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HEART FAILURE: PATHOPHYSIOLOGY AND MANAGEMENT

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Abstract:

Context: *Heart failure (HF) is defined as a clinical syndrome that is caused by mal-structural and malfunctional changes in the myocardium resulting in an impairment of ventricular filling or the ejection fraction. There are many causes of HF such as reduced ventricular function, ischemia related malfunction, and hemodynamic overload. HF is mostly clinically diagnosed and classified, but laboratory markers help in confirming the diagnosis.*

Methodology: *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: heart failure, ventricular dysfunction, classification of heart failure, clinical evaluation, diagnosis of heart failure, management of heart failure*

Aim: *In this review, we aim to study the classification, pathophysiology, and clinical presentation of heart failure. We will also study the appropriate methods of diagnosis and management.*

Conclusion: *Heart failure is a complicated disease and a major cause of morbidity and mortality in developing and developed countries. The pathophysiology behind it is various. A standardized medical therapy has been successful in the early stages of HF. The management is different according to the presented symptoms and the advanced stages of HF require frequent hospitalization due to the presence of severe HF and or associated co-morbid condition. The management plan differs whether the patient is in admission or in outpatient settings.*

Keywords: *heart failure, cardiac emergencies, management of hear failure*

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INTRODUCTION:

Heart failure (HF) is defined as a clinical syndrome that is caused by mal-structural and malfunctional changes in the myocardium resulting in an impairment of ventricular filling or the ejection fraction. There are many causes of HF. The most common cause of HF is reduced left ventricular myocardial function. Other causes of HF include diseases of the pericardium, myocardium, heart valves, endocardium or great vessels. The mechanisms behind HF are numerous. The most important pathogenic mechanisms leading to HF are the ischemia-related dysfunction, hemodynamic overload, excessive neuro-humoral stimulation, ventricular remodeling, abnormal myocyte calcium cycling, accelerated apoptosis, genetic mutations, and excessive or inadequate proliferation of the extracellular matrix [1].

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: heart failure, ventricular dysfunction, classification of heart failure, clinical evaluation, diagnosis of heart failure, management of heart failure

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

Classification of Heart Failure

There are different ways to classify HF. The clinically relevant classification is based on the failing chamber. It includes predominantly left ventricular, right ventricular or biventricular based on the location of the deficit. Depending on the time of onset, HF can be classified as acute or chronic. Another clinical classification includes tw major types based on the functional status of heart or the ejection fraction; heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). HFpEF patients are usually females and older adults. EF is often more than 50% with normal volume of the left-ventricular (LV) cavity, however, the LV wall is stiff and thickened; So, the ratio of LV mass/end-diastolic volume is higher than normal [2]. HFpEF can be further classified as borderline HF when the EF is between 41% and 49% and improved HF if EF is more than 40%. While, patients diagnosed with HFrEF, the ratio of LV mass/end-diastolic volume is either normal or reduced due to LV cavity dilatation. Histologically, the diameter of cardiomyocytes and the volume of myofibrils are higher in HFpEF than in HfrEF [1].

Moreover, HF can also be categorized based on the cardiac output. There are two main types. The high-output failure and low-output failure. High-output failure is a less common disorder characterized by an elevated resting cardiac index of greater than 2.5–4.0 L/min/m^2 and low systemic vascular resistance. The common pathological causes of high output failure include but not limited to: vascular shunting commonly occur after trauma, severe anemia, hyperthyroidism and vitamin B1 deficiency. The mechanism behind it is mainly due to ineffective blood pressure and/or volume. When there is ineffective blood volume or pressure, the renin-angiotensin-aldosterone system (RAAS) is activated by the sympathetic nervous system. This cause the stimulation of the posterior pituitary gland and the release of antidiuretic hormone (ADH), ultimately leading to ventricular enlargement, negative ventricular remodeling and HF. Low cardiac output failure is more common and is characterized by less effective cardiac output, especially during exertion or increased metabolic demand. large MI, right ventricular dysfunction can lead to left ventricular dysfunction, in addition to acute pulmonary embolus and biventricular dysfunction are important causes of low output failure [3].

