Figure: 4 Non-Effervescent FDDS

Effervescent FDDS[5]

This system made to float in the stomach by incorporating floating chamber, which may be filled with vacuum, air or inert gas. This system uses matrices prepared with swellable polymer and effervescent components. The matrices are formulated in such a way that when they reach into the stomach carbon dioxide is liberated by acidlity of gastric content. This carbon dioxide is

entrapped in the hydrocolloid causes the upward movements of the dosage form and maintain its buoyancy.

This system is divided in to two classes: 1) volatile liquid/ vacuum system and 2) gas generating system.

Volatile liquid/vacuum system[5]

It is osmotically controlled floating system. This system consists of two chambers which are separated by pressure sensitive, impermeable, movable bladder and bio erodible plug which gradually release the gas./ The drug and volatile liquid is placed in first and second chamber respectively. Upon administration, the drug is continuously released from the chamber into the gastric fluid.

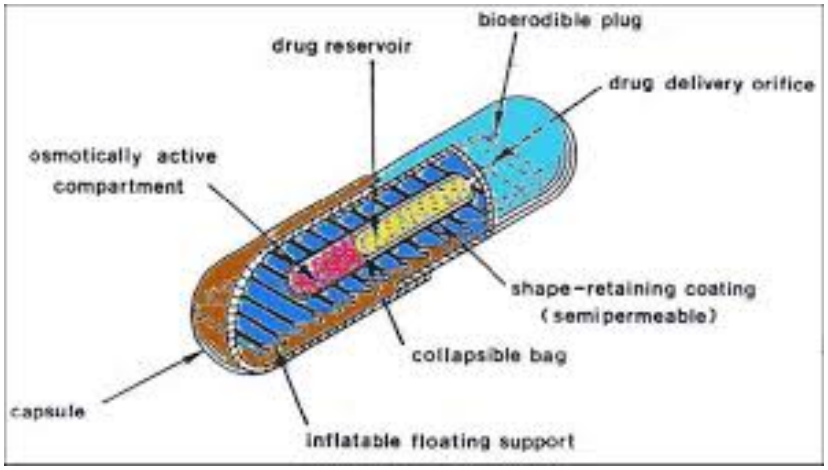


Figure: 5 Volatile Liquid / Vacuum System

Gas generating system[5]

This system uses effervescent reaction between carbonate/bicarbonate salt and citric/tartaric acid which liberate carbon dioxide. This carbon dioxide gets entrapped in the hydrocolloid layer of the system and thus decreases the specific gravity of the system which makes it to float over the gastric fluid.

Figure: 6 Gas Generating System

Mucoadhesive System[5]

Mucoadhesion means attachement of the drug to the mucus coat. This approach helps to increase the gastric residence time of the dosage from by binding them to the gastric mucosa. The adhesion is favoured by rapid hydration. This mucoadhesive system is not that much feasible as the bond formation for mucoadhesion is prevented by the acidic environment and presence of thick mucus in the stomach. Polymers used for this purpose may include polycarbophil, carbopol, CMC, chitosan, lectin etc.

Raft Forming System[5]

This system focus more for delivery of antacid and delivery of drugs used to treat gastrointestinal infection and disorders. The basic mechanism involves formation of viscous cohesive gel when the system comes in contact with gastric rfluid. In this each portion of liquid swells and forms a continuous layer of gel known as raft. The raft floats because of buoyancy created by formation of CO2. This raft acts as a physical barrier to prevent the reflex of gastric content into the oesophagus. This system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for making the system less dense than the gastric fluid and to float on the gastric fluid.

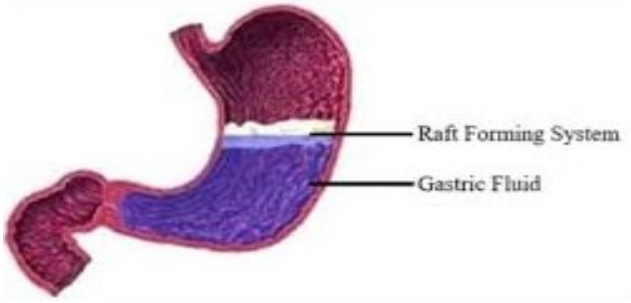


Figure: 7 Raft Forming System

Expandable system[5]

This system may be of two types: 1) Unfoldable system and 2) Swellable polymer.

- **Unfoldable systems** uses biodegradablke polymer. This concept uses carrier such as capsule in which compressed system is incorporated which extends in the stomach.
- **Swellable systems** are retained due to their mechanical property. The swelling is resulted from absorption of water.
- The resultant bulk enbles gastric retention and maintains the stomach in the fed condition.
- The whole expandable system is coated with the polymeric membrane. This outer coat is permeable to both, drug and body fluid. This outer coat also controls the drug release.
- This system is gradually reduced in the size and rigidity. This results in reduction of drug and expanding system. This results in elimination of system.

Super porous hydrogel[5]

Conventional hydrogel have pore size ranging from 10 mm to 10µm. This hydrogel possess very slow process of water absorption and require several hours to attain equilibrium state. In contrast to conventional hydrogel, superporous hydrogel have average pore size >100µm. Superporous hydrogel swells to equilibrium to equilibrium size within minute. This occurs because of rapid water uptake by capillary wetting through numerous interconnected open pores. Superporous hydrogel swells to large size and have sufficient mechanical strength to withstand the pressure created by gastric contraction. This approach is based on the principle that encapsulation of drug within the microporous compartment which having pores on the top and on the bottom wall. Peripheral walls are completely scaled to prevent any direct contact of gastric fluid to the undissolved drug. As delivery system contains entrapped air chamber, when it reaches into the stomach, floating of the system of the gastric fluid takes place Gastric fluid enters into the pores and dissolves the drug which causes release of dissolved drug.

Magnetic system[5]

This approach of increased gastric retention time is based on the principle that dosage form contains a small internal magnet. A magnet is placed in abdomen over the position of stomach that retains dosage form in the gastric region.

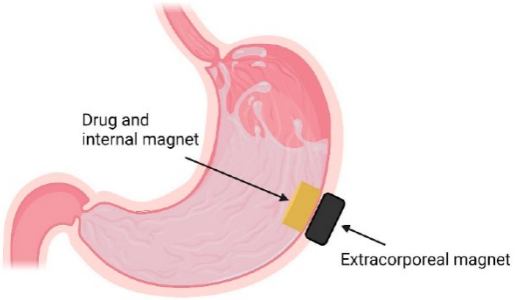


Figure: 8 Magnetic System

High density system[5]

This system possesses a density of about 3g/cm3 which are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements. This system is prepared by coating a drug on a heavy core or mixed with the inert material such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. The major drawback with such system is that it is technically difficult to manufacture formulation with high amount of drug and to achieve density of about 2.8g/cm3.

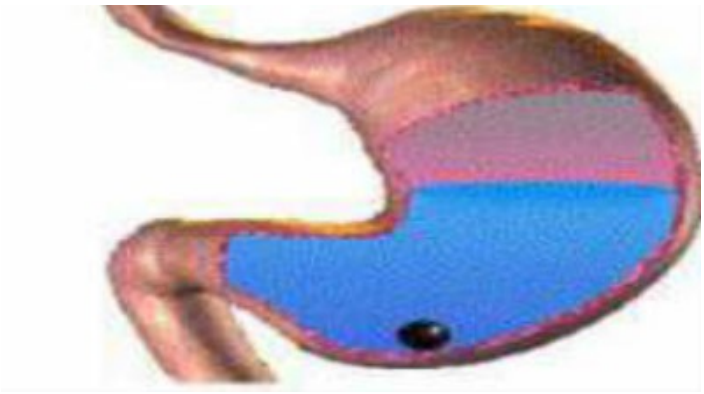


Figure: 9 High Density System

Introduction to muciadension[6]

An adhesive is a material that attaches to another substrate surface and resists separation. Adhesion involves the formation of attractive bonds between two substrates that resist separation.

Bioadhesion is a specific case of adhesion in which at least one of the two substrates involves a biological tissue. Furthermore, if the adherent

substrate surface is a mucosal surface, e.g., a mucosal membrane, bioadhesion is specifically referred to as mucoadhesion.

The use of mucoadhesive materials for the enhanced delivery of therapeutic agents has been of interest for severalyears sowing to several important advantages concerning the in-vitro and in-vivo performance of dosage forms. Mucoadhesive formulations are capable of providing localized drug release in desirable regions such as nasal cavity, eye, mouth, stomach, intestine, and vagina to enhance their clinical efficacy.

The employment of mucoadhesive materials in formulations may modify the permeability of mucosal tissue or membranes and hence facilitate the adsorption of macromolecules, e.g., peptides. Furthermore, the interaction between mucoadhestive form at the site of application, therbyreducintg the dosing frequency and increasing patient compliance.

Theories of mucoadhesion[6][7]

1) Wetting theory of mucoadhesion[6]

The wetting theory attributes the bonding between the formulation and the surface tissue to intermolecular interation and interfacial tension. This theory is usually applied for liquid or low viscosity mucoadhesive systems and is essentially a measure of the "spreadability" of a drug delivery system across the bioglogical substrate. The spreadability of the system is indicative of interactions and can be measured by the liquid-soild contact angle.

Adhesive forces between a liquid and solid enable a liquid drop to spread across the surface, whereas, cohesive forces within the liquid cause the drop to ball up and avoid contact with the surface.

Contact angle	Indication
90^0	The wetting of the surface is favourable, and the liquid tends to spread out to a large area
$>90^0$	The wetting of the surface is unfavourable; the interaction aming liquid molecules maintains the shape of the droplet and minimizes its contact area to the solid surface

Table 1: Contact angle for mucoadhesion

To work done is related to the surface tension of both the adhestive and the substrate, as given by Dupre's equation;

$Wa = \gamma_b + \gamma_1 - \gamma_b$(1)

Where,

Wa- the specific thermodynamic work of adhesion

γ_b- t3he surface tensions of the bioadhesive polymer

γ_t– the substrate

γbt – the interfacial tension

The adhesive work done is a sum of the surface tensions of the two adherent phases, less the interfacial tensions apparent between both phases.

Figure: 10 shows a drop of liquid bioadhesive spreading over a soft-tissue surface

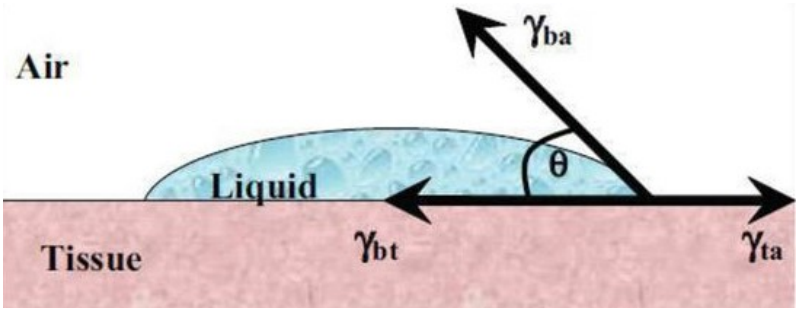


Figure: 10 Bioadhesive Spreading on Soft Tissue

The contact anlgle may be experimentally measured from which interfacial tension (Y)

May be derived using the Young equation,

$\gamma SG = \gamma SL + yLG\cos\theta$ (2)

Where,

γSG – The interfacial tension between solid and gas

γSL – the interfacial tension between solid and liquid

γLG – the interfacial tension

θ – Contactangle between solid and liquid interface

Contact anlge	Indication
$0 = 0^0$	Wetting is complete, the liquid having fully spread across the surface of the substrate
$0 = 180^0$	Non wettability

Table 2: Contact Angle and Indication

2. Electrostatic Theory Of Mucoadhesion[7]

According to electrostatic theory, transfer of electrons occurs across the adhesive interface and adhering surface. This results in the establishment of the electrical double layer at the interface and a series of attractive forces responsible for maintaining contact between the two layers.

3. Mechanical Interlocking Theory Of Mucoadhesion[6]

The mechanical interlocking theory ordy considers the adhesion between liquid and a rough surface or a surface rich in pores and essentially proposes that the adhesion between the two substrates is due to mechanical interlocking of the adhesive into the irregularities of the substrate surface. Adhesion between the Mucoadhesive system and the rough surface typically occurs within a diverse biological environment.

4. Diffusion Theory Of Mucoadhesion[7]

Diffusion theory describes that polymeric chains from the bio adhesive interpenetrate into glycoprotein mucin chains and reach a sufficient depth within the opposite matrix to allow formation of a semi-permanent bond. The process can be visualized from the point of bioadhesive into the mucus network and the glycoprotein mucin chains into the bioadhesive matrix until an equilibrium penetration depth is achieved.

5. Adsorption Theory Of Mucoadhesion[7]

According to the adsorption theory, after an intial contact between two surfaces, the materials adhere because of surface forcea acting between the chemical structures at the two surfaces. When plar molecules or groups are present, they re-oreientate at the interface. Chemisorption can occur when

adhesion is particularly strong. The theory maintains that adherence to tissue is due to the net result of one or more secondary forces (van der Wall's forces, hydrogen bonding, and hydrophobic bonding).

6. Fracture Theory Of Mucoadhesion[7]

This theory describes the force required for the separation of two surfaces after adhesion. The fracture strength is equivalent adhesive strength through the following equation. This theory is useful for the study of bioadhesion by tensile apparatus.

$$\sigma = (E \times e/L)^{1/2}$$

Where, a – fracture strength

e – fracture energy

E – young modulus of elasticity

L – critical crack length.

Polymers Used In Mucoadhesion[7]

Mucoadhesive polymers have numerous hydrophilic groups, such as hydropxyl, carboxyl, amide, and sulfate. These groups attach to mucus or the cell membrance by various interactions such as hydrogen bonding and hydrophobic or electrostatic interactions. These hydrophilic groups also cause ploymers to swell in water and, thus, expose the maximum number of adhesive sites.

An ideal polymer for a bio adhesive drug delivery system should have the following

Characteristics:

1. The polymer and its degradation products should be non-toxic and non-adsorbable.

2. It should be non-irritant.

3. It should preferably form a strong non-covalent bond with the mucus or epithelial cell surface.

4. It should adhere quickly to moist tissue and possess some site specificity.

5. It should allow easy incorporation of the drug and offer no hindrance to its release.

6. The polymer must not decompose on storage in during the shelf life of the dosage form.

7. The cost of the polymer should not be high so that the prepared dosage form remains competitive.

Polymers that adhere to biological surfaces can be divided into three broad categories.

1. Polymers that adhere through nonspecific, non-covalent interactions which are primarily electrostatic in nature.

2. Polymers possessing hydrophilic functioned groups that hydrogen bond with similar groups on biological substrates.

3. Polymers that bind to specific receptor sites on the cell or mucus surface.

Type	Common polymers
Anionic polymers	• Carbopol • Polycarbophil • Sodium alginate • Sodium carboxy methyl cellulose
Cationic polymers	• Chitosan
Non-ionic polymers	• Hydroxy propyl methyl cellulose • Hydrooxy propyl cellulose • Methyl cellulose • Polyethylene glycol • Polyvinyl pyrrolidone • Hydroxy ethyl cellulose
Stimuli-sensitive polymers	• Poloxamer

Table 3: Commonly Used Adhesive Polymer

Factors Affecting Mucoadhesion[7]

- Hydrophilicity
- Molecular weight

- Cross-linking and swelling
- Spatial conformation
- pH
- Concentration of active polymer
- Drug/ excipient concentration

Techiniques for the determination of mucoadhesion[7]

The evalution of bioahesive properties is fundamental to the development of novel bioadhesive delivery systems. These tests are also important to screen large number of materials and their mechanisms. Numerous methods have been developed for studying mucoadhesion. Since no standard apparatus is available for testing bioadhesive strength, an inevitable lack of uniformity between test methods has arisen. Nevertheless, three main testing models are recognized namely.

- Tensile strength
- Shear strength
- Peel strength

The most popular technique used for the determination of force of separation in bioahesive testing is the application of force perpendicularly to the tissue/adhesive interface, during which a state of **tensile stress** is set up. But during the **shear stress**, the direction of the forces is reoriented so that it acts along the joint interface. In both tensile and shear modes, and equal pressure is distributed over the contact area.

The **peel test** is based on the calculation of energy required to detach the patch from the substrate. The peel test is of limited use in most bioadhesive systems. However, it is of value when the bioadhesive system is formulated as a patch.

In **tensile and shear experiements**, the stress is uniformly distributed over the adhesive joint, whereas in the peel strength stress is focused at the edge of the joint. Thus tensile and shear measure the mechanical properties of the system, whereas peel strength measures the resistant of the peeling force.

The most common technique used for the measurement of bioadhesion test is **tensile strength method** McCarron et al. and Donnelly have reported extensively on the use of a commercial apparatus, in the form of a texture profile analyzer operating in bioadhesive test mode, to measure the force required to remove bioadhesive films from excised tissue in vitro.

The texture analyzer, operating in tensile test mode and coupled with a sliding lower platform, was also used to determine peel strength of similar formulations.

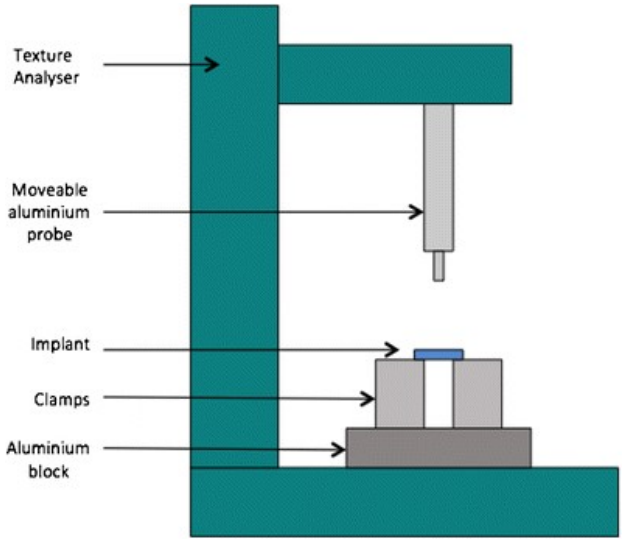
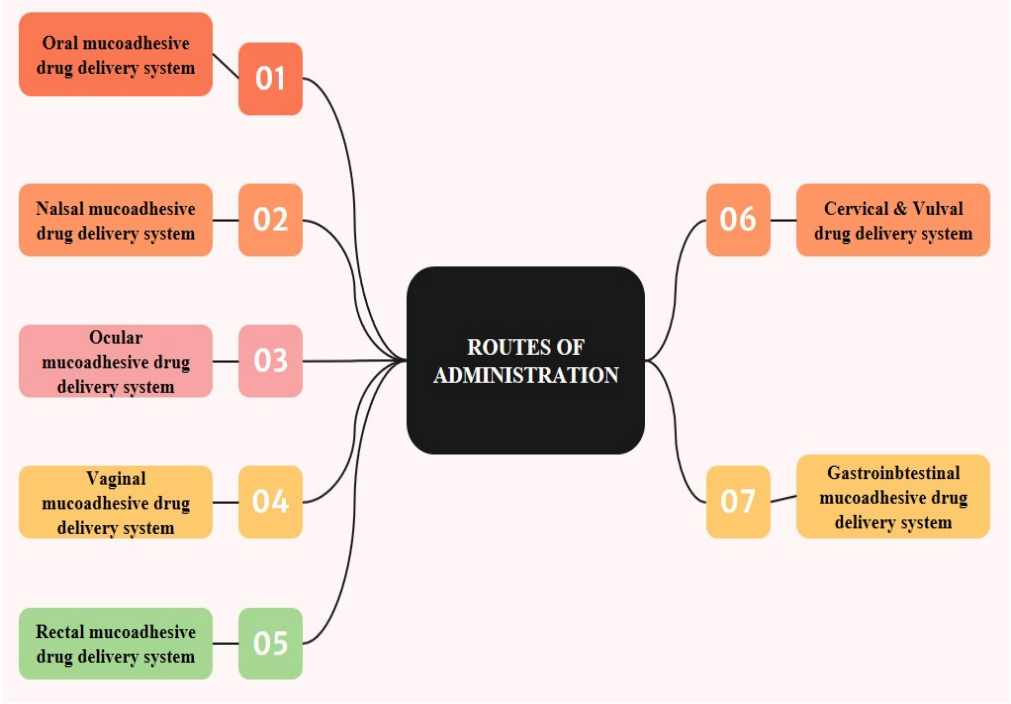


Figure 11: Analyser for tensile strength and shear strength

Routes of administration for mucoadhesive-based drug delivery system[7]



Conclusion

Gastro Retentive Drug Delivery Systems offer significant advantages in enhancing drug bioavailability and patient compliance by prolonging drug residence time in the stomach. While these systems show promising benefits, challenges such as variability in gastric emptying and potential for gastric irritation must be addressed. Ongoing research and technological advancements continue to improve the efficacy and application of GRDDS in pharmaceutical formulations.

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Robotic assistance in cardiac surgery glimpse into future

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Introduction

- The introduction of robot-assisted surgery and specifically the advanced set of instruments to use in performing robotic assisted minimally invasive surgery.
- Vinci surgical system used in an estimated 2lakhs surgery in 2012
- The first robotic assisted surgical uses of the robot was in orthopaedics, Neurosurgery , and cardiac surgery , General surgery, Gynaecology and Neck surgery
- The long term result and potential benefits or in robotic surgery

Defining Robotic assist:

Figure 1

- Robotic assistance refers to the use of robots to aid human in various tasks
- Minimally invasive approach to heart surgery surgeon perform this produce through small incision instrument and robot controlled tools
- Open heart surgery,larger incision reduced risk of complication
- In apollo hospital,make incision of 8mm using cutting ,robotic surgery
- Current status of robotic-assisted cardiac robotic surgery
- Robotic assisted surgery has significant advancement, making an integral part of various surgical speciality.

Evolution and innovation:

- 1960's robot assisted surgery have evolved significantly
- Modern robotic surgical system feature highly dexterous arm.
- Integration of imaging and visualization technology .
- Al-Artificial intelligence and machine learning aid in surgical decision

Challenges and Global doption:

- High costs of robotic system, maintenance and proply surgeon training
- Various clinical benefits procedures in robotic surgery
- Over 6000 robotic system surgery used across 66 countries
- More than 7.2million procure

Future Directions:

- Artificial Intelligence (AI) driven automation,no orbitsmicroscoficinesion surgery

Benefield for patient in robotic surgery:

Figure 2

- ❖ Minimally invasion robotic assisted surgery involves smaller incision in the less trauma to the body.
- ❖ Reduced rain and discomfort smaller incision typically
- ❖ Shorter hospital stay;
- ❖ Patient can often go home soon sometimes in a matter of days ;
- ❖ Faster recovery time ;
- ❖ Patient return to normal activities more quickly, week and months

Reduced Recovery Time Comparison: Robotic-Assisted Cardiac Surgery vs. Traditional Human Cardiac Surgery

Aspect	**Robotic-Assisted Surgery**	**Traditional Surgery**
Hospital Stay	3-5 days	5-7 days (or longer if complications arise)
Return to Normal Activities	2-4 weeks	6-8 weeks (or more) before resuming usual activities
Pain and Discomfort	Less pain and discomfort, quicker return to daily activities	More significant pain and discomfort, longer recovery periods
Physical Rehabilitation	Less intensive rehabilitation due to less invasive surgery	More extensive rehabilitation, extending recovery period
Benefits of Robotic Surgery	Smaller incisions, reduced trauma to the body	Quicker recovery, decreased infection risk, less blood loss

Economic impact of robotic assisted:

Numerous financial effects of robotically assisted heart surgery are felt by patients as well as healthcare systems. Long-term financial advantages can more than balance the sometimes substantial upfront outlay. Here is a thorough analysis of the effects on the economy

1. High Equipment Costs

Surgical robotic technologies, like the da Vinci Surgical System, are costly, frequently requiring millions of dollars in purchases. This financial load is increased by maintenance and upgrade expenses.

2. Training and Implementation

To use robotic systems efficiently, surgeons and operating room personnel need to undergo specialized training, which takes time and money.

Because robotic systems require specialized disposable instruments and longer setup periods, they may result in higher operational expenses.

3. Reduced Hospital Stay

Patients who get robotically assisted surgery spend less time in the hospital and pay less money for it. This lessens the financial strain on healthcare systems and frees up hospital resources.

4. Decreased Rates of Complications

Lower rates of postoperative complications result in decreased expenses for handling and treating complications. This involves a decreased requirement for follow-up visits, drugs, and operations.

5. Quicker Recoveries and Returns to Work

- Patients experience quicker recovery times, allowing them to resume regular activities and work sooner. By doing this, indirect costs related to missed work and decreased productivity are decreased.

6. Robotic

- Better results and more precision from robotically assisted surgery lead to lower readmission rates, which further cut down on medical expenses.

Cost-Effectiveness Studies:

1. **Comparative Studies**: Research contrasting robotic-assisted cardiac surgery with conventional surgery has demonstrated that, although having greater upfront costs, the procedure can be more cost-effective overall because of lower rates of complications, shorter hospital stays, and faster recovery periods.

2. **Long-Term Savings**: Long-term economic assessments indicate that the advantages of a faster recovery and fewer difficulties may outweigh the higher initial expenses associated with robotic systems.

Patient-Centric Economic Benefits

1. **Lower Out-of-Pocket Costs**: Patients may pay less out-of-pocket for hospital services and prescription drugs as a result of shorter hospital stays and fewer complications.

2.**Better Cosmetic Outcomes and Improved Recovery Experiences**:Improved recovery times and happier patients may spur demand for robotically assisted operations and provide justification for spending money on robotic technologies.

Broader Economic Impact

1. **Healthcare System Efficiency:** By relieving the strain on hospital resources and enabling the treatment of a greater number of patients in a given amount of time, robotically assisted surgeries can enhance the overall efficiency of the healthcare system.

2**. Technology Investment:** Hospitals that make investments in cutting-edge robotics may draw in more patients, especially those looking for innovative and high-quality healthcare, which will boost their bottom line.

3. **Economic Growth**: As robotic surgical systems are developed and used, the medical technology industry experiences innovation and economic growth that boosts employment and the economy.

Ethical and legal considerations:

Figure 3

Robotic-assisted surgery introduces several ethical and legal considerations that need careful examination to ensure the responsible and safe use of this advanced technology.

Here are the primary ethical and legal issues;

1.Ethical Considerations:

- Patient Consent and Autonomy1. Informed Consent -It is imperative to guarantee that patients are completely aware of the dangers, advantages, and alternatives associated with robotically assisted surgery in order to ensure Patient Consent and Autonomy.This involves describing the surgeon's
- Level of control and the function of the robot. Autonomy .
- Patients need to be able to make decisions about their care on their own, including whether or not to have robotically assisted surgery.

2. Access and Equity

Healthcare inequities-There's a chance that wealthy individuals or institutions won't be able to obtain robotic surgery, which would exacerbate already-existing healthcare inequities. - **Resource Allocation**- Allocating scarce healthcare resources, such as pricey robotic devices, presents moral dilemmas regarding justice and precedence.

Safety and Efficacy clinical Outcome- It is critical to guarantee that robotic surgery is just as safe and efficient as conventional techniques.

Training and competency- In order to guarantee patient safety, surgeons must obtain sufficient training and exhibit competency using robotic systems.

Patient-Physician Relationship and Trust and communication- The adoption of new technologies should not weaken the trust and communication between patients and their physicians. Surgeons must stay candid about their experience and the potential limitations of robotic surgery.

Ethical Use of Technology and Transparency- Clear communication regarding the use of technology in surgery, including potential limitations and risks, is crucial to maintain patient trust.

Avoiding Overuse-There is a possible ethical concern if robotic surgery is over-promoted or overused for commercial benefit rather than based on patient need and clinical evidence.

Legal considerations

1.Liability and Accountability:

- **Surgical Errors**-Determining liability in the event of a surgical error can be difficult, involving the surgeon, the hospital, and the manufacturer of the robotic system. –

- **Product Liability**-Manufacturers of robotic systems must ensure their goods are safe and effective. They can be held accountable for faults or failures that lead to patient damage.

2. Regulatory Compliance:

- Approval and Oversight- Robotic surgical systems must meet regulatory requirements imposed by entities like the FDA (Food and Drug Administration) in the U.S. or analogous agencies in other countries.

- Monitoring and Reporting-Continuous monitoring and reporting of adverse events connected to robotic surgeries are necessary to maintain regulatory compliance.

3. Privacy and Data Security:

- **Patient Data-** Robotic systems may collect and store sensitive patient data, raising concerns about data privacy and security.

- **Cybersecurity-** Protecting robotic systems from cyber threats is crucial to ensure patient safety and data integrity.

4. Standards and Guidelines:

- Professional Standards- Developing and adhering to professional standards and guidelines for robotic-assisted surgery assures uniformity and safety in its implementation

-Certification and Credentialing- Surgeons should be qualified and credentialed to perform robotic-assisted procedures, ensuring they have the requisite skills and knowledge

5. Insurance and Reimbursement:

- **Coverage-** Insurance companies must decide whether to pay the costs of robotic-assisted surgeries, which can be more expensive than traditional treatments.

- Reimbursement Rates: Determining suitable reimbursement rates for robotic surgeries is vital to balance cost and accessibility.

Conclusion

There are several ways that robotically assisted heart surgery affects the economy. Healthcare systems and patients may save a substantial amount of money over time by using robotic technology, even when the initial expenses are considerable. These savings are a result of shorter hospital stays, fewer complications, faster healing periods, and higher patient satisfaction. Additionally, the broader economic impact includes growing the medical technology industry and improving healthcare delivery efficiency.

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Fractional Flow Reserve (FFR): Clinical applications and implications

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Abstract

Fractional flow reserve (FFR) offers a precise assessment of the extent of ischemia resulting from coronary stenoses in the myocardial areas located downstream. Interventional cardiology data have indicated advantages of using an FFR-guided percutaneous coronary intervention (PCI) approach. There is a scarcity of evidence on the utilization of FFR to direct coronary artery bypass grafting (CABG). Recent results indicate that FFR may streamline CABG procedures and enhance the durability of artery grafts, while its effect on clinical outcomes remains uncertain. The objective of this review was to provide a concise summary of the existing information on FFR-based CABG and analyze the reasoning and possible outcomes of transitioning to a surgical revascularization strategy based on FFR.

Introduction

Fractional Flow Reserve (FFR) is a highly regarded and indispensable tool in the domain of interventional cardiology. This chapter examines the fundamental principles, techniques, clinical uses, and consequences of FFR, emphasizing its significance in directing therapy choices for individuals suffering from coronary artery disease.

Fractional flow reserve (FFR) is a precise technique used to evaluate the functional importance of blockages in the coronary arteries. FFR is the ratio of the maximum possible blood flow in a coronary artery to the hypothetical maximum achievable blood flow in the same artery if there were no narrowing. The value is obtained by dividing the average pressure in the distal coronary artery by the average pressure in the aorta at the time of maximum hyperemia. Initial research indicated that a cut-off value of 0.75 was a dependable means of identifying lesions that cause ischemia. Subsequently, other outcome studies

confirmed the validity of the threshold value of 0.80, which is currently widely acknowledged.

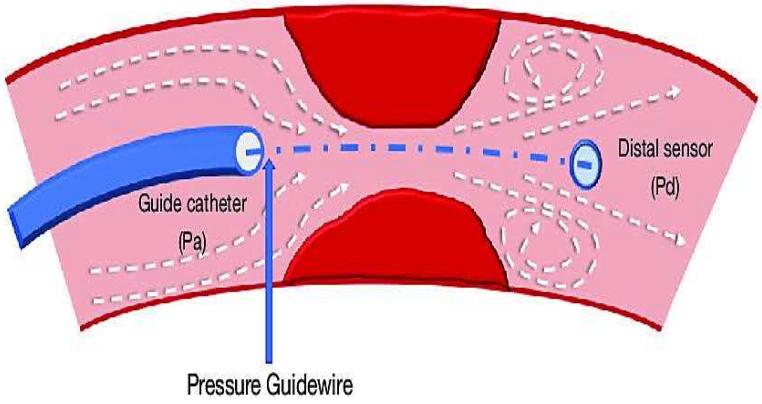

Figure1

Principle of FFR

FFR is based on the idea that not all blockages in the coronary arteries are equally important in producing reduced blood flow to the heart muscle. This procedure quantifies the decrease in pressure across a blockage in the coronary artery at maximum blood flow, offering a physiological evaluation of the severity of the blockage. FFR is determined by dividing the average distal coronary pressure by the average aortic pressure during hyperemia. A FFR result lower than 0.80 often suggests the presence of a clinically significant narrowing of blood vessels, which can help guide decisions regarding treatment.

FFR Measurement

Guide wire insertion involves the threading of a pressure-sensing guidewire through the coronary artery, specifically across the stenosis that is of interest.

Maximal coronary hyperemia is created by administering intravenous adenosine in order to replicate conditions of heightened demand.

Measurements of pressure: FFR is calculated by concurrently measuring distal coronary pressure and aortic pressure. The formula for fractional flow reserve (FFR) is calculated by dividing the distal coronary pressure (Pd) by the aortic pressure (Pa).

The acceptable range for a typical outcome is between 0.94 and 1. Any number below that indicates the need for therapy since it signifies insufficient

blood flow. For instance, if your fractional flow reserve (FFR) is 0.75, it indicates that the constricted portion of your coronary artery is resulting in a 25% reduction in pressure.

If the results of your fractional flow reserve indicate that your coronary artery blockage is not severe, then there is no need for you to undergo angioplasty and receive a stent. Instead, you have the option to consume medication.

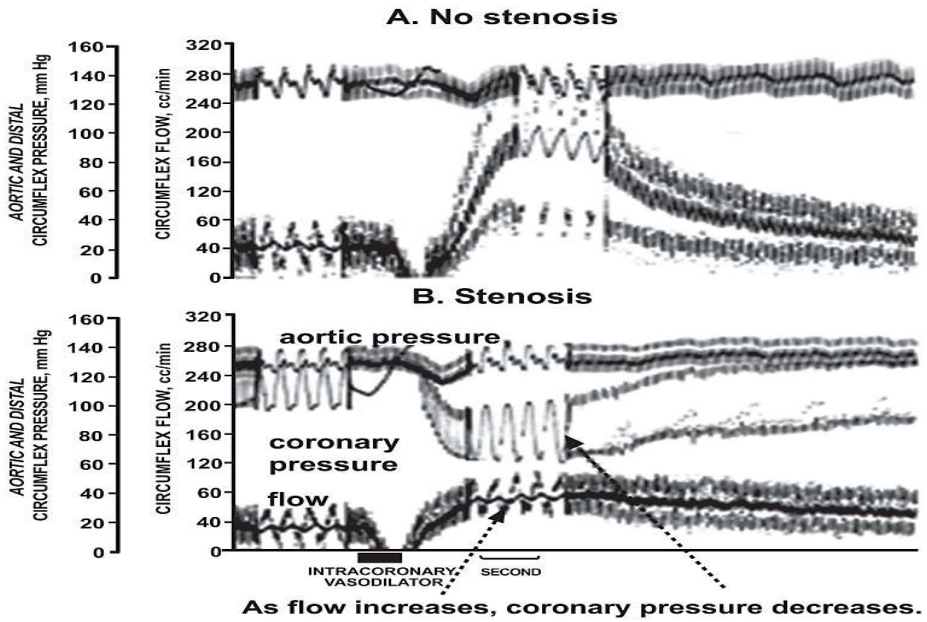

Figure 02: Tracings demonstrating fractional flow reserve

Tracings illustrating the use of fractional flow reserve (FFR) as a means to assess coronary flow reserve. Displayed are recordings of coronary blood flow and pressure tracings in a dog with a healthy coronary artery (A) and a dog with a significant narrowing of the coronary artery (B). The bar at the bottom of the picture indicates the hyperemic reaction that was caused by the coronary vasodilating impact of a contrast injection. In the absence of stenosis (A), the administration of contrast resulted in a significant augmentation of coronary blood flow, with minimal deviation of pressures. Nevertheless, in the presence of stenosis (B), the administration of contrast resulted in a slight enhancement in coronary blood flow, accompanied by a significant rise in the pressure difference between the aorta and the distal part of the coronary artery. FFR represents the ratio of coronary pressure to aortic pressure during maximum hyperaemia, and it indicates the flow reserve.

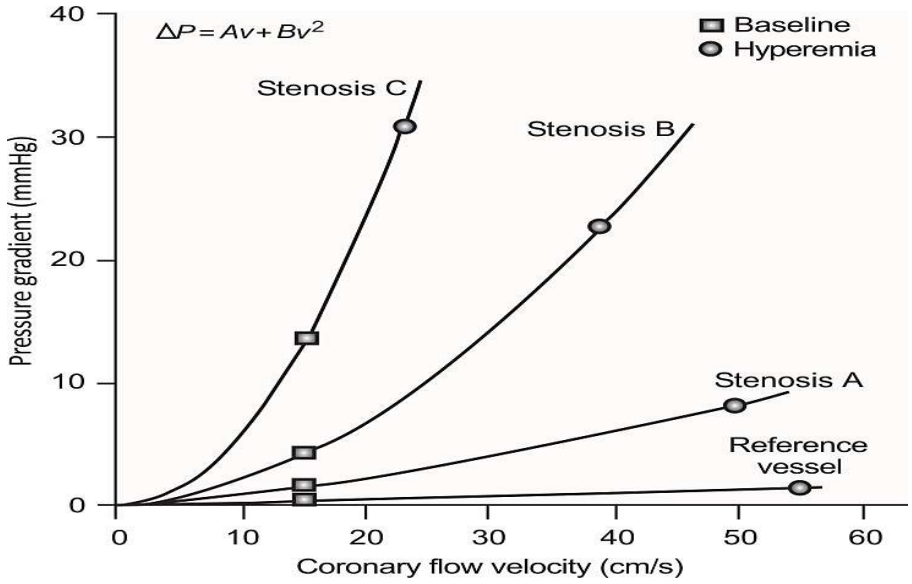

Figure 03: Correlation between Coronary Flow Velocity and Pressure Gradient.

The pressure drop (Δ P) across a myocardial stenosis is directly proportional to the flow velocity (v) in the coronary artery. The degree of incline in this correlation intensifies as the severity of stenosis increases (from Stenosis A to C). The pressure gradient at baseline (square) for a given stenosis is influenced by the resting microvascular resistance. On the other hand, the pressure gradient at maximal hyperemia (circle) is primarily determined by the vasodilator capability of the downstream resistance vessels, although the physical factors mentioned in the text may impose a limitation. The link between the change in pressure (Δ P) and velocity (v) is determined by the equation displayed at the top of the picture. The initial and subsequent terms denote the decrease in pressure due to viscous friction and the reduction in pressure at the exit of the stenosis, respectively. The values of coefficients A and B are established based on the geometry of the stenosis and the rheological properties of the blood.

Clinical applications

- Identifying Hemodynamically Significant Stenoses: FFR assists in distinguishing between anatomically significant lesions and those that induce ischemia, aiding treatment decisions.

- Optimizing Revascularization: FFR guides interventional cardiologists in selecting lesions that would benefit most from revascularization, minimizing unnecessary procedures.
- Deferred Revascularization: Lesions with FFR > 0.80 are often managed conservatively, avoiding interventions and their associated risks.
- Multi-Vessel Disease: FFR helps prioritize lesions in multi-vessel disease, determining which lesions require immediate intervention.
- Serial Assessment: FFR can monitor lesion progression over time, informing treatment strategies and assessing the success of prior interventions.
- Enhanced Decision-Making: FFR provides objective data to guide treatment choices, leading to more informed and evidence-based decisions.
- Risk Stratification: FFR values are associated with long-term outcomes, aiding in risk stratification and treatment planning.
- Cost-Effectiveness: FFR minimizes unnecessary interventions, optimizing resource utilization and reducing healthcare costs.
- Patient-Centered Care: FFR contributes to personalized care by tailoring interventions to the individual patient's needs and physiology.

Limitations and considerations

Three Relative contraindications for intravenous injection of adenosine include second- and third-degree atrioventricular blocks, sick sinus syndrome without pacemaker, prolonged QT-interval, severe hypotension, cardiac failure, and obstructive pulmonary disease. Invasive diagnostic techniques should generally not be performed unless there are invasive treatment options available.

FFR test measurements are restricted in patients with conditions such as small-vessel disease, diffuse coronary artery disease, and left ventricular hypertrophy.The number is 18. These circumstances can cause an overestimate of the degree of coronary stenosis because they impede blood flow following pharmacological vasodilation and result in a drop in distal coronary blood pressure.

Various coexisting medical conditions can have an impact on the effectiveness and safety of FFR examinations.Three Age-related alterations in microvasculature can compromise the accuracy of FFR testing in older individuals, resulting in elevated FFR scores that are not necessarily indicative of the severity of stenosis. Patients with diabetes mellitus may experience

inaccurately high FFR scores as a result of microvasculature disease and reduced responsiveness to vasodilators given during the test. Using FFR readings as guidelines may result in less treatment for elderly and diabetic individuals.

While there is ongoing debate about the precise impact of diseased microvasculature on FFR values, research has demonstrated that PCI interventions guided by FFR are equally advantageous for patients aged 65 and above with multivessel disease as they are for younger patients with the same condition. This holds true for patients with and without diabetes, when compared to PCI guided solely by angiography.

Adenosine reaction: Adenosine can elicit different reactions in patients, which may have an impact on FFR readings.

Microvascular Disease: Fractional Flow Reserve (FFR) may provide an inaccurate assessment of the severity of stenosis when there is microvascular dysfunction.

Lesion Location: FFR may not completely include the impact of collateral circulation and side branches on the total flow of blood in the coronary arteries.

Emerging trends and future directions

Instantaneous Wave-Free Ratio (iFR) is a method that is similar to Fractional Flow Reserve (FFR), but it involves taking pressure measurements at a different point in the cardiac cycle. This technique has the potential to decrease the requirement for adenosine administration. Virtual FFR (vFFR) is a method that uses computational fluid dynamics and sophisticated imaging to predict FFR values without the need for invasive procedures. This approach improves clinical decision-making.

Conclusion

Fractional Flow Reserve (FFR) is a significant breakthrough in the field of interventional cardiology, as it helps to connect the evaluation of coronary lesions in terms of both their anatomy and physiology. The clinical uses and consequences of this have revolutionized the approach of cardiologists to coronary artery disease, resulting in more accurate treatment decisions, enhanced patient outcomes, and a patient-focused approach to care. With the advancement of technology, Fractional Flow Reserve (FFR) remains an essential tool in guiding therapies by assessing the physiological importance of coronary lesions.

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"Genomic insights and the future of cardiac therapy: Deciphering the genetic code of cardiovascular disease".

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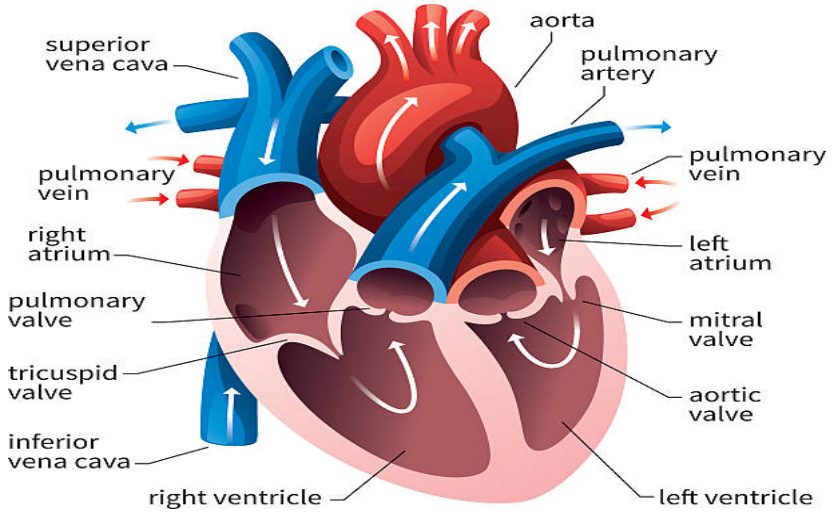
Introduction

Cardiovascular disease (CVD) is a leading health problem, affecting majority of individuals in all over the world. CVD comprises a broad range of the vasculature, the myocardium, the heart electrical circuit, congenital heart disease. Known risk to its development are lifestyle choices, ages, sex and inherited genetic variants. Enormous effort has been invested in understanding the genes and specific DNA sequence variants responsible for this heritability.

We consider the approaches used to discover genes for human CVD, the lessons learned from the study of mendelian and complex forms of CVD and take a look for research driven by next generation techniques ,this includes sequencing and modeling human genetic disease in cells. molecular genetics and pharmacogenetics play a key role in the diagnosis, prevention and treatment of CVD.

Genetic testing is used to identify the underlying genetic etiology in patients with suspected cardiovascular disease such as hypertropic cardiomyopathy or familial hypercholesterolemia and to determine who in the family has interited the causal variant and is therfore at risk of developing CVD.

Anatomy of heart



History of Genetics :

Genetics is the study of genes ,genetic variation ,and heredity in organism .heredity ,also called inheritance or biological inheritance ,is the passing on of traits from parents to their offspring ,either through asexual or sexual reproduction , the offspring cell or organism acquire the genetic information of their parents .

Gregor mendel is known as the "father of genetics ".His experiments showed that the inheritance of certain traits in pea plants follows particular pattern,subsequently becoming the foundation of modern genetics and leading to the study of heredity.

Family history and cardiovascular disease:

Genetics can influence the risk for heart disease .A family history of cardiovascular disease (CVD) modifies future risk of CVD depending on the number and age of affected first degree relatives. A genetic variation (mutation) in a single gene can affect the likehood of developing heart disease. It is likely that people with a family history of heart disease share common environment and other factors that may increase the risk of CVD. However, genes do not act alone –lifestyle, diet, and exercise modify the risk of CVD.

In the Framingham study , there were 2302 male and female offspring study participants with a parental history of premature CVD (FATHERS <55 Years and mothers <65 years)and they were analyzed for CVD risk .After 8

years of follow up , CVD increased 75% with paternal and about 60% with maternal history of premature CVD. The Framingham study found also that CVD increased about 40% in those whose siblings had CVD .

Cardiovascular disease:

The disease and conditions affecting the heart are collectively known as heart disease. Heart conditions that include diseased vessels , structural problems and blood clot is called cardiovascular disease . The person may be symptomatic or asymptomatic. There are many different types of cardiovascular disease;

1. coronary heart disease(CAD) ,
2. Arrhythmia ,
3. Rheumatic heart disease (RHD),
4. Cardiomyopathy,
5. Congenital heart disease ,
6. Endocarditis ,
7. High blood pressure ,
8. Peripheral artery disease ,etc.

Risk factors of cardiovascular disease :

A person is more likely to develop cardiovascular disease if they have risk factors such as :

1. High blood pressure (hypertension)
2. High cholesterol (hyperlipidemia)
3. Tobacco use
4. Type 2 diabetes
5. Family history of heart disease
6. Lack of physical activity
7. Obesity

Causes of cardiovascular disease :

The most common cause behind the cardiovascular disease is the development of plaque in the arteries and blood vessels that led to the heart ,other common factors related to cardiovascular disease are ;

- Uncontrolled diabetes
- Obesity
- Genetic
- Smoking
- High level cholesterol

- Excessive drinking
- Unhealthy life style

Role of genetics in cardiovascular disease:

Genetic factors play a role in a persons risk of developing certain heart diseases. Hereditary traits can increase the risk of heart disease or other related health conditions. A person may have certain gene alterations that affect their heart and heart functioning. These genes may make them more susceptible to developing heart disease. For health conditions that follow a dominant inheritance pattern, a parent has a 1 in 2 chance of passing these genes onto their child. Different gene variation can cause certain heart conditions. For example, the following genes have a link with the development of cardiomyopathies .

1. MYH7
2. MYBPC3
3. TNN2
4. TNNI3
5. LMNA

Other genes can also cause associated conditions that may increase the risk of heart disease , such as familial hypercholesterolemia (FH):

1. LDLR
2. APOB
3. PCSK9

Monogenic and polygenic disorders:

These disorders are caused by a mutation in a single gene (monogenic) or several genes (polygeneic) .polygenic disorders also be caused by a combinational effect of gene mutations and environmental factors or by damage to chromosomes . Genetic disease are caused by multiple environment agents ,internal or external , which interact giving way to a sick phenotype .These genomic alterations have a hereditary pattern and according to the amount of genes involved are divided into ;

- **Monogenic diseases :** caused by alterations in the DNA of a single gene .
- **Polygenetic diseases:** are the product of the combination of mutations in the DNA of several genes, generally on different chromosomes .

GENETICS AND HEART DISEASE

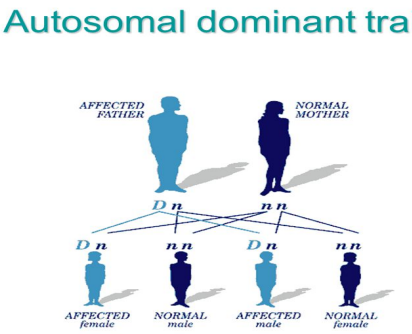
RARE MONOGENIC DISORDER

a. Hypertropic cardiomyopathy
b. Long QT syndrome
c. Familial dilated cardiomyopathy
d. Arrhythmogenic right ventricular Cardiomyopathy(CPVT)

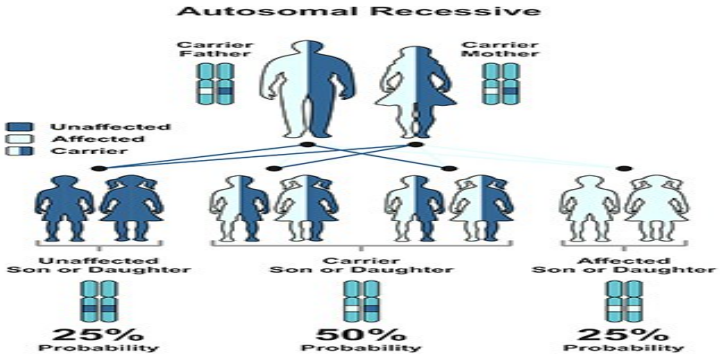
COMMON MULTIFACTORIAL CONDITION

a. Hypercholesterolemia
b. Hypertension
c. coronary artery disease
d. atrial fibrillation

Monogenic disorder



Multifactorial disorder



Role of genetics in coronary artery disease :

Genetic factors contribute importantly to the risk of CAD .The heritability of CAD has been estimated between 40% and 60%, on the basis of family and twin studies .populations of affected and unaffected individuals could be studied by genotyping common single nucleotide polymorphisms(SNPs) within a gene and its regulatory sequences .Although economically attractive, this approach had many limitations. By definition ,studies are limited to genes with a known or suspected role in defining a phenotype and do not provide new insight or into biological pathways leading to disease. With the exception of rare monogenic disorders of lipid metabolism, such as familial hypercholesterolemia, there is as yet little support for a role of single gene disorders in coronary atherosclerosis or plaque rupture .

Genome – wide association studies :

To understand the genetic of cardiovascular disease and other complex diseases has been driven by technological advances , including high – throughput DNA microarray technology using chips containing up to a million DNA markers consisting of a single nucleotide polymorphism (SNPs).In commercial arrays used for genome –wide association studies (GWASs),(SNPSs) are used to tag common variation across the human genome .comparison of the allele frequency of each SNP in cases and controls as part of GWAS provides an agnostic approach that involves no underlying assumption on candidate genes or pathways .

Testing for inherited heart diseases :

Genetic testing is the process of taking a sample of a persons DNA to look for changes that could cause inherited heart disease .Important changes in genes are called pathogenic mutations .**The term pathogenic means disease causing .**

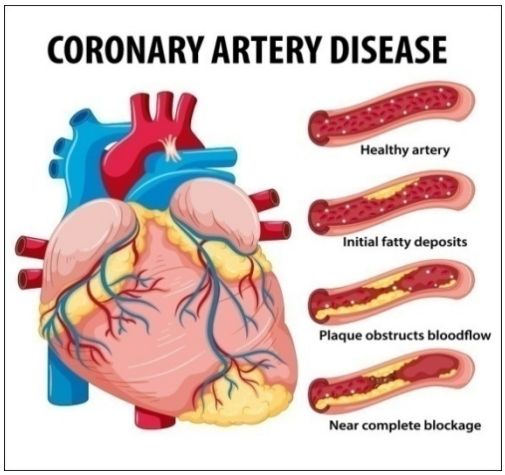
Genetic testing can be used to :

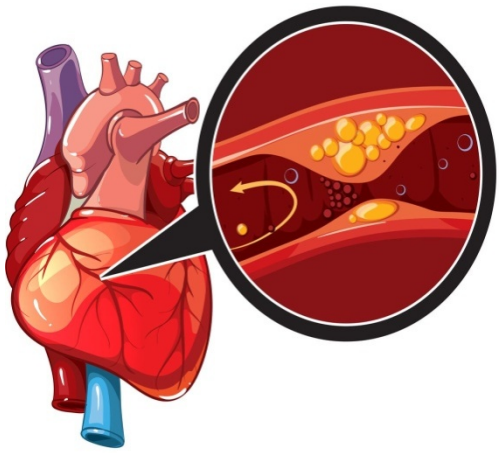
- Identify the cause of heart disease in a family ,
- Predict which family members are at risk to develop the family's heart condition .

People with a family history of heart diseases can collect information from their close relatives . Doctors can use this data to help reduce someone's heart disease risk .

Coronary Artery Disease (CAD):

Coronary artery disease is the narrowing or blockage of the coronary arteries ,usually caused by atherosclerosis ,It affects the main blood vessels that supply blood to the heart . coronary artery disease often develops over many years .symptoms are from the lack of blood flow to the heart .They may include chest pain and shortness of breath .A complete blockage of blood flow can cause a heart attack.





Causes :

Coronary artery disease is caused by the built up of fats , cholesterol ,and other substance in and on the walls of the heart arteries . this condition is called atherosclerosis .the buildup is called plaque. This cause arteries to narrow and blocking blood flow .some causes of atherosclerosis and CAD are ;

- Diabetes or insulin resistance
- High blood pressure
- Smoking and tobacco use

Risk factors :

- **Age** –getting older increase the risk of damaged and narrowed arteries .
- **Birth sex** – men are generally at greater risk of CAD . however , women increase the risk after menopause .
- **Family history –** A family history of heart disease makes more likely to CAD.
- **Chronic kidney disease –**Having long term kidney disease increase the risk of coronary artery disease .

- **Diabetes-** Type 2 diabetes and coronary artery disease share some risk factors ,such as obesity and high blood pressure .

Risk factors often happen together .one risk factor may trigger another .when together ,make more likely to develop coronary artery disease .For example, metabolic syndrome is a group of condition that include high blood pressure, high blood sugar ,too much body fat and high triglyceride levels . metabolic syndrome increase the risk of coronary heart disease .

- **Increased high sensitivity c- reactive protein (hs- CRP).**
- **High triglycerides .**
- **High level homocysteine .**
- **Certain autoimmune disease .**
- **Breathing pauses during sleep ,called obstructive sleep apnea .**

Complications:

Complications of coronary heart disease may include ;

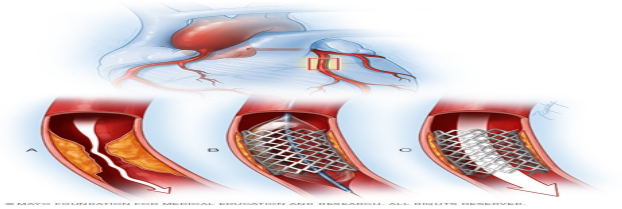
- **Chest pain also called angina –** This is a symptom of coronary artery disease .but it also can be a complication of worsening CAD.
- **Heart attack –** A clot can block the blood flow .The lack of blood can damage the heart muscle .
- **Heart failure –** narrowed arteries in the heart can slowly make the heart weak or stiff. This can make it harder for the heart to pump blood.

Medical management:

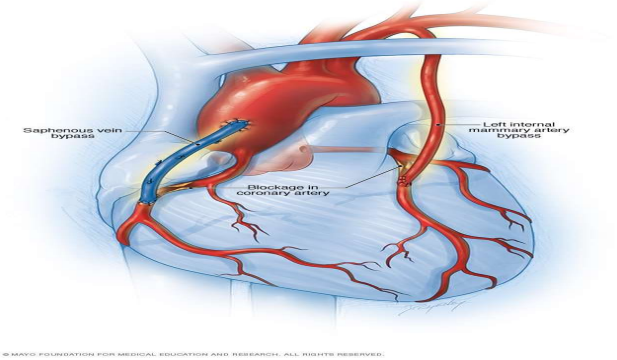
1. Vasodilators – Act as blood vessel dilator.
2. Beta blockers – decrease work load in the heart.
3. Calcium channel blockers – to improve coronary blood flow.
4. Anti hypertensive drugs – to treat high blood pressure.
5. Anticoagulants.
6. Opiate analgesic – for reduce pain.
7. Thrombolytic drugs.

Surgical management:

1. Angioplasty and stent placement



2. coronary artery bypass surgery – **also called coronary artery bypass graft.**



Cardiomyopathy :

Disease of the heart muscle in which the heart loses its ability to pump blood effectively. The heart muscle becomes enlarged or abnormally thick or rigid .

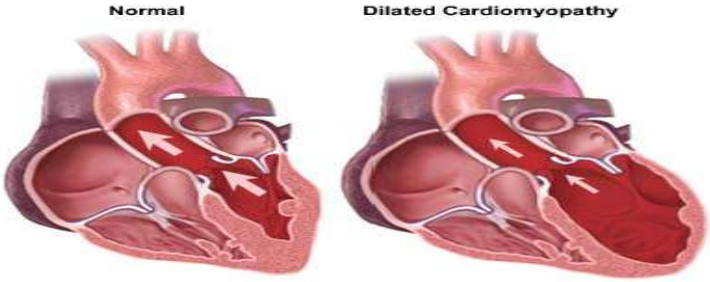
Classification :

The 3 main types of cardiomyopathy are;

- ✓ Dilated cardiomyopathy
- ✓ Hypertrophic cardiomyopathy
- ✓ Restrictive cardiomyopathy

1. Dilated cardiomyopathy :

A condition in which the hearts ability to pump blood is decreased because the hearts main pumping chamber , the left ventricle is enlarged or weakened .This is the most common form of cardiomyopathy . generally occurs in adults aged 20 to 60 years .more common in men .



Role of genetics in dilated cardiomyopathy:

Major genes associated with dilated cardiomyopathy

Geneprotein

- SCN5A - Sodium channel protein type 5, α subunit .
- TTN -Titin
- MYH7 - β –Myosin heavy chain, sarcomere .
- MYPN - Myopalladin

TTN truncating variants are th most common cause of DCM .Titin is the giant protein that encodes the TTN gene ,the largest known protein expressed in the heart .Titin has 4 major protein domains (the Z-disk,the I – band , the A band , and the M band)that are located on either side of the length of the sarcomere cases .LMNA variants are the second most common cause of DCM , accounting for 5 to 10 % of DCM cases.

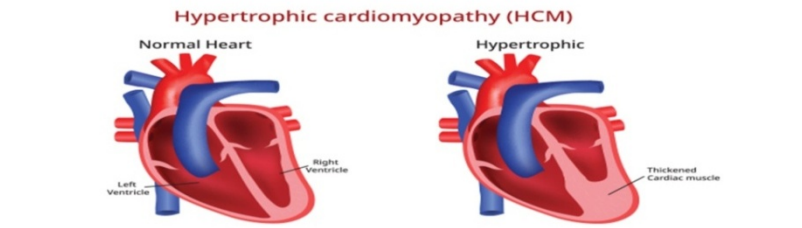
Medical management:

- Nitrates
- Loop diuretics
- ACE inhibitors
- Beta adrenergic blockers
- Anticoagulants
- Cardiac glycosides

Surgical management: Heart transplantation .

2. Hypertrophic Cardiomyopathy:

Assymetric left ventricle hypertrophy without ventricle dilation .when the septum between the two ventricles become enlarged and obstructs the blood flow from the left ventricle .it is known as the hypertrophic obstructive cardiomyopathy.



Role of genetics in hypertrophic cardiomyopathy:

The genetic basis for hypertrophic cardiomyopathy was the first described in 1990.A patient with more limited hypertrophy , only a wall thickness of 13 – 14 mm ,can also be diagnosed with HCM when present in conjunction with a family history of HCM or a positive genetic test . HCM is typically inherited in an autosomal dominant pattern , but there is considerable variation in its expression and penetrance .

The offspring of each affected family member has a 50%chance of inhering the genetic variant . in the case of HCM , the chance of developing the disease is significantly increased among family members who carry a pathogenic variant , but the age at which the disease manifest in an individual is variably distributed . the mechanism are not clear, but these genetic alteration result in the characteristic pathological and morphological features of HCM . Around 60%of patients HCM have clearly identifiable familial disease .

Pathogenic variant in genes encoding sarcomeric proteins have been implicated in the majority of HCM cases .Among the known causal genes ,the β-mysosin heavy chain (MYH7), and myosin binding protein C (MYBPC3) are the two most common followed by PVs in the genes encoding cardiac troponin T (TNNT2),cardiac troponin I (TNNT2),cardiac troponin I (TNNI3),and α-tropomyosin (TPM1).

Medical management :

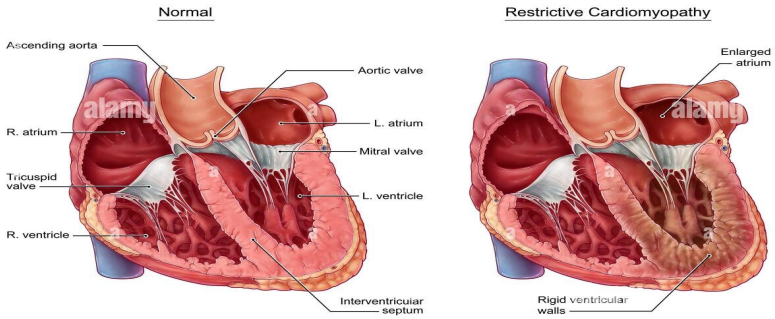
- ❖ calcium channel blockers
- ❖ beta adrenergic blockers
- ❖ antidysrhythmic drugs

surgical management :

- ❖ septal myectomy
- ❖ septal ablation

3. Restrictive cardiomyopathy :

It is characterized by diastolic dysfunction caused by rigid ventricular walls that impair diastolic fillings and ventricular stetch .



Role of genetics in restrictive cardiomyopathy:

The frequency of RCM is extremely low , which has limited understanding its genetic characteristics to assessing a small number of genes in small patient group . Familial RCM is usually passed on in an autosomal dominant manner , but other possible modes of inheritance include autosomal recessive and compound heterozygous forms .sarcomeric variants appear to be associated with severe disease expression and premature death or heart transplantation in childhood . nonsarcomeric variants have also recently been identified in RCM .

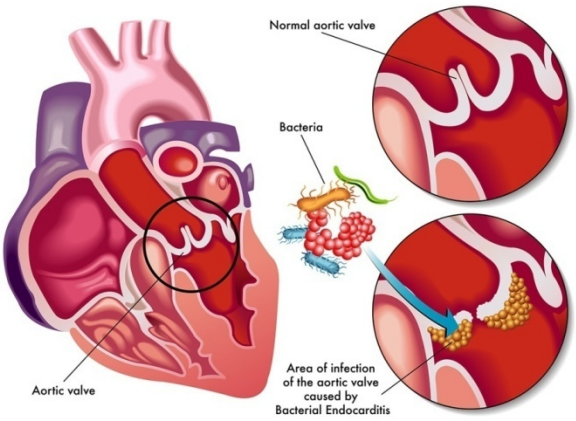
Medical management :

- Beta adrenergic blockers
- Calcium channel blockers
- Antidysrhythmic drugs

Surgical management: Heart transplantation .

Rheumatic heart disease :

Rheumatic heart disease is a chronic condition resulting from rheumatic fever which involves all layers of the heart and is characterized by scarring and deformity of the heart valves . Rheumatic fever is a diffuse inflammatory disease characterized by a delayed response to an infection by group A beta hemolytic streptococci in the tonsilopharyngeal area, affecting the heart , joints , central nervous system , skin and subcutaneous tissue .



Features:

- **syndenhem chorea**
- **warm and swollen joints (polyarthritis)**
- **subcutaneous nodules (hard , painless nodules , over extensor surface of extremities)**
- **erythema marginatum (transient mesh like macular rash on the trunk and extremities)**

Jones criteria:

Mnemonic: "JONES CAFE PAL "

Major criteria:

J	joint involvement
O	o looks like heart = myocarditis
N	Nodules, subcutaneous
E	erythema marginatum
S	Syndehem chorea

Minor criteria :

C	CRP increased
A	Arthralgia
F	Fever
E	Elevated ESR
P	Prolonged PR travel
A	Anamnesis of rheumatism
L	Leukocytosis

Signs and symptoms:

People with heart damage includes chest pain, fatigue, heart murmur, shortness of breath, swelling in the hands or feet, palpitations or cardiac arrhythmias. Rarely, symptoms can include nodules near joints or rashes.

Diagnosis:

- WBC count and ESR is elevated.
- C – reactive protein is positive
- Cardiac enzymes levels may increase in severe carditis.
- Anti streptolysin – o titer is elevated 95%of patients with in 2 months onset.

Throat cultures growing GABHS or elevated anti streptolysin o titers +

2 major criteria or 1 major and 2 minor criteria.

Rf and RhD – genetic susceptibility:

Genes involved with development of rheumatoid fever and rheumatoid heart disease. several genes controlling innate and / or adaptive immune response are involved with the development of the disease .

INNATE IR ⟵	CYTOKINES ⟶	ADAPTIVE IR
MBL – 2 : alleles A/O	TNF-alpha	HLA class II alleles
TLR-2	TGF- beta	CTLA-4
FCN2	IL-1RA	
FcR II A	IL-10	

Medical Management:

- **Corticosteroids –** used to treat carditis
- **Diuretics**
- **Salicylates like aspirin –** to promote comfort

Surgical management:

- Percutaneous balloon valvuloplasty
- Mitral valve replacement

Congenital heart disease (CHD):

Congenital heart disease ia one or more problems with the heart's structure that are present at birth . congenital means born with the condition . A congenital heart condition can change the way of blood flows through the body .There are different conditions of congenital heart defects some of those are :

Types :

s.no.	DEFECTS
1.	Atrial septal defect
2.	Ventricular septal defect
3.	Double outlet right ventricle
4.	Coarctation of aorta
5.	Eisenmenger syndrome
6.	Patent ductus arteriosus
7.	Pulmonary valve stenosis
8.	Total anomalous pulmonary venous return (TAPVR)

Genetics in congenital heart disease:

Familial CHD mutations occurs as autosomal dominant , autosomal recessive ,or X linked traits that are expressed with high penetrance and with variable clinical manifestations . CHD is genetically heterogeneous . that mutation is different genes cause an identical malformation .The spectrum of heart malformation that arise for an identical gene mutation implicates genomic context ,maternal fetal environment , cardiac biomechanics , and other factor as important influences that impact the clinical consequences of CHD mutations.

Aneuploidy or abnormal chromosomal number ,accounts for a significant proportion of CHD.

Hundreds of autosomal dominant or X linked mutations have been identified in familial forms of CHD. Autosomal recessive or somatic mutation and polygenic variants pose alternative genetic models to account for the population prevalence of CHD. In addition to defining CHD genes ,copy number variant (CNVs)can be used to assess developmental networks using bioinformatic repositories of biological interactions and functional annotaons , as well as gene –gene and protein –protein relationships.

Some of the Genes associated with CHD are :

- LOF mutation in GATA4 typically cause ASDs
- Mutation in NKX2-5 and TBX5 cause cardiac mal formation
- Mutations in MYH11 are reported to cause dominant thoracic aortic aneurysm ,ect.

(LOF: loss of function)

Signs and symptoms:

Common congenital heart disease symptoms in adults include irregular heart beats called arrhythmias ,blue or grey skin , lips and finger nails due to low oxygen levels , shortness of breath,feeling tired very quickly with activity , swelling due to fluid collecting inside body tissues called edema .

Diagnosis of cardiovascular disease:

- **Blood test** – Measures substances that indicate cardiovascular health , such as cholesterol , blood sugar level and specific protein .
- **Ankle brachial index (ABI)-** Compares the blood pressure in your ankle and arms to diagnose peripheral artery disease .
- **Electrocardiogram (EKG)-** records your heart's electrical activity .
- **Ambulatory monitoring –** uses wearable devices that track your heart rhythm and rates .
- **Echocardiogram –** uses sound waves to create an image of your heart beat and flow .
- **Ultrasound** –uses sound waves to check blood flow in your legs or neck .

- **Cardiac computerized tomography** (CT)- uses x ray and computer processing to create 3D images to your heart and blood vessels
- **Cardiac magnetic resonance imaging (MRI)** –uses magnets and radio waves to create highly detailed image of the heart .
- **Cardiac catheterization** – uses a catheter (thin ,hollow tube)to measure pressure blood flow in your heart .

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Advantages and challenges of stem cell therapy for dilated cardiomyopathy

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Introduction

Evaluating the methodological and technological elements of using cardiac stem cells to treat cardiomyopathy is the goal of this study. We also review many CSC subtypes' previous 10 years, and provide an update on recent cell tracing experiments that raise questions about the genesis. With 17.9 million fatalities per year, cardiovascular disease is the leading cause of illness and death worldwide. The primary cause of death globally is ischemic heart disease. The chronic loss of cardiomyocytes brought on by an ischemic myocardial infarction leads to heart failure and unwanted hypertrophy. Even though studies on the growth and regeneration of heart cells are still in their infancy, it is imperative to close any gaps and correct any mistakes in this field.

The potential for therapeutic applications of stem cell plasticity has been recognized by researchers within the past 20 years. It has been demonstrated that many stem cell types, including circulation-derived progenitor cells, induced pluripotent stem cells, and mesenchymal stem cells obtained from bone marrow and adipose tissue, can be therapeutically effective in treating ischemic heart disease."

Bone marrow cells appear to be the conduit for the release of chemicals with physiological activity that prevent heart injury. Unfortunately, bone marrow cells from individuals with long-term diseases rarely mature properly and may even die at a young age. There are important obstacles that need to be overcome in order to progress the use of stem cells in heart repair. In order to maximize the potential of stem cells to attract chemoattractants to infarcts, these challenges include figuring out which stem cells, if any, are suitable for transplantation without requiring host immune suppression, when to transplant stem cells, and precisely how to inject stem cells for cardiac repair. The development of strategies to improve stem cell formation and survival in the

heart is imperative for researchers. The interaction and transfer of perspectives between scientists and physicians will be key to this research.

Cardiomyopathy

A disease of the heart muscle is identified as cardiomyopathy. It renders it more challenging for the heart to pump blood to the body's various tissues, which can end up in heart failure symptoms. Several more significant cardiac conditions are additionally relied via cardiomyopathy. Distinct cardiomyopathies that have different forms. Dilated, hypertrophic, and confined cardiomyopathy represent the three primary varieties.

Symptoms

Symptoms of cardiomyopathy can include:

• Struggle with breathing or shortness of breath following activity or even after rest.
• Chest pain, especially when following vigorous activity or huge meals.
• Rapid, pounding, or fluttering heartbeats.
• Swelling around the veins in the neck area, stomach area, ankles, and feet.
• Inflammation in the stomach mainly an indication of accumulation of fluid.
• Cough while on your backside.
• Issues with sleeping flat.
• Fatigue, without resting.
• Feeling lightheaded.
• Falling asleep.

lacking medical attention, symptoms frequently intensify. In certain people, the illness deteriorates rapidly. In others, it may require an extended period for conditions to become terrible.

Causes

Normal Heart Enlarged Heart muscle

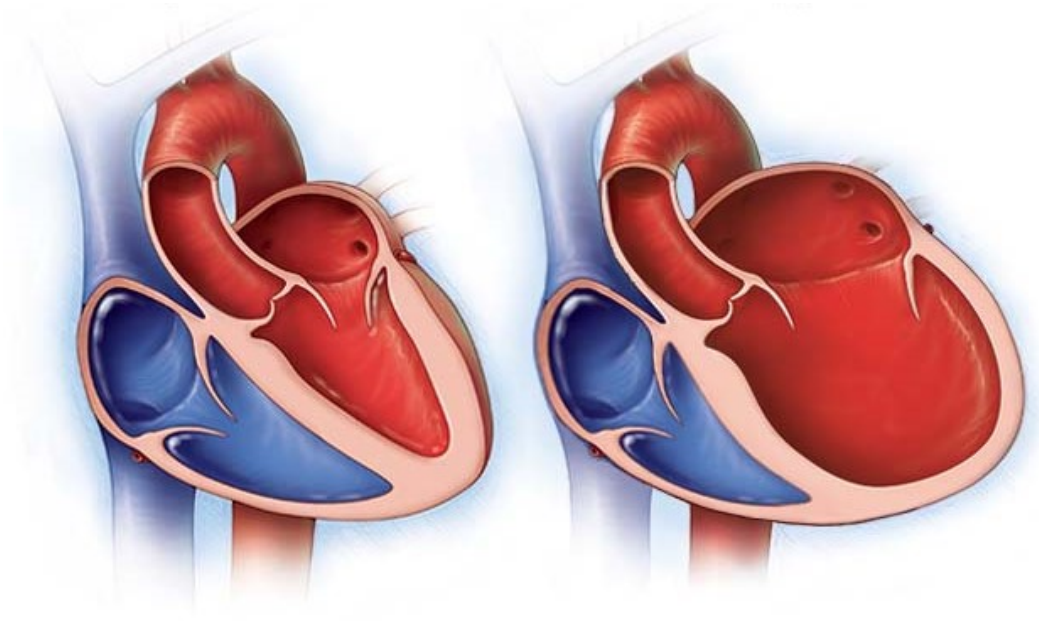

Figure: 1 A) Normal Heart B) Enlarged heart muscle

Dilated cardiomyopathy

The consequence of dilated cardiomyopathy results in an enlarging of the heart chambers. Heart failure can arise with dilated cardiomyopathy when left untreated.

- Chronically high blood pressure constitutes a health condition or exertion that may result in acquired cardiomyopathy.
- Damage to cardiac tissue following a heart attack.
- Prolongedly high heart rate.
- Issues with the heart valve.
- The COVID-19 virus.
- A few infections, particularly those that result in cardiac inflammation.
- Metabolic conditions, including diabetes, thyroid problems, and obesity.
- Inadequate intake of certain important vitamins and minerals, like thiamine (vitamin B-1).

The problems of pregnancy.

• Hemochromatosis, or iron accumulation in the heart muscle.
• The development of granulomas, which are microscopic masses of inflammatory cells, anywhere in the body. Sarcoidosis is the term for this condition that affects the heart or lungs.
• Amyloidosis, a medical disorder where abnormal protein deposits in the organs proliferate.
• Disorders of the connective tissues.
• excessive alcohol consumption.
• Cocaine usage,

Risk Factors

Many factors, such as heart failure, sudden cardiac arrest, and a family history of cardiomyopathy, might increase an individual's chance for developing cardiomyopathy.

• Chronically elevated blood pressure;

• Heart-related conditions. These include coronary artery disease, an infection in the heart, or a family history of heart attacks.
• Obesity, resulting in greater the workload of the heart.
• Chronic alcohol abuse.

Illegal drug use, including the use of cocaine, amphetamines, and anabolic steroids; cancer treatment comprising radiation and specific chemotherapeutic medication.

Cardiomyopathy is additionally connected with several types of disorders, including diabetes.

• Diseases of the thyroid.
• Hemochromatosis, the body's storage of excess iron.
• Amyloidosis, an illness that occurs when a certain protein aggregates in organs.
• Sarcoidosis, a medical disorder in which tiny areas of inflamed tissue form inside organs.
• Disorders of the connective tissues.

Complications

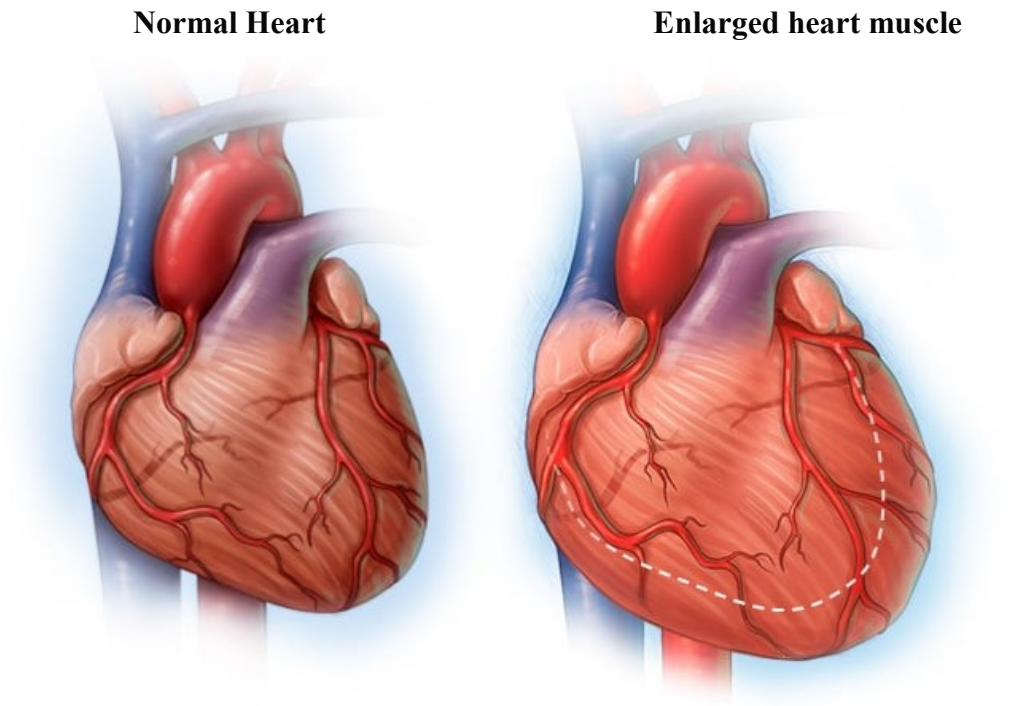

Figure :2 A) Normal Heart B) Enlarged heart in heart failure

Enlarged heart, in heart failure

If the heart weakens, as it can with heart failure, it begins to enlarge. This forces the heart to work harder to pump blood to the rest of the body.

Cardiomyopathy can lead to serious medical conditions, including:

- **Heart failure.** The heart can't pump enough blood to meet the body's needs. Without treatment, heart failure can be life-threatening.
- **Blood clots.** Because the heart can't pump well, blood clots might form in the heart. If clots enter the bloodstream, they can block the blood flow to other organs, including the heart and brain.
- **Heart valve problems.** Because cardiomyopathy can cause the heart to become larger, the heart valves might not close properly. This can cause blood to flow backward in the valve.
- **Cardiac arrest and sudden death.** Cardiomyopathy can trigger irregular heart rhythms that cause fainting. Sometimes, irregular heartbeats can cause sudden death if the heart stops beating effectively.

Prevention

Inherited types of cardiomyopathy can't be prevented. Let your healthcare professional know if you have a family history of the condition.

- Stay away from alcohol or illegal drugs such as cocaine.
- Control any other conditions you have, such as high blood pressure, high cholesterol or diabetes.
- Eat a healthy diet.
- Get regular exercise.
- Get enough sleep.
- Lower your stress

Stem cell therapy

Unspecialized cells in the body are called stem cells. They also possess the ability to differentiate into any type of cell and, in certain situations, to continuously reproduce.

Embryos and adult cells both contain stem cells. Pluripotent and somatic are the two categories of stem cells.

The two types of pluripotent stem cells are induced pluripotent stem cells and embryonic stem cells. Any of the body's cells can develop from these cells. Adult stem cells, or somatic stem cells, are able to develop into individual tissues or complete organs.

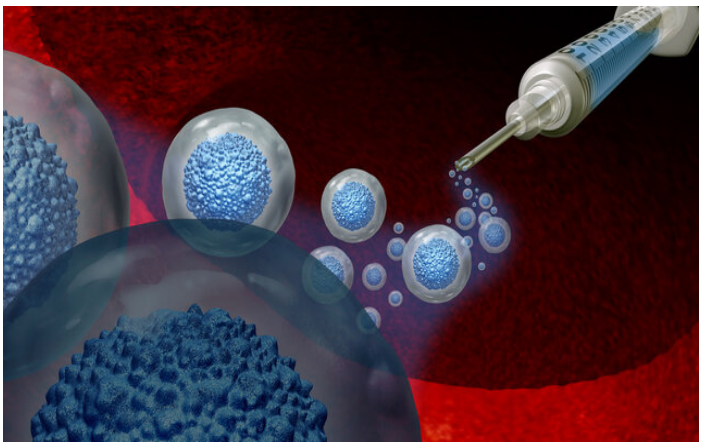

Figure: 3 Infusion of stem cell therapy

Types of Stem Cell Therapy

Stem cells are administered via an intravenous (IV) line inserted into a vein during stem cell therapy. The bone marrow, the umbilical cord, and blood are the three sources of blood-forming stem cells.

The transplants may consist of:
• Autologous: the individual receiving treatment has their own stem cells extracted.

• Allogeneic: An individual donates their own stem cells.
• Syngeneic: If the individual has an identical twin, the stem cells are derived from that twin.

The benefits of stem cells are wide-ranging and include:

1.Potent analgesic
2. Improves movement and function in many body regions
3. Short recovery periods
4. Non-invasive care that maintains effectiveness
5. Potential to aid in the recovery of complicated injuries
6. Avoid nerve injury
7. No chance of rejection
8. No requirement for a general anaesthetic
9. There is no danger of infectious illnesses

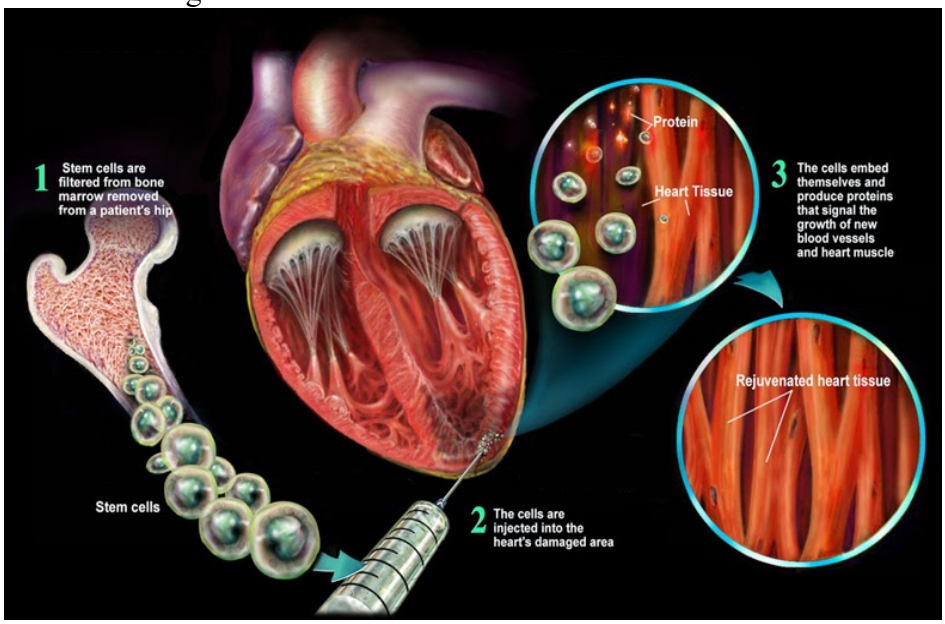

Figure : 4 steps of stem cell infusion at damaged heart

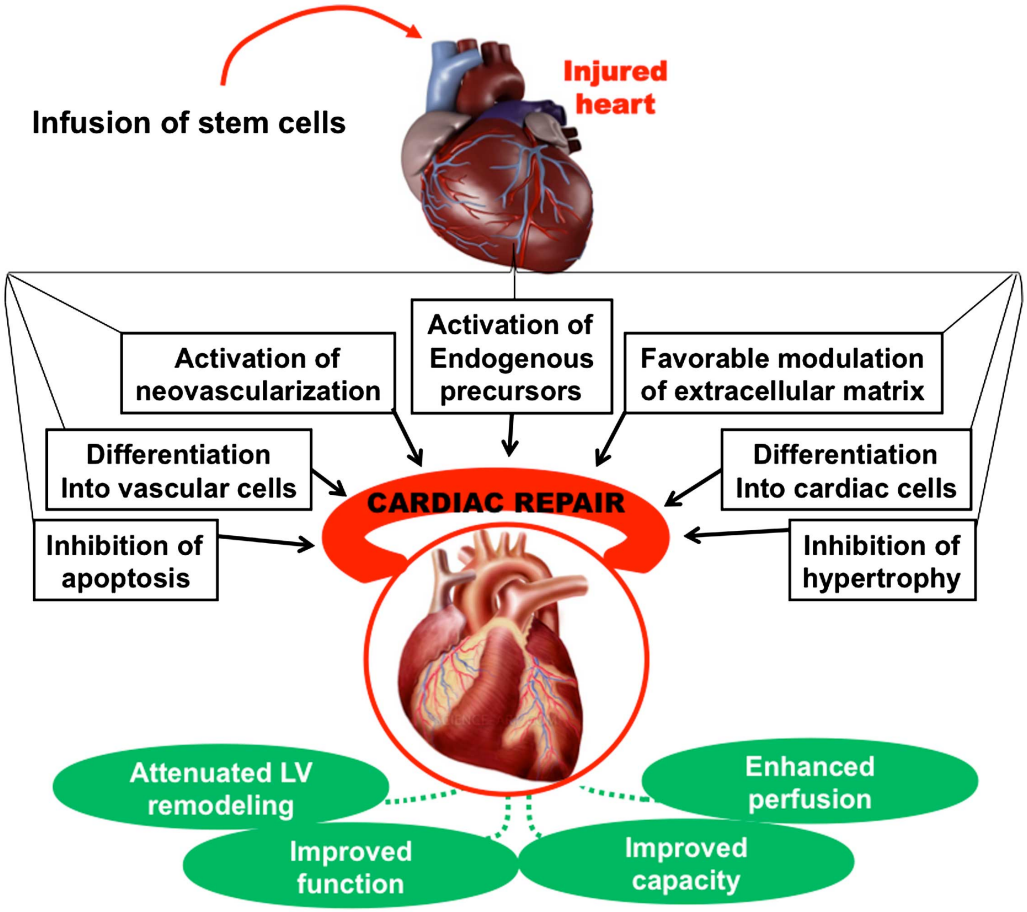

Figure: 5 Advantages of stem cells

How stem cells function at injured heart?

Ifwe infuse stem cells at injured heart it activates neovascularization(natural formation of new blood vessels), endogenous precursors

And it inhibits apoptosis and hypertrophy, it differentiatevascular and cardiac cells and favourable for extracellular matrix.

Conclusion

Research on stem cells is intricate and evolving quickly. Stem cells may one day simply replace damaged tissues and organs, but for now, medicine primarily aims to maintain or treat them. Stem cell therapy is compared to a soldier armed with a weapon. The battle will only be won if the soldier (a

skilled physician), the weapon (technology), and the ammunition (stem cells) are all in one hand.

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Promote biomarkers in cardiovascular diseases

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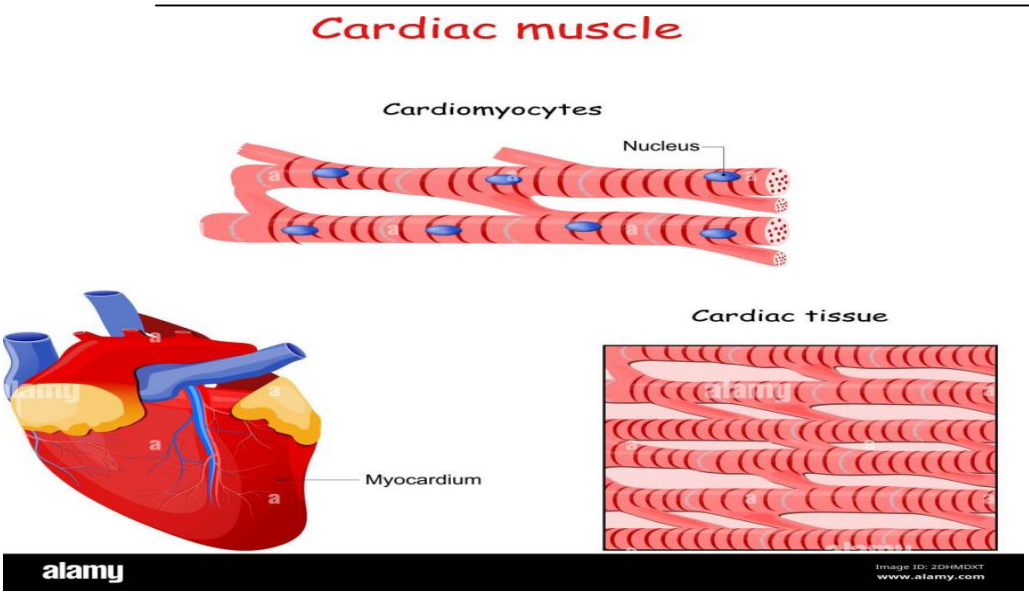
Introduction

A biological molecule that indicates a sickness or disease or is present in blood or any other bodily fluids or tissues. To determine how well the body reacts to an ailments or condition's intervention, a biomarker may be utilized. Also known as a signature molecule or molecular marker.

A major cause of death globally, cardiovascular disease (CVD) is becoming more widespread than it was in earlier decades, partly due to an aging worldwide population.Atherosclerotic CVD develops progressively and begins at a fairly young age, giving enough time for screening and early diagnosis. Over the past 30 years, improvements on CVD and advances in biomarker research have resulted in more focus on its early identification and detection, as well as enhanced treatments leading to better clinical outcomes for the population. However, scientists have been investigating the use of biomarkers for various purposes in CVD for a long time, and many new improvements are currently being made in this vital field of research.

Cardiovascular Tissue

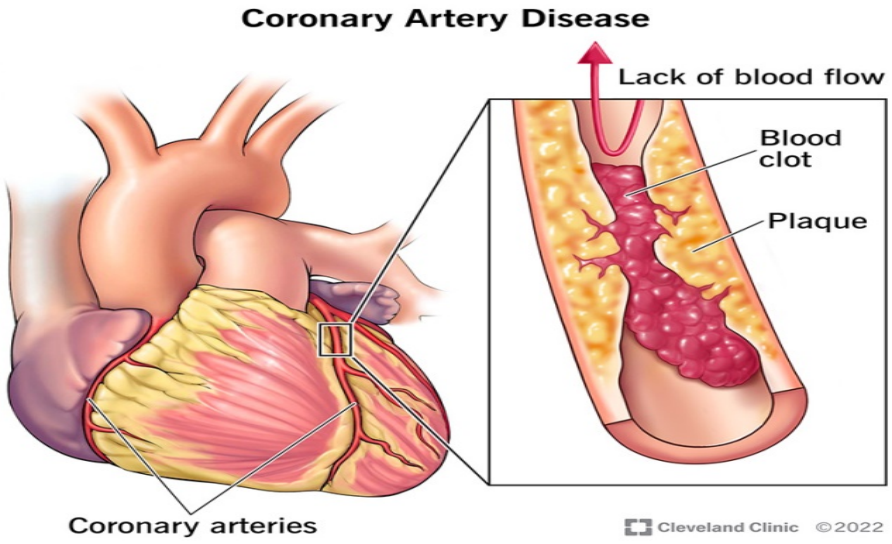
As a way maintain the human body's homeostasis, cardiovascular tissue performs a crucial role in the circulation of blood. Blood contains nutrients, oxygen, carbon dioxide, blood cells, and hormones. Vascular tissue is an organ that is necessary for human survival, consequently sickness or damage can have serious adverse effects on health. The primary cause of fatalities in the United States in 2011 was cardiovascular-related disorders, resulting in nearly 596,000 deaths, reported to the Centers for Disease Control and Prevention (CDC).



Cardiovascular Diseases

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels. They include:

DISEASES	AFFECTED ORGANS
1.Coronary heart disease	which affects the blood vessels supplying the heart muscle;
2.Cerebrovascular disease	which affects the blood vessels supplying thebrain
3.Peripheral arterial disease	which affects the blood vessels supplying the arms and legs;
4.Rheumatic heart disease	which results from streptococcal bacteria-induced damage to the heart muscle and heart valves;
5.Congenital heart disease	which is a birth defect resulting from malformations of the heart structure from birth
6.deep vein thrombosis and pulmonary embolism	which are blood clots in the leg veins that can become dislodge and travel to the heart and lungs.



Blood clots form when plaque accumulates in the arteries supplying blood to the heart, a condition known as coronary artery disease.

Risk factors of CVD

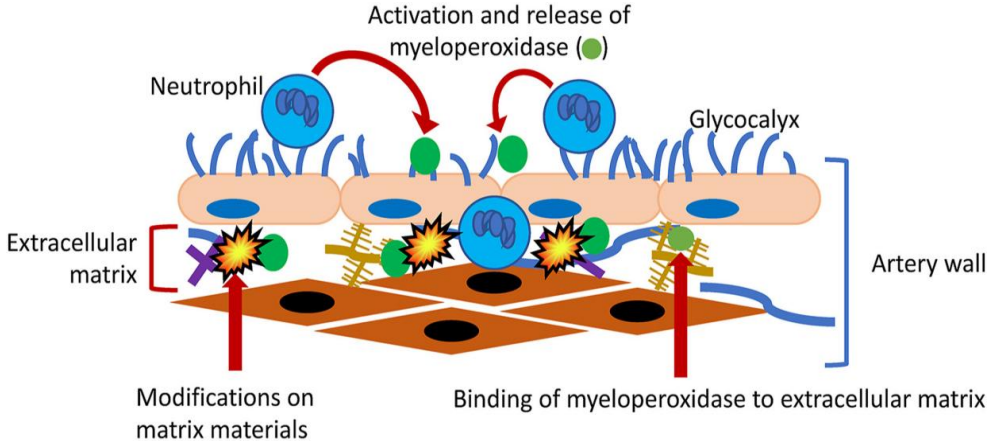
The following risk factors for CVD were identified during baseline screening:

- height and weight used to calculate body mass index (BMI);
- resting electrocardiographic (ECG) findings;
- age,
- gender,
- race,
- education level;
- blood pressure;
- total serum cholesterol level;
- smoking status; and medical history of drug treatment for diabetes or hypertension.