The New York Heart Association (NYHA) functional classification defines four functional classes as [4]:

- Class I: HF does not cause limitations to physical activity; ordinary physical activity does not cause symptoms.
- Class II: HF causes slight limitations to physical activity; the patients are comfortable at rest, but ordinary physical activity results in HF symptoms.
- Class III: HF causes marked limitations of physical activity; the patients are comfortable at rest, but less than ordinary activity causes symptoms of HF.
- Class IV: HF patients are unable to carry on any physical activity without HF symptoms or have symptoms when at rest.

The American College of Cardiology/American Heart Association (ACC/AHA) staging system is defined by the following four stages [5]:

- Stage A: High risk of heart failure, but no

structural heart disease or symptoms of heart failure;
- Stage B: Structural heart disease, but no symptoms of heart failure;
- Stage C: Structural heart disease and symptoms of heart failure;
- Stage D: Refractory heart failure requiring specialized interventions.

Pathophysiology of Acute Heart Failure

Acute heart failure or exacerbation attack is often described as a new-onset or deteriorating of symptoms and signs of HF, requires rapid therapy and usually the patient is admitted for proper therapy. The typical exacerbation attack of AHF presents with symptoms or signs related to volume overload and congestion rather than to hypoperfusion. Congestion is responsible for the major AHF cases. It is extremely essential that physicians understand the pathophysiologic mechanisms behind the congestion and AHF because it makes difference with the therapy. Moreover, the prognosis depends on the number of congested organs in the body which is relevant to the degree of AHF [6].

Pathophysiology of Congestion

In patients with cardiac dysfunction, the neuro-humoral pathways get activated to counter the negative effects of HF on perfusion and oxygen delivery to the peripheral tissues. These mechanisms include: the activation of sympathetic nervous system, the renin-angiotensin-aldosterone system and the arginine-vasopressin system [7].

While the neuro-humoral activation in HF may lead to impaired regulation of sodium excretion through the kidneys which results in sodium and, secondarily, fluid accumulation which exacerbate the condition. Indeed, significantly increased cardiac filling pressures and venous congestion are frequently observed days or weeks before the overt clinical decompensation [8].

When the transudation of fluid from extracellular compartments of the capillaries into the interstitium is more than the drainage capacity of the lymphatic system, edema occurs. Transudation of plasma fluid into the interstitium occurs due to relation between hydrostatic and oncotic pressures in the capillaries and in the interstitium in addition to the interstitial compliance. Edema is promoted by other mechanisms such as the increased transcapillary hydrostatic pressure gradient, decreased transcapillary oncotic pressure gradient and increased interstitial compliance [7].

In healthy subjects, the increased amount of the total body sodium is usually not accompanied by edema formation due to a large quantity of sodium get compensated by interstitial glycosaminoglycan networks without water retention. In addition, the interstitial glycosaminoglycan networks have low compliance which prevents fluid accumulation in the interstitium [8].

In HF, the normal physiology is interrupted by sodium accumulation, moreover the glycosaminoglycan networks become dysfunctional resulting in reduced compensatory capacity and increased compliance. In AHF, pulmonary or peripheral edema are poor indicators and reflect problems with left- and right-sided filling pressures, however, in case of dysfunctional glycosaminoglycan networks sometimes even mildly elevated venous pressures can lead to pulmonary and peripheral edema. Moreover, the excess amount of sodium being stored in the interstitial glycosaminoglycan networks does not reach the kidneys because it escapes renal clearance and is difficult to be removed from the body[8].

In addition, the persistence activation of the neuro-hormones can lead to maladaptation in the process leading to the remodeling of the ventricles and consequently myocardial dysfunction. The Pharmacological therapy is based on this fact. Inhibition of the sympathetic and renin-angiotensin-aldosterone systems with beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists and more recently the angiotensin receptor neprilysin inhibitor LCZ696 are the mainstays medications in the management of chronic HF [9].