Mechanism and action of biomarkers

Oxidative damage to lipids and proteins is an important component of atherosclerotic cardiovascular disease (CVD). Studies of oxidation-related molecules are helping to define atherosclerotic mechanisms, and measurements of circulating levels of specific oxidant compounds may improve cardiovascular risk assessment.

For example, plasma levels of the enzyme **myeloperoxidase,** which generates the strong oxidizing agent hypochlorous acid, have been found to be correlated with risk for myocardial infarction and endothelial dysfunction.



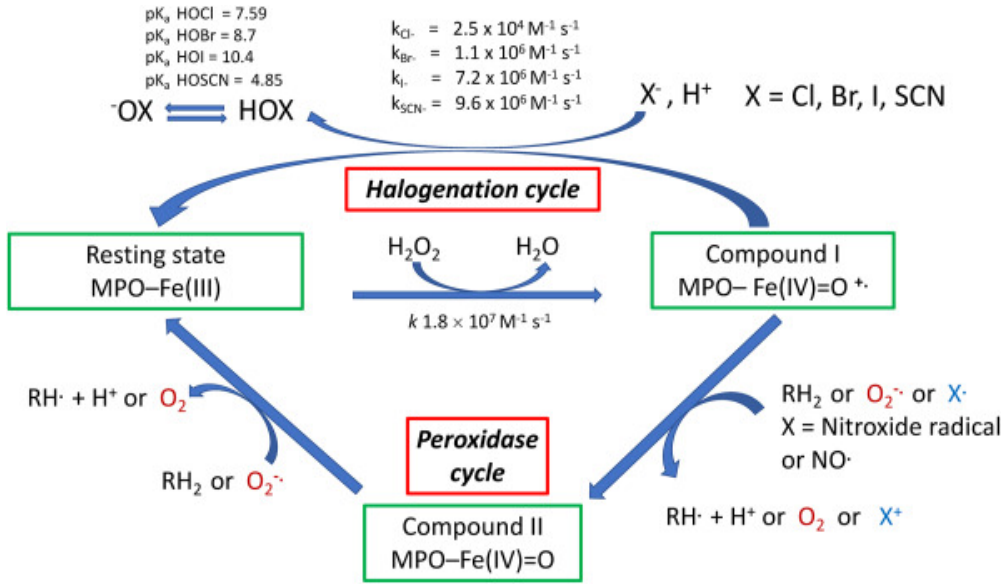


Fig. 1. Catalytic cycles of myeloperoxidase (MPO). The two major catalytic cycles (halogenation, top part of figure; peroxidase, lower part of figure) are illustrated together with selected rate constant data for the initial formation of Compound I by H_2O_2, and generation of the halogenating oxidants from this species. The pKa values of the resulting hypohalous acids are also provided. For original literature citations, see main text. It should be noted that both the resting state enzyme, and the Compound I and II intermediates, can also under go additional reactions (see text).

Uses Of Biomarkers In CVD

Types of biomarkers

There are mainly four types of biomarkers,

1. Genomic biomarkers

This is analyze DNA by identifying irregularsequences in the genome,typhically single nucleotide polymorphin

2. Transcriptomic biomarkers
3. Proteomic biomarkers
4. Metabolic biomarkers

This test measures the levels of cardiac biomarkers in your blood. These markers include enzymes, hormones, and proteins.

Blood samples containing cardiac biomarkers are produced when the heart is significantly stressed and undergoes damage from inadequate oxygenation. It could be the result of a heart attack. These levels, however, may be raised for different causes. It is frequently possible to rapidly determine the extent of an attack and how badly it damaged the heart by looking at the levels of biomarkers.

A heart attack can be diagnosed using these cardiac biomarkers:

1.Cardiac troponin. This protein is by far the most commonly used biomarker. It has the highest known sensitivity. It enters into your bloodstream soon after a heart attack. It also stays in your bloodstream days after all other biomarkers go back to normal levels. Two forms of troponin may be measured: troponin T and troponin I. Troponin I is highly specific to the heart and stays higher longer than creatinine kinase-MB. Current guidelines from the American Heart Association (AHA) say this is the best biomarker for finding a

heart attack. The AHA says to limit use of the other biomarkers. These include CK, CK-MB, and hemoglobin.

2. **Creatinine kinase (CK).** This enzyme can also be measured several times over a 24-hour period. It will often at least double if you've had a heart attack. But because levels of CK can go up in many other conditions besides a heart attack, it is not very specific.

3. **CK-MB.** This is a subtype of CK. It is more sensitive for finding heart damage from a heart attack. CK-MB rises 4 to 6 hours after a heart attack. But it is generally back to normal in a day or two. Because of this, it's not helpful when a healthcare provider is trying to figure out if your recent chest pain was a heart attack.

4. **Myoglobin.** This is a small protein that stores oxygen. It is measured occasionally. Myoglobin is sometimes measured in addition to troponin to help diagnose a heart attack. It is also not very specific for finding a heart attack

Diagnosis

Cardiogram (also known as ECG or EKG).The electrical signals in the heart can be monitored by a simple and painless assessment called an ECG. It has the ability to recognize a heartbeat that is irregular. **Holterobservation**.AHolter monitor is a wearable, portable ECG that records the heart's activity while an individual goes about their everyday activities for up to a day. An irregular heartbeat that is not discovered during a routine ECG examination can be recognized with this test.

An echocardiography.With this non-invasive examination, comprehensive images of the beating heart can be acquired using sound waves. It illustrates the flow of blood via the heart's valves. The presence of narrowing or leakage in a valve can be diagnosed with an echocardiography.

Do stress or exercise evaluation.These kinds of tests frequently entail stationary riding or walking on a treadmill while the heart is tracked. Exercise testing can show whether signs of heart disease develop during exercise and how the heart reacts to vigorous activity. Medication may be prescribed if you are reluctant to exercise.

A cardiac catheter is installed.This test has a capability to reveal cardiac artery blockages. A catheter is a thin, flexible, long tube that is led to the heart by being put into a blood an artery, typically in the wrist or groin. The catheter permits dye to flow through the heart's arteries. During the screening, the dye becomes the arteries more visible on X-ray imagesinside a machine

designed like a muffin. The instrument moves an X-ray tube around your body to take pictures of chest and heart.

An MRI, or magnetic resonance imaging, scan of the cardiac muscle. A magnetic field and radio waves generated by a computer are combined in a cardiac MRI to provide highly detailed pictures of the heart.

Treatment

Heart disease treatment depends on the cause and type of heart damage. Healthy lifestyle habits, such as eating a low-fat, low-salt diet, getting regular exercise and good sleep, and not smoking are an important part of treatment.

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"Harmonizing Hearts: The Symphony of IABP"

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Abstract

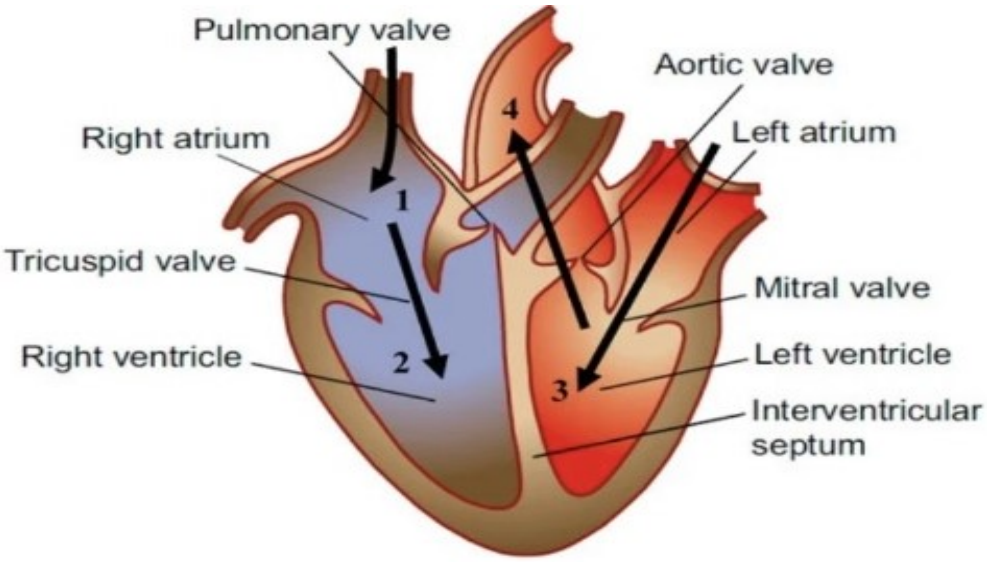
Various mechanical alternatives exist in the twenty-first century to assist a deteriorating heart. An ancient technique is the intra-aortic balloon pump (IABP), commonly referred to as "counterpulsation." Although there are many other options available, the IABP is still the most commonly used assist device for several reasons. It is a minimally invasive procedure that does not involve handling blood outside of the body. It also causes minimal damage to red blood cells and can be inserted in various settings such as the catheterization lab, operating room, and intensive care unit. Both surgeons and interventional cardiologists are capable of performing the insertion. This chapter will examine the reasons for using IABP counterpulsation, explain the physiological principles that justify its use, describe the procedure for inserting it, including possible difficulties, and ultimately discuss the results reported by clinical trials.

Keywords: Intra-Aortic Balloon Pump, Extracorporeal, Haemolysis, Cardiologists and Clinical Trials.

Introduction

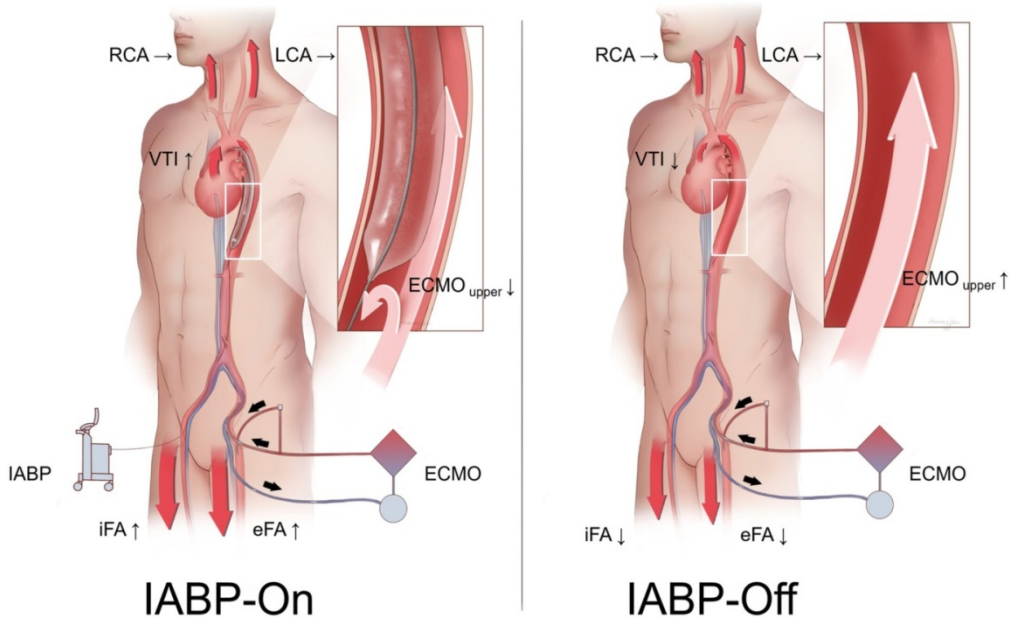
The Intra-Aortic Balloon Pump (IABP) is a mechanical device used for many years to enhance heart function in critically ill patients as a form of circulatory support. It functions as a transient instrument to enhance blood flow to the heart and alleviate stress on the heart muscle in different medical situations. The cardiovascular system is a vital system in the human body, with the heart serving as a crucial organ for optimal performance. It facilitates the transportation of blood, oxygen, and nutrients to various regions of the body. The heart requires a precise quantity of oxygen to maintain its appropriate functioning, known as myocardial oxygen demand. Additionally, there exists a maximum amount of oxygen that may be supplied to the heart through the blood, referred to as myocardial oxygen supply. If the heart lacks a precise

equilibrium between supply and demand, it would be deemed feeble and necessitate aid. Physicians often recommend the use of an intra-aortic balloon pump (IABP) for individuals with a heart problem, such as heart failure. The Intra-Aortic Balloon Pump (IABP) is a slender and elongated balloon designed to regulate blood flow within the aorta. The gadget aims to equilibrate the supply and demand of blood and oxygen required for the heart. In order to comprehend the functioning of the device, it is important to get a thorough understanding of the basic principles of hemodynamics and the specific location where the IABP will be integrated. The blood flow through the heart commences with deoxygenated blood entering the right atrium (1). Subsequently, the tricuspid valve opens, allowing the blood to pass into the right ventricle (2). From there, the blood proceeds through the pulmonary valve and enters the lungs, where it undergoes oxygenation. Subsequently, the blood is directed towards the left atrium where the mitral valve promptly opens, facilitating the passage of blood into the left ventricle (3). Subsequently, the heart propels the blood via the aortic valve and into the aorta, facilitating the distribution of oxygenated blood to various body regions (4). The Intra-Aortic Balloon Pump (IABP) is inserted into the aorta to provide mechanical circulatory assistance for the treatment of heart disorders. This chapter seeks to offer a thorough examination of the mechanics, applications, and therapeutic considerations associated with IABP therapy.



Mechanism of action

The IABP operates on the principle of counterpulsation, where a balloon is synchronized with the cardiac cycle to assist the heart's pumping action. During diastole, the balloon inflates, reducing aortic pressure and enhancing coronary perfusion. This inflation also leads to an increase in diastolic pressure, which helps improve myocardial oxygen supply. As systole begins, the balloon deflates rapidly, lowering resistance in the aorta and reducing afterload. This aids the heart in pumping blood with more efficiency and reducing the burden on the myocardium.



Indications for IABP

- **Cardiogenic Shock:** In cases of severe myocardial infarction, myocarditis, or acute heart failure, the IABP can provide temporary hemodynamic support until the underlying cause is addressed.
- **High-Risk Cardiac Procedures:** IABP can stabilize patients undergoing high-risk coronary interventions or cardiac surgeries.
- **Unstable Angina:** For patients with refractory angina, IABP therapy can improve oxygen supply and alleviate symptoms.

- **Bridge to Recovery or Transplant:** IABP can serve as a bridge for patients awaiting heart transplantation or those with reversible cardiac dysfunction.
- **Weaning from Cardiopulmonary Bypass:** Post-cardiopulmonary bypass, IABP support can assist the heart in regaining normal function.

Insertion and monitoring

IABP insertion involves the placement of a catheter with an inflatable balloon tip into the aorta, typically via the femoral artery. Proper positioning is confirmed through radiography or fluoroscopy. Hemodynamic monitoring, including arterial pressure, ECG, and continuous waveform analysis, guides the timing of balloon inflation and deflation, ensuring synchronization with the cardiac cycle.

Clinical considerations

- **Patient Selection:** Appropriate patient selection is crucial. IABP is most effective in conditions with reversible cardiac dysfunction, and careful evaluation of the underlying etiology is necessary.
- **Timing:** Early initiation of IABP therapy in cardiogenic shock can impact patient outcomes. Timely intervention improves coronary perfusion and prevents further deterioration.
- **Complications:** Potential complications include limb ischemia, bleeding, infection, and vascular injury. Regular assessment and vigilant monitoring are essential.
- **Weaning and Removal:** Gradual weaning off IABP is necessary to assess the heart's ability to function independently. Abrupt removal can lead to hemodynamic instability.
- **Alternative Therapies:** While IABP has been a cornerstone in circulatory support, newer devices like ventricular assist devices (VADs) and extracorporeal membrane oxygenation (ECMO) offer more robust support for advanced heart failure patients.

Contraindications of IABP

Absolute contraindications	**Common complications**
• Aortic regurgitation • Aortic aneurysm • Aortic dissection • Severe sepsis • Uncontrolled coagulopathy **Relative contraindications** • Atherosclerosis and arterial tortuosity • Left ventricular outflow tract obstruction • Contraindications to anticoagulation	Mild limb ischaemia - 2.9% Balloon leak - 1.0% Major limb ischaemia - 0.9% Haemorrhage - 0.8% Leg amputation due to ischaemia - 0.1% **Rare complications** Atheromatous cholesterol emboli Aortic or arterial dissection Cerebrovascular accident Thrombocytopenia Haemolysis Helium embolis

Conclusion

The Intra-Aortic Balloon Pump is a useful device for treating acute heart problems by providing temporary circulatory assistance. Healthcare practitioners involved in the care of critically ill cardiac patients must have a thorough understanding of the mechanisms of action, indications, insertion techniques, monitoring protocols, and potential consequences associated with the treatment. As technology progresses, the function of IABP (Intra-Aortic Balloon Pump) continues to develop alongside other sophisticated mechanical circulatory support alternatives.

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Books

1. Textbook of Clinical Application of Intra-Aortic Balloon Pump, 3rd Edition
2. Textbook of Hemodynamic Monitoring and Therapy (Chapter-32 Intra-aortic Balloon Pump)
3. Textbook of Care of patients connected to IABP
4. Textbook of Fast facts for cardiac surgery.

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Global trends in Emerging Cardiac Xenotransplantation

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Introduction

- In our global trends, the medical treatment for advanced heart failure is very actually successful. The last option for the patient with last stage heart disease (end – stage heart disease) is HTx.
- Therefore, now we are investigating the advanced technique of XTxshows that crossing the species has not always been a something/somebody. In fact, to be successful in humans, XTxmust overcome the from the issues of transplant rejection.
- As early as the1960's Organ Xenotransplantation were unsuccessfully attempted in one speciesto another species with so many failures and disappointments. The first transplantation in humans were used animal organs without any knowledge of species barriers. To explore this technique in further review of transplantation from animal to humans.

Abbreviations

- **HTx-** Heart transplantation
- **XTx -** Xenotransplantation
- **TAVR –**Transcatheter Aortic Valve Replacement
- **HLM –** Heart lung machine
- **HLHS-** Hypoplastic left heart syndrome
- **VSD**- Ventricular septal defect
- **PERV-** Procine endogenous retrovirus

Organ transplantation:

- Organ Transplantation is the unique one among medical/surgical procedure. Moving of an organ from one body to another , when the purpose of recipient. (Fig.1)
- The recipient's organ is damaged or failing, be replace with a working one from the donor site to the recipient. Organ donors can be living or deceased.

- ❖ Donors and recipient's may be in same location, or organs may be transported.
- ❖ Here, the types of transplantation are;

1.Autograft

2. Allograft

3. Xenograft

4. Isograft

Autograft:

Is the transplant of tissues from one part of the body to another in the same individual or same body (tissues from same body .

For example:

- Skin Graft
- CABG Surgery

Allograft:

Transplant of tissues or organ from a genetically non- identical genes of same species (tissues taken from another person)

Allograft is also known as '**Allotransplantation'**.

For example:

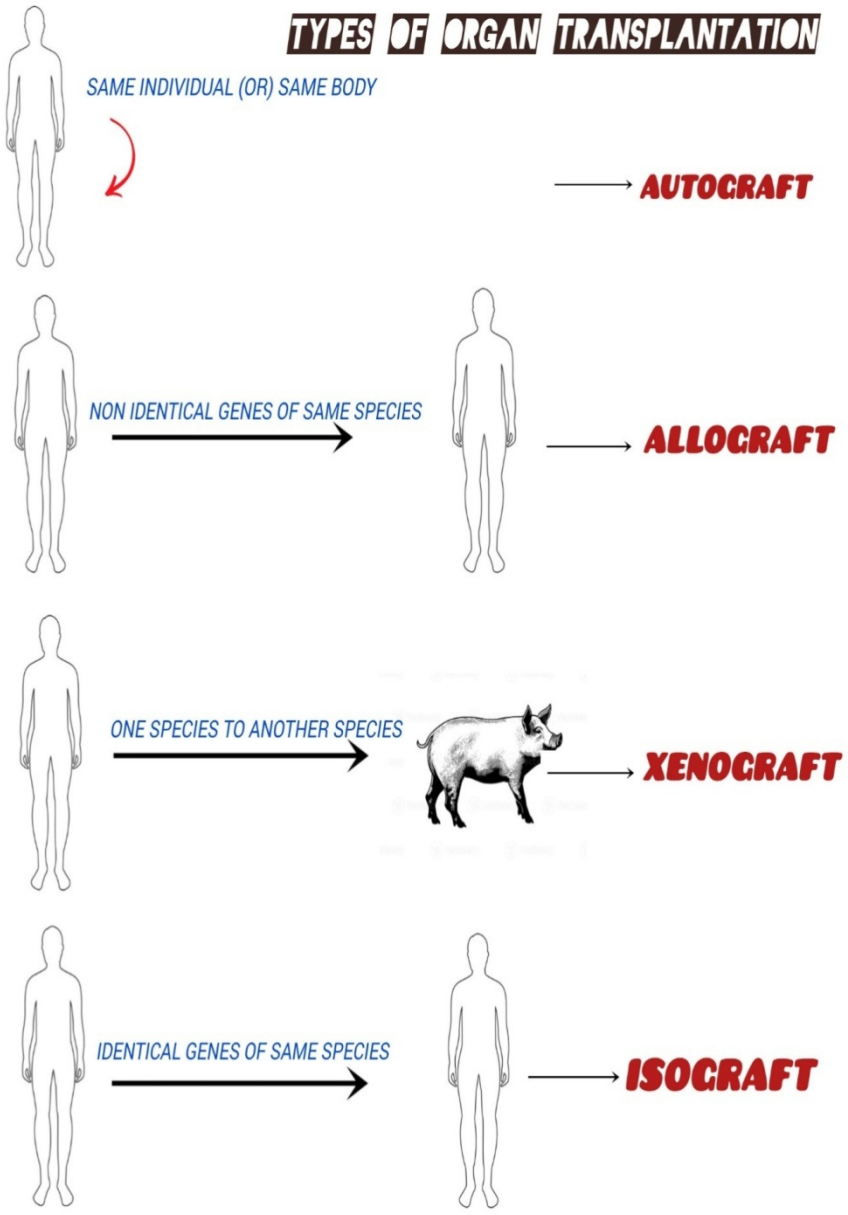
- Heart
- Liver
- Kidney
- Cornea

Isograft:

Transplant of tissue or organ from a genetically identical genes of same species.

For example:

Identical twins



(FIG: 1 Organ Transplantation)

Xenograft:

Transplant of organs from different species. Organ transplant from one species to another species .

Mainly from pig to human.

Then, Tissue is chemically treated to make '**Procine Heart Valves'** (during **TAVR**).

This is also known as **Xenotransplantation(XTx).**

For example:

- Monkey
- Pig
- Chimpanzee
- Baboons

What is xtx?

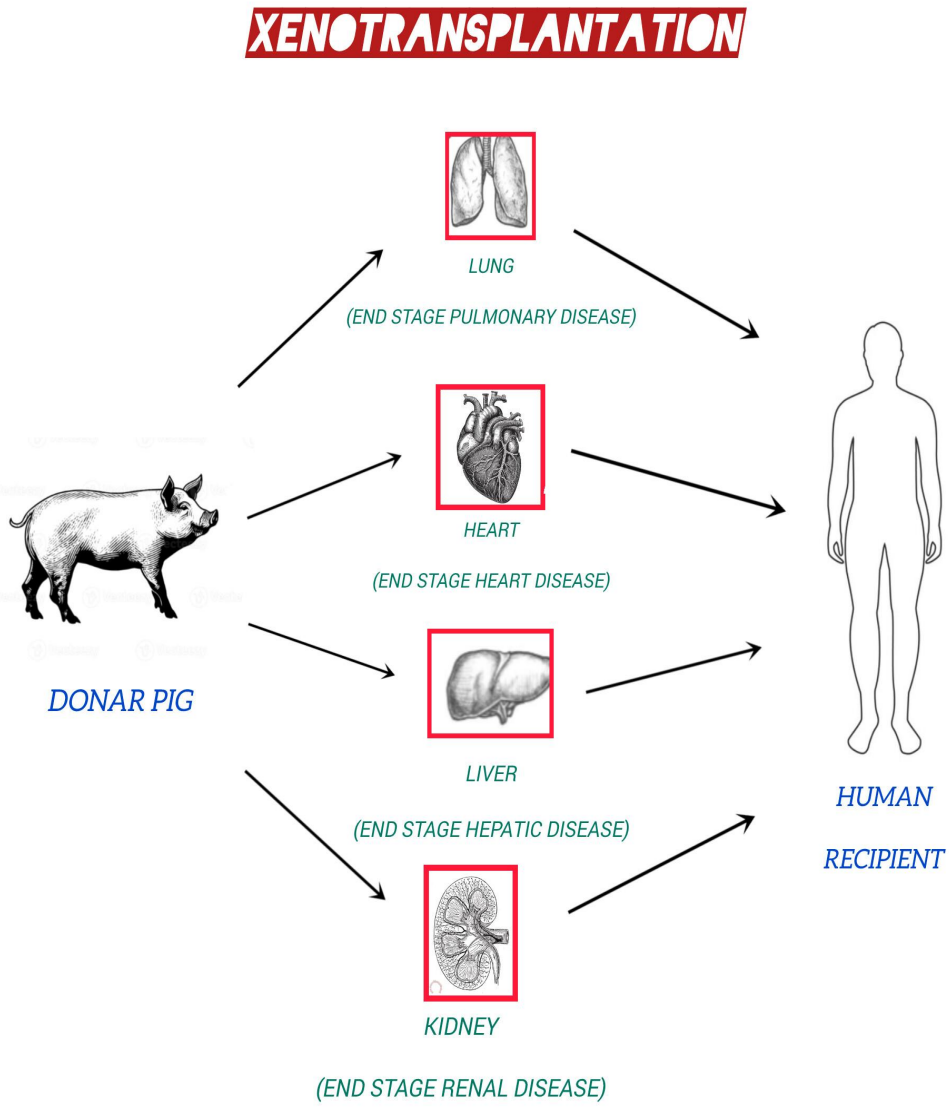
- ❖ XTx is surgical procedure to transplantation, implantation the tissues, cells or organs into the human recipient from non- human animal cell or tissues or organs .(Fig .2)
- ❖ Currently, **more than ten patient's**die every day in **US** for waiting to receive the vital organs for life saving.
- ❖ Today, Moreover, Recent evidence has suggested the cells or tissues or Organ Transplantation.
- ❖ In 1961, **Peter Gorer** proposed to replace the term **'Heterotransplantation'** with **'Xenotransplantation'.**

For example:

- **Transplantation**of heart, kidney or pancreatic tissue to organ failure species (humans).
- **Implantation** of neural cells to neurological disease affected person.

Importance of xenotransplantation:

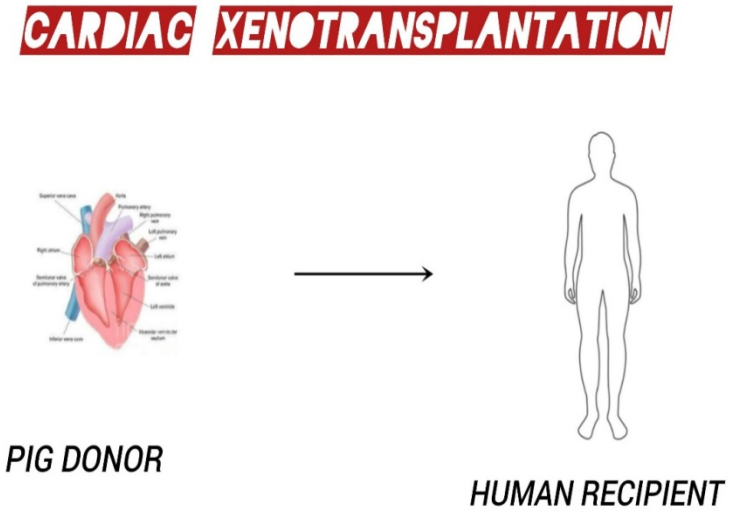
- ❖ Overcome the shortage of organ for implantation in worldwide.
- ❖ People with **diabetes**, **Alzheimer's** or **Parkinson's disease** treatment could provide through cellular transplants.
- ❖ Organ XTx include **heart**, **lungs**, **liver**, **kidneys**, **pancreas**.
- ❖ **Corneal transplant** for visually difficulties, **Bone transplants** for reconstructing limbs, **Skingraft** for burn patient.



(FIG 2: Xenotransplantation)

Cardiac xenotransplantation

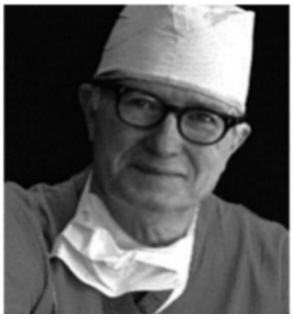
When the hear is deceased or failing to work the recipient person is in the end stage heart disease. Heart transplant from one species (non-human) to another species (humans).(Fig: 3)



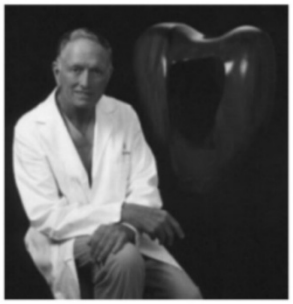
(FIG:3 –Cardiac Xenotransplantation)

History of cardiac xenotransplantation:

- On **Jan 23,1964 JAMES HARDY** (USA) (fig :4) attempted the first heart transplantation , he gave Chimpanzee (Bino) heart to the 68 yrs old man (Boyd Rush) in the cardiogenic shock stage (cardiomyopathy) . But the patient died after 3 hrs.
- On **Dec 3, 1967 CHRISTIAAN BARNARD** (Africa) clearly understood that the first same species (human) Lung transplantation done. After 18 days, the patient was affected by lung infection and died.



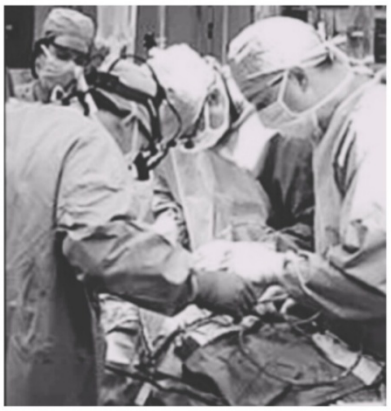
(FIG 4 : James Hardy (USA)**.**



(FIG 5: Denton Cooley (USA)

- In **1968, DONALD ROSS,** Perfused a pig heart with human blood without transplanted again Heart has stopped beating immediately. As the same day, **ROSS** Performed the Heterotrophic heart transplantation in patient with the support of HLM (Cardio pulmonary bypass machine). After 4 mins Heart stopped beating.
- In**1969, DENTON COOLEY** (USA) (fig.5) transplant the heart between one species (sheep) to different species (human) 48 yrs old is in ischemic cardiomyopathy. After the circulation is restored transplantation failed within 10 minutes.
- In **1969, A. BERTOYE** and **PIERRE MARIOR** (Lyon, France) attempted the heart transplantation for Chimpanzee to young woman .After that MVR is failured
- In **1977, CHRISTIAAN BARNARD** (South Africa)(fig.6) attempted Heterotrophic heart transplantation with the supported by HLM for two patients.**1.** In the **first case**, 30 kg baboon heart was transplanted to 25 yrs old woman. After 51/2yrs, the heart stopped beating. Because of different size of heart. **2.** In **second case**, with same procedure with supported by HLM. Chimpanzee heart is transplant to 60 yrs old man. After the transplant 4 days after inspite of strong immunosuppression rejection caused death.

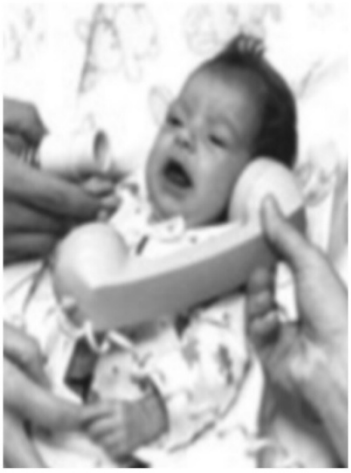
(**FIG 6**: **Christiaan Barnard** (South Africa).



(**FIG** 7: **Heart Xenotransplantation)**

- On **Oct 26, 1984 LEONARD BAILEY** (USA) (fig 8) Clearly understood that the most famous Xenotransplantation (fig 7) 12 days old girl named **BABY FAE** (fig 9)**,** Born prematurely with malformed heart HLHS Received a heart from a baboon. Despite the use of immunosuppressive drug CYCLOSPORINE (Organ rejection post-transplant). After the surgery, **FAE** lived only 20 days. She died on **Nov 15.** Due to graft rejection, caused mainly by an ABO Blood type mismatch.

(FIG 8: Leonard Bailey (USA)**).**



(FIG 9: Baby Fae)

- In **1992, ZIBIGNIEW RELIGA** (Poland) transplanted a pig heart to the human (man) affected with Marfan's Syndrome (connective tissues caused by mutation in the FBN1 Gene). Later 23 hrs the patient was died with rejection. Because the heart is in small size.
- On **Dec 31, 1996 DHANI RAM BARUAH** (India) transplanted the pig heart to 32 yrs old man (Purno Saikia) Patient with affected by VSD. After 1 week the patient was died with septic shock.**(IN INDIA, FIRST HEART XENOTRANSPLANTATION)**

Note: BARUAH was arrested by the **HUMAN ORGAN TRANSPLANTATION ACT (1994)** for violating.

Pig heart recipients:

World first recipient:

On **Jan 7, 2022 BARTLEY P GRIFFITH** (USA) transplanted the pig heart to 57 yrs old man (David Bennett). He was suffered with advanced heart failure (cardiac arrhythmias). Bennett's got approved **from FOOD AND DRUG ADMINISTRATION (HUMAN ORGAN TRANSPLANTATION ACT, 1994)**to perform a pig heart transplant. But he survived for 60 days.

World second recipient:

In **2023, BARTLEY P GRIFFITH and Team** (USA) transplanted the pig heart to 58 yrs old man (Lawrence Faucette) affected with heart disease . But he survived for 40 days.

Immunological barriers: (Transplantation rejection)

1. Hyperacute xenograft rejection (HXR)
2. Acute vascular xenograft rejection (ACXR)
3. Cellular xenograft rejection
4. Chronic xenograft rejection

1. Hyperacute xenograft rejection:

- To make something different, the recipient by reducing naturally occurring **antibodies** against **α-Gal antigen** to xenograft recipient.
- It occurs **within a minute to hours before the surgery,** as pre existing antibodies.(fig 10)
- For overcoming, the potential for the human recipient to be infected by endogenous retrovirus from the pig XTx.

2. Acute vascular xenograft rejection:

- It occurs **in first week (2-3 days) after the surgery.**
- Depletion of **anti-Gal antibodies (XNAs)** such as a technique of immunosuppression (adsorption) to prevent endothelial cell activation.
- Inhibits the activation of macrophages and white blood cell.
- **T-cell mediated** immune response directed against the **foreign MHC (major histocompatibility complex).**

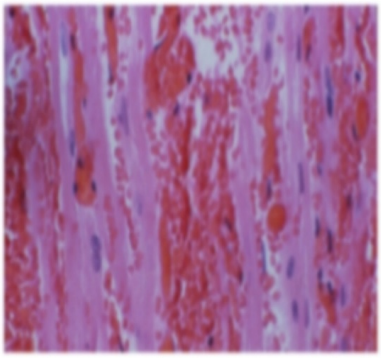
3. Cellular xenograft rejection:

- Cellular rejection mediated by **natural killer cells** which is accumulated in damage the xenograft.
- **T- lymphocytes** which are activated by **MHC.**

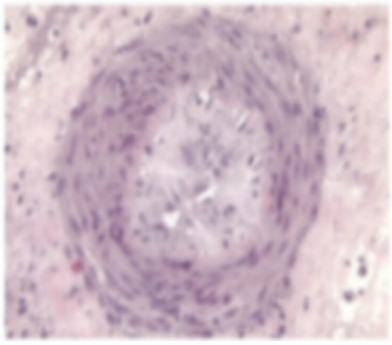
- Donor stem cells are introduced into the bone marrow of the recipient and that co-exist in the stem cells and that cause donor reactive T- cells to considered as normal and controlled of organism growth.

4. Chronic xenograft rejection:

- It occurs over **several years after the surgery.**
- Major cause is **Arteriosclerosis.(fig 11)**
- **Lymphocytes (INBC)** activated by antigens in Graft vessel wall.
- Activated Macrophages to secrete smooth muscles



(FIG 10 : Hyperacute rejection).



(FIG 11: Chronic Rejection)

Benefits of choosing pigs:

- ✓ **98% DNA** matched (pig and human) for Xenotransplantation.
- ✓ Sterile living conditions
- ✓ Bread intensively
- ✓ Do not resemble humans
- ✓ Accepted for food production

Note: Small difference between the human and pig is (humans have 4 pulmonary valves but pigs have 2 pulmonary valves, pig heart is located horizontally but humans heart are located vertically)

Ethical issues:

1. Risk of diseases:

Infectious disease transfer from animals to humans **(Xenozoonosis).**

2. Medical implications:

Even well matched human donor organs can be rejected after the transplantation and with animal organs the danger is likely to be higher.

Such treatments are very risky, some medical ethicists but they should still go ahead if the patient knows the risk.

3. Individual rights:

Should have no outside influencing their choice .

Should understand the risk and benefits of transplantation.

Lifetime monitoring should be required.

4. Animal rights:

People for the ethical treatment of animals (PETA) has condemned pig heart transplant as "**unethical, dangerous".**

5. Religion belif:

XTxfrom pigs may affects the **Jewish andMuslim** dietary laws, whose religions have strict rules on animals, which prohibited the consumption of pork.

When and why XTX banned?

All Xenotransplantation was banned **worldwide in 1997.** Because of **PERV** pig virus being transmitted to humans. Some countries allowing XTx research to continue on a case by case basis **(some countries are US, UK** and **NEW ZEALAND).**

Future of xenotransplantation:

Xenotransplantation has the ability to be very useful in society today. At this stage cell based xenotransplant are easily to treat the diseases and very protected from the side of recipient. In fact, treating diabetes pig cell transplants could be available for next **5-10 years.** Organs are more different to protect. Unfortunately, the research and discoveries is very long. If scientists can find a way to solve the complications for transplanting the non-human (animal) organs could save so many lives.

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Revolutionizing Cardiovascular Disease Treatment with Stem Cells

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Introduction

Heart disease is still the most common cause of mortality (41.2%), followed by coronary heart disease. This emphasizes the necessity of complementary therapies like stem cell therapy. Multipotent stem cells can self-renew, differentiate into end-organ tissue cells, and live inside the body without triggering an immune reaction. Numerous stem cell types have been investigated for use in treating ischemic heart disease (IHD), congenital heart disease (CHD), and dilated cardiomyopathy (DCM), conditions for which there are currently no effective, expensive, or comprehensive treatments. However, because of their questionable long-term safety and potential for differentiation, the use of adult cell-derived stem cells has generated controversy. The goal of this review is to thoroughly examine the research on the application of adult stem cells to these cardiac diseases.

Stem cells:

Undifferentiated or partially differentiated cells with the ability to differentiate into a variety of tissues and cell types are known as stem cells. There are two primary kinds: adult stem cells, which come from fully grown organs including bone marrow, adipose tissue, and the umbilical cord, and embryonic stem cells, which come from embryos that are not used. In clinical research, stem cells are utilized to create specialized cells, such as heart or nerve cells, without the need for patient tissue. They can also be used to replace damaged tissues.

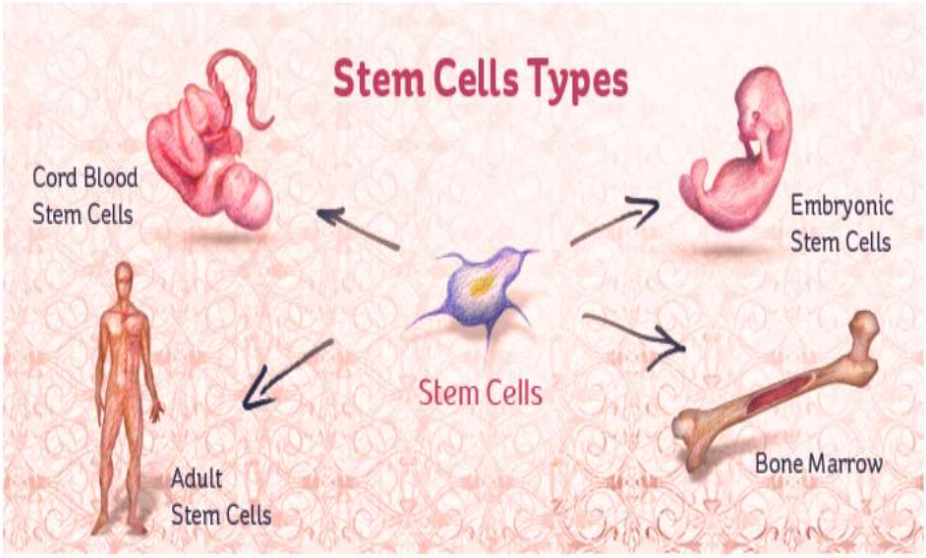

Figure 1: Stem cell types

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Stem cell therapy for the treatment of heart diseases:

A viable substitute for conventional cardiac illness and heart attack therapies, which frequently include drugs, surgery, or interventional procedures to control symptoms or enhance heart blood flow, is stem cell therapy. Although these therapies have the potential to be beneficial, they may not completely restore cardiac function because they do not address the underlying issue of tissue damage. On the other hand, by encouraging tissue repair and regeneration, stem cell therapy has the ability to directly target the underlying cause of cardiac or heart disease.

Process of stem cell therapy in cardiac treatment:

- **Stem Cell Harvesting:** Adult stem cells can be obtained from various sources, including bone marrow, adipose tissue, and circulating blood. These cells are typically harvested through a minimally invasive procedure, such as a bone marrow aspiration or fat tissue biopsy. The cells can also be sourced from a donor, as is the case for umbilical cord tissue-derived stem cells.

- **Isolation and Processing:** Once harvested, the stem cells are processed in a laboratory to isolate the desired cell population. Techniques such as centrifugation or filtration may be used to concentrate the stem cells.
- **Delivery to the Heart:** The stem cells are typically delivered to the heart through a catheter-based procedure. The catheter is guided into the coronary arteries or directly into the myocardium (heart muscle), where the stem cells are injected. Alternatively, they can be injected during open-heart surgery if the patient is undergoing a procedure like coronary artery bypass grafting (CABG).
- **Engraftment and differentiation of stem cells:** The stem cells need to engraft—that is, adhere to and become integrated with the surrounding tissue—after being injected into the wound site. After that, they differentiate—becoming distinct cell types—and repair damaged tissue.
- **Integration and Healing:** The injected stem cells may become integrated with the injured cardiac tissue. They can facilitate tissue repair and regeneration through numerous processes, such as differentiation into heart cells, production of growth factors, and activation of local progenitor cells.
- **Monitoring and Follow-Up:** Following the surgery, patients are constantly observed to evaluate their overall health and cardiac function. Additional testing like cardiac catheterization, MRI scans, and echocardiography may be performed to assess how well the treatment is working.

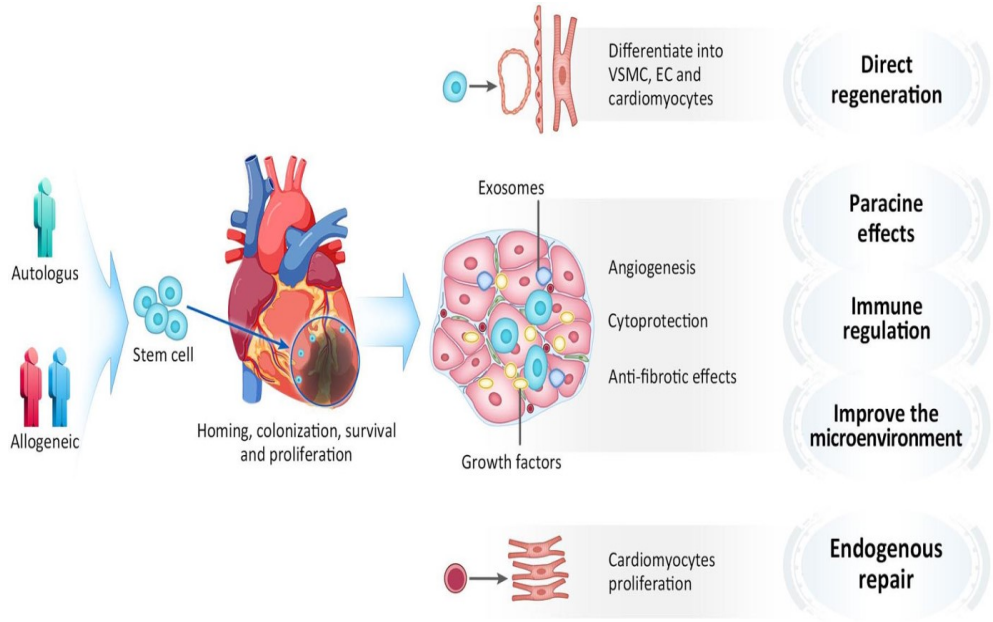

Figure 2: Mechanisms of stem cell therapy. VSMC, Vascular Smooth Muscle Cell; EC, Endothelial Cell.

https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.636136/full

Uses of stem cell therapy in cardiac treatment:

- **Treatment for low ejection fraction:** Stem cell therapy for low ejection fraction in cardiac patients is an evolving treatment approach aiming to address the underlying myocardial damage and dysfunction. Typically, stem cells are harvested from the patient's bone marrow or adipose tissue, processed to isolate specific cell types, such as mesenchymal stem cells (MSCs), and then reintroduced into the heart via intracoronary infusion or direct myocardial injection. These stem cells have the potential to promote tissue regeneration, modulate inflammation, and enhance vascularization in the damaged myocardium. Clinical studies and trials have shown promising results in improving ejection fraction, reducing heart failure symptoms, and potentially reversing heart remodeling. However, challenges such as variability in patient responses, optimal cell types and delivery methods, and long-term safety concerns remain significant areas of ongoing research. The field continues to advance with

the aim of establishing stem cell therapy as a viable treatment option for patients with low ejection fractions, complementing traditional cardiac interventions.

- **Ischemic Heart Disease:** Atherosclerosis causes left ventricular cell death and dysfunction by gradually decreasing coronary flow and, consequently, oxygenation of cardiac tissue, which leads to infarction of the heart. Since present treatments for IHD only manage symptoms without correcting cardiac damage, stem cells' regenerative characteristics have been utilized as prospective remedies. Historically, intracoronary or intramyocardial pathways have been the main ways to transport stem cells to the heart.
- **Congestive heart failure:** When the heart is unable to pump blood efficiently, it can cause congestive heart failure, which can cause fluid to accumulate in the lungs and other areas of the body. Patients with heart failure and congestive heart failure may benefit from stem cell therapy. Heart cells are among the many cell types that stem cells can differentiate into. Research has demonstrated that in patients suffering from congestive heart failure, stem cells can enhance cardiac function. It has been demonstrated that stem cells can promote the development of new heart muscle cells and blood arteries, which enhances cardiac function, blood flow, and heart inflammation.
- **Cardiomyopathy:** Stem cell therapy for cardiomyopathy involves using stem cells, such as mesenchymal stem cells (MSCs), to regenerate and repair damaged heart muscle. These cells are believed to promote tissue healing, reduce inflammation, and enhance cardiac function by integrating into the myocardium and supporting its regeneration. Clinical trials have shown promising results in improving heart function and reducing symptoms in patients with various types of cardiomyopathy, although further research is needed to establish long-term safety and efficacy conclusively. The therapy holds potential as a regenerative approach to complement existing treatments for managing cardiomyopathy and improving overall heart health.
- **Electrical Conduction Disorders:** Research explores the use of stem cells to regenerate cardiac electrical pathways, potentially correcting arrhythmias and improving heart rhythm.

Challenges to stem cell therapy:

- **Delivery and Engraftment:** Efficiently delivering stem cells to the damaged heart tissue and ensuring they engraft and survive is difficult. Cells can be lost due to the heart's dynamic environment and immune responses.
- **Differentiation:** Making sure stem cells, like cardiomyocytes, develop into the appropriate cell type after transplantation presents another difficulty. Although some research has demonstrated that stem cells can develop into cardiac muscle cells, this process is not very effective. Depending on the particular stem cell type and surroundings, it could change.
- **Safety Concerns:** Risks include the potential for tumor formation, abnormal growths, or arrhythmias. Ensuring the safety and long-term stability of the therapy is crucial.
- **Cost and accessibility**: Developing, producing, and administering stem cell therapies is expensive, potentially limiting accessibility for many patients.

Conclusion

To sum up, stem cells have a great deal of promise for treating cardiac conditions like coronary artery disease and heart failure. Even the reversal of coronary heart disease may be achievable. Alterations in lifestyle are also essential for heart regeneration.

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Cardiorenal Syndrome: A Comprehensive Overview

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Introduction

Cardiorenal syndrome is an appellation pursued to signify a bilateral malfunction of the kidney and heart, that kicks off a feedback cycle causing harm to both organs and corresponds to undesirable clinical ramifications. Cardiorenal syndrome has a dynamic, multifaceted, and intricate pathogenesis. Enhanced comprehension of the disease mechanisms will facilitate the creation of focused pharmaceutical and nonpharmacologic treatments for the management of this ailments. There has been a growing usage of the term "cardiorenal syndrome" without a standard definition. An innovative categorization of the cardiorenal syndrome was proposed, which includes five distinct categories that symbolizes the nature, duration, and pathophysiology of concurrent cardiac and renal dysfunction. This allowed for the inclusion of the wide range of interrelated disorders and emphasized the reciprocal nature of heart-kidney interactions.An autoimmune disorder of the cardiovascular system and renal system, sometimes called cardiorenal syndrome, tends to be defined by the possibility of acute or chronic fall apart in one organ causing acute or

chronic dysfunction in the other. It has become widely recognized that hindered kidney function may interfere with cardiac function, even though cardiorenal syndrome has historically been characterized as acute kidney dysfunction following acute cardiovascular disease.

Key Points: Acute kidney injury (AKI); cardiorenal syndrome (CRS); diagnosis; pathophysiology; treatment.

Definition:

"Any serious or intermittent problem in the cardiovascular system or the renal system that may culminate in an acute or chronic problem of the other" is the precise meaning of cardiorenal syndrome. CRS embraces atmospheres in which acute or persistent problems with the renal system or cardiovascular system can lead to problems with the other organ.

Classification based on the primary organ involved:

The cardiorenal syndrome is divided into five subtypes:

Type 1: a drastic drop in renal function as a result of an enormous decrease in cardiac function
Type 2: a progressive decline in renal function brought on by chronic cardiovascular insufficiency
Type 3: a sudden collapse in cardiac function as a result of an extreme decrease in renal function
Type 4: an recurrent reduction in the renal system leading to persistent heart dysfunction
Type 5: widespread diseases that cause problems with the cardiac system and the renal system

Type of CRS	Pathophysiology
Type 1 CRS (Acute CardiorenalSyndrome)	- **Hemodynamic Mechanisms**: Reduced cardiac output (CO) and increased central venous pressure (CVP) impair renal perfusion. - **Neurohumoral Activation**: RAAS (renin-angiotensin-aldosterone system) and sympathetic nervous system contribute to

Type of CRS	Pathophysiology
	vasoconstriction and sodium retention. - **Inflammation**: Systemic inflammatory response affects both heart and kidneys. - **Oxidative Stress Imbalance**: Increased reactive oxygen species (ROS) and reduced nitric oxide (NO) bioavailability[2].
Type 2 CRS (Chronic Cardiorenal Syndrome)	- **Hemodynamic Factors (HFrEF)**: Decreased cardiac output, venous congestion, neurohormonal activation, and chronic inflammation. - **HFpEF**: Increased filling pressures, compromised cardiac filling, and inadequate stroke volume reserve[9].
Type 3 CRS (Acute Renocardiac Syndrome)	- **AKI Trigger**: Acute kidney injury (AKI) superimposed on chronic kidney disease (CKD). - **Sensitive Nephrons**: Nephrons are sensitive to ischemia and nephrotoxins. - **Clinical Context**: Often occurs in acute decompensated heart failure (ADHF)[5].
Type 4 CRS (Chronic Renocardiac Syndrome)	- **Multifactorial Mechanisms**: Not fully understood. - **Oxidative Stress**: Major connector in development and progression. - **Cardiovascular Involvement**: Occurs in patients with chronic kidney disease[11].
Type 5 CRS (Secondary CRS)	- **Systemic Diseases**: Induced by conditions like sepsis, hepatorenal syndrome, and immune-mediated diseases. - **Simultaneous Cardiac and Renal Involvement**: Complex

Type of CRS	Pathophysiology
	interactions between heart and kidney due to underlying systemic disorders[14].

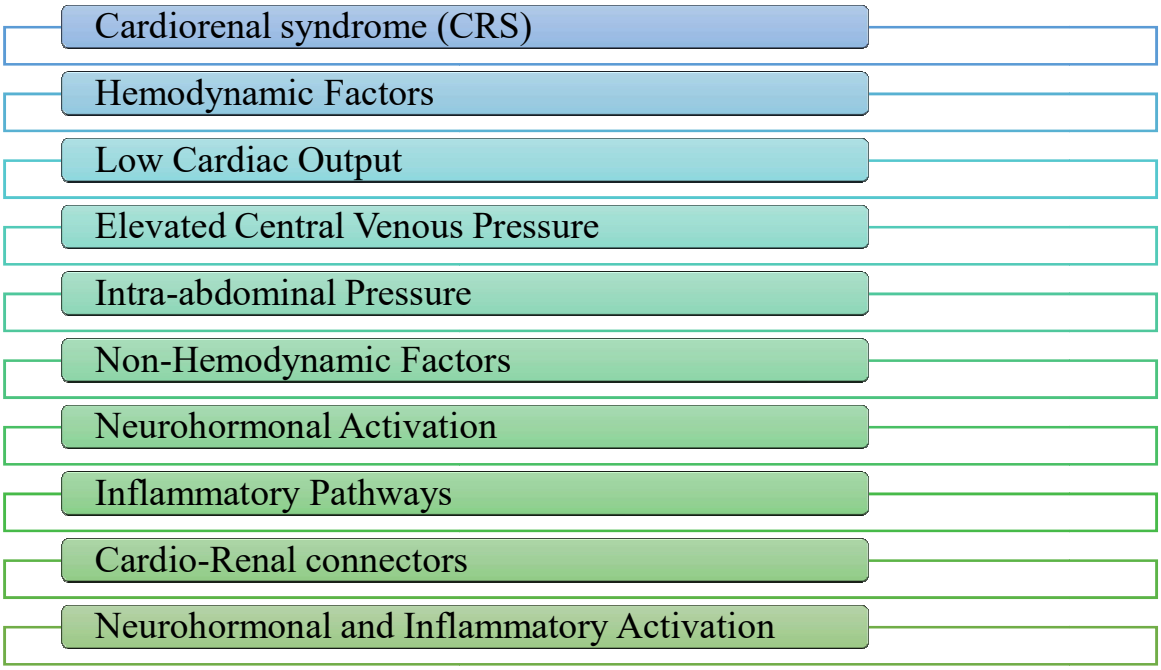
Indications, such as:

• Increased jugular vein pressure;

• Widespread edema and swelling with "third spacing," manifesting as ascites, peripheral edema, or pleural effusion.

• Patients may also exhibit signs of reduced cardiac output, such as weariness, reduced peripheral pulses, irregular heart rates (either tachycardia or bradycardia), crackles or rales on lung auscultation.

Pathophysiology:



Other possible signs indicating a primary renal cause of cardiorenal syndrome **may include:**

- Watching for oliguria or anuria prior to cardiac failure;
- pallor from anemia

1. Mechanisms:

Acute CRS:

- Systemic congestion increases renal venous pressure,
- Reducing renal perfusion.

Chronic CRS:

- Neurohormonal activation,
- inflammation,
- oxidative stress play key roles.

2. Clinical Presentation:

- Fatigue,
- Dyspnea,
- Reduced urine output,
- Peripheral edema,
- Palpitations.
- Diagnosis involves assessing cardiac and renal function,
- Fluid status,
- Biomarkers.

3. Causes and Risk Factors:

- Heart failure (most common cause).
- Kidney disease (e.g., glomerulonephritis, diabetic nephropathy).
- Diabetes, hypertension, obesity, and vascular disorders increase risk

4. Inflammation and Oxidative Stress:

Both heart failure and kidney disease are associated with increased levels of pro-inflammatory cytokines and oxidative stress markers. Inflammation and oxidative stress can cause endothelial dysfunction, promoting vascular damage and fibrosis in both organs.

5. Uremic Toxins:

In CKD, the accumulation of uremic toxins (e.g., indoxylsulfate and p-cresylsulfate) can have direct cardiotoxic effects, promoting myocardial fibrosis and arrhythmias. Diagnosis and Management Diagnosis:

Radiology plays a crucial role in diagnosing and managing CRS. Diagnostic imaging techniques used include:

Echocardiography:

- Evaluates heart function, structure, and hemodynamics.
- Detects left ventricular dysfunction, valvular diseases, and signs of heart failure.

Renal Ultrasound:

- Assesses kidney size, structure, and possible obstructions.
- Helps identify chronic kidney disease, renal artery stenosis, and acute kidney injury.

Chest X-Ray:

- Evaluates pulmonary congestion and cardiac size.
- Identifies signs of heart failure such as pulmonary edema and cardiomegaly.

Magnetic Resonance Imaging (MRI):

- Cardiac MRI provides detailed images of cardiac anatomy, function, and myocardial tissue characterization.
- Renal MRI assesses renal perfusion, structure, and function.

Computed Tomography (CT):

- Cardiac CT evaluates coronary artery disease and calcifications.
- Renal CT assesses renal masses, obstructions, and vascular abnormalities.

Nuclear Imaging:

- Myocardial perfusion imaging evaluates coronary artery disease and myocardial viability.
- Renal scintigraphy assesses renal function and perfusion.

Management and Treatment

Managing CRS involves a multidisciplinary approach to address both cardiac and renal dysfunctions:

Medications:

- Diuretics to manage fluid overload.
- ACE inhibitors or ARBs for heart failure and hypertension.
- Beta-blockers and aldosterone antagonists for heart failure management.

Interventions:

- Renal replacement therapy in severe kidney dysfunction.
- Percutaneous coronary interventions or surgery for coronary artery disease.

Lifestyle Modifications:

- Dietary modifications to manage fluid and electrolyte balance.
- Monitoring and managing comorbid conditions like diabetes and hypertension.

Conclusion

CRS remains a challenging clinical entity, requiring a multidisciplinary approach. By understanding its pathophysiology and implementing evidence-based strategies, healthcare providers can improve outcomes for patients with cardiorenal syndrome.

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Acute Coronary Syndromes - An overview

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Introduction

The term acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischaemia and covers the spectrum of clinical conditions ranging from unstable angina (UA) to non-ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI). Unstable angina was the term used earlier and now NSTEMI is used more commonly. The present chapter deals with UA and NSTEMI which are closely related conditions but they differ in severity.

Epidemiology

According to OASIS registry, Indian patients are 7 to 8 years younger than Western patients with mean age of 57 years as against 65 years in Western population. In additional , our patients are more often diabetic. A large registry – CREATE registry was done in 2008, involving 20,000 patients admitted in multiple centres in India. 37% of these patients were less than 50 years of age. Patients of NSTEMI/STEMI reached hospital later as compared to the Western patients. In young patients coming from poorer socio-economic strata, smoking was the risk factor in 50% of the patients. In older individuals from rich areas, diabetes and hypertension were more important risk factors. The mortality rate of NSTEMI in CREATE registry was 4% which is 1% more than in Western registries.

Pathophysiology

Atherosclerosis is the process of plaque formation that involves primarily the intima of large and medium-sized arteries; the condition progresses overtime. The pathogenesis of ACS involves an interplay among the endothelium, the inflammatory cells, and the thrombogenicity of the blood(Figure 1)

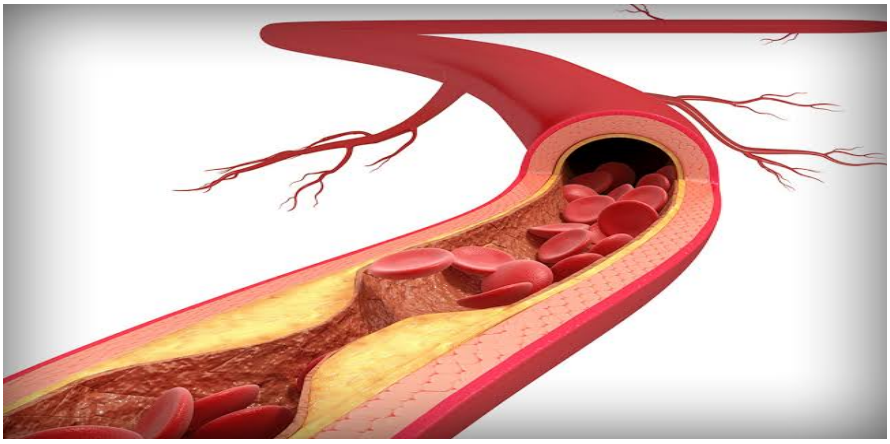


Figure 1: Atherosclerotic Plaque formation

After plaque rupture (or endothelial erosion), the subendothelial matrix (which is rich in tissue factor, a potent procoagulant) is exposed to the circulating blood; this exposure leads to platelet adhesion followed by platelet activation and aggregation and the subsequent formation of a thrombus .

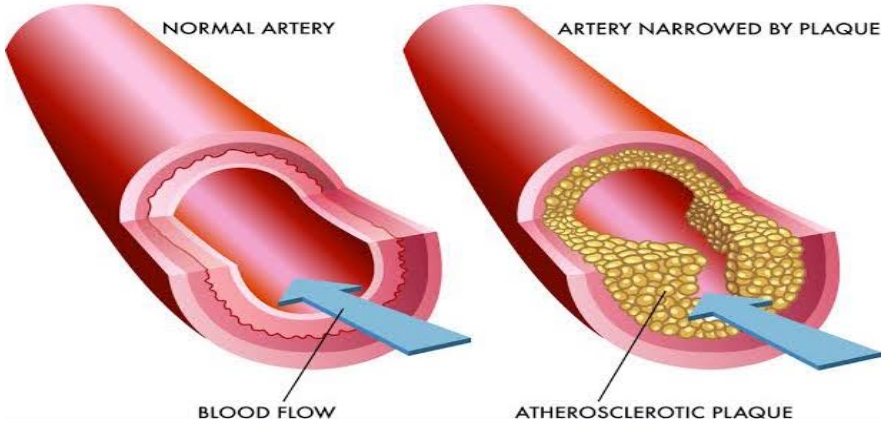


Figure 2: Vessel wall occlusion by plaque

Types Of Thrombus

Two types of thrombi can form: a platelet-rich clot (a white clot) that forms in areas of high shear stress and partially occludes the artery, or a fibrin-rich clot (a red clot) that is the result of an activated coagulation cascade and decreased flow in the artery.

Figure 3 - White Thrombus

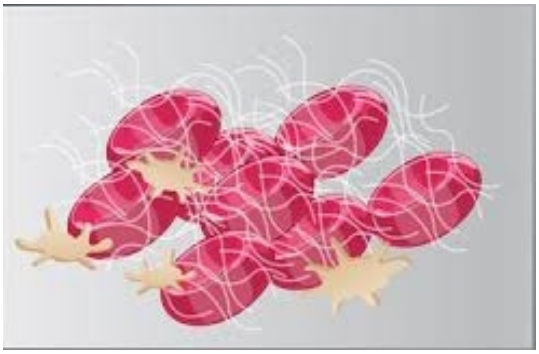


Figure 4 - Red Thrombus

Platelets are main cellular components of white Thrombus, which tends to form in arterial system.

Red blood cells predominate in red Thrombus, in veins.

Acute Coronary Syndrome are frequently superimposed on white clots, and cause *total occlusion* resulting in STEMI. When occlusion is *subtotal*, UA/ NSTEMI are usually the result(Figure 5) .

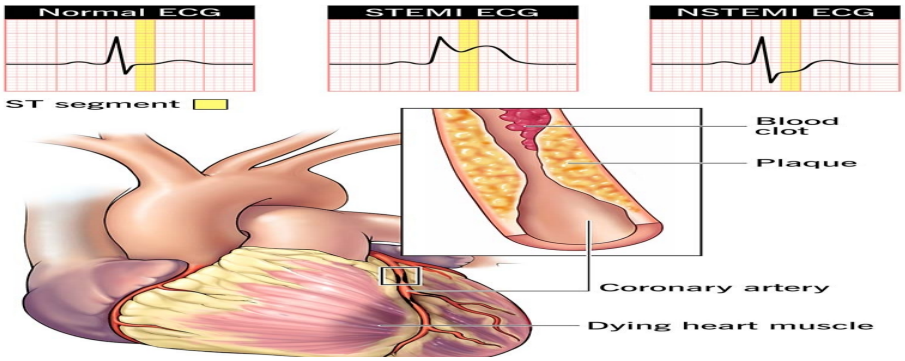


Figure 5 - STEMI & NSTEMI

Plaques are characterised by a large lipid core, thin fibrous caps, a high density of macrophages and T lymphocytes, a relative paucity of smooth muscle cells, locally increased expression of matrix metalloproteinases that degrade collagen, eccentric outward remodelling, and increases in plaque neovascularity and intraplaque haemorrhage. Inflammation, an important determinant of the 'vulnerability' of plaques, is related to an increase in the activity of macrophages at the site of plaque. 70 % of lesions on coronary angiography that cause ACS are less than 50 per cent stenosis of arterial diameter. So most ACS episodes are due to rupture of non-obstructive plaques(Figure 6).

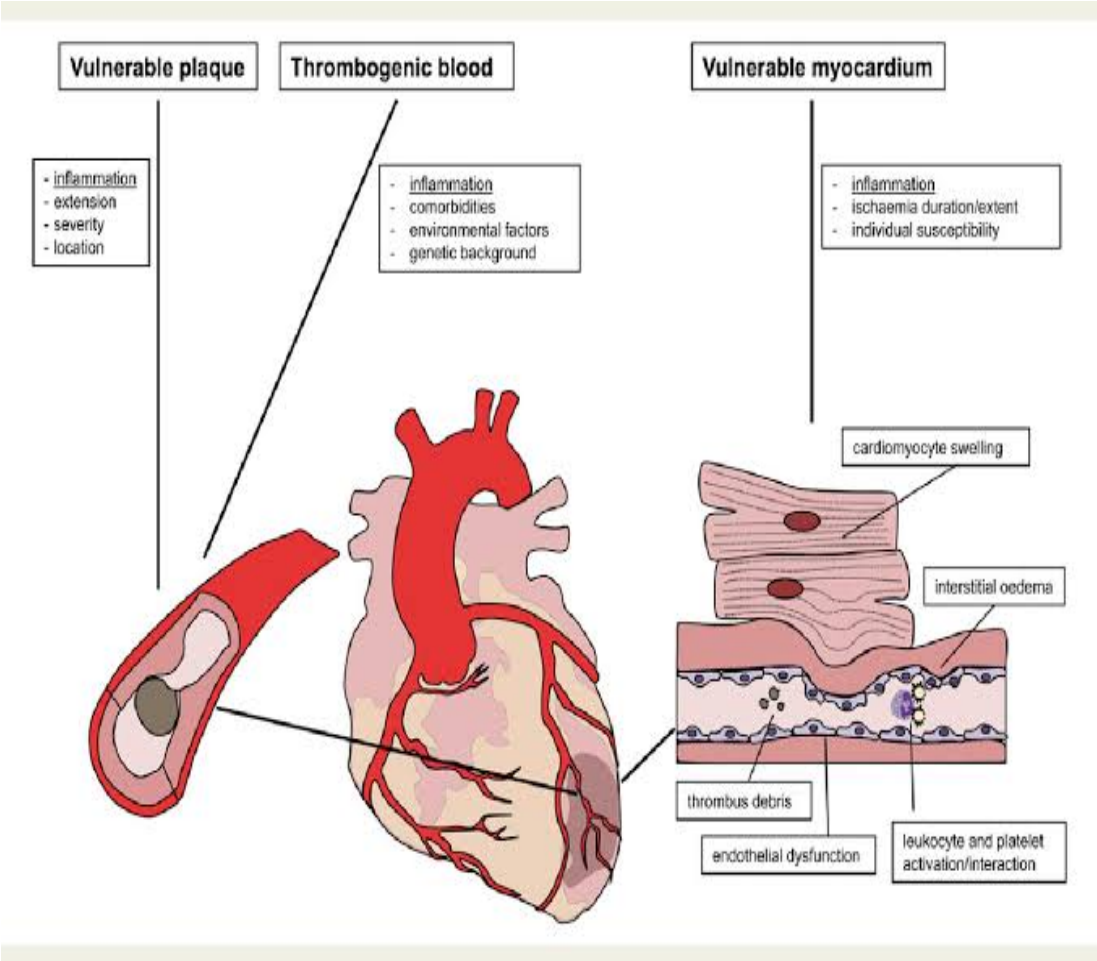


Figure 6 - Pathogenesis of Atherosclerosis

Clinical Features

- ACS occurs more commonly in males.
- As compared to stable angina, the chest discomfort associated with UA is more severe, occurs at rest, lasts longer and is usually described as frank pain
- It is located in the substernal region or epigastric area radiates to the neck, jaw, left shoulder, and left arm.
- The discomfort is often accompanied by burping and eructations and is at time mistaken as 'gas' by the patients.
- Some patients may present with symptoms other than chest discomfort; such 'angina equivalents' symptoms include dyspnoea (most common), nausea and vomiting, diaphoresis, and unexplained fatigue.
- Atypical presentations are more common among women, elderly people and in diabetics. Rarely, syncope may be the presenting symptom of ACS.
- Besides characteristics of pain other factors that help to identify pain of CAD are older age, male sex, a history of CAD and number of traditional risk factors present.

Table 1: Braunwald Clinical Classification of Unstable Angina

	Secondary UA (A)	Primary UA (B)	Post-MI Angina (C)
New onset angina (I)	I A	I B	I C
Angina at rest not within preceding 48 hours (II)	II A	II B	II C
Angina at rest within 48 hours (III)	III A	III B-T Positive III B-T Negative	III C

Arrow indicates that with increasing severity prognosis worsens.

Figure 7: Braunwald Clinical Classification of Unstable Angina

Clinical Examination

The cardiovascular examination is mostly normal. The findings that indicate a large area of ischaemia and high-risk include;

- Pale, cool skin & diaphoresis
- Sinus tachycardia
- Third or fourth heart sound
- Basilar rales;
- Hypotension.

Investigations

Electrocardiography

Findings on ECG associated with Unstable Angina include ST-segment depression, transient ST-segment elevation, T-wave inversion, or some combination of these changes.

Depending on the severity of the clinical presentation, these findings are present in 30% to 50% of the patients. New ST-segment deviation, even of only 0.05 mV, is an important and specific measure of ischaemia and prognosis. T wave inversion is sensitive for ischaemia but is less specific. Patients with no ECG changes are at a lower risk of complications than those with ECG changes. Myocardial ischaemia is dynamic and patients hospitalised for Unstable Angina /NSTEMI should undergo serial ECG tracings or continuous ST segment monitoring

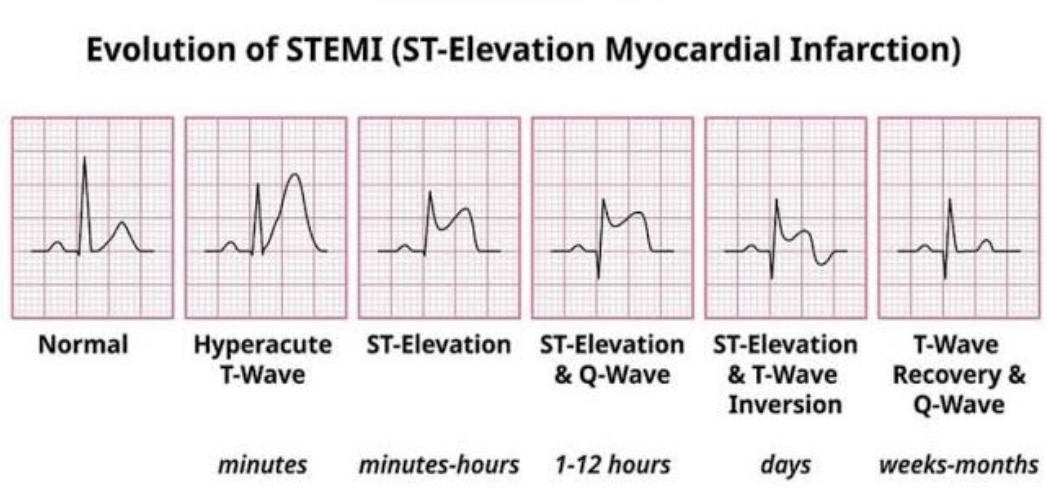


Figure 8 : Braunwald Clinical Classification of Unstable Angina

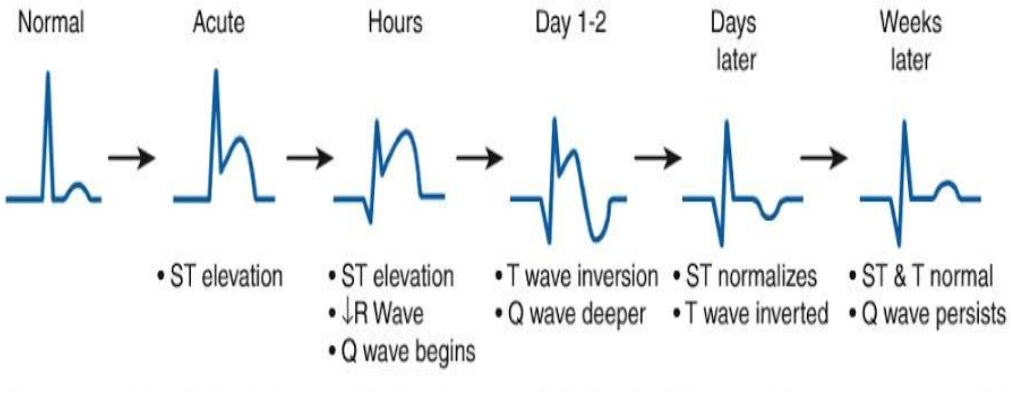


Figure 9 : Evolution of STEMI

ECG changes in MI

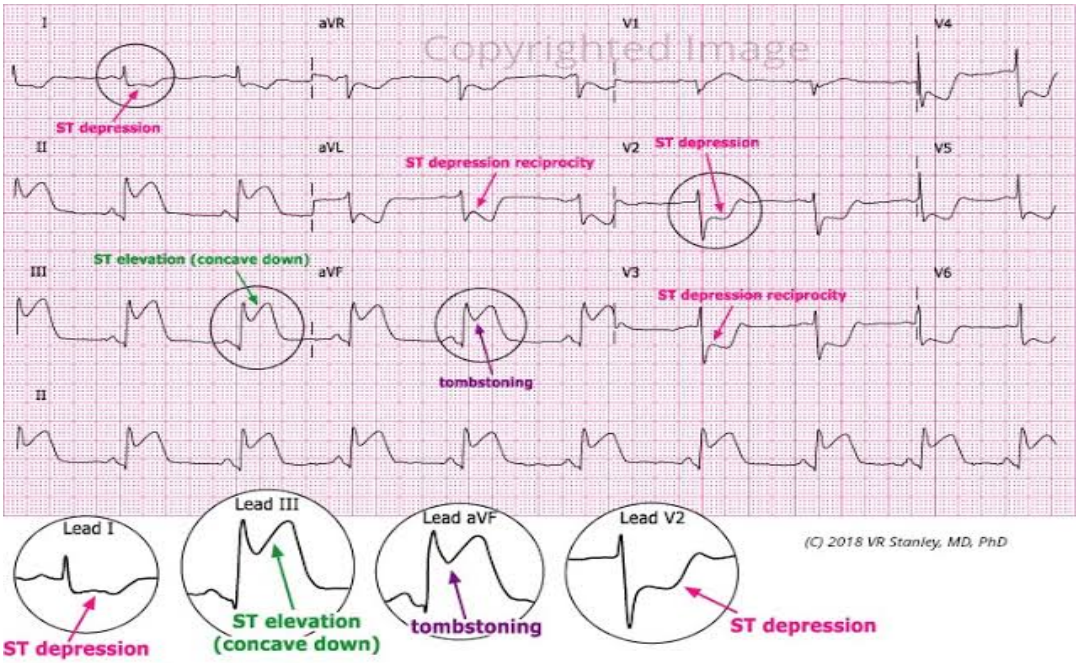


Figure 10 : Various ECG Changes in MI

a)Anteroseptal wall MI :

Impression : ST Elevation in v1-v4 , Reciprocal ST T changes in Lead II,III,aVF

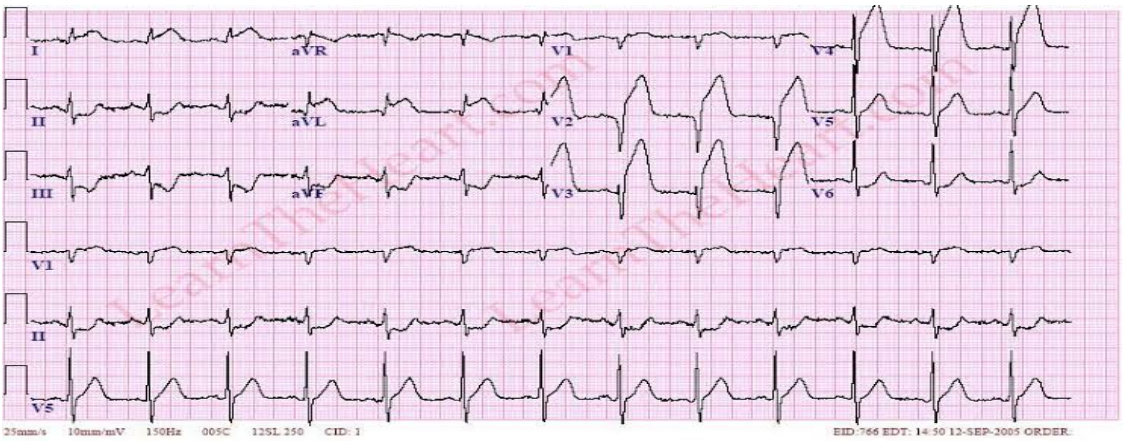


Figure 11 : ECG Changes in Anteroseptal wall MI..

b)Right ventricular MI:

Impression: ST Elevation lead I , Lead V4R , Lead III , Reciprocal ST depression in lead I & aVL .

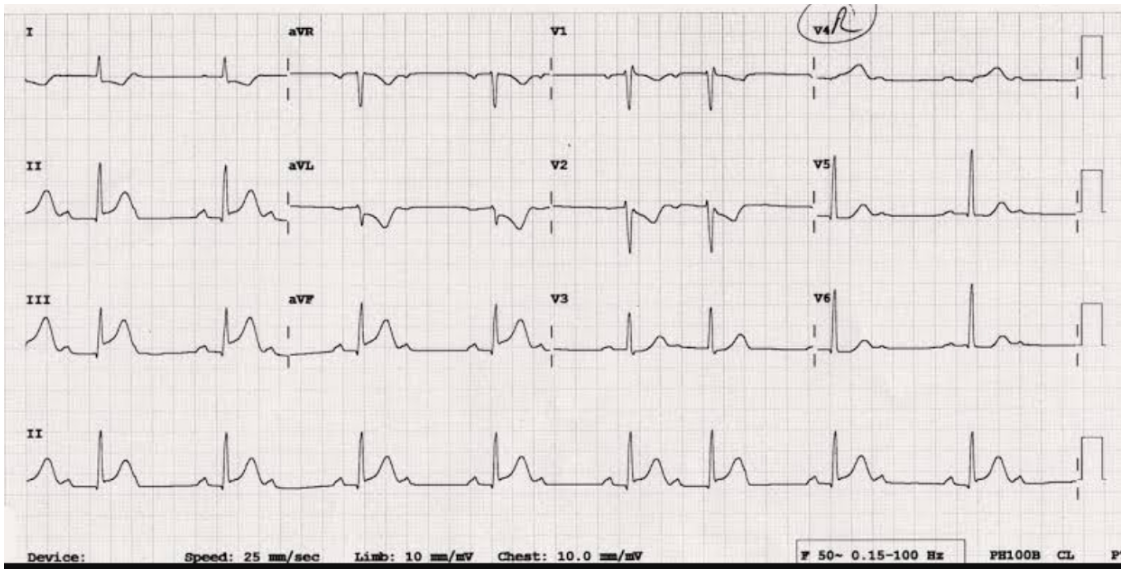


Figure 12 : ECG Changes in Right ventricular MI

c)Inferior wall MI :

Impression: ST Elevation in lead II ,III, V4,V5,V6 , aVF & Reciprocal ST depression in V1, V2

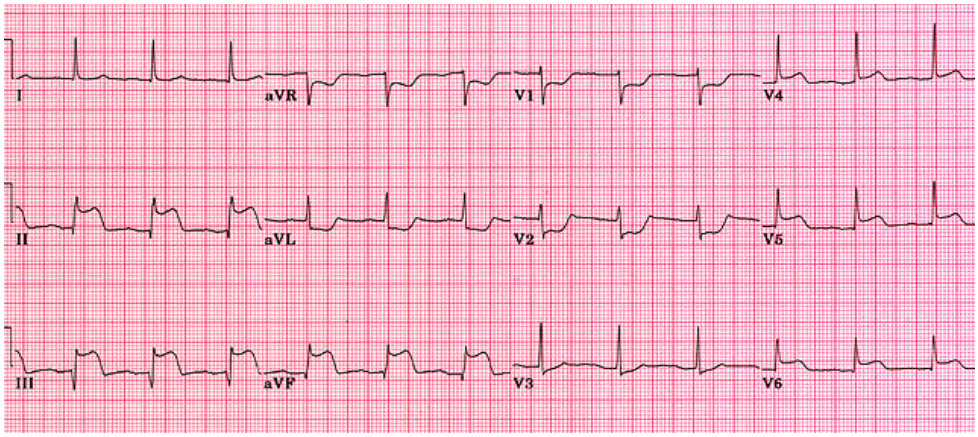


Figure 13 : ECG Changes in Inferior wall MI

d)Posterior wall MI:

Impression : ST elevation in V 7,8,9 and reciprocal ST depression in v1- V3

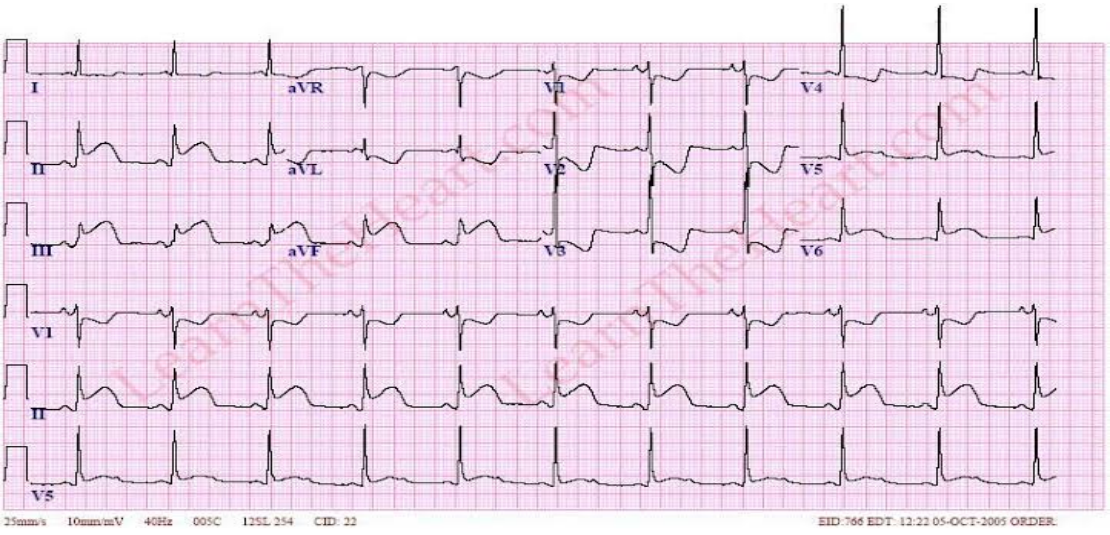


Figure 14 : ECG Changes in posterior wall MI

e)Lateral wall MI:

Impression : ST Elevation in Leads I, aVL , V5,V6

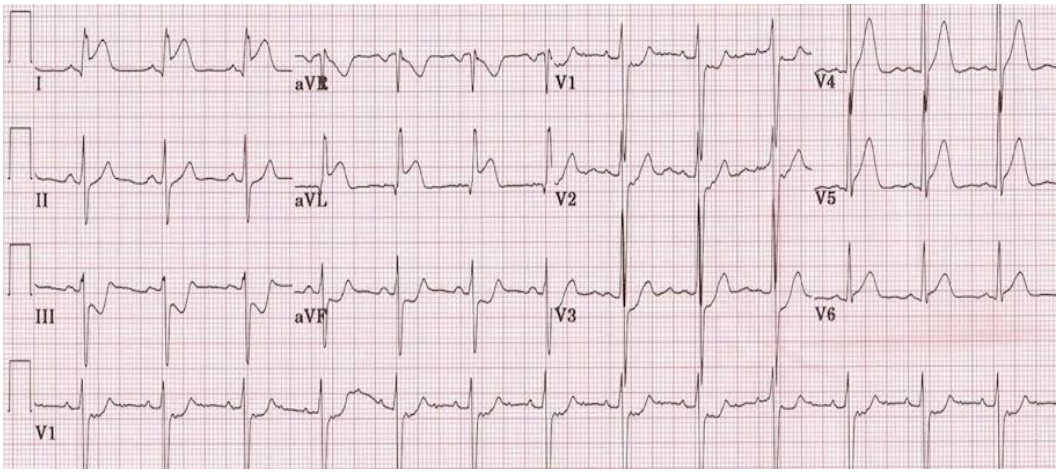


Figure 15: ECG Changes in Lateral wall MI

f)Non ST Elevation MI(NSTEMI):

Impression : ST depression in lead II, III , aVF , V2,V3 ,V4 ,V5

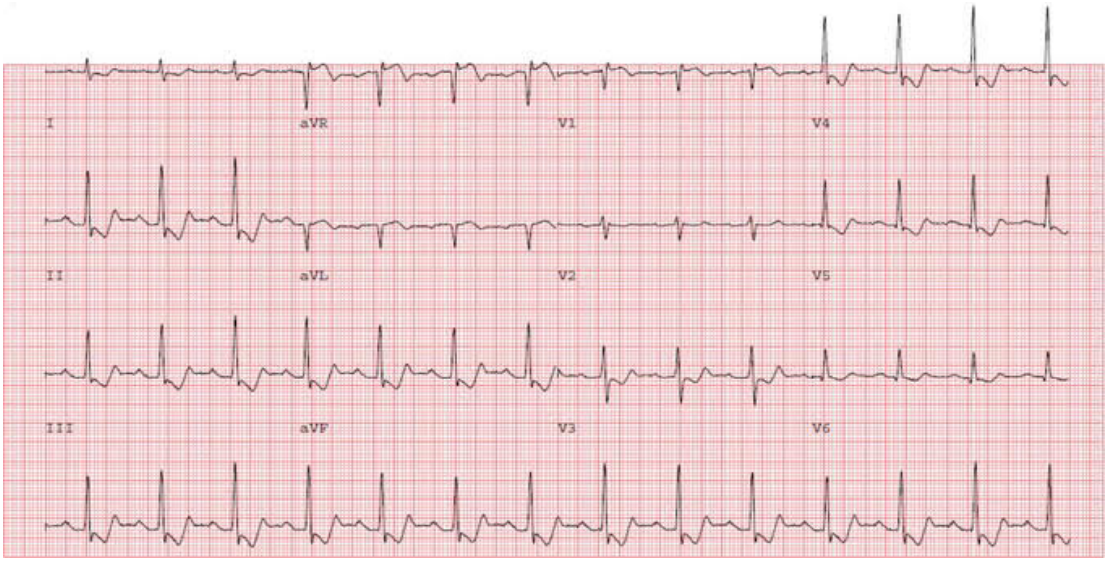


Figure 16: ECG Changes in Non ST elevation MI

Localisation of MI

localisation	ST elevation	Reciprocal ST depression	coronary artery
Anterior MI	V1-V6	None	LAD
Septal MI	V1-V4, disappearance of septum Q in leads V5,V6	none	LAD-septal branches
Lateral MI	I, aVL, V5, V6	II,III, aVF	LCX or MO
Inferior MI	II, III, aVF	I, aVL	RCA (80%) or RCX (20%)
Posterior MI	V7, V8, V9	high R in V1-V3 with ST depression V1-V3 > 2mm (mirror view)	RCX
Right Ventricle MI	V1, V4R	I, aVL	RCA
Atrial MI	PTa in I,V5,V6	PTa in I,II, or III	RCA

Figure 16: Localisation of MI with St elevation & possible Reciprocal changes with Artery involved .

Cardiac biomakers:

A diagnosis of NSTEMI can be made when the ischaemia is sufficiently severe to cause myocardial damage that results in the release of a biomarker of myocardial necrosis into the circulation (cardiac-specific troponins T or I, or muscle and brain fraction of creatine kinase [CK-MB]).

Cardiac biomakers should be measured in all patients of acute coronary syndromes and include

- CK- MB
- Troponin I / T

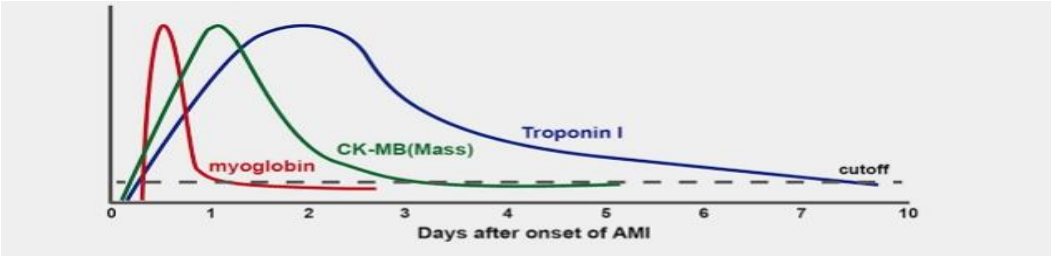
Tropnin I/T

They are used for the diagnosis of NSTEMI and for prognostication. Troponins are more sensitive and specific than any other biomarker. Both qualitative as well as quantitative measurements are available. There is a direct relationship between the degree of troponin elevation and mortality. Patients with elevated Troponin levels have 25% risk of death or MI at 6 months as

compared to less than 5% risk in patients with normal Troponin levels. Troponins are not released before 4 to 5 hours of symptoms, so these should be measured after 4 to 5 hours of symptom onset and if results are negative, these are measured after 8 to 12 hours of symptom onset. Troponins remain elevated up to 10 to 14 days of symptom onset.

CK-MB :

Levels of CK-MB start increasing after 10 to 12 hours of symptom onset and remain elevated for 24 to 36 hours. It is rapid, cost- efficient and detects early reinfarction but lacks specificity in setting of skeletal muscle.



Enzymes	Time of Hours	Peak time	Fall to Normal
Trop I& T	3 – 12 hours	24 hours	2 weeks
Creatine kinase	3-12 hours	24 hours	48-72 hours
Lactate Dehydrogenase	After 24 hours	36-48 hours	14 days
Myoglobin	Within first few hours	7-8 hours	Within 24 hours

Figure 16: Various Cardiac Biomarkers

Other lab investigations

Elevated CRP levels relate to an increased risk of mortality. B-type natriuretic peptide (BNP) provides useful prognostic information across the entire spectrum of patients with ACS as a marker of heart failure which may be associated in some highrisk patients.

Risk Stratification

Patients of ACS have variable prognosis. At one end of spectrum are young patients with new onset angina, no ECG changes, non-elevated biomarkers and no haemodynamic instability. These patients are managed pharmacologically and they should undergo non-invasive testing (TMT, stress echocardiography) after 10 days of symptom onset. At the other end are patients with history of recurrent/rest angina, fresh ECG changes, elevated biomarkers and, haemodynamically unstable patients who need early invasive treatment strategy in the form of PCI.

Table 1:Selection of Initial Treatment Strategy: Invasive versus Conservative

Selection of Initial Treatment Strategy: Invasive versus Conservative
Invasive
Recurrent angina or ischaemia at rest or with low level activities despite intensive medical therapy,Elevated cardiac biomarkers (TnT or TnI), New or presumably new ST-segment depression, Signs or symptoms of HF or new or worsening mitral regurgitation
High-risk findings from non-invasive testing, Haemodynamic instability Sustained ventricular tachycardia PCI within 6 month Prior CABG High-risk score (e.g. TIMI, GRACE) Reduced left ventricular function (LVEF < 40%)
Conservative
Low-risk score (e.g. TIMI, GRACE) Patient or physician preference in the absence of high-risk feature

CABG = Coronary artery bypass grafting; GRACE = Global registry of acute coronary events; HF = Heart failure; LVEF = Left ventricular ejection fraction;

Patients with ACS are risk stratified on the basis of certain criteria, to assess which of them would benefit from early invasive therapy (percutaneous coronary intervention) and who will be managed conservatively (Table 1). Many risk profile models like TIMI (Table 2), GRACE have been proposed for triage assessment. The TIMI risk score is determined by seven variables, each of which is assigned one point. Patients with scores of five or more have been shown to have a higher risk of adverse events and a higher mortality and these patients should be considered for early coronary angiography and revascularisation.