The pathophysiology of AHF cannot be explained by fluid accumulation solely. In fact, the majority of AHF patients show only minimal increase in body weight (<1 kg) before hospital admission. In these particular patients, fluid redistribution is responsible for the congestion rather than accumulation. Moreover, Sympathetic stimulation induce a transient vasoconstriction resulting in acute distribution of volume from the splanchnic and peripheral venous system to the pulmonary circulation, without exogenous fluid retention. Regardless, fluid redistribution requires the presence of a certain amount of peripheral and splanchnic congestion [6].

Physiologically, the capacity of the venous system constitutes one fourth of the total blood volume and is responsible for a great amount of the preload stabilization leading to buffering of the volume

overload. In patient with concurrent hypertension and AHF, there is increased afterload and decreased venous capacity i.e. increased preload. This lead to alteration and mismatch in the ventricular-vascular coupling relationship [10].

Accumulation of fluid and fluid redistribution both are responsible for the production of increase in cardiac load and congestion in AHF, however their importance is likely to change according to the clinical situation. In some case the fluid accumulation is more common in decompensations of congestive heart failure (CHF) with reduced ejection fraction, in other cases fluid redistribution might be the predominant pathophysiological mechanism in AHF with preserved ejection fraction. Therefore, the therapy should be personalized according to the clinical scenario presented. While diuretics might be useful in some cases like fluid accumulation, vasodilators might be more appropriate in cases of fluid redistribution [7].

Moreover, the recent studies from human models reveal that venous congestion is not simply an epiphenomenon secondary to cardiac malfunction but has an active crucial role in the pathophysiology of AHF inducing pro-oxidant, pro-inflammatory and hemodynamic stimuli that contribute to acute exacerbation or decompensation attacks. The pathophysiological changes remain a controversial subject and incompletely explained however the biomechanical forces generated by congestion contribute significantly to the endothelial and neuro-humoral stimulation. In fact, endothelial stretch stimulates an intracellular pathway that stimulates the endothelial cells to change its phenotype and switch to a pro-oxidant, pro-inflammatory vasoconstricted state [10].

Diagnosis

Early introduction of therapy in AHF should be in three parts: triage, diagnosis and initiation of treatment, and reassessment. Because AHF is a life-threatening condition, current guidelines recommend the early management of AHF, specifically in the first 30–60 min after hospital admission or even earlier [1].

Clinical Evaluation

Patients presented with dyspnea should be initially evaluated to (i) assess severity of AHF (ii) establish or confirm the diagnosis of AHF and (iii) identify precipitating risk factors of AHF.

Patient history and physical examination should focus on the presence of congestion because congestion is the main feature of AHF, this would support the diagnosis of AHF. Symptoms of left-sided congestion include but not limited to dyspnea, orthopnea, bendopnea, paroxysmal nocturnal dyspnea. Additional symptoms and signs include cough, tachypnoea, pathological lung auscultation (rales, crackles, wheezing) and hypoxia. If there were no rales even with normal chest x-ray, the diagnosis of left sided congestion cannot be excluded. In fact, around 40–50% of patients with increased pulmonary-artery wedge pressure have completely normal chest radiography. In contrast, the right-sided congestion present with symptoms of increased body weight, bilateral peripheral edema, decreased urine output, abdominal tenderness, nausea and vomiting, jugular vein distension or positive hepato-jugular reflux, ascites, hepatomegaly, icterus [11].

The presence of signs and symptoms of hypoperfusion strongly indicate severity. These include but not limited to hypotension, tachycardia, weak pulse, mental confusion, anxiety, fatigue, cold sweated extremities, decreased urine output and angina due to myocardial ischemia. Cardiogenic shock (which is the most severe form of cardiac) is defined as the presence of inappropriate stroke volume and clinical and biological signs of hypoperfusion in AHF. Cardiogenic shock can lead to acute myocardial infarction and associated with in-hospital mortality rates of 40–50% but accounts for less than 10% of AHF cases [12].

Patients with AHF may be categorized in four groups according to the presence of clinical symptoms or signs of organ congestion to wet, dry, cold or warm. Two thirds of AHF patients are classified ‘wet-warm’ (congested but well perfused), about one of four are ‘wet-cold’ (congested and hypoperfused) and only a minority are ‘dry-cold’ (not congested and hypoperfused). The fourth groups ‘dry-warm’ represent the compensated (decongested, well-perfused) status. This classification can help with guiding initial management plan and consists of vasodilators and/or diuretics [13].