Table 2: The TIMI Risk Score TIMI Risk Score

The TIMI Risk Score TIMI Risk Score	
TIMI Risk Score. No. Of Risk Factors	Risk of Death, MI, or Urgent Revascularisation (%)
0 or 1	~ 5%
2	~10%
3	~15%
4	~20%
5	~25%
6.	~40%

Coronary Angiography :

Coronary angiography is done in all patients who are stratified as high-risk by risk profile models as described above. Angiography is the key in diagnosing the extent, location and severity of lesions and in planning revascularisation [percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)]. More than 80% patients withUnstable Angina /NSTEMI show significant coronary lesions on coronary angiography.

Management

The principles of management are

- General measures
- Pharmacological therapy
- Revascularisation.

General Measures

Patients with definite ACS are admitted to the hospital for further treatment. Admission to the coronary care unit (CCU) is recommended if there is an evidence of active, ongoing ischaemia or haemodynamic or electrical instability. The other measures include bed rest till patient is pain free for at least 24 hours, mild sedation, quiet environment, morphine or pethidine if pain is not substantially relieved by nitrates and beta-blockers and stool softeners to avoid straining.

Pharmacological Therapy

Loading Dose :

- ASPIRIN 325 mg
- CLOPIDOGREL 300 mg
- ATORVASTATIN 80 mg

Dual antiplatelet therapy :

Dual anti-platelet therapy includes aspirin and clopidogrel

Aspirin blocks the synthesis of thromboxane A2 by irreversibly inhibiting cyclooxygenase 1, thereby diminishing platelet aggregation. Randomised trials demonstrate that, compared with placebo, aspirin *reduces the risk of death or MI by more than 50%* for patients presenting with UA/NSTEMI.

Clopidogrel is a thienopyridine derivative that blocks the P2Y12 adenosine diphosphate (ADP) receptor on platelets. This action decreases platelet activation and aggregation, increases bleeding time, and reduces blood viscosity. Therapy with clopidogrel and aspirin is recommended for essentially all patients with UA/NSTEMI.

Several large trials involving patients with UA/NSTEMI have shown that the GP IIb/IIIa inhibitors are of substantial benefit for patients at high-risk, those undergoing PCI, or both. Three agents are currently available for use: abciximab, eptifibatide, and tirofiban.

Anticoagulant Therapy :

Low molecular weight heparins (LMWH)have several advantages over conventional heparins, including ease of administration (twice a day), a lower rate of thrombocytopaenia, more bioavailability, and less binding to plasma proteins, a factor that renders monitoring the level of anticoagulation unnecessary.

Nitrates act as vasodilator, thereby reducing myocardial oxygen demand via venodilatation and enhance myocardial oxygen delivery by dilating large coronary arteries and improving collateral flow to ischaemic areas. Nitrates relieve chest pain but do not reduce mortality in ACS.

Revascularisation:

Revascularisation consists of measures to open the culprit vessel/(s) to improve the perfusion to the ischaemic myocardium, after identification of the location and extent of the lesions on coronary angiography (CAG). It can be done by percutaneous coronary

Intervention (PCI), i.e. percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG).

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Heart Failure- An Impending Doom

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Introduction

Heart failure is a complex clinical syndrome in which the heart fails to meet the metabolic demands of the body, in the form of any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

A Diagnosis of heart failure is based on the presence of a triad:

1. Typical symptoms :Shortness of breath on exertion and at rest, fatigue
2. Signs: Tachycardia, tachypnoea, raised jugular venous pressure, peripheral oedema, and pulmonary congestion
3. Objective evidence of a structural or functional cardiac abnormality : Cardiomegaly, abnormal echocardiogram, raised natriuretic peptide concentration

Pathophysiology:

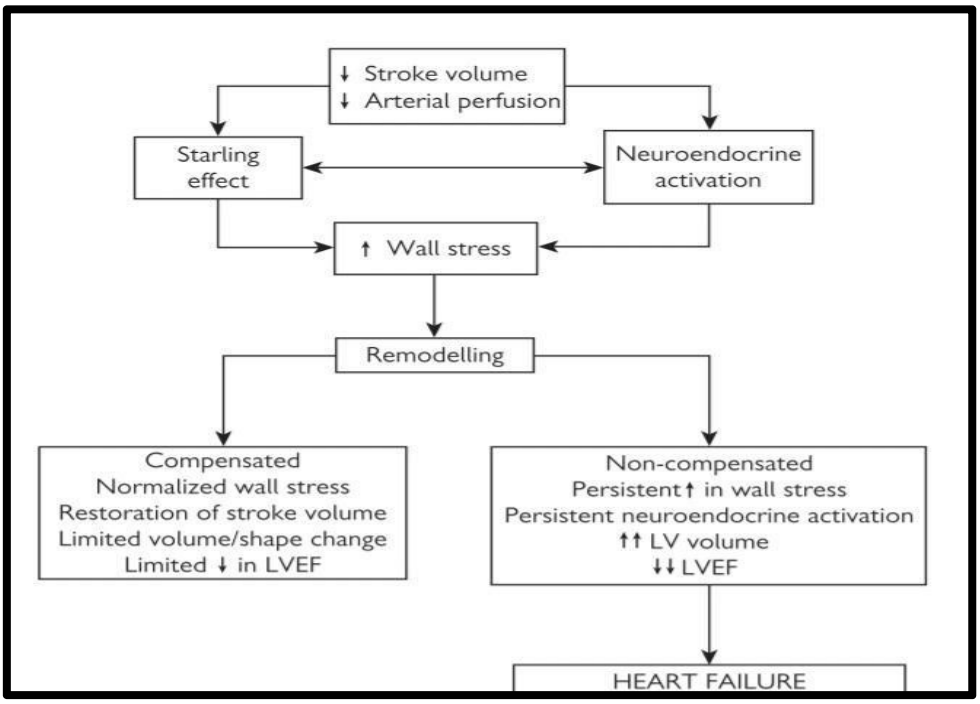

Figure 1: Pathophysiology of Heart Failure

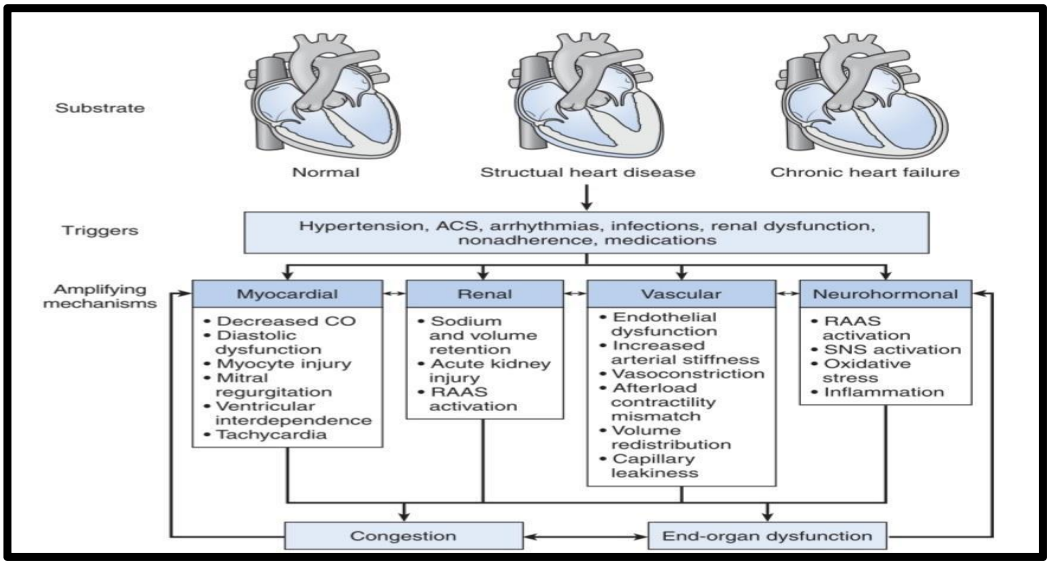

Figure 2: Pathophysiology of Heart Failure

Conditions mimicking heart failure

- Obesity
- Chest disease — including lung, diaphragm, or chest wall
- Venous insufficiency in lower limbs.
- Drug-induced ankle swelling (e.g. dihydropyridine calcium blockers)
- Drug-induced fluid retention (e.g. NSAIDs)
- Hypoalbuminemia
- Intrinsic renal disease
- Intrinsic hepatic disease
- Pulmonary embolic disease
- Depression and/or anxiety disorders
- Severe anaemia
- Thyroid disease
- Bilateral renal artery

Signs and symptoms

The evaluation of a heart failure patient with a comprehensive history and clinical examination.

Primary symptoms can be attributed to either reduced cardiac output or fluid accumulation include:

- ❖ Fatigue
- ❖ Dyspnoea (on exertion or at rest)
- ❖ Orthopnoea
- ❖ Paroxysmal nocturnal dyspnoea
- ❖ Peripheral oedema
- ❖ Chest pain
- ❖ Palpitations (tachycardia)
- ❖ Hypotension
- ❖ Raised jugular venous pressure (JVP)
- ❖ Displaced apex beat
- ❖ Gallop rhythm (3rd heart sound)
- ❖ Cachexia.

Gastrointestinal symptoms secondary to congestive hepatomegaly, ascites, reduced bowel perfusion, and oedema (abdominal distension and pain, anorexia, bloating, nausea,constipation, jaundice)

Genitourinary symptoms secondary to impaired renal perfusion: Oliguria/anuria, urinary frequency, nocturia

Cerebrovascular symptoms secondary to cerebral hypoperfusion

Electrolyte abnormalities: Confusion, memory impairment, anxiety, headaches, insomnia, bad dreams or nightmares, psychosis with disorientation, delirium, or hallucinations

Musculoskeletal symptoms : Gout, carpal tunnel syndrome, muscle cramps

NYHA Classification of heart failure

Class I : No limitation of physical activity.
Class II : Slight limitation of physical activity — symptoms with ordinary levels of exertion (e.g. walking up stairs)
Class III : Marked limitation of physical activity — symptoms with minimal levels of exertion (e.g. dressing)
Class IV : Symptoms at rest

Stages of heart failure' proposed by the AMERICAN COLLEGE OF CARDIOLOGY (ACC) and THE AMERICAN HEART ASSOCIATION (AHA):

Stage A: At high risk for developing heart failure (HF) but without identifi ed structural or functional heart disease, symptoms or signs of HF e.g. patients with: hypertension, atherosclerosis, diabetes, obesity, metabolic syndrome
Stage B: Structural or functional heart disease but without symptoms or signs of HF e.g. previous MI, left ventricular hypertrophy, reduced EF, valvular lesions

Stage C: Structural or functional heart disease with current or prior symptoms or signs of HF e.g. known structural heart disease with associated dyspnoea,fatigue, oedema
Stage D: Refractory HF symptoms despite maximal medical therapy e.g. marked symptoms on minimal exertion or at rest, hospitalized patients

Diagnostic criteria:

HF is a clinical diagnosis based on history and physical examination findings:

Although there are no universally agreed-upon diagnostic criteria for HF, The FRAMINGHAM criteria require two major or one major and two minor criteria:

MAJOR CRITERIA:	MINOR CRITERIA:
❖ Paroxysmal nocturnal dyspnea ❖ Jugular venous distention ❖ Crackles, cardiomegaly ❖ Pulmonary edema ❖ Presence of S3 ❖ Positive hepatojugular reflux ❖ Weight loss with diuresis (>4.5 lb)	❖ Lower extremity edema ❖ Nocturnal cough ❖ Dyspnea on exertion ❖ Hepatomegaly ❖ Pleural effusions ❖ Tachycardia ❖ Decrease in vital capacity

The diagnosis of HF is further supported by laboratory values (elevated brain natriuretic peptide [BNP] or N-terminal proBNP [NT-proBNP]), ECG, and imaging studies.

Types of clinical presentation of heart failure:

1. Warm and wet: volume overloaded but with adequate perfusion
2. Cold and wet: volume overloaded with poor cardiac output
3. Cold and dry: euvolemic with poor cardiac output
4. Warm and dry: appropriate cardiac output and are clinically euvolemic. Look for noncardiac etiologies of their hospital presentation.

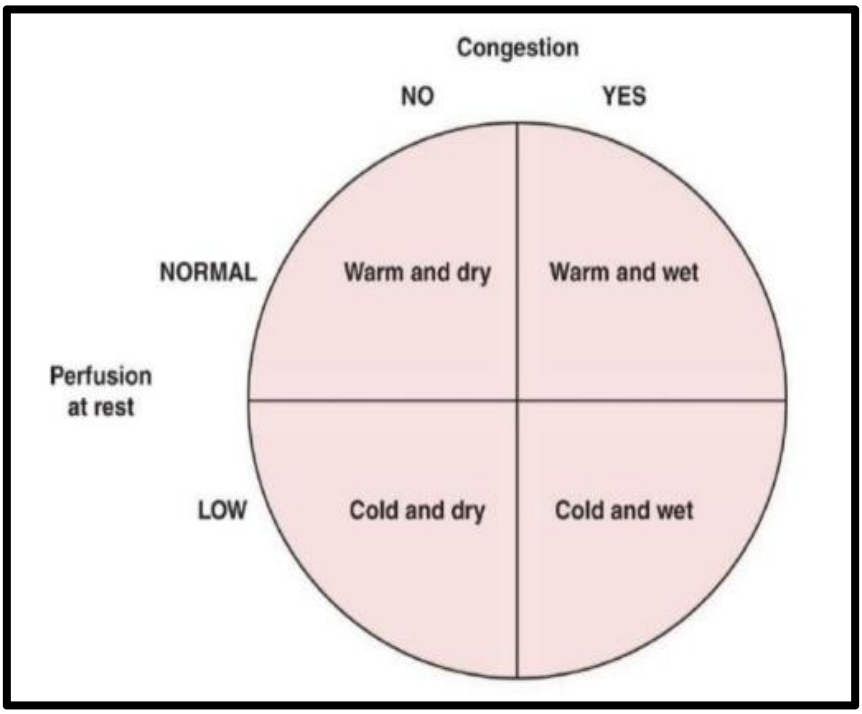

Figure 3: Types of clinical presentation of heart failure

Latest classification of heart failure by ejection fraction

- HFrEF (Heart failure with reduced Ejection fraction): symptomatic HF with LVEF ≤ 40%
- HFmrEF (Heart failure with Mid range Ejection fraction: symptomatic HF with LVEF 41–49%

- HFpEF (Heart failure with Preserved Ejection fraction: symptomatic HF with LVEF ≥ 50%.
- HFimpEF (HF with improved EF): symptomatic HF with a baseline LVEF ≤ 40%, a ≥ ten-point increase from baseline LVEF, and a second measurement of LVEF > 40%

Diagnosis of heart failure:

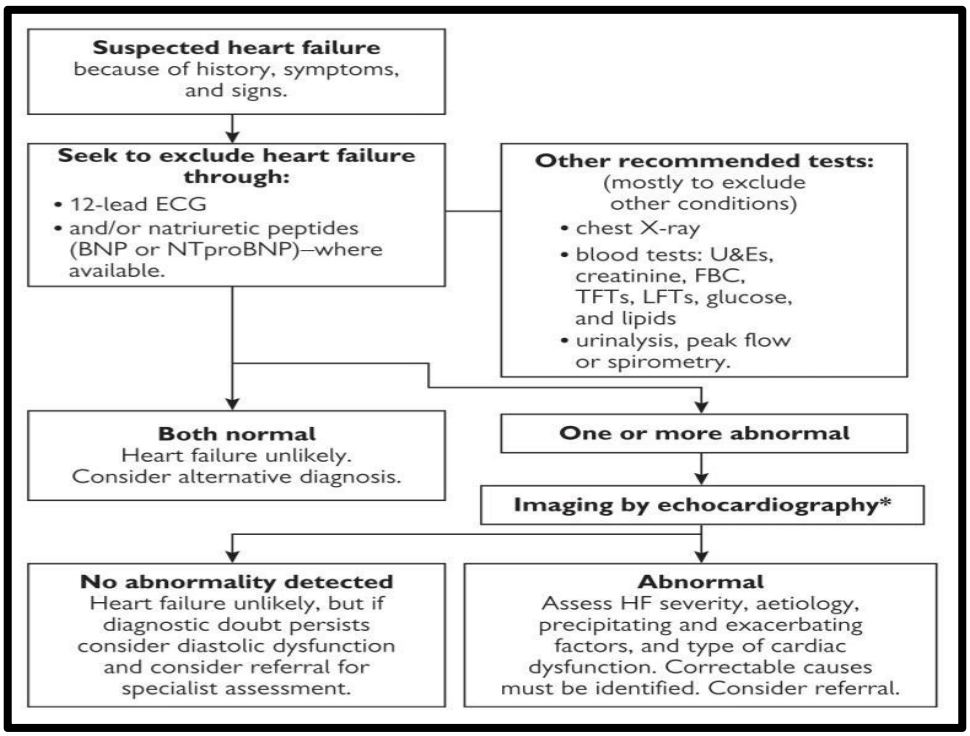

Figure 4: Diagnosis of heart failure:

Investigations:

ECG : although there are no specific changes in heart failure

Common findings include:

- Sinus tachycardia/bradycardia
- Arrhythmias : SUPRAVENTRICULAR/VENTRICULAR
- Voltage criteria for left ventricular hypertrophy (LVH) : INCREASED VOLTAGE

- Evidence of current or past ischaemia/infarction : ST-T CHANGES/Q WAVE
- Conduction system defects : PR INTERVAL, QRS
- Infiltration : REDUCED VOLTAGE

CHEST X-RAY (CXR):

Permits assessment of pulmonary congestion and may demonstrate other non-cardiac causes of dyspnoea

Common findings include:

- Cardiomegaly
- Pulmonary congestion with alveolar oedema, prominent upper lobe vessels, 'bat's wings' and Kerley B lines
- Pleural effusions

ECHOCARDIOGRAPHY (ECHO):

Key investigation in patients with HF and is mandatory for confirming the diagnosis.

Apart from documenting systolic and diastolic left ventricular function, the scan is useful in the identification of various causes or complications of heart failure

ECHOCARDIOGRAPHIC FINDINGS	EXAMPLES OF POSSIBLE AETIOLOGY
Identification of anatomical defects	Atrial septal defect (ASD), ventricular septal defect (VSD)
Valvular pathology	Aortic valve or mitral valve stenosis or insufficiency
Pericardial disease	Acute or chronic pericarditis, Constrictive pericarditis, Pericardial effusion

Identification of regional ventricular wall motion abnormalities	Ischaemic heart disease
Altered myocardial architecture	Hypertrophic cardiomyopathy, Infiltrative diseases (amyloidosis)
Estimation of pulmonary artery pressure	Pulmonary hypertension (cor pulmonale as a result of primary pulmonary hypertension or secondary to lung disease)
Identifying complications of reduced ventricular function	Intramural thrombus secondary to ventricular dilatation, reduced contraction, or aneurysm

NATRIURETIC PEPTIDES: evidence exists supporting the use of plasma concentrations of natriuretic peptides for diagnosing, staging, or even identifying patients at risk for clinical events.

BLOOD TESTS: CBC, U&Es, LFTs, TFTs, Glucose, Uric acid

INVESTIGATIONS TO CONSIDER FOR SELECTED PATIENTS WITH HEART FAILURE

- Blood tests: troponin I or T
- Iron studies
- Serum Folate, Vitamin B 12
- Autoimmune screen
- Immunoglobulins
- Protein electrophoresis
- Serum ACE
- Viral titres
- Urine sample: albumin/creatinine ratio, 24-hour urine collection for protein, catecholamines, Bence–Jones protein
- Arterial blood gases

- Pulmonary function tests
- Exercise testing
- Ambulatory ECG monitoring (QT dispersion, heart-rate variability)
- Stress imaging
- Radionuclide ventriculography
- Cardiac magnetic resonance
- Coronary angiography (computed tomography (CT) or conventional)
- Myocardial biopsy
- Right-heart catheterization

MANAGEMENT OUTLINE IN HEART FAILURE:

- Establish a firm diagnosis of HF
- Determine the etiology and the severity of HF
- Correct precipitating or exacerbating factors
- Multidisciplinary approach to treatment
- Education of the patient and relatives
- Monitor progress

OBJECTIVES OF TREATMENT

- Reduce mortality
- Reduce morbidity (to improve quality of life by relieving symptoms, increasing exercise capacity, reducing the need for hospitalization and providing end-of-life care)

1980s PRE-PHARMACOLOGIC ERA	1990s PHARMACOLOGIC ERA	2000s DEVICE ERA	2010s & 2020s RENAISSANCE ERA	2030s PRECISION ERA
1.Bed rest Fluid restriction 2.Diuretics 3.Digitalis 4.Vasodilators	Triple neurohormonal blockade: 1.ACEI/ARB 2.BBs 3.MRAs	1.Implantable cardiac defibrillators 2.Cardiac Resynchronization Therapy 3. Left Ventricular Assist Device	Quadruple foundational therapy 1.ARNI 2.BBs 3.MRAs 4.SGLTs inhibitors	Phenotype-specific approaches

Table 1: Evolution of Heart Failure Treatment

PREVENTION

1. Prevention of cardiovascular risk factors that may lead or contribute to the development of heart failure, i.e. hypertension, diabetes, obesity

2. Prevention of progression of myocardial damage, remodeling, and recurrence of symptoms once HF is established

LIFESTYLE/RISK MODIFICATION DIET

❖ DIETARY INSTRUCTION regarding sodium and fluid intake is critical in volume management in patients with HF.

❖ SODIUM INTAKE should generally be limited to 2 to 3 g per day, though more severe restriction to <2 g per day is necessary with moderate-to-severe HF.

- ❖ FLUID INTAKE must also be limited, with 1.5 to 2 L per day recommended for those with hyponatremia or edema despite aggressive diuretic usage.

- ❖ IF APPROPRIATE, EXERCISE TRAINING can be started, preferably in a monitored setting to facilitate understanding of exercise expectations and to increase duration and intensity to a general exercise goal of 30 minutes of moderate activity/exercise, 5 days per week with warm-up and cool-down exercises.

- ❖ OUTPATIENT EXERCISE-BASED CARDIAC REHABILITATION improves HF patient quality of life, functional capacity, and clinical outcomes. Unfortunately, cardiac rehabilitation is underused

GUIDELINE-DIRECTED MEDICAL THERAPY(GDMT) OPTIMIZATION, TITRATION, AND MONITORING

Four classes of GDMT HF medication are now recognized to offer substantial benefit to patients with HFrEF and should be prescribed unless a contraindication exists.

1. Angiotensin-converting enzyme inhibitors (ACEIs).Angiotensin-receptor blockers (ARBs),ARNIs
2. β-Blockers
3. Aldosterone antagonists
4. Sodium glucose cotransporter 2 inhibitors (SGLT2i)

Diuretics are used as needed to control volume status

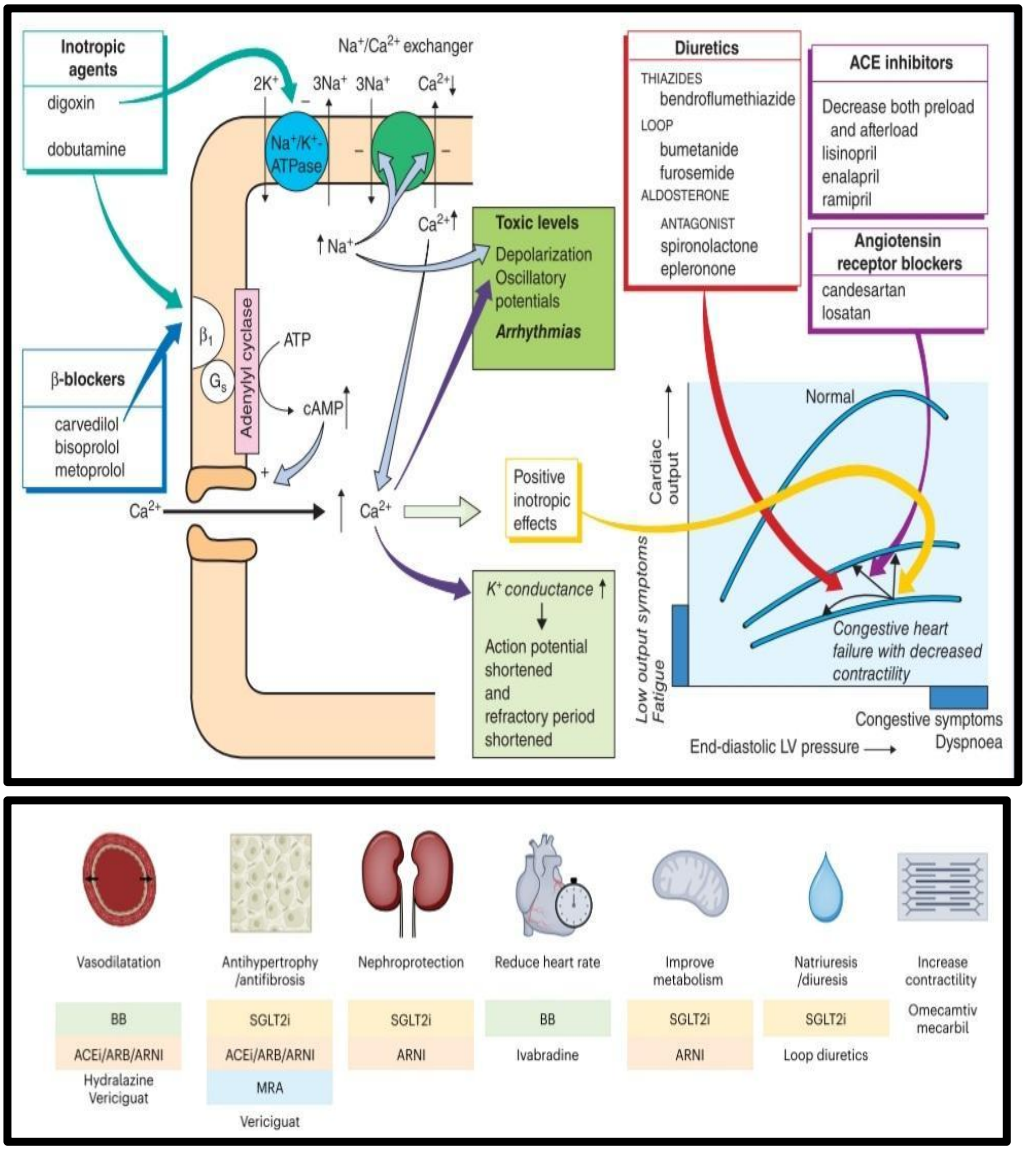

Figure 5: Guideline-Directed Medical Therapy for Heart Failure

ACE INHIBITORS AND ARBS:

- ACE inhibitors inhibit ACE, thus blocking the conversion of angiotensin I to angiotensin II.
- ACE is predominantly found in the pulmonary and to a lesser extent in the renal endothelium.

- By decreasing the production of angiotensin II
- ACE inhibitors attenuate sympathetic tone, decrease arterial vasoconstriction, and attenuate myocardial hypertrophy.
- Because angiotensin II stimulates aldosterone production, circulating levels of aldosterone are reduced.
- This results in decreased in sodium chloride absorption, decreased potassium excretion in the distal tubules, and decreased water retention.
- Through a decrease in antidiuretic hormone (ADH) production, ACE inhibitors also decrease water absorption in the collecting ducts.
- ARBs selectively block the binding of angiotensin II to the AT1 receptor, thereby blocking the effect of angiotensin II on end organs.
- The net effect of decreased angiotensin II on end organs of both classes of medications results in attenuation of sympathetic tone, decrease in arterial vasoconstriction, and attenuation of myocardial hypertrophy.
- Because angiotensin II stimulates aldosterone production, circulating levels of aldosterone are reduced.
- This results in a decrease in sodium chloride absorption, potassium excretion in the distal tubules, and water retention

ARNI: DOSING REGIMEN OF SACUBITRIL AND VALSARTAN:

- For patients being switched from an ACE inhibitor to sacubitril/valsartan, the product package insert recommended starting dose is 49/51 mg (sacubitril/valsartan) twice daily.
- A washout period of 36 hours between discontinuation of the ACE inhibitor and initiation of sacubitril/valsartan is recommended.
- It is recommended to double the dose of the drug combination after 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated.
- It is recommended that the starting dose be reduced to 24/26 mg twice daily for:
- Patients not currently taking an ACE inhibitor or ARB or previously taking a low dose of these agents.

- Patients with severe chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] ,30 mL/ min/1.73 m2).
- Patients with moderate hepatic information.
- Sacubitril/valsartan should not be used in patients with severe liver disease, pregnancy, concomitant use of ACE inhibitors (allow a washout period of 36 hours), and those with a history of angioedema related to previous ACE inhibitor or ARB therapy.
- Important side effects of the drug combination include hyperkalemia, renal impairment, hypotension, and angioedema.

BETA BLOCKERS:

- β-Blockers act by inhibiting the adverse effects of the sympathetic nervous system activation in patients with systolic HF.
- Long-term benefits of β-blockade include an increase in ejection fraction, a decrease in left ventricular volumes and in mitral regurgitation, and a reversion of the left ventricle to a more elliptical shape.
- Administration of β-blockers is associated with an early deterioration in cardiac function (consistent with the negative inotropic effects), followed by return to baseline values after 1 month and an increase in the ejection fraction after 3 months of treatment with further improvement for up to a year.

ALDOSTERONE ANTAGONISTS:

- ARBs block the mineralocorticoid receptor in the distal renal tubules, thereby decreasing sodium chloride absorption, potassium excretion, and water retention.
- In addition, they block the direct deleterious effects of aldosterone on the myocardium and may thus decrease myocardial fibrosis and its consequences.
- dosing of aldosterone antagonists in heart failure?
- Dosing of aldosterone antagonists in heart failure is as follows:
- Spironolactone: 12.5 to 25 mg daily, increased to up to 25 mg twice daily.
- Eplerenone: 25 mg daily, increased to 50 mg daily

COMMON ADVERSE EFFECTS OF ACE INHIBITORS, ARBS, AND ALDOSTERONE ANTAGONISTS INCLUDE THE FOLLOWING:

- ACE inhibitors: hypotension, worsening renal function, hyperkalemia, cough and angioedema (uncommon).
- ARBs: hypotension, worsening renal function, and hyperkalemia.
- Aldosterone antagonists: hyperkalemia, worsening renal dysfunction, hypotension, and hyponatremia

SGLT2 INHIBITORS

- SGLT2 inhibitors are now established as safe and effective drugs for the treatment of HF across the entire spectrum of LVEF
- The use of SGLT2 inhibitors was not associated with a clinically relevant risk of hypotension, volume depletion or renal adverse events.
- Dapagliflozin improved all key domains of health status irrespective of LVEF
- Empagliflozin also reduced the progression to macroalbuminuria and the risk of acute kidney disease.
- Empagliflozin led to a significant increase in albumin levels and was beneficial irrespective of baseline liver function.
- The benefits of SGLT2 inhibitors were not influenced by background therapy or by the baseline history of AF.

DIURETICS:

- Diuretics provide rapid symptomatic relief of congestive symptoms by promoting excretion of sodium and water and lowering plasma volume, thus reducing congestion in the pulmonary and systemic vascular beds and improving symptoms and functional capacity.
- Diuretics are tightly bound to plasma proteins and are actively secreted into the proximal tubular lumen.
- Diuretics should be used in all patients with evidence of volume overload; in an acutely decompensated state, a higher dose of oral diuretics or intravenous diuretics (starting with twice the home dose) or a combination of loop and thiazide diuretic is needed to achieve euvolemia

DIGOXIN:

- The beneficial effects of digoxin in HF are due to the attenuation of the activation of neurohormonal systems.
- Clinically, the beneficial effects in patients with systolic HF and sinus rhythm include improved HF symptoms, increased exercise time, modestly increased ejection fraction, enhanced cardiac output, and decreased HF hospitalizations.
- The benefits of digoxin are higher in patients with more symptomatic HF

IVABRADINE:

- Ivabradine is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with LVEF =35% who are in sinus rhythm with a resting HR 70 beats/min and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.
- Contraindications to ivabradine include acute decompensated heart failure, hypotension, sick sinus syndrome, third-degree heart block (unless a pacemaker is present), resting HR ,60 beats/min, severe liver disease, and pacemaker dependence (HR maintained exclusively by a pacemaker).
- The recommended starting dose of ivabradine is 5 mg twice daily. After 2 weeks of treatment, the dose can be adjusted based on HR.
- The maximum drug dose is 7.5 mg twice daily. In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, the initial recommended dose is 2.5 mg twice daily.

SUGGESTED DOSE ADJUSTMENTS ARE AS FOLLOWS:

- HR .60 beats/min: increase dose by 2.5 mg (given twice daily) up to a maximum dose of 7.5 mg twice daily.
- HR 50 to 60 beats/min: maintain current dose.
- HR ,50 beats/min or signs/symptoms of bradycardia: decrease dose by 2.5 mg (given twice daily); if current dose is 2.5 mg twice daily, discontinue therapy.

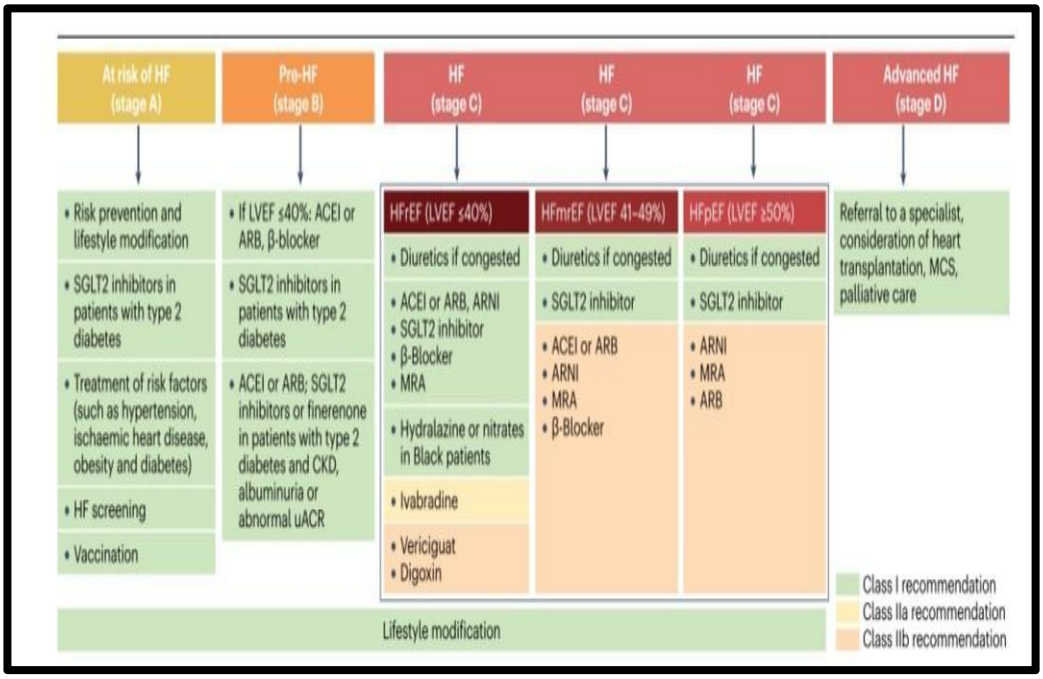

Figure 6: Treatment of Heart Failure

RECENT UPDATES IN HEART FAILURE:

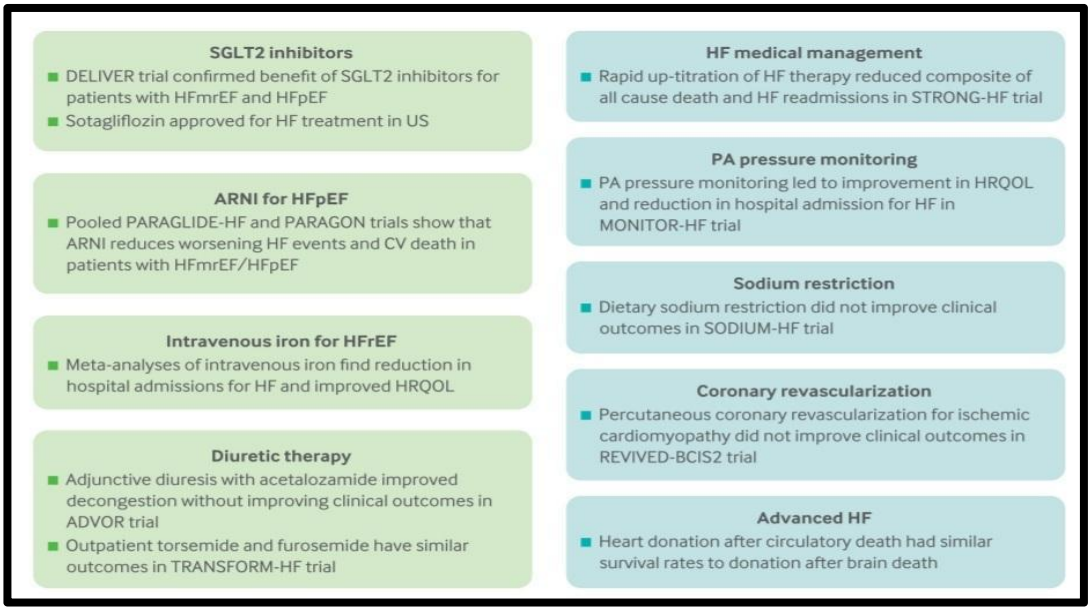

Figure 7: Recent updates in the management of Heart Failure

IRON THERAPY IN HEART FAILURE:

- Iron deficiency is present in 50-75% of individuals with HFpEF with a slightly higher frequency compared to HFmrEF or HFrEF patients
- Iron deficiency in HF was linked to lower peak oxygen consumption, increased dyspnea, reduced 6-minute walk distance oxygen uptake, and diminished health-related quality of life
- The potential benefits of intravenous iron supplementation in Heart failure.
- INDICATIONS: Ferritin <100microgram/L or 100 to 299 microgram/L with transferrin saturation <20%

VERICIGUAT:

- An oral guanylate cyclase stimulator, reduced the incidence of death or hospitalization from HF in patients with NYHA II, III, or IV HF symptoms
- Four pillar heart failure (HF) therapy is often poorly tolerated by older patients, limiting adherence to treatment.
- Vericiguat shows promise for older and frail patients with worsening HF with reduced ejection fraction (HFrEF), targeting a new pathway in HF pathophysiology and offering a well-tolerated, more manageable option.
- Future studies to clarify the role of vericiguat in different HFrEF subgroups, particularly in older patients, are required.

OMECAMTIV MECARBIL:

- Myosin activators
- The selective cardiac myosin activator omecamtiv mecarbil might be more effective in patients with more severe HFrEF.
- These data are also confirmed by a pre-specified analysis of the GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in HF) trial that showed a greater effect of omecamtiv mecarbil on the primary composite outcome of a first HF event or CV death in patients with a higher baseline NT-proBNP.

SEMAGLUTIDE

- The glucagon-like peptide 1 (GLP-1) agonist semaglutide administered once weekly at a dose of 2.4 mg for 1 year significantly decreased body weight
- The main inclusion criteria were BMI above 30 kg/m2, NYHA Class II–IV, elevated natriuretic peptide levels (with thresholds stratified according to the BMI at baseline), LVEF > 45% and evidence of echocardiographic abnormalities.

CARDIAC CONTRACTILITY MODULATION (CCM):

- CCM may improve functional capacity and reduce HFHs

DEVICE-BASED PERCUTANEOUS TREATMENTS:

- Interatrial shunt devices might represent a new therapeutic strategy to decompress and reduce LA pressure

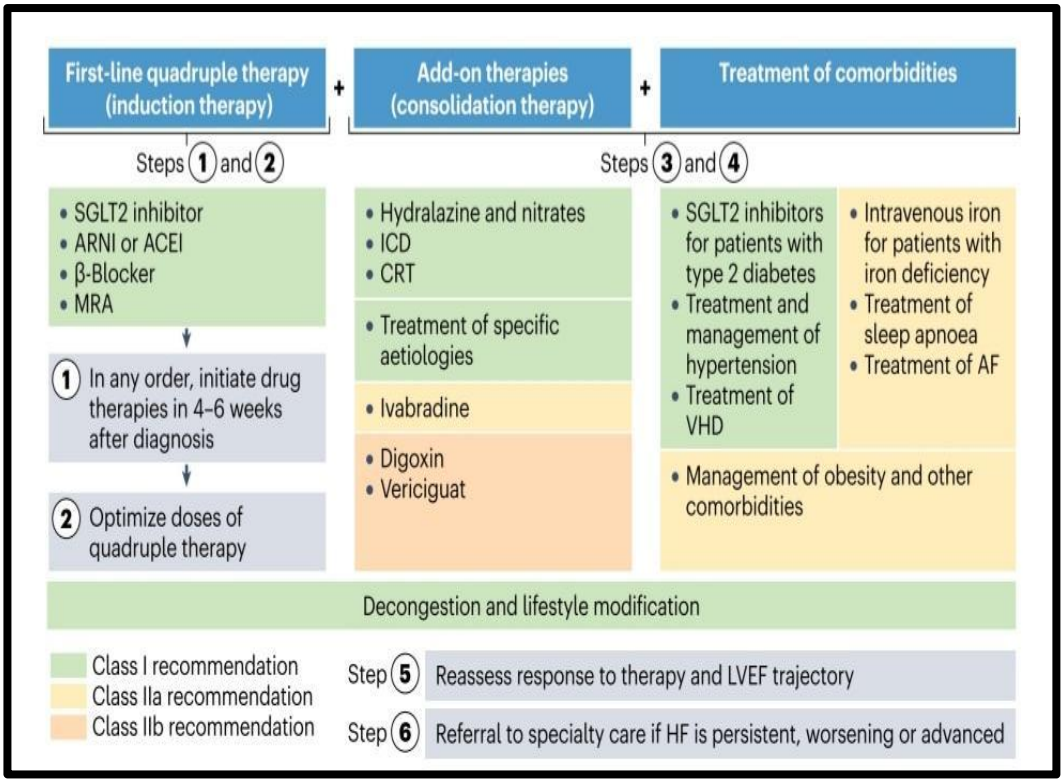

Figure 8: Treatment of heart failure with reduced ejection fraction - recent guidlines:

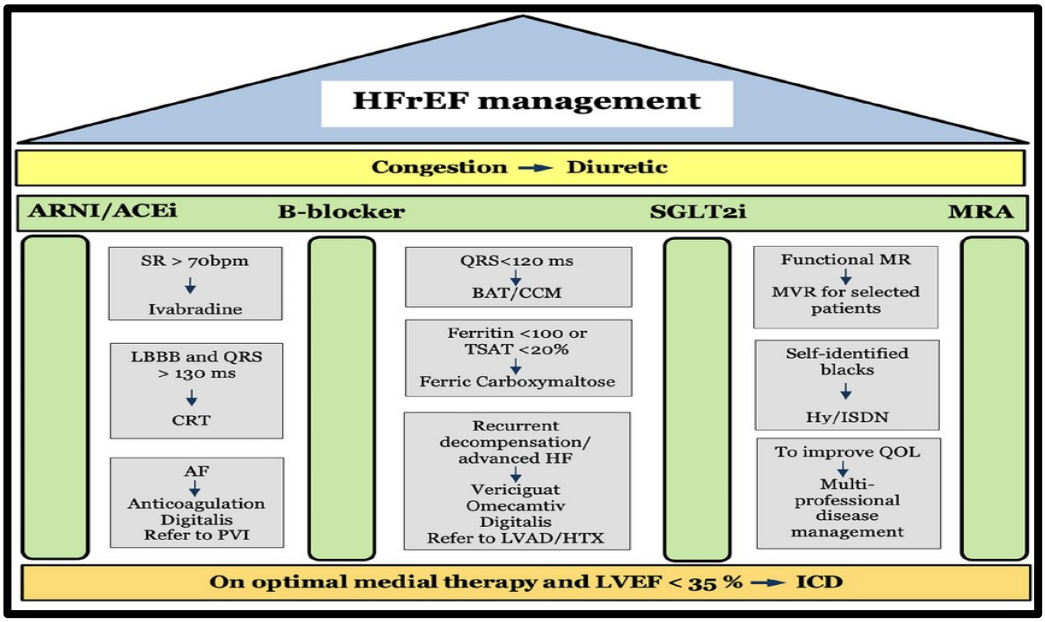

Figure 9: Treatment of heart failure with reduced ejection fraction

TREATMENT OF HEART FAILURE WITH PRESERVED AND MIDRANGE EJECTION FRACTION – RECENT GUIDELINES:

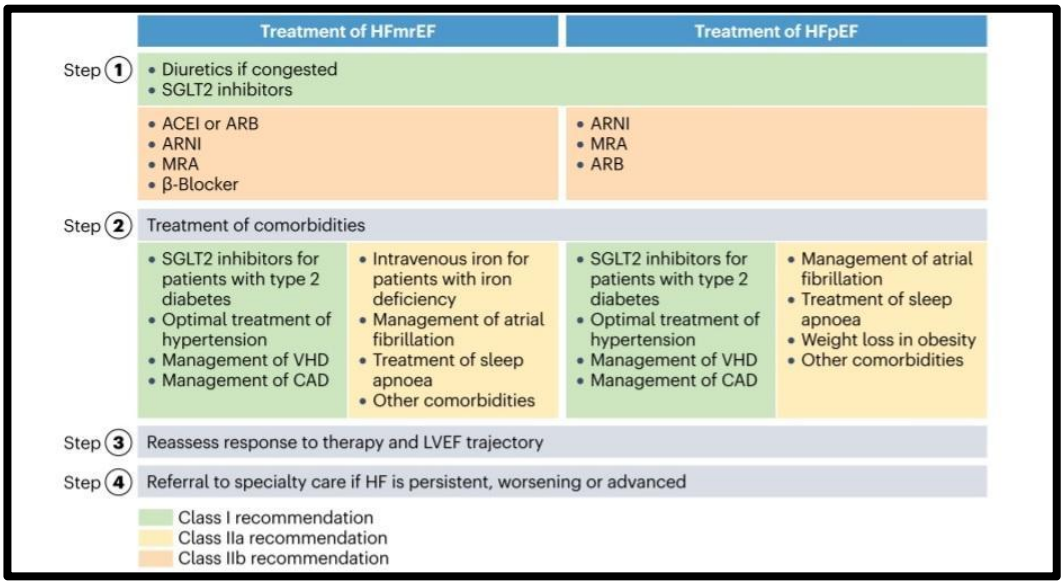

Figure 10: Treatment of heart failure with preserved & midrange ejection fraction

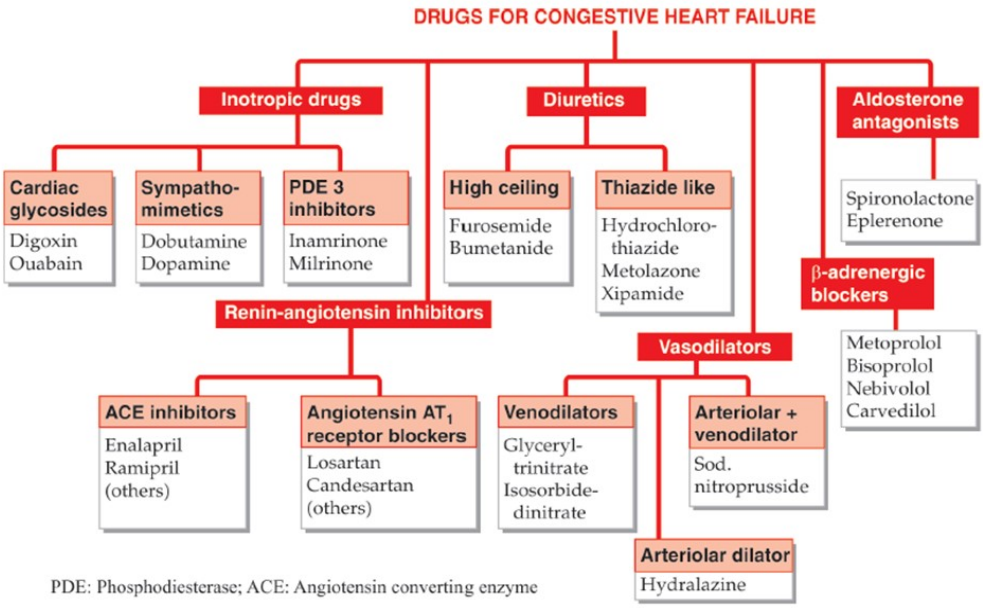

Figure 11: Drugs used in Congestive cardiac failure

NON-PHARMACOLOGICAL OPTIONS

DEVICE-BASED THERAPIES

ICD:

- It is used to prevent sudden death from life-threatening ventricular arrhythmias.
- ICD implantation should be considered for all HF patients with EF ≤35%.
- The VEST trial showed that in HF patients with recent MI, the wearable cardioverter-defibrillator did not reduce the rate of arrhythmic death.

CRT :

- It is designed to resynchronize ventricular contraction and improve cardiac function in patients with HF and dyssynchronous electromechanical activation of the LV.
- Biventricular pacing was associated with an improvement in symptoms and a reduction in hospitalizations compared to patients receiving medical therapy alone.

- The CARE-HF trial also demonstrated a marked decrease in mortality associated with biventricular pacing.
- CRT should be considered in patients with dyssynchrony (QRS > 120 ms) who have NYHA classes III to IV HF symptoms despite medical therapy. More recent indications have endorsed the use of CRT in patients with less severe HF (NYHA class I or II) but with more dyssynchrony (QRS > 150 ms).

MITRACLIP:

- Functional or secondary mitral regurgitation often develops in patients with significant LV dysfunction and remodeling and is associated with poor outcomes.
- Percutaneous transcatheter mitral valve repair using the MitraClip device was shown to decrease the primary end point of HF hospitalizations in patients with moderate-to-severe secondary mitral regurgitation in the COAPT trial.
- There was also an improvement in all-cause mortality.
- Patients should be treated with maximally tolerated medical therapy before considering MitraClip.

ADVANCED HEART FAILURE IS RECOGNIZED WHEN HEART FAILURE PATIENTS FOLLOW THE BELOW CLINICAL PATTERNS:

- More than two hospitalizations or emergency room visits in the past 1 year for heart failure symptoms.
- Progressive decline in renal function.
- Progressive weight loss without other identifiable cause, known as cardiac cachexia.
- Intolerance to beta-blockers due to worsening heart failure or hypotension.
- Frequent systolic blood pressure less than 90 mm Hg.
- Frequent dyspnea during dressing or bathing requiring rest.
- Inability to walk one block on level ground due to dyspnea or fatigue.
- Progressive decline in serum sodium, usually less than 133 mEq/L.

- Frequent ICD shocks.
- Need to escalate diuretic therapy to maintain volume status, usually reaching an equivalent daily dose of .160 mg furosemide/day and/or need for daily supplemental metolazone therapy.

MECHANICAL CIRCULATORY SUPPORT

- Mechanical circulatory support (MCS) can be considered in select patients with acute or chronic end-organ hypoperfusion from cardiac dysfunction.
- Ventricular support devices are designed for short- or long-term ventricular support.
- The HeartMate III is the only long-term left ventricular assist device (LVAD) currently being implanted (MOMENTUM).
- Devices previously used in the US include the HeartMate II, HVAD, or pulsatile devices (Thoratec VAD and HeartMate IP, VE, and XVE and WorldHeart Novacor).
- Compared to HeartMate II LVAD, the HeartMate III LVAD is a fully magnetically levitated centrifugal flow pump with superior survival-free time from stroke or reoperation for pump dysfunction.
- LVADs are implanted as a bridge to transplant or are destination therapy for those who are not the transplant candidates.
- Two randomized trials of destination therapy LVADs in end-stage HF patients (REMATCH and INTrEPID studies) compared LVAD to standard medical therapy in patients with advanced HF.

Many patients in cardiogenic shock may require temporary mechanical circulatory support (MCS). Short-term devices include the PERCUTANEOUSLY INSERTED PNEUMATIC INTRA-AORTIC BALLOON PUMP (IABP), the AXIAL FLOW IMPELLA, IMPELLA RP (for right heart support), PROTEKDUO (for right heart support), VA ECMO (biventricular support), or TANDEMHEART. These devices can provide cardiac support for up to 1 to 2 months. Each device requires anticoagulation, is susceptible to hemolysis, and requires prolonged ICU care.

WHATS NEW IN HEART FAILURE:

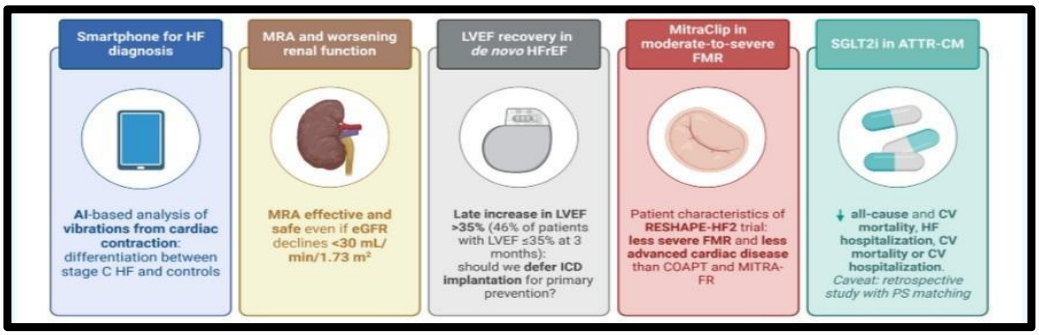

Figure 12: Newer options in management of Heart failure

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Cardiovascular Drug Safety: Monitoring, Reporting, and Managing Adverse Effects

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1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality globally, necessitating the widespread use of cardiovascular drugs such as antihypertensives, antiplatelets, and statins. While these medications are crucial for managing CVDs, they are also associated with a range of adverse effects that can compromise patient safety. Adverse drug reactions (ADRs) in cardiovascular therapy can lead to hospitalization, increased healthcare costs, and, in severe cases, death. (Alomar, M. J,2016)

The importance of monitoring, reporting, and managing these ADRs cannot be overstated. Pharmacovigilance, the science and activities related to the detection, assessment, understanding, and prevention of adverse effects, plays a critical role in ensuring drug safety. This chapter provides a comprehensive overview of the mechanisms of ADRs in cardiovascular therapy, the strategies for effective monitoring and reporting, and the management practices to minimize the risk to patients. (Bavishi, C,2016)

2. Mechanisms of Adverse Drug Reactions in Cardiovascular Therapy

Adverse drug reactions in cardiovascular therapy can arise from various mechanisms, including pharmacokinetic and pharmacodynamic interactions, patient-specific factors, and drug formulation issues.

2.1 Pharmacokinetic Interactions

Absorption, Distribution, Metabolism, and Excretion (ADME): Cardiovascular drugs may interact with other medications, leading to altered pharmacokinetics. For example, the co-administration of statins with certain antibiotics can inhibit cytochrome P450 enzymes, leading to increased statin levels and a higher risk of myopathy.

Drug-Drug Interactions: Common in polypharmacy, particularly in elderly patients with multiple comorbidities, drug-drug interactions can significantly alter the efficacy and safety profile of cardiovascular drugs. For example, the concurrent use of warfarin and antiplatelet agents increases the risk of bleeding.

2.2 Pharmacodynamic Interactions

Synergistic and Antagonistic Effects: When cardiovascular drugs are used together, their effects can be synergistic (enhanced therapeutic effect) or antagonistic (reduced efficacy). For instance, combining ACE inhibitors with potassium-sparing diuretics can lead to hyperkalaemia.

Mechanism-Based Adverse Effects: Some ADRs are related to the primary mechanism of action of the drug. For example, beta-blockers can cause bradycardia due to their mechanism of slowing heart rate.

2.3 Patient-Specific Factors

Genetic Variability: Genetic polymorphisms can affect drug metabolism and response, leading to variability in ADRs. For example, patients with certain CYP2C9 variants may have an increased risk of bleeding with warfarin.

Age, Gender, and Comorbidities: These factors can influence the pharmacokinetics and pharmacodynamics of cardiovascular drugs, leading to a higher risk of ADRs in certain populations, such as the elderly or those with renal impairment. (Eguale, T,2015)

2.4 Drug Formulation and Delivery Issues

Bioavailability: Variations in drug formulation can affect the bioavailability of cardiovascular medications, potentially leading to subtherapeutic or toxic effects.

Drug Delivery Systems: The method of drug delivery (e.g., oral, transdermal, intravenous) can impact the incidence of ADRs. For example, transdermal nitro-glycerine patches may cause less gastrointestinal upset compared to oral formulations.

3. Monitoring Adverse Drug Reactions in Cardiovascular Therapy

Effective monitoring of ADRs is critical for ensuring patient safety in cardiovascular therapy. (Chowdhury, R,2013)This section discusses the tools and strategies used in ADR monitoring.

3.1 Role of Pharmacovigilance Systems

National and International Pharmacovigilance Programs: Systems such as the FDA's MedWatch and the WHO's Uppsala Monitoring Centre collect and analyze data on ADRs, providing essential information for drug safety monitoring. (Hauben, M,2009)

Post-Marketing Surveillance: After a drug is approved and marketed, post-marketing surveillance is crucial for detecting ADRs that may not have been evident in clinical trials. This involves the continuous monitoring of ADRs through spontaneous reporting, registries, and observational studies.(Dal Pan, G. J,2015)

3.2 Electronic Health Records (EHRs)

Real-Time ADR Monitoring: EHRs enable the real-time monitoring of patient data, allowing for the early detection of ADRs. Automated alerts and decision support systems within EHRs can notify healthcare providers of potential drug interactions or contraindications.

Data Mining and Signal Detection: Advanced data mining techniques, such as disproportionality analysis, are used to detect signals of potential ADRs within large EHR databases.

3.3 Patient-Reported Outcomes

Patient Engagement: Involving patients in ADR reporting through patient portals and mobile health apps can improve the detection of ADRs. Patients are often the first to notice side effects, and their reports can provide valuable insights. (Davies, E. C,2009)

Quality of Life Assessments: Tools such as the SF-36 Health Survey can be used to assess the impact of ADRs on patients' quality of life, helping to guide treatment adjustments.

3.4 Role of Healthcare Professionals

Pharmacists: Pharmacists play a crucial role in identifying and reporting ADRs. Their expertise in drug interactions and patient counselling is vital for preventing and managing ADRs in cardiovascular therapy.(Khan, M. U,2015)

Nurses and Physicians: Nurses and physicians are often the first to encounter ADRs in clinical practice. Their role in monitoring, documenting, and reporting ADRs is essential for effective pharmacovigilance.

4. Reporting Adverse Drug Reactions

Reporting ADRs is a fundamental component of pharmacovigilance. This section outlines the processes and challenges associated with ADR reporting.

4.1 Spontaneous Reporting Systems

Strengths and Limitations: Spontaneous reporting systems, such as MedWatch, are invaluable for detecting new and rare ADRs. However, they are subject to underreporting and reporting bias, which can limit their effectiveness. (Evans, S. J.M,2001)

Encouraging Reporting: Strategies to encourage healthcare professionals and patients to report ADRs include education, simplification of reporting procedures, and integrating reporting systems into EHRs. (Kalaba, M,2017)

4.2 Structured Reporting Systems

Standardized Reporting Forms: Structured forms, such as the CIOMS form used by the WHO, provide a consistent framework for reporting ADRs. This standardization facilitates data collection and analysis.

Regulatory Requirements: Regulatory agencies require pharmaceutical companies to report ADRs as part of their post-marketing surveillance obligations. Failure to comply can result in penalties and impact drug approval status. (Thayer, S. G,2016)

4.3 Big Data and Artificial Intelligence in ADR Reporting

Data Integration: AI tools can integrate data from multiple sources, including EHRs, social media, and clinical trial databases, to identify ADRs. This can enhance the sensitivity and specificity of ADR detection. (Xu, Q,2018)

Natural Language Processing (NLP): NLP algorithms can analyze unstructured data, such as clinical notes and patient narratives, to identify potential ADRs that might not be captured in structured data. (Weiss, J,2016)

4.4 Global Collaboration in ADR Reporting

International Databases: Collaboration between national pharmacovigilance centres and international organizations, such as the WHO, enables the sharing of ADR data across borders. This global collaboration enhances the detection of ADRs and the development of safety guidelines.

5. Managing Adverse Drug Reactions in Cardiovascular Therapy

Once ADRs are detected, effective management strategies are essential to mitigate their impact on patients.

5.1 Risk Mitigation Strategies

Dose Adjustment and Drug Substitution: Adjusting the dose or switching to an alternative medication can help manage ADRs. For example, in patients who experience bradycardia with beta-blockers, a dose reduction or switching to a different class of antihypertensives may be necessary. (Man, K. K,2019)

Monitoring and Follow-Up: Regular monitoring of patients on cardiovascular drugs, including laboratory tests and clinical assessments, is essential for early detection and management of ADRs. (Rodenburg, E. M,2010)

5.2 Patient Education and Counselling

Informed Consent: Educating patients about the potential risks and benefits of cardiovascular drugs, including possible ADRs, is crucial for informed consent and shared decision-making.

Self-Monitoring: Encouraging patients to monitor their symptoms and report any unusual effects can lead to earlier detection and management of ADRs. (Gagne, J. J,2011)

5.3 Interdisciplinary Collaboration

Team-Based Care: Collaboration among healthcare professionals, including cardiologists, pharmacists, and primary care providers, ensures comprehensive management of ADRs. This team-based approach can improve patient outcomes and reduce the incidence of serious ADRs. (Murphy, S. P ,2018)

Consultation with Specialists: In cases of severe or complex ADRs, consultation with specialists, such as clinical pharmacologists or toxicologists, may be necessary to guide management.

5.4 Use of Technology in ADR Management

Clinical Decision Support Systems (CDSS): CDSS can provide healthcare professionals with evidence-based guidelines for managing ADRs. These systems can also alert clinicians to potential ADRs based on patient data.

Mobile Health Applications: Mobile apps can assist patients in tracking their medications and reporting ADRs in real-time. These apps can also provide education on managing common ADRs associated with cardiovascular drugs.

6. Emerging Trends and Future Directions

As the field of drug safety continues to evolve, several emerging trends are shaping the future of ADR monitoring and management in cardiovascular therapy. (Patel, H,2015)

6.1 Pharmacogenomics

Personalized Medicine: Pharmacogenomic testing can identify genetic variations that influence drug metabolism and response, allowing for personalized drug therapy that minimizes the risk of ADRs. For example, genetic testing for CYP2C19 variants can guide the use of antiplatelet agents like clopidogrel. (Saito, Y,2016)

6.2 Artificial Intelligence and Big Data

Predictive Analytics: AI and big data analytics are being used to develop predictive models that identify patients at high risk for ADRs before they occur. These models can inform proactive interventions to prevent ADRs in vulnerable populations.(Weiss, J,2016)

Real-World Evidence: The use of real-world data from EHRs, registries, and patient-reported outcomes is becoming increasingly important in ADR monitoring and management. This data provides insights into drug safety in diverse patient populations and real-world settings. (Mascolo, A,2017)

6.3 Regulatory Innovations

Adaptive Licensing: Regulatory agencies are exploring adaptive licensing models that allow for the continuous assessment of drug safety and efficacy throughout a product's lifecycle. This approach enables faster access to innovative therapies while ensuring ongoing monitoring of ADRs.

Patient-Cantered Approaches: There is a growing emphasis on involving patients in drug safety decision-making. Patient-reported outcomes and preferences are increasingly being considered in the regulatory evaluation of drug safety.

7. Conclusion

Cardiovascular drug safety is a critical aspect of patient care, requiring vigilant monitoring, reporting, and management of ADRs. Healthcare professionals play a pivotal role in ensuring drug safety by staying informed about the mechanisms of ADRs, utilizing pharmacovigilance tools, and engaging patients in their care. Emerging technologies, such as AI and

pharmacogenomics, hold promise for enhancing drug safety and personalizing cardiovascular therapy. As the field continues to advance, a collaborative and multidisciplinary approach will be essential for minimizing the risks associated with cardiovascular drugs and improving patient outcomes.

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Advancing Nuclear Cardiology Diagnostics through Innovative Imaging Solutions

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Introduction

Cardiovascular nuclear medicine has evolved significantly over nearly a century, becoming a cornerstone of clinical practice, with rapid advancements accelerating its development more than ever before. While traditional techniques like flow measurements have improved precision in diagnosing cardiovascular diseases (CVD), the introduction of newer nuclear cardiology diagnostics enhancesnon-invasive imaging by targeting subtle molecular pathologies. These innovations allow for a deeper understanding of integrative biology, enabling early disease detection, targeted treatments, and precise therapy monitoring. This review highlights these advancements, focusing on the transformative role of innovative imaging technologies and artificial intelligence (AI) in advancing nuclear cardiology diagnostics.

Nuclear cardiology

Nuclear cardiology is a subspecialty of cardiology that utilizes radioactive substances and advanced imaging techniques to evaluate, diagnose, and manage a variety of heart conditions. This imaging modality specifically assesses blood flow to the heart muscle during both rest and stress conditions, identifying areas at risk of ischemia or damage. A pivotal component of nuclear cardiology is cardiac radionuclide imaging, which offers a non-invasive approach to assess myocardial perfusion and function, enabling comprehensive evaluations without the need for surgical interventions.Figure 1 illustrates the many facets of nuclear cardiology, particularly in the context of heart failure. Panel **A** showcases perfusion imaging for the detection of ischemia, comparing the efficacy of SPECT and PET methods. Panel **B** focuses on imaging myocardial viability, highlighting the perfusion/metabolism mismatch that indicates hibernating myocardium. Panel **C** demonstrates

imaging of sympathetic innervation, presenting planar and SPECT images from a patient with preserved (left) and impaired (right) innervation. Finally, panel **D** emphasizes the application of nuclear cardiology in imaging myocardial inflammation, especially in cases of sarcoidosis. Collectively, these applications exemplify the versatility and significance of nuclear cardiology in enhancing patient care within modern cardiovascular medicine.

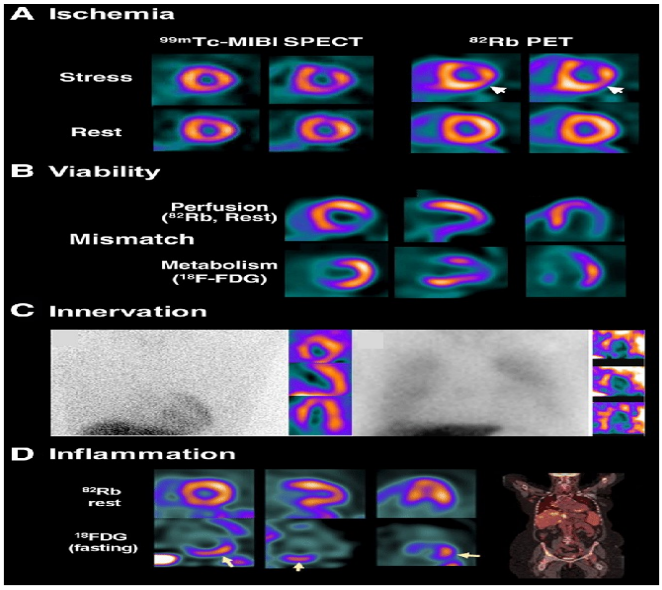

Figure 1 : The many faces of nuclear cardiology in heart failure. (A) Perfusion imaging for detection of ischemia. Comparison of SPECT and PET (B) Imaging of myocardial viability. Perfusion/metabolism mismatch indicating hibernating myocardium (C) Imaging of sympathetic innervation. Shown are planar and SPECT images in a patient with preserved (left) and impaired (right) innervation. (D) Imaging of myocardial inflammation in sarcoidosis

Nuclear Imaging Techniquesin Cardiology

1. Myocardial Perfusion Imaging (MPI)

Myocardial perfusion imaging is currently the most widely used technique in nuclear cardiology. It involves assessing blood flow to the heart muscle during rest and stress conditions, utilizing radiotracers to visualize myocardial perfusion. The technique helps identify areas with reduced blood supply, indicating ischemia or previous myocardial infarctions.

2. Positron Emission Tomography (PET)

PET is a sophisticated imaging modality that provides detailed information about cardiac blood flow and metabolic activity. By using radiotracers such as Fluorine-18 fluorodeoxyglucose (FDG), PET can discern between viable and non-viable myocardium, enabling targeted treatment planning for revascularization procedures.

3. Single Photon Emission Computed Tomography (SPECT)

SPECT is commonly employed for evaluating myocardial perfusion and function. This technique utilizes gamma cameras to detect gamma rays emitted from radiotracers injected during the imaging process, allowing assessment of cardiac physiology non-invasively. SPECT is often used in conjunction with pharmacological or exercise challenges to stimulate the heart and evaluate blood flow.

4. Radionuclide Ventriculography

This technique assesses the pumping function of the heart using a radiotracer to visualize the four heart chambers. It accurately measures the ejection fraction and helps in understanding the heart's performance after an event such as a heart attack or during treatment for heart diseases.

5. Cardiac Scintigraphy

Cardiac scintigraphy involves injecting radiolabelled tracers to visualize various cardiac conditions. Techniques include assessing for myocardial infarction, infection, and evaluating cardiac masses. This method is notable for its ability to complement other imaging modalities by providing functional insights that are often missed by anatomical imaging alone.

6. Dual-Tracer Techniques

In specific conditions such as cardiac sarcoidosis, dual-tracer PET techniques are utilized, involving the administration of two different radiotracers to detect inflammation and assess perfusion simultaneously. This method enhances the diagnostic accuracy for conditions where both perfusion and metabolic activity are crucial.

7. Quantitative Myocardial Perfusion Imaging

Innovations in quantitative myocardial perfusion imaging (MPI) have emerged, focusing on the precise measurement of blood flow into the heart muscles. Techniques using advanced algorithms and novel approaches allow for accurate assessments of myocardial blood flow, which provide critical

information for risk stratification and treatment planning. Quantitative methods enable physicians to evaluate coronary flow reserve and better identify patients at risk for cardiac events.

Innovation in nuclear cardiology

1. Hybrid Imaging Systems

Recent innovations in imaging techniques for nuclear cardiology prominently feature hybrid imaging systems, such as SPECT-CT and PET-CT. These sophisticated systems integrate anatomical and functional imaging, significantly enhancing diagnostic accuracy by providing detailed insights into both myocardial perfusion and cardiac anatomy. This integration allows for improved detection of coronary artery disease, as it combines the strengths of traditional nuclear imaging with the anatomical clarity provided by computed tomography (CT). The inclusion of CT in these systems is particularly beneficial for attenuation correction, helping to mitigate artifacts and other discrepancies that can arise in imaging results. Figure 2 illustrates how SPECT/CT fusion imaging offers substantial advantages over SPECT alone, particularly in the imaging of cardiac amyloidosis, as it effectively reduces false positives. Overall, these hybrid modalities represent a significant advancement in the field, enabling more accurate diagnoses and better patient management in nuclear cardiology.

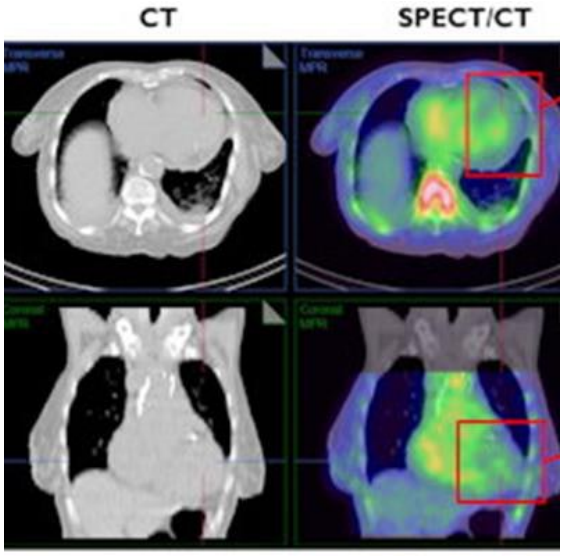

Figure 2: SPECT/CT fusion imaging(Hybrid Imaging) offers significant advantages over SPECT alone for imaging cardiac amyloidosis by reducing false positives

2. Advanced Detector Technology

The introduction of solid-state detectors, specifically those made with cadmium-zinc-telluride (CZT), has revolutionized imaging quality in nuclear cardiology. These advanced detectors provide superior energy resolution and sensitivity compared to traditional scintillation detectors, enabling clearer imaging while concurrently reducing the amount of radiotracer required for procedures. This reduction enhances diagnostic efficacy and allows imaging to be conducted with lower radiation doses, significantly improving patient safety. Figure 3 illustrates two different CZT cameras: **A**: Discovery NM 530C and **B**: D-SPECT, both of which utilize multiple CZT detectors. These cameras focus specifically on cardiac imaging and acquire data simultaneously, offering high spatial and energy resolution that further enhances the clarity and reliability of nuclear cardiology assessments.

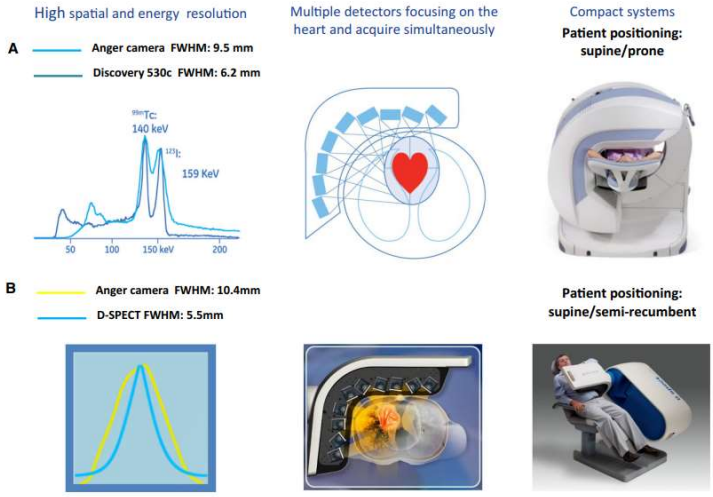

Figure 3 : Two different CZT cameras: A discovery NM 530c, and B D-SPECT that use multiple CZT detectors focusing on the heart and acquire data simultaneously, providing high spatial and energy resolution

3. Novel Radiotracers

Recent advancements have also led to the development of innovative radiotracers that enhance the diagnostic capabilities of nuclear cardiology. For instance, PET tracers targeting specific cardiac pathologies, such as 18F-fluorodeoxyglucose (FDG) for inflammation assessment or 18F-sodium fluoride (NaF) for calcification visualization, are proving invaluable in the diagnosis and management of conditions like cardiac sarcoidosis and atherosclerosis. These new agents allow clinicians to gather more specific

information about myocardial viability and pathology.In addition to these established tracers, emerging PET agents like 13N-ammonia and 82Rubidium are gaining traction due to their unique properties. For example, 13N-ammonia specifically measures myocardial blood flow and is characterized by relatively rapid clearance, which contributes to clearer imaging results. Conversely, while 82Rubidium PET provides good qualitative assessments of perfusion defects, it suffers from limitations such as lower contrast and resolution.Moreover, visual representation of the performance of these radiotracers can significantly aid in their evaluation. Figure 4 illustrates qualitative images of various PET tracers, highlighting their distinct characteristics: 82Rubidium PET shows relatively low lesion contrast with low spatial resolution, while 13N-NH3 PET demonstrates clear images owing to its rapid clearance from the blood pool.

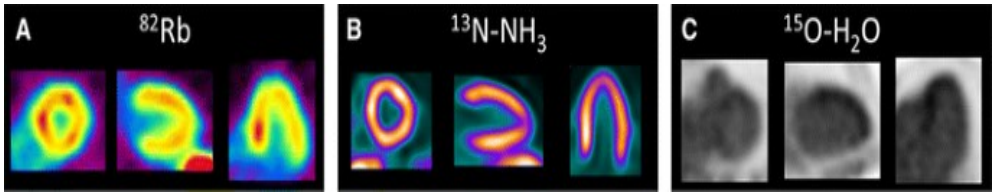

Figure 4: Qualitative images of PET tracers ^{82}Rb PET has relatively low lesion contrast with low spatial resolution. ^{13}N-NH$_3$ PET shows clear images due to rapid clearance from the blood pool. With ^{15}O-H$_2$O PET, it is difficult to distinguish between myocardium and blood pool.

4. Artificial Intelligence in Imaging

The application of artificial intelligence (AI) in nuclear cardiology is gaining ground, particularly for image analysis and processing. AI algorithms assist in automating tasks such as motion correction and image registration, resulting in improved diagnostic accuracy and workflow efficiency are discussed in Figure 5. These advanced AI tools can analyze complex datasets and help in the identification of previously unrecognized patterns in imaging, leading to more timely and precise diagnoses.

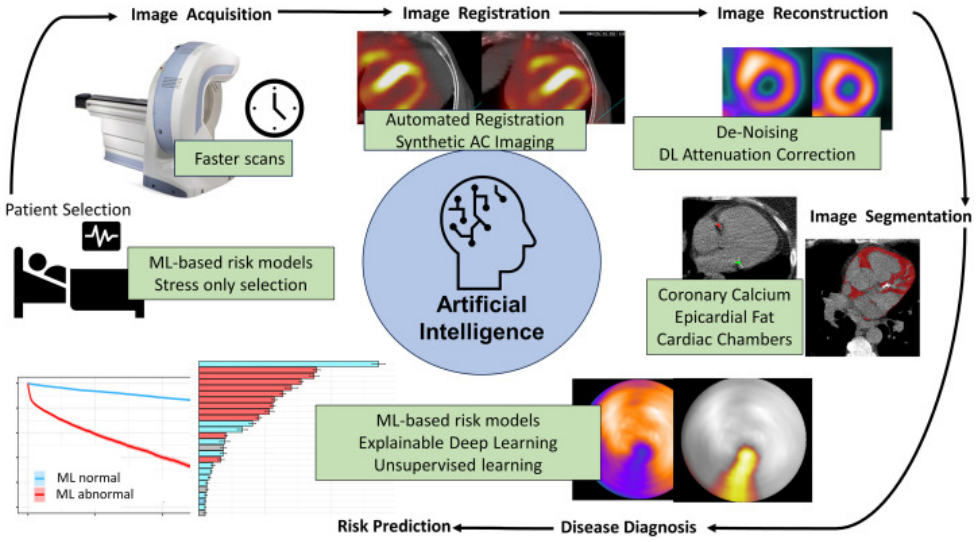

Figure 5 : Role of Artificial Intelligence in Nuclear Cardiology (Improving Image Acquisition Times and Image Quality,Image Registration,AI-Derived Attenuation Correction,Disease diagnosis and Risk prediction).

Challenges in innovation in nuclear cardiology

1. Integration with Advanced Imaging Modalities

One of the primary challenges in nuclear cardiology is the integration of new imaging technologies, such as advanced CT and MR studies. These modalities have gained prominence, presenting a serious challenge to nuclear cardiology by making it essential to demonstrate clear advantages of nuclear methods over these competitors.

2. Patient Radiation Exposure

Despite advancements aimed at reducing radiation exposure, nuclear cardiology still faces scrutiny regarding the doses that patients receive during imaging procedures. As safety is a major concern, the field must continuously adapt and implement techniques that limit radiation exposure while maintaining or improving imaging quality.

3. Adoption of New Technologies

The integration of advanced imaging systems and techniques, such as solid-state imaging devices and AI, requires significant investment in both time and resources. Many labs struggle to keep pace with technological advancements, leading to lagging adoption rates of potentially beneficial innovations.

4. Standardization of Protocols

Ensuring consistency in imaging protocols across different laboratories remains a challenge. Variability in the application of newer technologies, such as the use of cadmium-zinc-telluride (CZT) SPECT cameras or advanced post-processing techniques, can lead to disparities in patient care and outcomes. The nuclear cardiology community must develop standardized guidelines to optimize equipment usage and image quality.

Conclusion

The advancement of nuclear cardiology diagnostics is significantly driven by innovations in imaging technologies and the integration of artificial intelligence (AI), which enhances accuracy, enables targeted treatments, facilitates early disease detection, and allows for precise therapy monitoring. Despite several challenges, future developments in this field have the potential to improve patient outcomes and solidify its role in the future of cardiovascular health management.

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Advancing Perioperative medication strategies in Xenotransplantation: A contemporary approach

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Introduction

The US Food and Drug Administration (FDA) specifies xenotransplantation as "any the process that comprises the transplantation, implantation, or diffusion into a human recipient of either (a) currently reside cells, tissues, or organs from a source made up of nonhuman animals, or (b) human organism fluids, cells, tissues, or organs that have had ex vivo contact with live inanimate animal cells, tissues, or organs."

The fabrication of cross-species experimental models retains promise for the advancement of xenotransplantation (XTx) entering healthcare environments as an effective solution for the current worldwide organ shortage.

The University of Maryland (UMD) recently unveiled the early success of a pig-to-human HT, focusing on the great hope of xenotransplantation in the modern era.

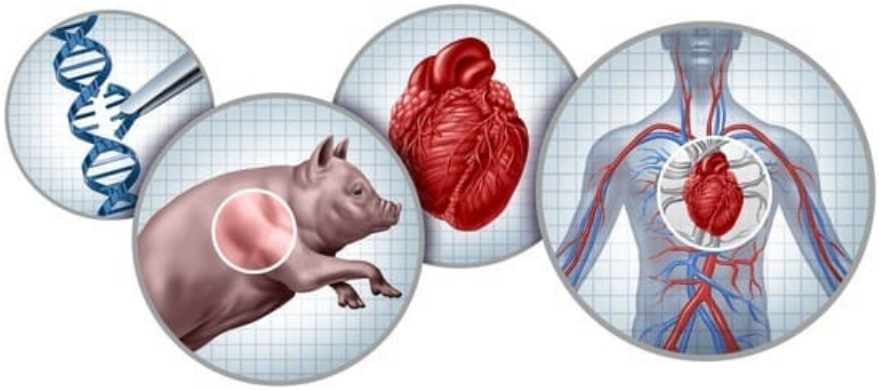
Xenotransplantation products utilize nonhuman animals that can be transgenic or nontransgenic, in addition to composite commodities that come together xenotransplantation products with prescription drugs or health care equipment. outlined are some examples:

Fetal brain neurons of porcines Porcine islet cells encapsulated Animals such as cattle adrenal chromaffin cells encapsulated Bone marrow of the baboon Using swine liver or hepatocytes, external liver-assist devices A variety of challenges to the success of xenotransplantation have been encountered during the past few years. This include in, but are not limited to,

Overcoming severe rejection minimizing rapid cardiovascular issues induced through acute rejection or severe technical generates Guiding the body's immune system to modify itself acquiring tolerance to

immunity Controlling amplification of viruses from xenografts towards individuals addressing the ethical issues related to xenograft animal products and recipient selection (retaining in the knowledge that xenotransplantation is still experimental)

The reason supporting cross-plantation Supply and demand assess the willingness to use animal sources for organ or tissue transplantation. As of November 8, 2018 [14], 114,518 the United States (approximate 32% of them were under 50 years in age) were on the United Network for Organ Sharing (UNOS) list of patients waiting for donor organs. 34,770 humans received transplants in 2017.



The story of extension:

Alexis Carrel's groundbreaking research with vascular techniques brought about himself the reputation of founding father of experimental organ transplantation. Throughout 1904 and 1906, Carrel and Guthrie contributed major improvements to the area of transplant science. They designed the widely used patch-graft procedure for expanding limited blood vessels, executed autogenous vein organ transplantation, and rebuilt dogs' legs. They also performed experimental transplantation using a heterotopic way. A larger dog's neck has been altered to fit the parts of a tiny dog. For the reason minimize thrombus improvement, they designed the buttonhole technique for kidney transplant recipient and donor vessel anastomosis.

Jaboulay attempted transplants of kidneys into humans in 1906 employing organs from goats, sheep, and monkeys. These kidney xenografting investigations failed to succeed. A man having kidney failure received a nonhuman kidney in Unger in 1910; the guy died suddenly a little within a day

after the transplant was performed. A patient who was experiencing mercury poisoning received a lamb kidney transplanted in Neuhof in 1932. The patient survived for an appropriate nine-day period. Demikhov transplanted a heterotopic heart and lung in 1946; the animal survived for nine hours after the procedure.

Following an increasing number of disappointing results and an understanding that transplant failure was caused by robust, mysterious forces—later revealed to be the body's immune system—clinical interest in xenotransplants dropped. It failed until the 1950s when researchers started displaying significant interest in this area following safely transplanted identical twin kidneys. In Paris in 1952, Michon and Hamburger succeeded in carrying out a kidney transplant by applying a living related donor; in 1954,

Merrill and Murray completed the first kidney transplant between monozygotic twins with no using any sort of immunosuppression.

Immunosuppressive drugs and transplant immunobiology had been fairly fresh fields to be researched at the time of their development. The deep medical use of allografting was severely restricted due to a comparatively small amount of knowledge when it comes to the procurement and place of storage of organs. At this time, chimpanzees or baboons had been utilized in xenotransplantation research by Starzl and colleagues, along with by other groups.

The discovery of the porcine retrovirus in the 1990s stopped the development of xenotransplantation. The risk of cross-species infections lead to the termination of xenotransplantation clinical trials.

Selecting the donor species

A xenotransplant can be categorized as concordant or discordant according to the relationship between the donor and recipient species. Phylogenetically closely related species are identified as concordant species. These species combinations include human to nonhuman primate as well as presumably, baboon to cynomolgus monkey, or mouse to rat. On the other hand, discordant species—such as pigs and mice or humans—do not belong to an intimate relationship.

It is clear that utilizing nonhuman primates would simplify the procedures of obtaining a xenotransplant a lot easier. But one might be curious which species would provide a suitable donor. Actually, the use of a chimpanzee kidney to treat a patient suffering kidney failure was found to be successful for more than nine months before rejection—this was even before

the arrival modern immunosuppression. In addition, by using a mixed chimerism approach similar to to that one has been successfully used for allogeneic kidney transplants, tolerance of donated kidneys from baboons to monkeys has been successfully established.

The domestic pig (Sus scrofa domestica) was chosen by majority of investigators to make a more desirable potential donor for organ xenotransplantation to human recipients.

Table 1 Survival of organs from genetically modified pigs into non-human primates

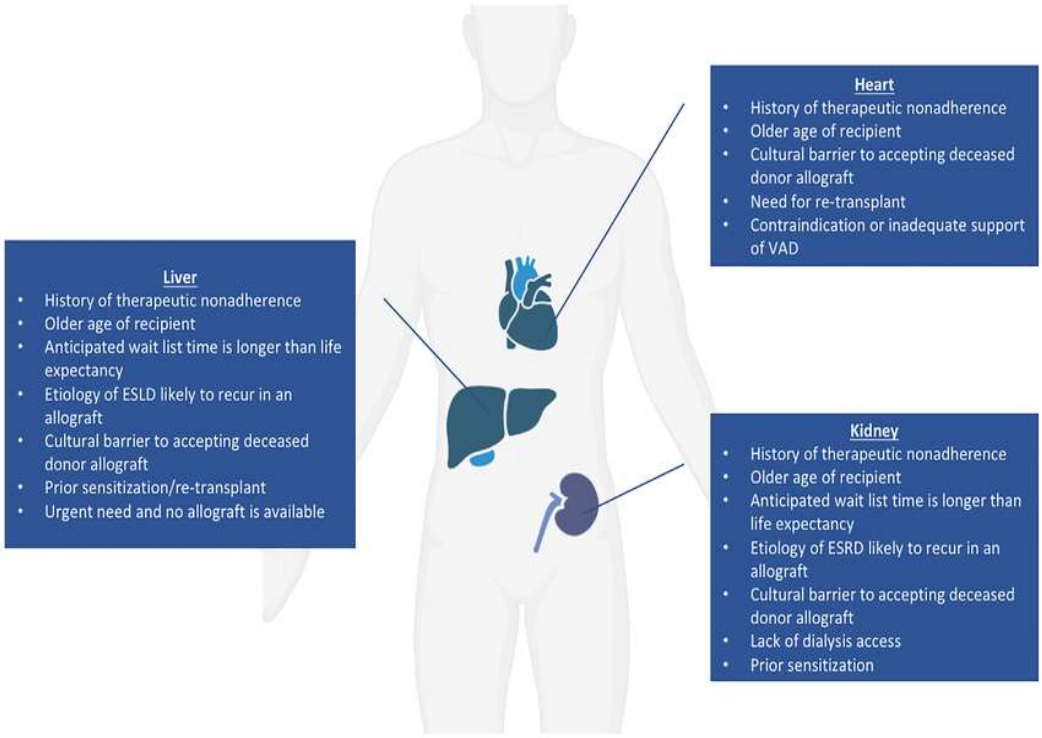
Type of graft	Type of genetic modification	Immunosuppression	Longest survival time (days)
Heart (heterotopic transplantation)	GTKO, CD46, TM	ATG, CD20, CVF, CD40, MMF, CS	945
	GTKO, CD46	ATG, CD20, CD154, CVF, MMF, CS	236
	GTKO	ATG, TI, CD2, CD154, CVF, MMF, MP	179
Heart (orthotopic transplantation)	CD46	ATG, or CyP, CD20, TAC, Rapa	s57
	GTKO, CD46, TM	CD40, ATG, CD20, MMF; non-ischemic preservation technique	40
	CD55	CyP, CsA, MMF, CS	39
Kidney	GTKO, CD55	CD4, CD8, CD154, MMF, CS	310
	GTKO, CD46, CD55, EPCR, TFPI, CD47	ATG, CD20, CD40, Rapa, CS	237
	CD55	ATG, MMF, CS, CD2, CD154, TAC, CyP, CVF, thymectomy or thymic irradiation	229
	GTKO, CD46, CD55, TM, EPCR, CD39	ATG, CD20, CD40, Rapa, MP, CVF,	136

Liver (orthotopic transplantation)	GTKO	ATG, CVF, CTLA4-Ig, TAC, CS	25
	CD55	CyP, CsA, CS	8
Lung (orthotopic transplantation)	vWF-KO	CsA, INN, AZA, CS, macrophage-depleted, antibody immunoabsorption	109 h
	GTKO, CD46	CS + CsA + AZA, macrophage-depleted	48 h

. In the case of lung xenotransplants, survival is given in hours

. *ATG* antithymocyte globulin, *AZA* azathioprine, *CD154* antihuman CD154 (CD40L), *CD2* rat antihuman CD2 (LoCD2b), *CD20* antihuman CD20 (rituximab), *CD4* anti-CD4, *CD40* antihuman CD40, *CD8* anti-CD8, *CS* corticosteroids, *CsA* cyclosporin, *CVF* cobra venom factor, *CyP* cyclophosphamide, *INN* indomethacin, *MMF* mycophenolate mofetil, *MP* methylprednisolone, *Rapa* rapamycin (sirolimus), *TAC* tacrolimus (FK-506)

Selection the recipient:



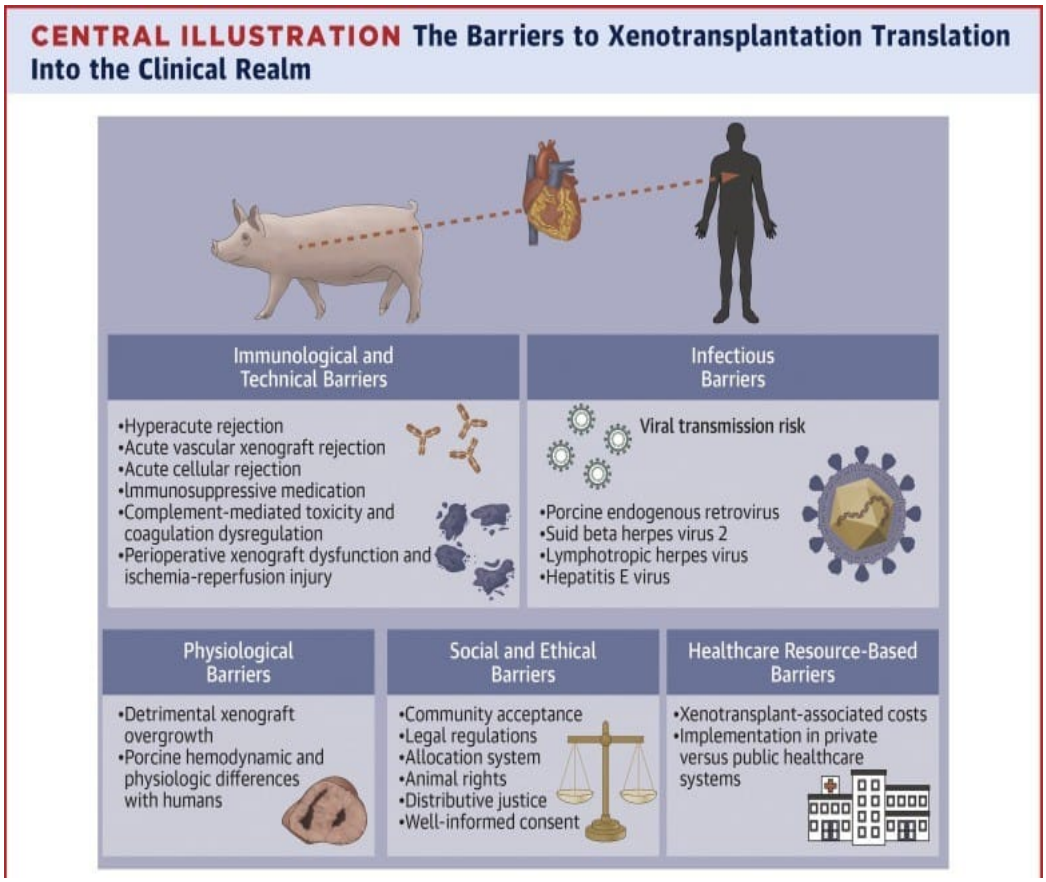
Need and treatment condition:

Condition Severity: The majority of patients have conditions that have not gotten better with prior treatments or severe, end-stage organ failure.