Noteworthy, the using inotropes is preferably limited to patients presented with signs of cardiogenic shock or AHF and hypoperfusion to maintain end-organ function, because studies showed that often the inappropriate use is associated with increased morbidity and mortality. In most of the cases the presentation of acute heart failure consists of acute decompensation of chronic HF (ADHF) or, occasionally might occur in patients without previous history of symptomatic HF or *de novo* AHF. It is important to distinct between these two clinical

scenarios due to the deference in the underlying mechanisms leading to AHF and subsequently affects the management plan. In fact, *de novo* AHF is typically induced by severe alteration in the hemodynamic circulation mostly secondary to the initial insult. Common causes of *de novo* AHF include acute myocardial infarction, severe myocarditis, acute valve regurgitation and pericardial tamponade. On the other hand, ADHF may be precipitated by several clinical conditions, while in some patients; no precipitant can be identified [13].

The fast identification of the risk factors that precipitate AHF is very critical in the management in order to optimize patient care. The most common risk factors that precipitate the AHF include but are not limited to myocardial ischemia, arrhythmias (especially paroxysmal atrial fibrillation), sepsis and/or pulmonary disease, uncontrolled hypertension, non-compliance with medical prescriptions, renal dysfunction and iatrogenic causes. Early identification of precipitants risk factors of AHF can help with detecting whether the cause is reversible or treatable and often assists in determining prognosis. In fact, initial management should include, also specific treatments directed towards the underlying causes of AHF in addition to the vasodilators and/or diuretics. In cases of AHF precipitated by acute coronary syndrome, early coronary angiography with revascularization is recommended. While antiarrhythmic treatment and/or electrical cardioversion are recommended in AHF precipitated by arrhythmia. If sepsis is suspected, early and rapid initiation of antimicrobial therapy is often recommended. Moreover, risk stratification should be carried out; this is often accomplished by identification of precipitants of AHF. The prognosis can differ with the initial cause. In AHF caused by acute coronary syndrome or infection is often associated with poorer outcomes whereas outcomes tend to be better in AHF precipitated by atrial fibrillation or uncontrolled hypertension [14].

Investigations

Laboratory tests are extremely helpful in the evaluation of patients presented with AHF. There are many tests help with the diagnosis of AHF including natriuretic peptides, including B-type NP (BNP), amino-terminal pro-B-type NP (NT-proBNP) and mid-regional pro-atrial NPs (MR-proANP). The sensitivity and specificity is different from one another. Some of them show high accuracy and excellent negative predictive value in differentiating AHF from non-cardiac causes of acute dyspnea. Natriuretic peptide levels in HFpEF are lower than in HFrEF. Low circulating NPs (thresholds: BNP <100 pg/mL, NT-proBNP <300 pg/mL, MR-proANP <120 pmol/L) make the diagnosis of AHF unlikely. This is true for both HFrEF and HFpEF. A recent meta-analysis indicated that at these thresholds BNP and NT-proBNP have sensitivities of 0.95 and 0.99 and negative predictive values of 0.94 and 0.98, respectively, for a diagnosis of AHF. MRproANP had a sensitivity ranging from 0.95 to 0.97 and a negative predictive value ranging from 0.90 to 0.97 [15].

Elevated levels of NPs cannot confirm the diagnosis of AHF, as they are also increased in other variety of cardiac and non-cardiac causes. These include but not limited to atrial fibrillation, age, and renal failure. Natriuretic peptides should be measured in all patients regardless upon presentation [16].

Cardiac troponins are helpful to exclude myocardial ischemia and myocardial infarction as precipitating factor of AHF. but, cardiac troponin, in particular when measured with high-sensitive assays, is often high in patients with AHF, even without myocardial ischemia. In fact, the reason for that might be attributed to the fact that AHF is characterized by remodeling and accelerated myocardial necrosis. Many biomarkers are independent predictors of in-hospital complications and longer-term outcomes in AHF syndromes, but their impact on management has not been adequately established. The easy-to perform AHEAD score based on the analysis of co-morbidities provide relevant information on short and long term prognosis of patients hospitalized for AHF [17].