Lack of Alternatives: People usually do not have access to successful alternative treatment, such as compatible human donation of organs.

Pre-existing Immune Conditions: Patients getting medications to treat autoimmune diseases or other immune system dysfunctions may be more susceptible to certain risks and complications. It's essential to analyze the immune system thoroughly.

Barrier in xenotransplantation:



Immunological barrier:

Hyperacute rejection

Pre-formed antibodies that the recipient has against the donor before to transplantation are the cause of hyperacute rejection.When these antibodies attach to the graft organ's vascular epithelium, a series of rapid events take place, causing the graft to thrombose. In allogenic transplantation, this kind of rejection may also happen if tissue matching is not done.

Acute rejection of the vessels

A more delayed kind of immunologic reaction eventually causes thrombosis of the graft between hours to days if the transplanted organ is not rejected within minutes to hours. This process is referred to as acute vascular rejection (AVR) or delayed xenograft rejection (DXR).

Rejection of Cellular Xenografts:

The immune system of the recipient, in particular the activities of T cells, natural killer (NK) cells, and macrophages, is the main mediator of this kind of rejection.

Immunological Response: The xenograft triggers an immunological response since the recipient's immune system perceives it as foreign.The innate and adaptive immune systems are also involved in this.

T lymphocytes: CD4+ and CD8+ In order to mediate cellular rejection, T lymphocytes are essential.They harm tissue by infiltrating the transplant.

Macrophages and natural killer cells: By targeting the xenograft and secreting inflammatory cytokines, these cells also play a role in the rejection process.

Coagulation dysfunction:

1. **Thrombotic Microangiopathy:** This illness causes ischemia and graft failure by causing tiny blood clots to form in the xenograft's blood vessels.

2. **Consumptive Coagulopathy:** This systemic disease is marked by bleeding and thrombocytopenia, which can lead to serious consequences and the loss of a graft.

3. **Molecular Incompatibilities:** These coagulation problems are made worse by variations in the coagulation factors of the donor (a pig, for example) and the recipient (a human).

4. **Platelet Activation:** In various coagulation diseases, platelets are essential. To address these concerns, efforts are being made to modify the genetic makeup of donor animals so that they express human coagulation-regulatory genes (such as thrombomodulin and endothelial protein C receptor).

Transmission of viruses

Porcine Endogenous Retroviruses (PERVs): These viruses can infect human cells and are included into the genome of all pigs. The potential for PERV transmission to human recipients makes xenotransplantation risky. Among the viruses that should worry transplant recipients the most are herpesviruses and retroviruses. To lower the danger, they can be tested for and removed from the donor pool.

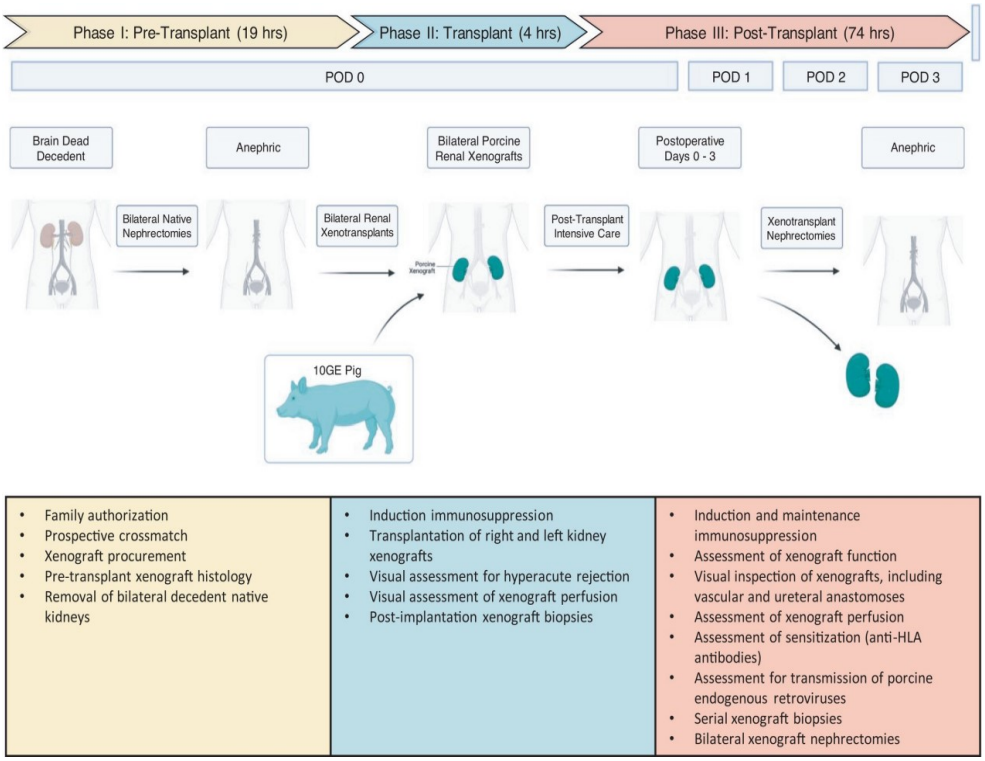
Zoonotic Transmission: Viral infections have the potential to transmit from the recipient to other people in a zoonotic transmission. Despite being regarded as modest, this danger is really concerning.

Growth of xenograft

Growth Hormone Receptor Modifications: By removing or changing growth hormone receptors in donor animals, for example, it may be possible to regulate the xenograft's growth. By doing this, the transplanted organ is kept from expanding excessively following the transplant.

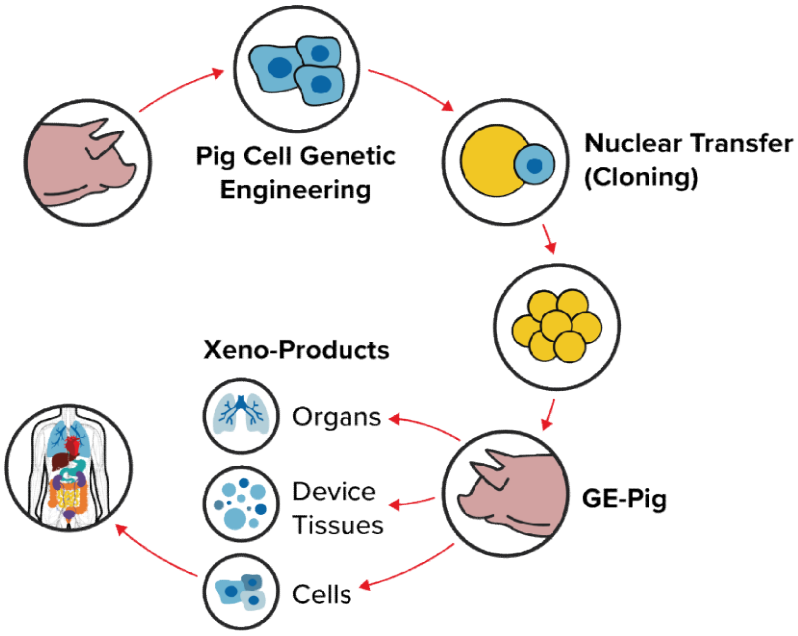
Control of Organ Dimensions: It is vital to make sure the transplanted organ's size fits the human recipient. This entails the appropriate age and size selection of donor animals in addition to the use of genetic engineering to control organ growth2.

Perioperative medication strategies in xenotransplantation:



1. **Genetic Engineering of Donor Animals:** The development of genetically engineered pigs has been made possible by developments in gene-editing technologies, such as CRISPR-Cas9.By lowering the expression of antigens that cause immunological reactions, these changes can improve the organs' compatibility with human recipients. human recipients.

Figure 1: Xenograft Platform



2. **Immunosuppressive Therapies:**

Initiate or continue to prevent rejection.

It's normal practice to use immunosuppressive medications to reduce the recipient's immunological reaction.These medications aid in preventing xenograft rejection by the immune system.

Training the recipient's immune system to recognize the xenograft as "self" as opposed to alien is known as tolerance induction.Methods like mixed chimerism, in which bone marrow cells from the donor animal are delivered to the recipient, are under investigation.

A typical immunosuppressive medication

1. Tacrolimus: An inhibitor of calcineurin that inhibits T-cell activation1.

2. Mycophenolate mofetil (MMF): An antiproliferative medication that prevents T and B cells from proliferating.

3. Sirolimus (Rapamycin): An inhibitor of mTOR that stops T-cell growth.

4. Corticosteroids: They lower immunological response and inflammation; one example is prednisone.

5. Monoclonal antibodies: These antibodies, such as CD40 or CD154, target certain immune cells.

Immunosuppressive medication	POD 0	POD 1	POD 2	POD 3
Anti-Thymocyte Globulin (Rabbit)	175 mg	175 mg	175 mg	—
Rituximab	1800 mg	—	—	—
Tacrolimus	—	1 mg AM	1 mg AM	2 mg AM
	1 mg PM	1 mg PM	2 mg PM	—
Mycophenolate mofetil	—	1000 mg AM	1000 mg AM	1000 mg AM
	2000 mg PM	1000 mg PM	1000 mg PM	—
Methylprednisolone[a]	500 mg	250 mg	125 mg	90 mg

Abbreviations: POD AM, morning of post-operative day; POD PM, afternoon of post-operative day.

[a] Additional methylprednisolone given for brain death management.

3. Frequently used anticoagulant medications:

Anti-coagulant therapy:

Heparin: Used to stop blood clots from forming during and right after surgery.

Vitamin K antagonist Warfarin is prescribed for prolonged anticoagulation.

The usage of direct oral anticoagulants (DOACs), such as apixaban and rivaroxaban, is growing because of their convenient dosage forms and predictable pharmacokinetics.

4. **Frequently used antiviral medications and vaccines:**

Drug	Mechanism of Action	Dose	Use	Adverse Effects
Acyclovir	Acyclovir is a nucleoside analogue that inhibits viral DNA polymerase by incorporating into the viral DNA chain, leading to chain termination.	·**Herpes Simplex Virus (HSV) Infection:** • Oral: 200 mg every 4 hours while awake for 5-10 days. • IV: 5-10 mg/kg every 8 hours for severe infections. ·**Varicella-Zoster Virus (VZV):** • Oral: 800 mg five times daily for 7-10 days.	·HSV infections (oral and genital herpes) ·VZV infections (chickenpox and shingles) ·CMV infection in immunocompromised patients (less common)	·Nausea, diarrhea, headache ·Renal toxicity (if IV administration is too rapid) ·Neurotoxicity (e.g., tremors, confusion) with high doses or rapid infusion
Valacyclovir	Valacyclovir is a prodrug that is converted to acyclovir in the body. Its mechanism of action is similar to acyclovir.	·**HSV Infection:** 500 mg to 1 g twice daily for 7-10 days. ·**VZV Infection:** 1 g three times daily for 7 days	• ·HSV infections (oral and genital herpes) • VZV infections (shingles and chickenpox) • Prevent	·Headache, nausea, dizziness ·Gastrointestinal symptoms (e.g., abdominal pain, diarrhea) ·Rarely, renal toxicity and neurotoxicity

			recurrence of HSV infections ··	
Ganciclovir	· Ganciclovir is a nucleoside analogue that inhibits CMV DNA polymerase, leading to inhibition of viral DNA replication. ···	·**CMV Retinitis:** • IV: 5 mg/kg every 12 hours for 14-21 days, followed by maintenance. ·**CMV Prophylaxis:** • Oral: 1000 mg twice daily.	CMV infections (especially in immunocompromised patients)	·Bone marrow suppression (e.g., neutropenia, anemia) ·Fever, rash, gastrointestinal symptoms ·Renal toxicity
Valganciclovir	Valganciclovir is a prodrug converted to ganciclovir. Its mechanism of action is the same as ganciclovir.	• ·**CMV Retinitis:** 900 mg twice daily for 21 days, then once daily for maintenance. • **CMV Prophylaxis:** 900 mg once daily.	·CMV infections (prevention and treatment) ·CMV retinitis in immunocompromised patients	bone marrow suppression, gastrointestinal issues, renal toxicity
Foscarnet	· Foscarnet inhibits viral DNA polymerase and reverse transcriptase directly, without requiring activation by viral kinases.	·**CMV Retinitis:** • IV: 60 mg/kg every 8 hours for 2-4 weeks, then reduced for maintenance. ·**HSV Infections:**	·Resistant CMV infections ·Resistant HSV and VZV infections	·Renal toxicity (nephrotoxicity) ·Electrolyte imbalances (e.g., hypocalcemia, hypomagnesemia) ·Central nervous system effects (e.g., seizures, confusion)

		• IV: 40 mg/kg every 8 hours for 10-14 days.		
Cidofovir	Cidofovir is a nucleotide analogue that inhibits viral DNA polymerase, leading to a reduction in viral DNA synthesis.	·**CMV Retinitis:** • IV: 5 mg/kg once weekly for 2 weeks, then every 2 weeks. ·**Other indications:** Adjust doses based on infection type and patient condition.	·CMV infections (especially in HIV/AIDS patients) ·Treatment of some other viral infections (e.g., adenovirus)	·Renal toxicity (nephrotoxicity) ·Uveitis ·Fever, headache

Vaccines are essential in xenotransplantation because they lower the possibility of virus transmission from donor animals to human recipients.

The swine Circovirus (PCV) vaccine is intended to guard against diseases brought on by swine circoviruses, which people can contract from pigs.

The Porcine Cytomegalovirus (PCMV) vaccine aims to prevent infections caused by the virus, which is a major risk in the process of xenotransplantation.

Despite its limited availability, research is being done to create vaccinations against the hepatitis E virus (HEV), which can be spread from pigs to humans.

5. **Antibiotics**: **Broad-Spectrum Antibiotics**: Drugs like ceftriaxone or piperacillin-tazobactam can cover a wide range of potential pathogens

6. **Pain Management**: Use appropriate analgesics considering overall condition.

·**Opioids**: Medications like fentanyl or morphine can be used, often in combination with other analgesics.

·**NSAIDs**: Nonsteroidal anti-inflammatory drugs (e.g., ketorolac) can help with inflammation and pain. However, use caution if there are concerns about renal function or bleeding risk.

·**Regional Anesthesia**: Techniques such as epidural analgesia or nerve blocks can provide effective pain relief and reduce the need for systemic opioids.

7. **Review All Medications**: Assess for interactions or adverse effects.

8. **Monitoring and Early Intervention:** Monitor blood pressure, fluid balance, and electrolytes.

Ethical worries:

It is believed that confinement is necessary for pigs reared for xenografts in order to lower the danger of infection and subsequent infection transfer to the intended recipient of the xenograft. By using CRISPR technology, a pig with all PERVs deactivated has been created, lowering the possibility of PERV infection during xenotransplantation and eliminating this ethical conundrum.

Because they are widely accepted as a food source in most modern societies, pigs are easily obtained, have favorable reproductive characteristics, can be bred in clean, controlled environments to avoid pathogens, are amenable to genetic engineering, and are less likely to raise ethical concerns about their use for this purpose.[21]Its physiological and anatomical characteristics are also comparable to those of humans.

Recent clinical trials for xenograft

Results of a very similar research conducted at UAB using a TKO pig kidney implanted in a brain-dead patient with seven additional genetic alterations (ten genetic modifications, or 10G-pigs) were published on January 20, 2022. Unambiguously observing the lack of HAR, the UAB researchers recorded this using negative flow crossmatches both prior to and following transplant (until 74 hours when the trial was terminated).

It is noteworthy that they employed rituximab in addition to normal immunosuppression, which included maintenance with mycophenolate mofetil, tacrolimus, and prednisone, as well as methylprednisolone taper, anti-thymocyte globulin at a dose of 6 mg/kg, and anti-CD20.Three important lessons were learned from this very first experience: 1) there was no

hyperacute rejection; 2) the biopsy revealed TMA; and 3) urine production.but no creatinine clearance.

The recipient was a brain-dead donor who had undergone bilateral native nephrectomy; these events may have compromised kidney function in any case and exacerbated pre-existing TMA, which was most likely due to the inflammatory-hypercoagulable state resulting from traumatic brain injury rather than antimicrobial resistance. Pig kidney xenografts appear to be able to clear creatinine in more stable conditions, according to extensive research in NHPs (84, 85) and other similar trials (7) that will probably soon be described in a scientific form.

While there is little doubt that these latest studies represent a major advancement in the industry, they also bring up several new scientific issues. However, there is a noticeable appetite among the scientific community for comprehensive accounts of these experiments.

Conclusion

In order for xenotransplants to be incorporated into routine clinical practice, the trials should ideally concentrate on establishing suitable recipient selection criteria and identifying an appropriate immunosuppression regimen for xenograft recipients. These are currently notable unknowns that need to be further investigated.

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Irregular Heartbeat, Regular Care:Managing Atrial Fibrillation - For a Healthier Life

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Definition

Atrial fibrillation(AF) is an arrhythmia where atria are disorganised and multiple atrial foci fire impulses at a rate of 350-600/minute.There is no atrial contraction but only fibrillation.The ventricles respond at irregular intervals, usually at a rate of 100-- 140/minute.

Epidemiology

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an overall prevalence of 0.5% in the adult population of the UK. The prevalence rises with age, affecting 1% of those aged 60–64 years, increasing to 9% of those aged over 80 years. It is associated with significant morbidity and a two fold increase in mortality. This is mainly because of its association with underlying heart disease but also because of its association with systemic embolism and stroke.

Classification Of Atrial Fibrillation

Atrial fibrillation can be paroxysmal, persistent or permanent.

- **Paroxysmal AF** means that terminates spontaneously or with intervention within 7 days of Onset.
- **Persistent AF** means that episodes last longer than 7 days or require an intervention, such as cardioversion, to restore sinus rhythm..
- **Long standing persistent AF**- Continuous AF of >12 months duration when decided to adopt a rhythm control strategy.

❖ **Permanent AF** means that the arrhythmia is continuous and interventions to restore sinus rhythm have either failed or not been attempted.

Other Special Types Of Atrial Fibrillation;-

❖ **Lone AF** occur in patients younger than 60 years who do not have hypertension or any evidence of structural heart disease .

❖ **Non-valvular AF** is used when it occurs in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

❖ **FIRST DIAGNOSED** - AF not diagnosed before, irrespective of its duration or the presence/severity of AF related symptoms.

❖ **Paroxysmal AF** is defined by episodes that start spontaneously and stop within 7 days of onset.It is initiated by small re-entrant or rapidly firing foci in sleeves of atrial muscle that extend into the pulmonary veins (PV).Catheter ablation that isolates these foci usually abolishes paroxysmal AF, although some patients also have initiating foci in other locations.

Persistent AF:

❖ Persistent AF has a longer duration, exceeding 7 days, and, in many cases, will continue indefinitely unless cardioversion is performed.

❖Cardioversion can be followed by prolonged periods of sinus rhythm.

❖ As for paroxysmal AF, episodes are often initiated by rapidly firing foci within PV, but Non- PV sites, including myocardial sleeves around the superior vena cava (SVC) or coronary sinus are encountered more often than when af is paroxysmal.

Long Persistent AF:

❖ In patients with longstanding persistent AF(>1 year), significant fibrosis is usually present and it is difficult to restore and maintain sinus rhythm.

❖ Some Patients progress over years from paroxysmal to persistent AF.

Risk factors &Aetiology of Atrial Fibrillation:

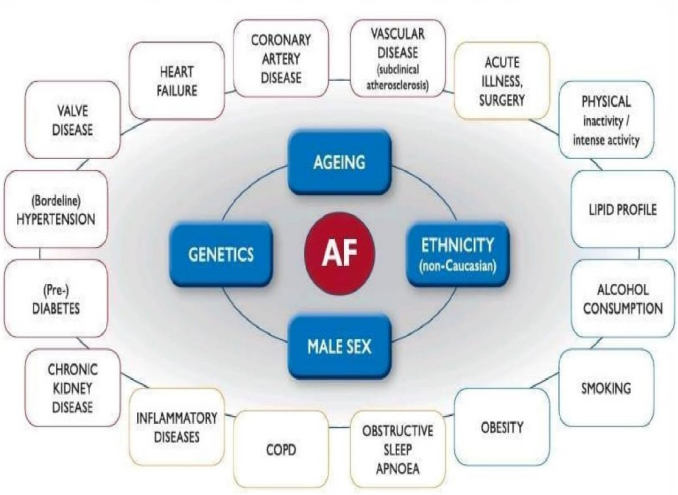
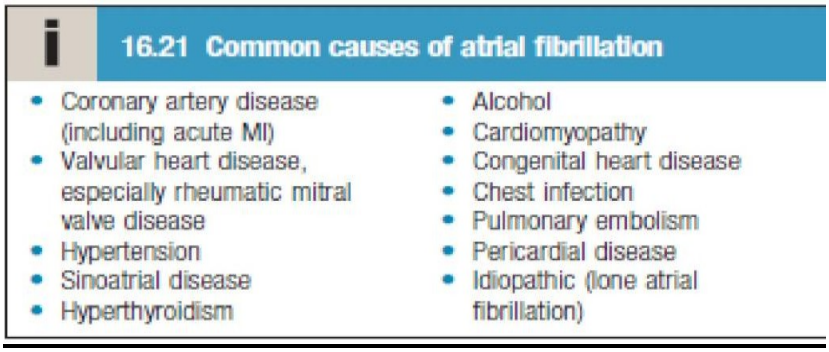


Figure 1: Risk Factors of AF



16.21 Common causes of atrial fibrillation

- Coronary artery disease (including acute MI)
- Valvular heart disease, especially rheumatic mitral valve disease
- Hypertension
- Sinoatrial disease
- Hyperthyroidism
- Alcohol
- Cardiomyopathy
- Congenital heart disease
- Chest infection
- Pulmonary embolism
- Pericardial disease
- Idiopathic (lone atrial fibrillation)

Figure 2: Aetiology of AF

Cardiac Causes Of AF:

- ❖ Coronary artery disease (including acute Myocardial Infarction)
- ❖ Valvular heart disease, specially rheumatic mitral valve disease
- ❖ Systemic Hypertension
- ❖ Sinoatrial disease
- ❖ Congestive Heart Failure
- ❖ Cardiomyopathy

- Congenital heart disease

Non cardiac causes of AF

- Alcohol
- Pulmonary causes like COPD, pneumonia, Pulmonary embolism
- Idiopathic (lone AF)
- Thyrotoxicosis
- Pheochromocytoma
- Sepsis

Pathophysiology and haemodynamics .

AF is a complex arrhythmia characterised by both abnormal automatic firing and the presence of multiple interacting re-entry circuits looping around the atria. Episodes of AF are initiated by rapid bursts of ectopic beats arising from conducting tissue in the pulmonary veins or from diseased atrial tissue. It becomes sustained because of re-entrant conduction within the atria or sometimes because of continuous ectopic firing.

Re-entry is more likely to occur in atria that are enlarged or in which conduction is slow, as is the case in many forms of heart disease. During episodes of AF, the atria beat rapidly but in an uncoordinated and ineffective manner. The ventricles are activated irregularly at a rate determined by conduction through the AV node.

Initiation of AF is commonly because of rapid, repetitive firing of an ectopic focus with in the pulmonary veins with fibrillatory conduction , to the bodies of the atria.Structural and electrical remodelling of the left atrium associated with cardiovascular disease promotes ectopic activity and heterogenous conduction patterns that provide the substrate for AF. Inflammation and fibrosis may play a major role in initiation and maintenance of AF.Inflammatory markers such as IL 6 and CRP are increased in AF.

Atria fire the impulses at a rate of 350-600/m.inute. Many of them reach the AV node in its refractory period and so not conducted. However, a variable number (about 100-- 140/minute) of impulses are conducted to the ventricles at irregular intervals. This accounts for the irregularly irregular rhythm of pulse and heart. The irregular rhythm of heart results in varying

durations of diastole (short, normal or long). The duration of diastole determines the volume of ventricular blood; the shorter the diastole, the lesser the ventricular volume, and the longer the diastole, the higher the ventricular volume. The ventricular volume in turn determines the cardiac output, which hence keeps varying. This varying cardiac output accounts for the varying volume of pulse and the pulse deficit (ventricular systoles that are so weak as to be not able to evoke a pulse.

Lack Of Atrial Contraction Results In The Following:

- ❖ Stasis of blood in the left atrium resulting in thrombus formation and subsequent dislodgment of the thrombus resulting in systemic embolisation.
- ❖ Disappearance of a waves from JVP (a waves are due to atrial contraction).
- ❖ Disappearance of a fourth heart sound if it was already present (S4 is due to atrial contraction).
- ❖ In some cases, disappearance of pre-systolic accentuation of mid-diastolic murmur of mitral stenosis (atrial contraction may contribute to PSA).
- ❖ Loss of "atrial booster effect" (atrial contraction in pre-systole) resulting in precipitation or Worsening of cardiac failure.
- ❖ Tachycardia-related cardiomyopathy in patients with poor rate control may further depress cardiac function.

Mechanism of AF:

- ❖ **Focal Activation** ;- AF originates from an area of focal activity which may be triggered due to increased automaticity , or from micro re-entry , usually in the pulmonary veins
- ❖ **Multiple Wavelets** ;-Multiple wondering small wave lets are formed and the fibrillation is maintained by reentry circuits formed by some wavelets. This is potentiated in the presence of dilated left atria due to larger surface facilitating Continuous wave form propagation

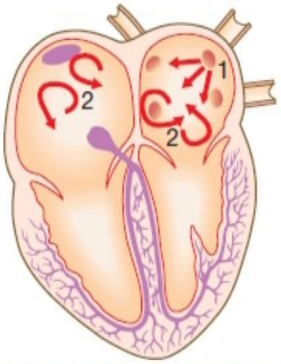


Fig. 16.36 **Mechanisms initiating atrial fibrillation.** (1) Ectopic beats, often arising from the pulmonary veins, trigger atrial fibrillation. (2) Re-entry within the atria maintains atrial fibrillation, with multiple interacting re-entry circuits operating simultaneously.

Figure 3

AF in Old Age:

16.22 Atrial fibrillation in old age

- **Prevalence**: rises with age, reaching 9% in those over 80 years.
- **Symptoms**: sometimes asymptomatic but often accompanied by diastolic heart failure.
- **Hyperthyroidism**: atrial fibrillation may emerge as the dominant feature of otherwise silent or occult hyperthyroidism.
- **Cardioversion**: followed by high rates (~70% at 1 year) of recurrent atrial fibrillation.
- **Stroke**: atrial fibrillation is an important cause of cerebral embolism, found in 15% of all stroke patients and 2–8% of those with transient ischaemic attacks (TIAs).
- **Anticoagulation**: although the risk of thromboembolism rises, the hazards of anticoagulation also become greater with age because of increased comorbidity, particularly cognitive impairment and falls.
- **Target INR**: if anticoagulation is recommended in those over 75 years, care should be taken to maintain an INR below 3.0 because of the increased risk of intracranial haemorrhage.
- **Directly acting oral anticoagulants**: alternatives to warfarin. No blood monitoring is required, there are fewer drug interactions, and fixed dosing may aid adherence. Dabigatran dose is reduced from 150 mg twice daily to 110 mg twice daily in those over 80 or if creatinine clearance is less than 30 mL/min. Rivaroxaban dose is reduced from 20 mg once daily to 15 mg once daily if creatinine clearance is 30–49 mL/min, and is contraindicated below 30 mL/min.

Figure 4: AF in Old Age

Clinical presentation and outcomes:

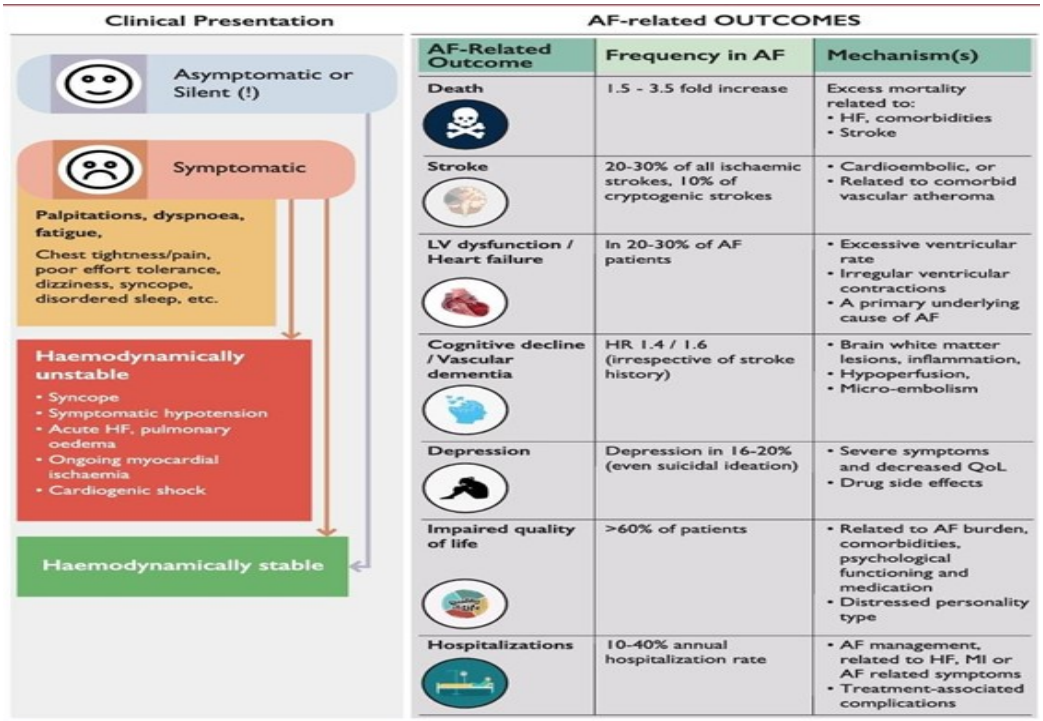


Figure 5: Clinical presentation and AF related outcomes

Risk of Stroke in Atrial Fibrillation

❖ In patients with non-valvular atrial fibrillation the average annual risk for arterial thromboembolism, including stroke, is 5%, and the risk is higher in patients older than 75 years of age.

❖ A risk index (CHA2DS2 - VASc) has been developed to determine the risk of stroke due to thromboembolism in patients with non-valvular atrial fibrillation.

❖ CHA2DS2 - VASc score of 9 predicts a stroke rate of 15.2% per year.

❖ Antithrombotic agents like warfarin are recommended for CHA2DS2 -VASc score >2 .

 In addition, echocardiographic demonstration of intra-auricular thrombus or an enlarged left atrium also indicates increased risk of emboli .

16.23 CHA_2DS_2-VASc stroke risk scoring system for non-valvular atrial fibrillation

	Parameter	Score
C	Congestive heart failure	1 point
H	Hypertension history	1 point
A_2	Age ≥75 years	2 points
D	Diabetes mellitus	1 point
S_2	Previous stroke or transient ischemic attack (TIA)	2 points
V	Vascular disease	1 point
A	Age 65–74 years	1 point
Sc	Sex category female	1 point
	Maximum total score	9 points

Annual stroke risk
0 points = 0% (no prophylaxis required)
1 point = 1.3% (oral anticoagulant recommended in males only)
2+ points = > 2.2% (oral anticoagulant recommended)

Figure 6: CHA2DS2-VASc Stroke risk scoring system for non-valvular AF

	Parameter	Score
H	Hypertension; current systolic blood pressure >160 mmHg	1 point
A	Abnormal liver function (cirrhosis OR bilirubin > twice upper limit of reference range or transaminases > three times upper limit of reference range	1 point
	Abnormal renal function (creatinine > 200 μmol/L (2.26 mg/dL)	1 point
S	Stroke history	1 point
B	Bleeding: prior major event	1 point
L	Labile INR on warfarin	1 point
E	Elderly: age ≥65 years	1 point
D	Drugs:	
	Use of antiplatelet drugs	1 point
	High alcohol consumption	1 point
	Maximum total score	9 points
HAS-BLED score of ≥3 points requires close patient monitoring		

Figure 7: HAS-BLED bleeding risk scoring system for patients receiving oral anti-coagulation

Symptoms:

- Palpitations.
- Fatigue.
- Dyspnea.
- Effort intolerance.

- ❖ Lightheadedness.
- ❖ Polyuria(bcoz of ANP release).
- ❖ Syncope.

Signs:

- ❖ Irregularly irregular pulse
- ❖ Varying volume of pulse.
- ❖ Pulse deficit
- ❖ Varying intensity of first heart sound
- ❖ Absence of 'a' waves in JVP
- ❖ Disappearance of fourth heart sound
- ❖ Hypotension
- ❖ Disappearance of the PSA of the mid-diastolic murmur of mitral stenosis (MS) in some cases.

Pulse Deficit (Apex-Pulse Deficit)

It is the difference between the heart rate and the pulse rate, when counted simultaneously for one full minute.

Causes of Apex-Pulse Deficit

- ❖ Atrial fibrillation
- ❖ Ventricular premature beats.

Differentiating Features between VPC and AF

Features	*Ventricular Pre-mature Beats (VPCs)*	*Atrial Fibrillation (AF)*
Pulse deficit	Less than 10 per min.	More than 10 per min.
'a' wave in JVP	Present	Absent
On exertion	Decreases or disappears	Persists or increases
Rhythm	Short pause (between normal beat and VPC) followed by a long pause (following VPC)	Pauses are variable and chaotic

Figure 8: VPC & VF

Investigations

Haemogram,

RFT - to rule out CKD,

LFT,

Serum electrolytes (HYPOKALEMIA, HYPOMAGNESEMIA),

ECG,

ABG,

Thyroid profile - to rule out THYROTOXICOSIS ,

Chest Xray - to rule out COPD, PNEUMONIA

2D-ECHO - to identify Structural heart disease mainly mitral valve

Electrocardiogram ECG ;- 3 criteria

- ❖ Absent P waves
- ❖ An irregularly irregular rhythm of QRS complexes
- ❖ Fibrillary waves

1)Small, irregular waves (fibrillary waves) at a rate of 350-600/minute that are difficult to see on ECG (fine atrial fibrillation)

2)At lower rates of 150-300, coarse fibrillary waves are seen (coarse atrial fibrillation)

Calculate Average Heart Rate In AF ;- Number of QRS complex in 6 seconds or 30 big squares and then multiply by 10.

Note: Patients with atrial fibrillation and digoxin toxicity may have regular R-R intervals due to development of AV block and junctional rhythm; P waves are absent.

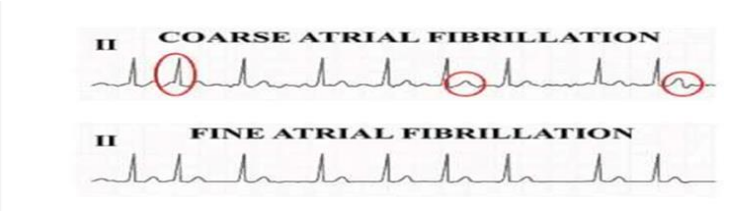


Figure 9: Coarse & Fine AF

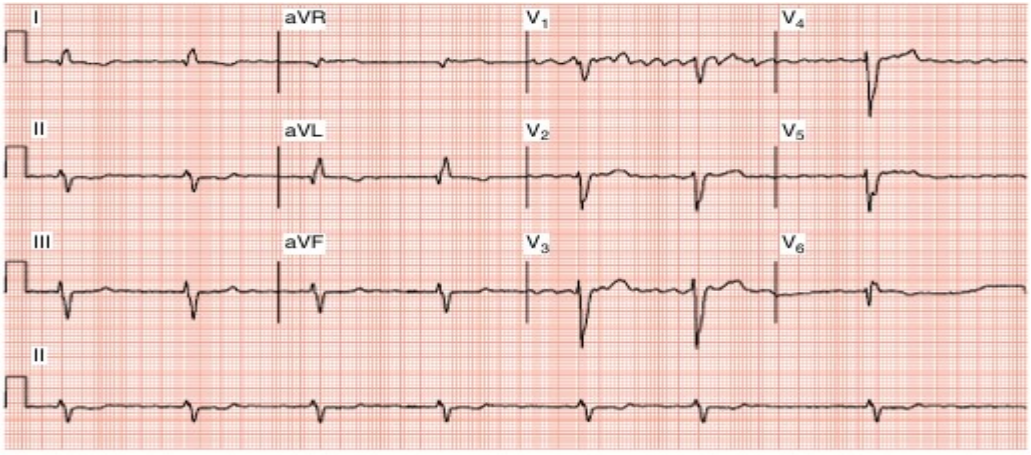


Figure 10: AF with slow ventricular response

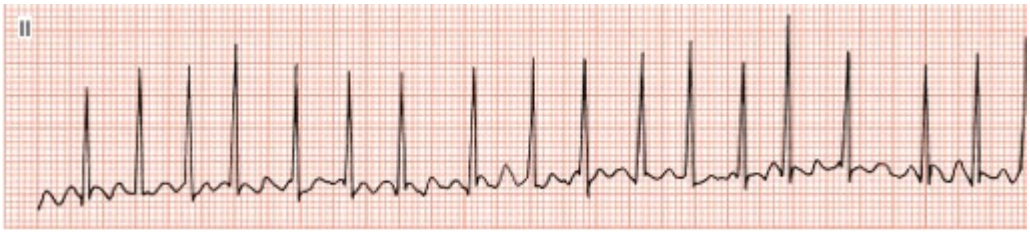


Figure 11: AF with Rapid ventricular response

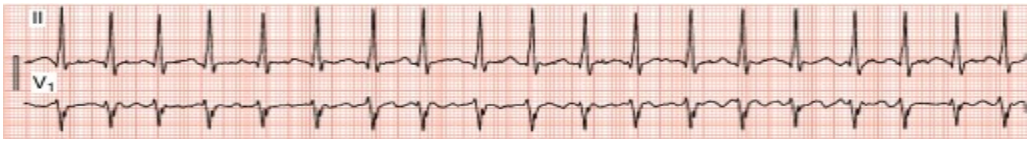


Figure 12: AF with Rapid ventricular response

Differential Diagnosis

- **Atrial flutter** with variable block: Prominent saw-tooth waves at lower rates of 250- 350/minute are seen in the ECG.
- **Atrial tachycardia with variable block**: Atrial rate is approximately 150/minute that is regular but the conduction to the ventricles is not regular producing irregular pulse.
- **Multifocal atrial tachycardia and wandering atrial** pacemaker can both have irregular ventricular responses; P waves of differing morphology are present.

Treatment:

Treatment of AF includes a holistic ABC approach

A = Avoid stroke/ anticoagulation

B= Better symptom control

C= Cardiovascular and comorbidity optimization

A – Avoid Stroke/Anticoagulation :

Overall, AF increases the risk of stroke five-fold, but this risk is not homogeneous, depending on the presence of specific stroke risk factors/modifier. Common stroke risk factors are summarized in the clinical risk-factor-based CHA2DS2-VASC SCORE. Female sex is an age-dependent stroke risk modifier rather than a risk factor per se.More complex clinical scores [e.G. Global anticoagulant registry in the FIELD - atrial fibrillation (garfield-af)]and those inclusive of biomarkers

Absolute Contraindications Of Oac

- ❖ Active serious bleeding
- ❖ Thrombocytopenia <50,000/ ul
- ❖ Severe anemia under investigation
- ❖ Recent high risk event such as intracranial hemorrhage

Stroke Prevention Therapies

- ❖ VIT K ANTAGONIST
- ❖ NEW ORAL ANTICOAGULANTS

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150mg bid	20mg od	5mg bid	60mg od
Lower dose	110mg bid			30mg od
Reduced dose		15mg od	2.5mg bid	30mg od /15mg od
Dose reucing criteria	Dabigatran 110 mg b.i.d. in patients with: • Age >_80 years • Concomitant use of verapamil, or • Increased bleeding risk	CrCl 15 - 49 mL/min	At least 2 of 3 criteria: • Age >_80 years, • Body weight<_ 60kg • Creatinine >_1.5 mg/dL (133 Imol/L)	If any of the following: • CrCl 30 - 50 mL/min, • Body weight <_60 • Concomitant use of verapamil, quinidine, or dronedarone

Figure 13: New Oral Anticoagulants

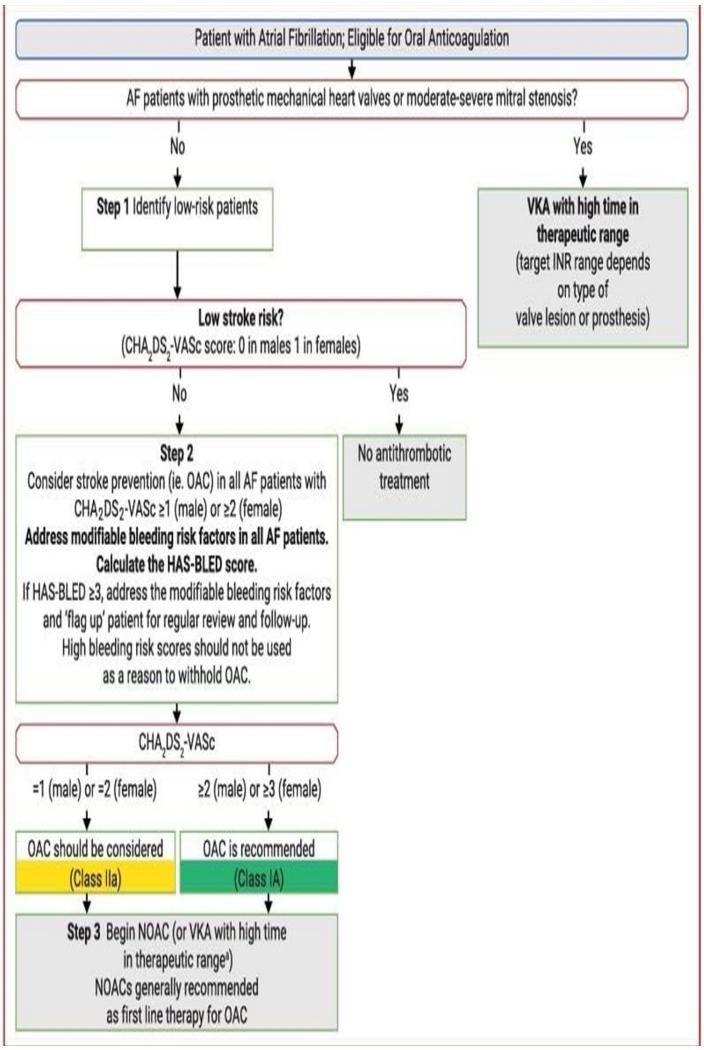


Figure 14: Algorithm to start oral anti-coagulation

B – Better Symptom Control:

❖ The optimal heart-rate target in AF patients is unclear.

❖ In the race (race control efficacy in permanent atrial fibrillation) ii RCT of permanent AF patients, there was no difference in a composite of clinical events, Newyork Heart Association(NYHA)class, or hospitalizations between the strict [target heart rate <80 beats per minute (bpm)at rest and <110 bpm during moderate exercise and lenient (heart-rate target <110 bpm)are

similar to ananalys is from the affirm (atrial fibrillation follow-up investigation of rhythm management) and race trials.

- ❖ Therefore ,lenient rate control is an acceptable initial approach, regardless of HF status (with the exception of tachycardia-induced cardiomyopathy),unless symptoms call for stricter rate control.

- ❖ Beta-blockers are often first-line rate-controlling agents, largely based on better acute rate control.

- ❖ Interestingly, the prognostic benefit of beta-blockers seen in hf with reduced ejection fraction (HFREF) patients with sinus rhythm has been questioned in patients with AF.

- ❖ Non-dihydropyridine calcium channel blockers (NDCC) verapamil and diltiazem provide reasonable rate control and can improve AF-related symptoms compared with beta blockers.

- ❖ Digoxin and digitoxin are not effective in patients with increased sympathetic drive.

- ❖ Amiodarone can be useful as a last resort when heart rate cannot be controlled with combination therapy in patients who do not qualify for no pharmacological rate control, i.E. Atrioventricular node ablation and pacing, not with standing the extracardiac adverse effects of the drug.

Acute Rate Control:

Acute hemodynamic instability (i.E. Syncope, acute pulmonary oedema, ongoing myocardial ischemia, symptomatic hypotension, or cardiogenic shock) in AF patients presenting with a rapid ventricular rate requires prompt intervention. In severely compromised patients, emergency electrical cardioversion should be attempted without delay, and anticoagulation should be started as soon as possible. In acute settings, physicians should always evaluate underlying causes, such as infection or anaemia. Beta-blockers and diltiazem/verapamil are preferred over digoxin because of their rapid onset of action and effectiveness at high sympathetic tone. The choice of drug and target heart rate will depend on the patient characteristics, symptoms, LVEF value, and haemodynamics, but a lenient initial heart-rate approach seems acceptable. Combination therapy may be required. In patients with HFREF, betablockers, digitalis, or their combination should be used. In critically ill patients and those with severely impaired LV systolic function, i.V. Amiodarone can be used

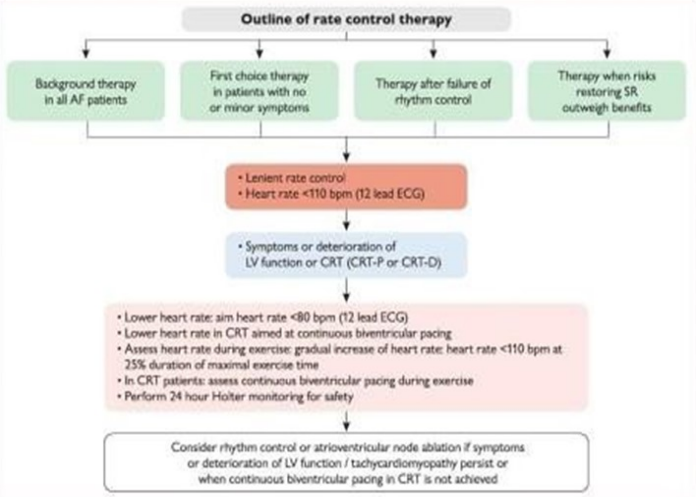


Figure 15: Outline of rate control therapy

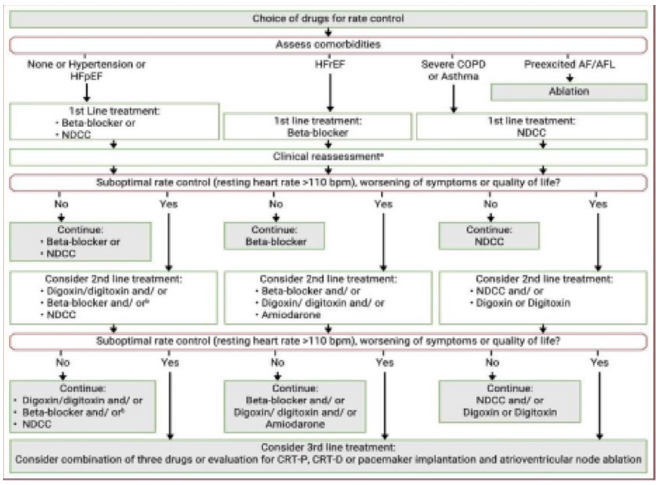


Figure 16: Choice of drugs for rate control

	Intravenous administration	Usual oral maintenance dose	Contraindicated
Beta-blockers[a]			
Metoprolol tartrate	2.5 - 5 mg i.v. bolus; up to 4 doses	25 - 100 mg b.i.d.	In case of asthma use beta-1-blockers Contraindicated in acute HF and history of severe bronchospasm
Metoprolol XL (succinate)	N/A	50 - 400 mg o.d.	
Bisoprolol	N/A	1.25 - 20 mg o.d.	
Atenolol[c]	N/A	25 - 100 mg o.d.	
Esmolol	500 µg/kg i.v. bolus over 1 min; followed by 50 - 300 µg/kg/min	N/A	
Landiolol	100 µg/kg i.v. bolus over 1 min; followed by 10 - 40 µg/kg/min[105]	N/A	
Nebivolol	N/A	2.5 - 10 mg o.d.	
Carvedilol	N/A	3.125 - 50 mg b.i.d.	
Non-dihydropyridine calcium channel antagonists			
Verapamil	2.5 - 10 mg i.v. bolusover 5 min	40 mg b.i.d. to 480 mg (extended release) o.d.	Contraindicated in HFrEF Adapt doses in hepatic and renal impairment
Diltiazem	0.25 mg/kg i.v. bolus over 5 min, then 5 - 15 mg/h	60 mg t.i.d. to 360 mg (extended release) o.d.	
Digitalis glycosides			
Digoxin	0.5 mg i.v. bolus (0.75 - 1.5 mg over 24 hours in divided doses)	0.0625 - 0.25 mg o.d.	High plasma levels associated with increased mortality Check renal function before starting and adapt dose in CKD patients
Digitoxin	0.4 - 0.6 mg	0.05 - 0.1 mg o.d.	High plasma levels associated with increased mortality
Other			
Amiodarone	300 mg i.v. diluted in 250 mL 5% dextrose over 30 - 60 min (preferably via central venous cannula), followed by 900 - 1200 mg i.v. over 24 hours diluted in 500 - 1000 mL via a central venous cannula	200 mg o.d. after loading 3 × 200 mg daily over 4 weeks, then 200 mg daily[228,d](reduce other rate controlling drugs according to heart rate)	In case of thyroid disease, only if no other options

AF = atrial fibrillation; b.i.d. = *bis in die* (twice a day); CKD = chronic kidney disease; HF = heart failure; HFrEF = HF with reduced ejection fraction; i.v. = intravenous; min = minutes; N/A = not available or not widely available; o.d. = *omni die* (once daily); t.i.d. = *ter in die* (three times a day).