An electrocardiography (ECG) can be helpful to diagnose arrhythmia, ischemia and to exclude ST-elevation myocardial infarction requiring immediate revascularization. However, ECG is rarely normal in AHF. Also, current guidelines do not recommend immediate echocardiography in all patients presenting with AHF. Immediate echocardiography (preferably within 24–48 h from admission) is only recommended to patients with cardiogenic shock or suspicion of acute life-threatening structural or functional cardiac abnormalities as well as *de novo* AHF and in those with unknown cardiac function [18].

Chest X-ray may be useful to assess the presence of interstitial pulmonary edema; ultrasound might be helpful as well. both techniques provide complementary information about the presence of pulmonary edema or pleural effusion. Chest X-ray may also be helpful to rule-out alternative causes of dyspnea such as pneumothorax and pneumonia [18].

Management

The target of managing AHF is to: (1) improve prognosis and reduce morbidity and mortality (2) relieve signs and symptoms and reduce morbidity through adequately reversing the cardiac and peripheral dysfunction. For hospitalized patients, additionally it is preferred to target the following as well: (1) prevent organ system damage (2) reduce the length of stay and subsequent readmission and (3) consider the co-morbidities that may contribute to poor prognosis [16].

In-Patient Management of HF

'In-patient' management of HF: It is advised to admit the patient in the telemetry bed or in ICU and the treatment is based on the following points [5].

- Provide noninvasive positive pressure ventilation (NIPPV) in the few cases with respiratory distress for respiratory support to avoid subsequent intubation.
- Monitor oxygen, whether PaO_2 < 60% or SaO_2 < 90%.
- Use the following pharmacological agents depending on the precipitating factors and symptoms/signs for congestion: Diuretics (thiazides, loop diuretics and potassium sparing): the aim is to reduce the edema by the reduction of blood volume and venous pressure and salt restriction in patients with current or previous heart failure symptoms and reduced left ventricular ejection fraction (LVEF) for symptomatic relief. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) to stop the neuro-hormonal effect, vasodilatation and improvement in LVEF. Beta-adrenergic blocker for neuro-hormonal modification, improvement in symptoms and LVEF, has a beneficial survival benefit, arrhythmia prevention and control of ventricular rate. Aldosterone antagonists, is used as an adjunct to other drugs for additive diuresis, heart failure symptom control, improved heart rate variability, decreased ventricular arrhythmias, reduction in cardiac workload, improved LVEF and an increase in survival. Digoxin, which can lead to a small increase in cardiac output, improvement in heart failure symptoms and a decreased rate of heart failure hospitalizations. Anticoagulants, if applicable, to decrease the risk of thromboembolism. Inotropic agents to restore organ perfusion and reduce congestion in patients with heart failure with reduced ejection fraction, so as to increase in cardiac output and reduce neuro-humoral activation. Some other agents have been described under clinical trial [19].

Out-Patient Management of HF

The outpatient management of HF includes the following: provide a comprehensive education and counseling individualized to the patient's disease and socio-economic and educational level Education/promotion of self-care, including self-adjustment of diuretic therapy in appropriate patients with the help of a family member/caregiver Early attention to signs and symptoms of fluid overload Emphasis on behavioral strategies to increase adherence Optimization of medical therapy Vigilant follow-up after hospital discharge or after periods of instability Increased access to providers or healthcare/social services Assistance with social and financial concerns [5].

CONCLUSION:

Heart failure is a complicated disease and so far has been a major cause of morbidity and mortality in developing and developed countries. The pathophysiology behind it is various. A standardized medical therapy has been successful in the early stages of HF. The management is different according to the presented symptoms and the advanced stages of HF require frequent hospitalization due to the presence of severe HF and or associated co-morbid condition. The management plan differs whether the patient is in admission or in outpatient settings. There are various diagnostic techniques that help with the diagnosis as well as establish the prognosis in patients presented with AHF.

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