[a]All rate control drugs are contraindicated in Wolff-Parkinson-White syndrome, also i.v. amiodarone.

[b]Other beta-blockers are available but not recommended as specific rate control therapy in AF and therefore not mentioned here (e.g. propranolol and labetalol).

[c]No data on atenolol; should not be used in HFrEF.

[d]Loading regimen may vary; i.v. dosage should be considered when calculating total load.

Figure 17: Drugs for rate control in AF

Acute Rhythm Control:

The 'rhythm control strategy' refers to attempts to restore and maintain sinus rhythm, and may engage a combination of treatment approaches, including cardioversion, anti arrhythmic medication, and catheter ablation, along with an adequate rate control, anticoagulation therapy and comprehensive cardiovascular prophylactic therapy (upstream therapy, including lifestyle and sleep apnoea management). Based on the currently available evidence from RCTS, the primary indication for rhythm control is to reduce AF-related symptoms and improve QOL.

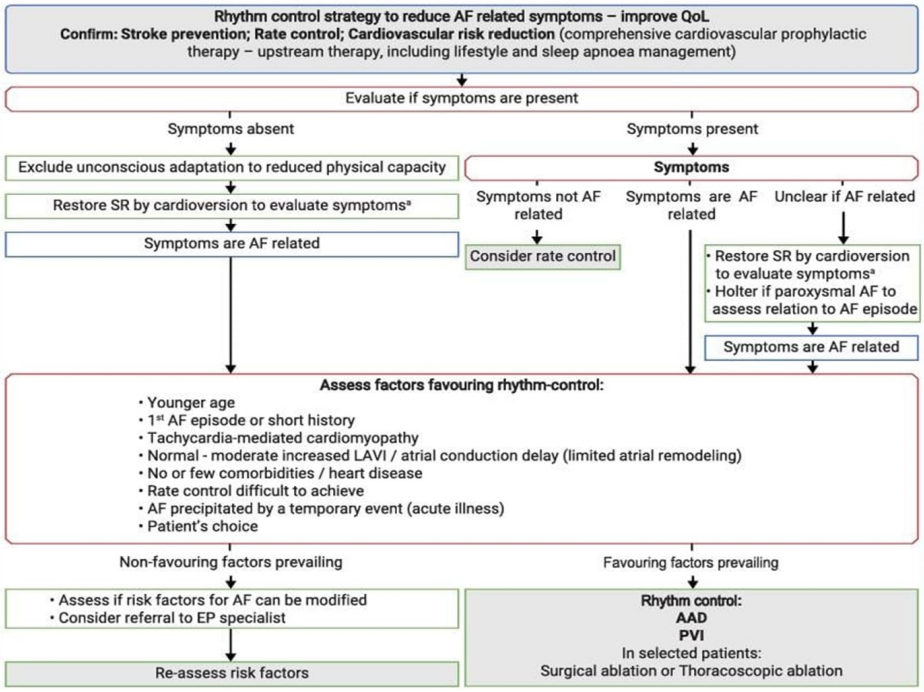


Figure 18: Rhythm control in AF

Cardioversion Acute rhythm control can be performed as an emergency

cardioversion in a haemodynamically unstable AF patient or in a non-emergenc
situation.Synchronized direct current electrical cardioversion is the preferred choice in haemodynamically compromised af patients as it is more effective than pharmacological cardioversion and results in immediate restoration of sinus rhythm. In stable patients, either pharmacological cardioversion or electrical ardioversion can be attempted; pharmacological cardioversion is less effective but does not require sedation. Of note, pre-treatment with aads can improve the efficacy of elective electrical cardioversion.

Electrical cardioversion. Electrical cardioversion can be performed safely in sedated patients treated with i.V. Midazolam and/or propofol or etomidate. Bp monitoring and oximetry during the procedure should be used routinely. Skin burns may occasionally be observed. Intravenous atropine or isoproterenol, or temporary transcutaneous pacing,should be available in case of post-cardioversion bradycardia. Biphasic defibrillators are standard because of their superior efficacy compared with monophasic defibrillators

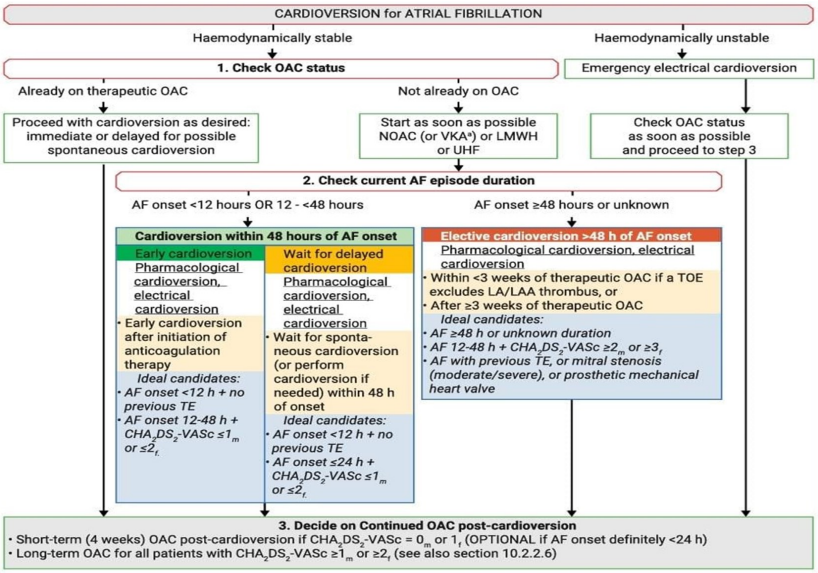


Figure 19: Cardioversion for AF

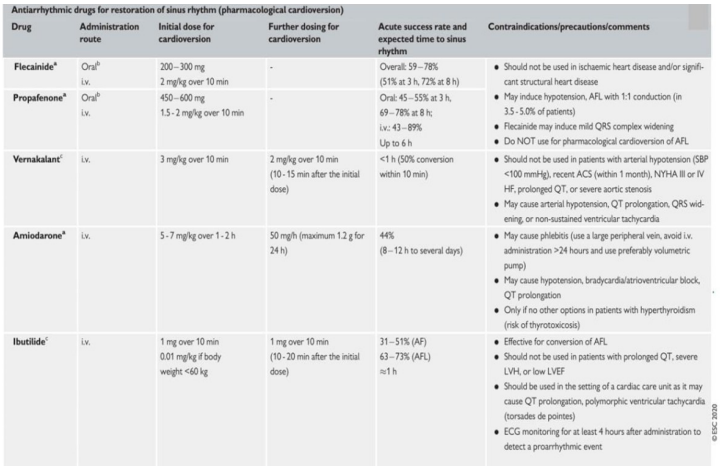
Factors Associated With An Increased Risk For Af Recurrence After Elective Cardioversion

- ❖ Older age
- ❖ Female sex,
- ❖ Previous cardioversion,
- ❖ Chronic obstructive pulmonary disease (COPD),
- ❖ Renal impairment,
- ❖ Structural heart disease,
- ❖ Larger LA volume index, and HF

Pharmacological cardioversion (including 'pill in the pocket'):

Pharmacological cardioversion to sinus rhythm is an elective procedure indicated in hemodynamically stable patients. Its true efficacy is biased by the spontaneous restoration of sinus rhythm within 48 h of hospitalization in 76 - 83% of patients with recent onset AF (10 - 18% within first 3 h, 55 - 66% within 24 h, and 69% within 48 h). Therefore, a 'wait and watch' strategy (usually <24h) may be considered in patients with recent onset AF as non inferior alternative option to early cardioversion. AF catheter ablation is a well-established treatment for the prevention of AF recurrences. When performed

by appropriately trained operators, AF catheter ablation is a safe and superior alternative to AADs for maintenance of sinus rhythm and symptom improvement. Indications for AF catheter ablation are presented for paroxysmal and persistent AF in patients with and without risk factors for post-ablation AF recurrence.



Antiarrhythmic drugs for restoration of sinus rhythm (pharmacological cardioversion)

Drug	Administration route	Initial dose for cardioversion	Further dosing for cardioversion	Acute success rate and expected time to sinus rhythm	Contraindications/precautions/comments
Flecainide[a]	Oral[b] i.v.	200–300 mg 2 mg/kg over 10 min	-	Overall: 59–78% (51% at 3 h, 72% at 8 h)	• Should not be used in ischaemic heart disease and/or significant structural heart disease
Propafenone[a]	Oral[b] i.v.	450–600 mg 1.5–2 mg/kg over 10 min	-	Oral: 45–55% at 3 h, 69–78% at 8 h; i.v.: 43–89% Up to 6 h	• May induce hypotension, AFL with 1:1 conduction (in 3.5–5.0% of patients) • Flecainide may induce mild QRS complex widening • Do NOT use for pharmacological cardioversion of AFL
Vernakalant[c]	i.v.	3 mg/kg over 10 min	2 mg/kg over 10 min (10–15 min after the initial dose)	<1 h (50% conversion within 10 min)	• Should not be used in patients with arterial hypotension (SBP <100 mmHg), recent ACS (within 1 month), NYHA III or IV HF, prolonged QT, or severe aortic stenosis • May cause arterial hypotension, QT prolongation, QRS widening, or non-sustained ventricular tachycardia
Amiodarone[a]	i.v.	5–7 mg/kg over 1–2 h	50 mg/h (maximum 1.2 g for 24 h)	44% (8–12 h to several days)	• May cause phlebitis (use a large peripheral vein, avoid i.v. administration >24 hours and use preferably volumetric pump) • May cause hypotension, bradycardia/atrioventricular block, QT prolongation • Only if no other options in patients with hyperthyroidism (risk of thyrotoxicosis)
Ibutilide[c]	i.v.	1 mg over 10 min 0.01 mg/kg if body weight <60 kg	1 mg over 10 min (10–20 min after the initial dose)	31–51% (AF) 63–73% (AFL) ≈1 h	• Effective for conversion of AFL • Should not be used in patients with prolonged QT, severe LVH, or low LVEF • Should be used in the setting of a cardiac care unit as it may cause QT prolongation, polymorphic ventricular tachycardia (torsades de pointes) • ECG monitoring for at least 4 hours after administration to detect a proarrhythmic event

Figure 20: Anti-arrhythmic drugs used in reversal of sinus rhythm

Af Catheter Ablation:

❖ It is a well-established treatment for the prevention of AF recurrences. When performed by appropriately trained operators, AF catheter ablation is a safe and superior alternative to AADs for maintenance of sinus rhythm and symptom improvement.

❖ Indications for AF catheter ablation are presented for paroxysmal and persistent AF in patients with and without risk factors for post-ablation AF recurrence.

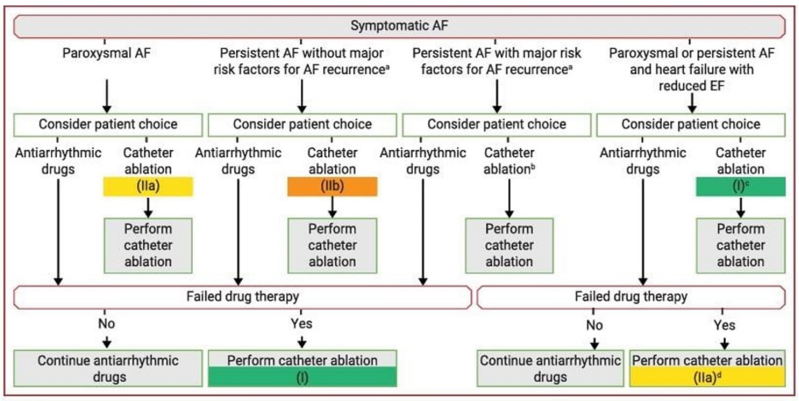


Figure 21: Indications for catheter ablation for symptomatic AF

C=Cardiovascular And Comorbidity Optimization

- ❖ Weight loss
- ❖ Avoid alcohol
- ❖ Given the importance of hypertension as a precipitating factor for AF, which should be regarded as a manifestation of hypertension target-organ damage,treatment of hypertension consistent with current BP guidelines is mandatory in AF patients, aiming to achieve BP <_130/80 to reduce adverse outcomes
- ❖ Diabetes control

Goals of Management:

- ❖ Haemodynamic stabilisation
- ❖ Control of ventricular rate
- ❖ Restoration of sinus rhythm
- ❖ Prevention of embolic complications
- ❖ Treatment of underlying cause

1. **If the patient's clinical status is severely compromised** (presence of hypotension, angina, syncope, pulmonary oedema or altered sensorium), synchronised DC cardioversion starting at 100 J (or 50 J using biphasic cardioverters) is the treatment of choice.

2. **If the patient's clinical status is not severely compromised**, treatment is in two steps:

a)**Slowing the ventricular rate** with verapamil, diltiazem, propranolol, esmolol or digoxin. The goal is to achieve a ventricular rate of less than 100/minute. Controlling the ventricular rate increases cardiac output, decreases the metabolic demand of the heart and avoids the potentially dangerous side effects of rhythm-control drugs. The doses of various drugs are:

Diltiazem: 10 mg intravenously over 2 minutes; repeat same dose in 15 minutes if required; start an infusion at 10-15 mg/hour to maintain ventricular rate below 100/minute.

Verapamil: 5-10 mg intravenously over 2 minutes; repeat in 30 minutes if required. Propranolol: 1 mg intravenously over 2 minutes; repeat every 5 minutes up to a maximum of 5 mg.

Digoxin: 0.25-0.5 mg intravenously, then 0.25 mg after 4-6 hours and another dose after another 12 hours. Peak effect not seen for hours and, therefore, less commonly used at present.

Amiodarone: 150 mg over 10 minutes, followed by 1 mg/minute over 6 hours and then 0.5 mg/minute for next 18 hours. Drug of choice in stable patients with known ejection fractions of less than 40%. Less likely to produce fall in blood pressure compared to other drugs.However, it may convert atrial fibrillation to normal rhythm that may lead to embolism.

Adverse effects of amiodarone include the following:

Hepatic toxicity characterised by hepatitis that can progress to cirrhosis.

Pulmonary toxicity can develop within 6 weeks or after years of therapy and most often manifests as cough and dyspnoea

Thyroid dysfunction (hypothyroidism, hyperthyroidism)

Sun sensitivity

Ocular symptoms

3. Converting rhythm to normal sinus rhythm

Pharmacological cardioversion to sinus rhythm with quinidine, ibutilide, flecainide, propafenone or amiodarone. The dose of amiodarone 5-7 mg/kg intravenously over 1 hour followed by 1.2-1.8 g/24-hour infusion. If medical cardioversion fails, electric cardioversion is performed after 3 weeks of warfarin therapy that is continued for another 4 weeks after

cardioversion.Anticoagulation is recommended increases risk of stroke, MI and death

4. **In patients in whom cardioversion is unsuccessful** or in whom atrial fibrillation is likely to recur, treatment consists of the following:

• Allowing the patient to remain in atrial fibrillation but reduce the ventricular rate by digitalis, diltiazem, verapamil or propranolol.

• Goal is to achieve a resting heart rate of 80/minute.

•Chronic anticoagulation

5. **Antithrombotic therapy**:

❖ Early medical or electric cardioversion may be done without prior anticoagulation therapy when atrial fibrillation has been present for less than 48 hours.

❖ If duration of atrial fibrillation exceeds 48 hours or is unknown, a transoesophageal echocardiography should be done to exclude an atrial thrombus. If no atrial thrombi are observed heparin is administered before cardioversion (if conversion to sinus rhythm is planned) that is followed by warfarin for 4 weeks.

❖ If atrial thrombi are seen on echocardiography, cardioversion should be delayed and anticoagulation with warfarin is administered for 3 weeks prior to cardioversion. Warfarin is continued for another 4 weeks after cardioversion.

❖ If cardioversion is unsuccessful and patient remains in atrial fibrillation, or cardioversion is not planned, longterm warfarin therapy is recommended if CHA2DSr VASc score 2. or patient has a previous history of stroke or transient ischaemic attack. • Thus, anticoagulants are required in all three types of atrial fibrillation i.e. paroxysmal, persistent and permanent.

❖ Anticoagulants include warfarin, dabigatran (a direct thrombin inhibitor) or apixaban (a direct factor Xa inhibitor).

❖ With warfarin, the INR should be maintained between 2.0 and 3.0 (between 2.5 and 3.5 if underlying valvular lesion is present).

6. **Aspirin**:

Aspirin 325 mg/day can be used as an alternative to warfarin in the following situations:

Contraindication/allergy to warfarin; or Age <75 years with no previous stroke or transient ischaemic attack; and no hypertension, diabetes or heart failure.

7. **Refractory cases** are managed with antitachycardia pacemakers or inducing complete heart block by ablation of bundle of His followed by permanent pacemaker implantation

Note: Rate-control strategies advocate medically slowing ventricular response to the fibrillating atrium and using anticoagulation to reduce stroke risk. On the other hand, rhythm- control strategies involve medical or electrical conversion to sinus rhythm to improve haemodynarnics and symptoms and, theoretically, reduce stroke risk. However, data available suggest no definite advantage of one approach over the other. Rate control along with chronic anticoagulation is possibly the best strategy for most patients with atrial fibrillation. In some select group patients (e.g. young patients or patients with left ventricular dysfunction producing symptoms) rhythm control may be tried, even though there is no data to support his line of action.

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Evolving paradigms in cardiac rehabilitation: Personalized patient care for tomorrow"

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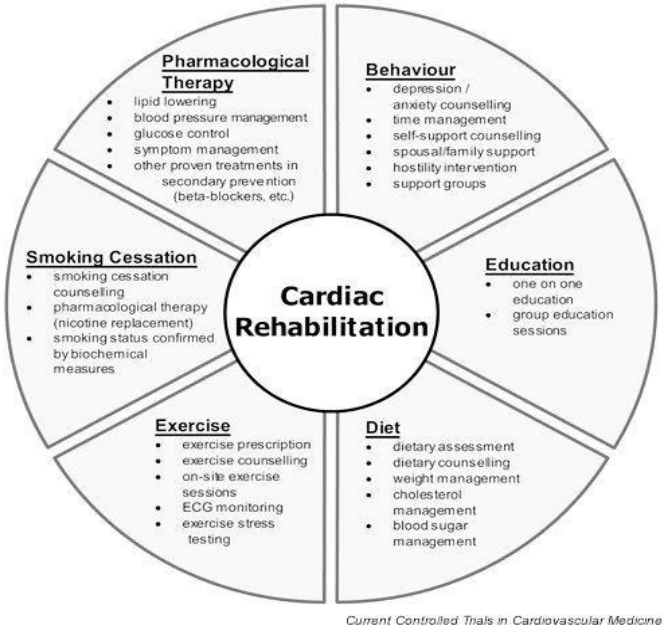
Introduction

In the last few decades, Cardiac Rehabilitation developed itself from a simple safe return to physical activity monitoring multidisciplinary strategy which focuses on patient education and individually adapted exercise training, modification of cardiac risk factors and overall well-being of cardiac patients. This has emerged as a useful tool for taking care of heart disease patients. The increasing evidence in the field of cardiac rehabilitation suggests that tremendous benefits can be derived from optimal utilization of cardiac rehabilitation in various cardiovascular pathologies including ischemic heart disease, heart failure, and post-heart surgery. Cardiac rehabilitation's positive

effect includes lower mortality rate among patients, s enhanced psychosocial wellness in general. Unfortunately, most often this valuable service is not used because people do not refer it enough or enroll to participate in it. Creating new approaches coupled with using trans telephonic EKGs and other forms of monitoring will help expand access to cardiac rehabilitation.

Objectives:

Heart-related healing has better over the last forty years from a simple watching Program for the safe return to physical activities to an (using different kinds of expert knowledge)Program including (after an operation) patient care, the optimization of medical treatment, (related To vitamins, protein, etc., in food) counseling, smoking ending, risk separation (into clear layers),Stress management, high blood pressure management and the control of (disease where blood Sugar swings wildly) or dyslipidemia. The World Health Organization offered a definition of heart-Related healing/repairing that summarizes very well its goals: the sum of activities demanded to influence positively/well the hidden (under) cause of the disease, as well as to make sure that the patient will getting better physical, mental and social conditions, so that they may, by their own efforts, preserve or resume when lost, as commonly regular a place as possible in the life of the community (World Health Organization 1993)



Current Controlled Trials in Cardiovascular Medicine

Indications:

- Acute myocardial infraction
- stable angina pectoris
- coronary artery bypass graft surgery [CABG]
- heart valve repair or replacement
- percutaneous transluminal coronary angioplasty [PTCA]
- Heart transplantation or heart lung transplantation
- Heart attack
- Cardiomyopathy
- Heart failure
- Angioplasty and stenting

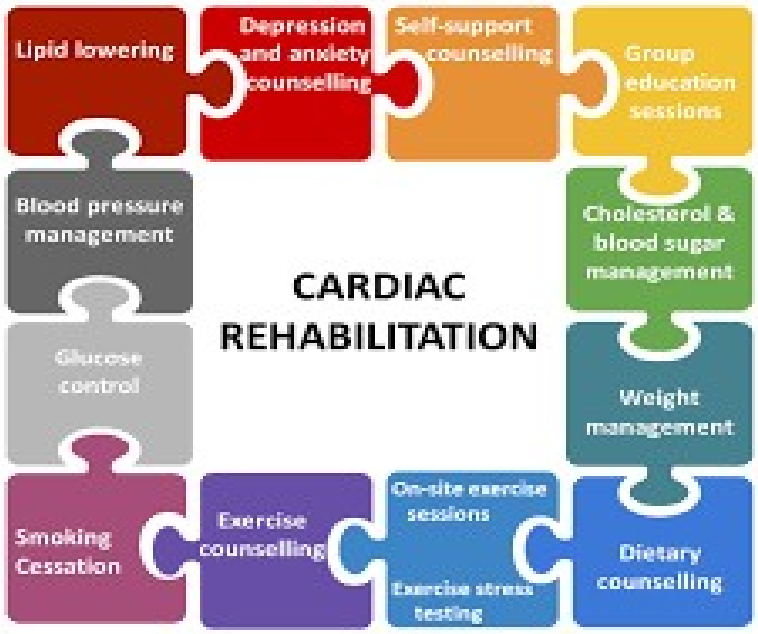
Individualized exercise training can also be beneficial for patients with peripheral artery disease (PAD), as PAD frequently coexists with coronary artery disease. One-third of individuals with documented coronary artery disease also have PAD, and half of patients with PAD have coronary artery disease. Sending these individuals to a program for heart-related healing or repair will ensure that they receive adequate secondary prevention.

Contraindications:

- Unstable angina
- Decompensated heart failure
- Ramified ventricular Arrhythmias
- Pulmonary arterial hypertension greater than 60 mm hg
- Intracavitary Thrombus
- Recent thrombophlebitis with or without pulmonary embolism
- Severe obstructive Cardiomyopathies
- Severe or symptomatic aortic stenosis
- Uncontrolled inflammatory or infectious pathologies
- Musculoskeletal condition that prohibits physical exercises.

Components of cardiac rehabilitation:

Core Components of Cardiac Rehabilitation/Secondary Prevention Programs: Blood Pressure Management, Lipid Management, Diabetes Management, Tobacco Cessation, Psychosocial Management, Physical Activity Counseling, and Exercise Training Cardiac Rehabilitation.



Phases of cardiac rehabilitation:

Cardiac rehabilitation consists of 3 phases

- Phase 1: Inpatient phase or Clinical phase
- Phase II: Outpatient cardiac rehabilitation
- Phase III: Post-cardiac rehab. Maintenance

Phase I:

This phase starts in the inpatient setting shortly after a cardiovascular event or intervention. Initially, the rehabilitation team, including therapists and nurses, evaluates the patient's physical Abilities and motivation for rehabilitation. They begin with gentle exercises at the bedside to Maintain range of motion and prevent hospital deconditioning. The team also focuses on activities of daily living (ADLs) and educates the patient on stress Management. Patients are advised to rest until any comorbid conditions or

post-operative Complications are treated. Additionally, the rehabilitation team assesses the need for assistive Devices, provides education to both patients and their families, and plans for the patient's Discharge.

Phase II: Outpatient cardiac rehabilitation :

After a patient is stabilized and cleared by cardiology, they can start outpatient cardiac Rehabilitation. Phase II usually lasts three to six weeks, but can extend up to twelve weeks. The Process begins with an assessment to identify physical limitations, participation restrictions due To other health issues, and activity constraints. Based on this assessment, a personalized therapy Plan is developed, including three components: information and advice, a customized exercise Program, and a relaxation routine. The goal of this phase is to encourage independence and Lifestyle changes, helping patients transition back to their daily lives at home.

Phase III: Post-cardiac rehab. Maintenance

Phase III focuses on greater independence and self-monitoring. The aim is to increase flexibility,Strengthen muscles, and improve aerobic fitness. Goal: Support long-term maintenance of lifestyle changes, track changes in risk factors, and Promote secondary prevention.

Team approach:

Cardiologist/Physician and co-coordinator to lead cardiac rehabilitation

- Clinical Nurse Specialist
- Physiotherapist
- Clinical nutritionist/Dietitian
- Occupational Therapist
- Pharmacist
- Psychologist
- Smoking cessation counselor/nurse
- Social worker
- Vocational counselor

Effective physiotherapy in cardiac rehabilitation:

- Warm up : 15 minutes

  Gradually increasing heart rate .

- Main exercise: 15 -40 Minutes

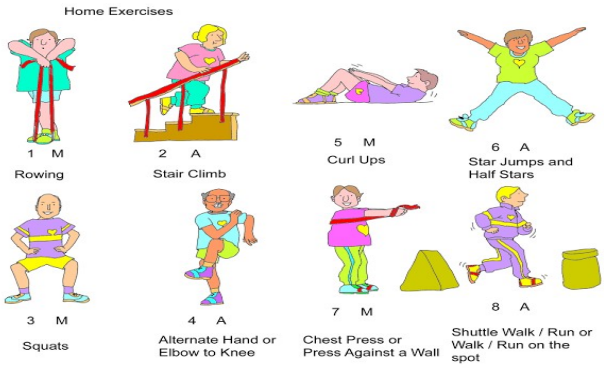
  Maintain target heart rate.

- Cool down : 10 -15 mins

  Gradually decrease heart rate

Exercises:

1. Warm up: walking and low level cycling
2. Main exercise: stretching activities :Upper back stretches, chest stretches, lower back Stretches
3. Cool down: walking and low level cycling.

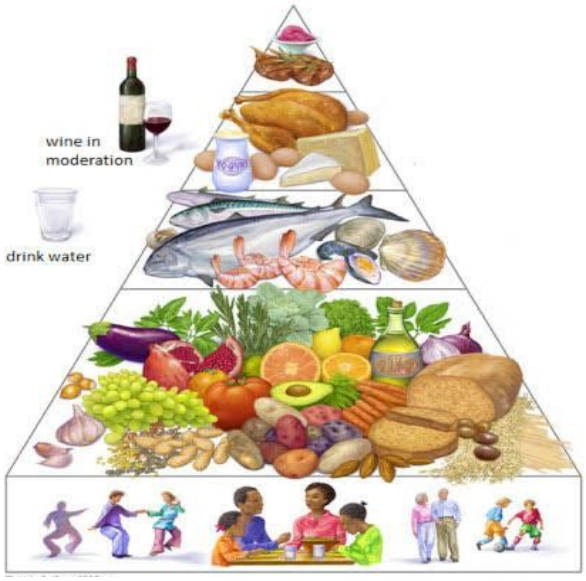


Right diet and proper nutrition:

Nutrition is important to reduce risk of recurrence of heart conditions and also helps in achieving Optimal recovery .Fruits , vegetables, whole grains , nuts legumes , fish ,low fat diary products , liquid Vegetable oil.

Recommended dietary allowance:

- Wheat, rice, jowar, bajra, maize, and a variety of dals and vegetables:400-500 g per day.
- Fresh fruits:300-500 g per day
- Low-fat diet:30-50 g per day
- Lean meat poultry/ chicken or fish:30-50 g per day.



These diet includes:

- Moderate amount of unsaturated fatty acids is important of lowering cholesterol.
- Lower amount of saturated, and trans fatty acids ,sugar and starch.

With diet and exercise health care provider will monitor heart health through series of lab tests in heart recovery program, a few lab tests are necessary to assess how well rehabilitation is Working for you.

Postoperative lab tests:

- ECG
- ECHO
- CHEST x ray

Heart recovery begins after surgery:

Postoperative follow up: heart recovery starts about 2-3weeks after discharge 12 week exercise program and basic parameters are assessed .ideally after 12 week program Patient will required to repeat all monitored test and come for follow up.

Benefits of cardiac rehabilitation:

- It focuses on safe, effective exercise.
- It encourages a heart healthy diet and lifestyle.
- It can help patients quit smoking
- Engaging in exercise safely.

Risks of cardiac rehabilitation:

Exercise during cardiac rehabilitation may very rarely result in harm or a hazardous cardiac rhythm. In order to treat you immediately, the cardiac rehab team will require you to stop exercising if this occurs. The cardiac rehab experts will consult with your primary healthcare provider or cardiologist as needed. Before you go back to cardiac rehabilitation, they might want to check you out or order additional testing.

Patient care:

Exercise instruction, psychological support, and lifestyle education about heart-healthy living are all part of cardiac rehabilitation. Maintaining a healthy weight, giving up smoking, and eating a balanced diet are examples of healthy lifestyle choices.

Conclusion

Even with proof of its advantages, cardiac rehabilitation is still not widely utilized. Heart-related It has been demonstrated that cardiac rehabilitation is a safe and efficient way to lower morbidity and mortality in individuals with cardiovascular disease and improve their quality of life. By enhancing referrals and participation in cardiac rehabilitation programs and customizing care based on the patient's profile, this affordable tool would help more patients.

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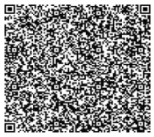	Subject: Cardiology
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New therapeutic approaches targeting inflammation in heart failure

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Introduction

Heart failure (HF) is a progressive and complex clinical syndrome with functional, atrial, and ventricular cardiac abnormalities that impair ventricular filling and ejecting of blood.(1,2) HF is classified into three groups based on left ventricular ejection fraction (LVEF), i) heart failure with reduced ejection fraction (HFrE), LVEF 25% to 40%, ii) heart failure with preserved ejection fraction (HFpEF), LVEF 50% to 65%) and heart failure with mildly reduced ejection fraction (HFmrEF), LVEF, 41% to 50%).(3–5)HFrEF is a spectrum of heterogenous disorders including ejection fraction less than 45%, impaired diastolic dysfunction, and other myocardial disorders.(6) Pathological causes of HF are diverse which include myocardial infarction, high blood pressure, cardiac valvular diseases, idiopathic cardiomyopathy, genetic mutation, and environmental mechanisms.(7) Several pathological mechanisms are involved in the pathogenesis of HF(8) which include necrosis, myocardial inflammation, and other comorbidities like diabetes mellitus, and hypertension.

The main molecular mechanism involved in the pathogenesis of HF is elevated OS and inflammation, which are upregulated in HF. These two mechanisms are closely interrelated with each other which forms a vicious cycle that contributes to HF pathogenesis.(9)OS is defined as an imbalance between antioxidants and detoxification of reactive oxygen species (ROS).(10,11)Overproduction of ROS results in cellular dysfunction, myocardial damage, DNA damage, and lipid peroxidation which leads to senescence.(10) OS(11) and inflammation(9) are the biomarkers that help to determine HF progression and the onset of HF.

Epidemiology

HF affects almost 23 million population all over the world. In this approximately 50% of the population is diagnosed with HFrEF. 5 to 7 percent per one lakh is reported annually. According to aging, the number of populations is increasing with HF. Based on sex, compared to women, men are more prominent to HFrEF. However, accurately determining the prevalence of HF is challenging, as it may be underreported or undiagnosed in underdeveloped countries, and disease penetrance that is not fully expressed or the manifestation of the disease occurring later in life may affect these figures.(12–14) HF is responsible for about 60 percent of young-aged cardiomyopathies with the highest incidence of kids under one year of age. The mortality rate for HF after diagnosis is around 60 to 70 percent of the population.(15)

Causes of heart failure

Hereditary, and systemic disease are the most common causes contributing to HF. The primary causes that lead to HF are ischemic heart disease, myocardial infarction, chronic obstructive pulmonary disease, and hypertensive diseases.(5,8,9) Secondary causes that lead to HF are dilated cardiomyopathy (DCM), peripartum cardiomyopathy, myocarditis, genetic causes, rheumatic heart disease, and valvular heart diseases.(11)

Signs and symptoms

In HF, cardiac output (CO) is decreased, and lack of venous return. Due to ineffective flow from the ventricle, pulmonary capillary wedge pressure (PCWP) increases resulting in dyspnea, asthma, and COPD. The right ventricle (RV) fails to accommodate the systemic venous returns which results in edema in the lower extremities. When CO is not maintained the metabolic needs throughout the body result in fatigue. Palpitation occurs when the heart rate increases due to a decrease in the CO.(4,16)

Symptoms are mainly classified based on the New York Heart Association (NYHA classification) (Table 2.1.3.1). Symptoms with class 1 have no limitation in regular physical activity, class II have minimal symptoms such as giddiness, breathlessness, and palpitation only during normal activity, class III patients have no symptoms during rest but have marked symptoms during daily physical activity, class IV patients have symptoms even during rest and high limitations.(17,18) American Heart Association (AHA) classification describes the symptoms based on the development and disease

progression (Table 2.1.3.2.) Stage A patients are at high risk for developing HF, but do not have any atrial and ventricular abnormalities, stage B patients have atrial and ventricular abnormalities with mild symptoms, stage C patients have underlying atrial and ventricular changes with previous history of symptoms, stage D indicates end-stage patients who need immediate therapy, both pharmacological as well as therapeutical.(19)

Class I	no limitation in regular physical activity
Class II	minimal symptoms such as giddiness, breathlessness, palpitation only during normal activity
Class III	no symptoms during rest but has marked symptoms during daily physical activity
Class IV	symptoms even during rest and high limitations

Table 1. New York Heart Association classification

Stage A	high risk for developing HF, but does not have any atrial and ventricular abnormalities
Stage B	atrial and ventricular abnormalities with mild symptoms
Stage C	underlying atrial and ventricular changes with a previous history of symptoms
Stage D	end-stage patients who need immediate therapy, both pharmacological as well as therapeutical

Table 2. American Heart Association classification

Pathophysiology

The mechanisms underlying HF are apoptosis of cardiac myocytes, volume or pressure overload, and impaired ventricular filling of the heart.(20,21) A decrease in stroke volume (SV) and end-diastolic pressure occurs when the myocardium fails to contract. This leads to HF. Several compensatory mechanisms are involved in reverse HF, such as frank starling law, neurohormonal activation, and ventricular remodeling.(21) According to Frank Starling's law, a change in the contractility of myocyte results in an increase in SV, CO, and venous return of the heart.(22) A decrease in the CO leads to sympathetic activation and stimulation of the renin-angiotensin-aldosterone system (RAAS) with retention of salt and water and an increase in

the circulating volume.(20) CO gets increased, by frank starling law. (figure 2.1.4)

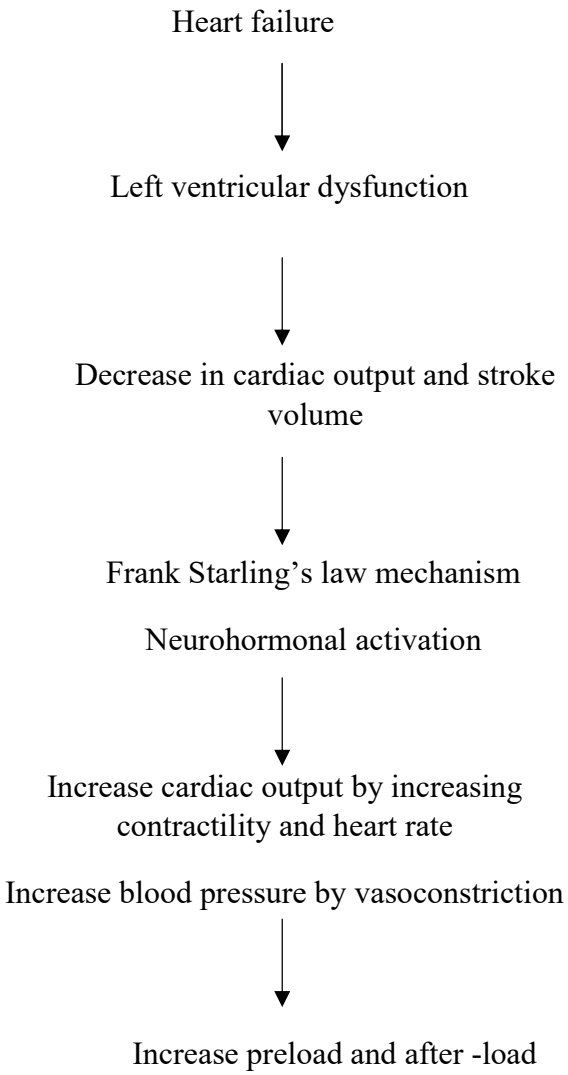

Figure 1 Vicious cycle of heart failure

Diagnostic Investigations

Chest X-ray is one of the standard methods for diagnosing HF. Chest radiographs often reveal cardiomegaly and redistribution of pulmonary venous blood flow, although pulmonary edema is less frequently observed. In chest x-ray, secondary to effusion volume overload, cardiomegaly and Kerley B -lines are observed. (23,24). Cardiac CT and cardiac MRI are precise evaluations of LV volumes, ventricular wall thickening, and pumping activity, in addition to offering tissue characterization. In MRI, the presence of delayed gadolinium indicates cellular death of the myocardium or scarring of the endocardium. When both death or thinning and edema (high signal T2 intensity) are detected, along with hyperemia (early gadolinium enhancement), it suggests the likelihood of myocardial inflammation.(25,26) The observation of effusion in the pericardium on cardiac MRI suggests the possibility of myocarditis.

Electrocardiogram (ECG) may exhibit nonspecific repolarization with LVH, and LAE abnormalities. Sinus tachycardia is the most common abnormality with reduced ejection fraction. Increased PR interval is the first indication of decreased ejection fraction. Prolonged QRS duration is a strong indicator of systolic HF. LBBB, AV block, and LAFB are other possible conduction abnormalities that can occur.

Echocardiography is the standard method for assessing the LV structure and function. A useful test for diagnosing HF, structural abnormalities, valvular abnormalities, cardiomyopathies, rheumatic heart disease, and congenital heart diseases. In HF patients, the structural abnormality is visualized in a 2D echocardiogram. Several views are used to diagnose HF.(27,28) Parasternal long axis view shows enlarged right and LV. In the parasternal short axis view, systolic dysfunction is assessed. In the apical four chamber view structural and functional abnormalities are diagnosed. Tissue doppler imaging evaluates the myocardial tissue velocities, which is used for assessing LV diastolic dysfunction. (29,30)

Oxidative stress and heart failure

In HF, OS correlates with LV dysfunction that occurs in the plasma and myocardium. Mitochondrial dysfunction, which can occur due to reduced ATP production, is a key factor in the development of OS. Mitochondria are the primary source of ROS production in cardiomyocytes, and mitochondrial dysfunction can lead to increased ROS production and OS. The effects of OS in HF are numerous and can include impaired mitochondrial function, cellular damage, and apoptosis. ROS can damage mitochondrial proteins, lipids, and

DNA, resulting in damage to mitochondrial work and producing decreased ATP.

ROS can also cause cellular damage, including lipid peroxidation and protein oxidation, leading to cellular dysfunction and apoptosis. Inflammation is another important factor in the development of OS in HF. Inflammatory cells can produce ROS, which can contribute to OS. In addition, chronic inflammation can lead to increased OS by inducing mitochondrial dysfunction and activating OS pathways. For example, tumor necrosis factor-alpha (TNF-α), a proinflammatory cytokine, can activate NADPH oxidase, leading to increased ROS production and OS.(31) ROS negatively alters calcium causing arrhythmia and contributes to remodelingof the heart. Endothelial cells are important for maintaining vascular function and protecting against OS.(32) Endothelial dysfunction, which can occur due to reduced NO production, can lead to increased ROS production and OS.

Biomarkers and HF Pathogenesis

Sirtuin1 (Sirt1),(33) nicotinamide adenine dinucleotide (NAD+),(34) asymmetric dimethylarginine (ADMA),(35) reduced glutathione (GSH) and oxidised glutathione (GSSG), the ratio of reduced glutathione to oxidized glutathione (GSH:GSSG ratio),(36,37) circulating levels of visfatin or nicotinamide phosphoribosyltransferase (NAMPT)(38) are the biomarkers which contribute to HF pathogenesis.

Therapeutic Strategy and Future Perspective

Therapeutic management is based on AHA guidelines. Initial management includes lifestyle modification such as weight loss, daily physical activity, stop smoking and alcohol, nutritional diet, and restriction of sodium and salt. Medical management includes treating hypertension, diabetes mellitus, dyslipidemia, and arrhythmias.(39)

Pharmacological management of HF includes medication that deteriorates compensatory mechanisms. Angiotensin converting enzyme inhibitors (ACE), diuretics, digoxin, angiotensin receptor-neprilysin inhibitors (ARNI), betablockers are the STD HF therapies.(39) ACE inhibitors such as captopril, and enalapril reduce the RAAS activation which prevents the conversion of angiotensin 1 to angiotensin II. ARNI is replaced by ACE inhibitors. ARNI such as valsartan, and sacubitril reduces the symptoms, treats hypotension, and treats hyperkaliemia. Diuretics such as furosemide which is a loop diuretic help to reduce edema and improve physical activity by increasing exercise tolerance. Digoxin is an inotropic agent that reduces the activation of

the sympathetic nervous system (SNS) and RAAS activation. Betablockers such as metoprolol, and carvedilol protect from the overstimulation of SNS and increase the contraction by improving heart rate. Aldosterone antagonists also inhibit RAAS activation.(6,40)

Surgical management includes cardiac vascularization, cardiac resynchronization therapy (CRT), ventricular assist device, and heart transplantation. CRT improves ventricular function by pacing on both ventricles. Ventricular assist device decreases the CO, whereas transplantation of the heart replaces the failing heart.(6,40)

Despite advancements in therapeutic approaches and prevention, the prognosis for heart failure remains poor because the treatments for heart failure do not address the underlying pathogenic mechanisms(8), although OS and inflammation are the main mechanisms contributing to HF pathogenesis.(9) Trimetazidine (TMZ), is an antianginal drug used for treating angina pectoris.(41) TMZ inhibits long-chain mitochondria 3-ketoacyl coenzyme A thiolase enzymeit improves myocardial metabolism by inhibiting fatty acid oxidation and promotes glucose metabolism via beta-oxidation, besides other cardiac benefits.(42) TMZ binds to mitochondria, increases the rate of glucose oxidation, and reduces the rate of fatty acid oxidation. Studies show that TMZ, a traditional HF treatment, enhances LV function in patients with HF of various etiologies.(43,44) The guideline of the European Society of Cardiology (ESC) includes TMZ for treating HF.(41) Together evidence suggestes that the additive effect of TMZ enhances LVEF in patients with myocardial infarction.(45)

Adjuvant therapy such as TMZ, N-acetylcysteine (NAC) which is an anti-inflammatory and antioxidant molecule, magnesium (Mg) which is a sirt1 activator, and niacin which is an NAD+ booster and acts as a vitamin B3 supplement address the mechanism that are involved in the underlying pathology of HF. The mechanisms involved in this pathogenesis are elevated OS, sirt1 deficiency increase in inflammation, thus TMZ decreases inflammation

Adjuvant therapy such as N-acetylcysteine (NAC) which is an anti-inflammatory and antioxidant molecule, magnesium (Mg) which is a sirt1 activator, and niacin which is an NAD+ booster and acts as a vitamin B3 supplement address the mechanism that are involved in the underlying pathology of HF. The mechanisms involved in this pathogenesis are elevated OS, sirt1 deficiency increase in inflammation, decreased NAD+ and increased circulating concentrations of visfatin.

Reports showed that Quercetin, an anti-inflammatory drug acts as a sirt1 activator, thereby decreasing the concentration of visfatin.(46) Based on these reports, by activating sirt1, (47) TMZ improves HF symptoms.(41)

Decrease in NAD+ and deficient in the Mg are most prevalent in HF. (48). Mg and NAC supplement helps with elevated OS and pro-inflammation. Cardiomyocyte senescence could be the cause for the increased circulating level of visfatin. Such senescence can be treated by supplementation of NAD+. Thus, an increase in the visfatin can be therapeutically treated with niacin, an NAD+ booster. Reports show that in invitro studies treating rats/mice with niacin restores the cardiac function(49). Thus supplementation of Mg and niacin could help in the restoration of HF.

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