Pathophysiology of heart failure and its relationship with interleukin - 1β sST2 receptors

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ABSTRACT

Objective: to establish, through a narrative-critical review, the pathophysiology, prevalence, diagnosis and therapeutic management of heart failure (HF). It also demonstrated the association of HF with cardiovascular biomarkers, such as interleukin 1β and its receptors. Methods: literature review based on scientific articles from the PubMed, LILACS and SciELO databases. Descriptors based on studies published in the years 2014 to 2023 and adherence to the theme "heart failure" were used. Studies without complete publications and without free availability on the data platform were excluded. Results: 204, 22 and 6 articles were obtained from the PubMed, LILACS and SciELO databases, respectively. Of these, 18, 2 and 2 articles from PubMed, LILACS and SciELO, respectively, stood out after evaluation and use of exclusion criteria. Finally, 17 articles and a textbook make up this study. Conclusion: HF is a syndromic pathology caused by a series of different etiological diagnoses. Patients with HF have several compensatory mechanisms, in addition to occasional cardiac remodeling and repair guided by inflammatory mediators. In this disease, biomarkers are very useful, being widely studied in recent years. An important highlight is the 1β interleukins, which are useful in the diagnosis and therapeutic management of HF.

Keywords: Heart Failure, Interleukin 1, sST2 Receptors.

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INTRODUCTION

Heart failure (HF) encompasses a series of clinical signs and symptoms originating from a series of different etiological diagnoses. It is difficult to establish this diagnostic identity as a specific disease. Therefore, HF can be considered as a syndromic finding originating from several distinct pathophysiological findings. In the scientific literature it is possible to find many definitions for heart failure. This happens due to the scope that each definition comprises in itself and the need to meet the demand of each clinical practice. Some definitions are focused on urgency and emergency guidelines, others are focused on their pathophysiology, and there are still others that are stricter to traditional medical school textbooks (HEIDENREICH et al., 2022; CANDICE and KOLODZIEJ, 2019).

According to the American College of Cardiology Foundation (2021), heart failure is a syndromic finding. HF results from any damage caused to the ventricular structure or function or damage during blood ejection. The fundamental symptoms of HF are dyspnea, edema, and fatigue. These symptoms have a relevant impact on tolerance to physical activity and fluid retention. It is common to find patients with pulmonary congestion and edema of the upper and lower limbs. The list of patients who report intolerance to physical exercise, but do not have peripheral fluid retention, is also classic (BOZKURT et al., 2021).

Many textbooks portray HF as a state where the heart cannot pump blood in the minimum amount necessary to maintain body homeostasis. According to this definition, in HF, many organs are unable to receive adequate oxygen supply to maintain many body functions. Therefore, constant fatigue, dyspnea, and intolerance to physical activity are justified. Although these books provide a clear definition of HF, this definition cannot reach all types of patients. This is the deficiency in this type of scientific literature (HEIDENREICH et al., 2022).

METHODS

The study prepared in this literature review was based on data obtained from bibliographic searches carried out in the PubMed, LILACS and SciELO databases. To obtain the articles, the following descriptors were defined: heart failure, interleukin 1 and sST2 receptors. Through PuBMed, LILACS and SciELO, 204, 22 and 6 articles were obtained, respectively. All according to the following search plan: heart failure AND interleukin 1 OR sST2 receptors (Heart Failure AND Interleukin 1 OR sST2 receptors). The selection criteria were adopted: publication in 2013 and 2023 and adherence to the theme "heart failure" as a minimum prerequisite for the study. Thus, 85, 9 and 0 articles were excluded, respectively. Of these, articles that were not freely available to the scientific community were disregarded. Finally, 69, 2 and 6 articles, respectively, were collected for analysis. 18 articles from PubMed, 2 articles from LILACS and 2 articles from SciELO were selected for

further analysis. In view of the heterogeneity of the articles, an explanatory/descriptive analysis was established with a subsequent narrative-critical review of the pertinent studies.

RESULTS AND DISCUSSION

The bibliographic study generated 22 articles. In view of these results, explanatory-descriptive analyses of all selected studies were performed. After evaluation and review of the findings, 17 articles and one textbook were highlighted to support the development of this literature review.

According to the European Society of Cardiology (2016), HF is a clinical syndrome consisting of dyspnea, swelling and fatigue. In addition to these symptoms, some specific signs may occur, such as: elevated jugular venous pressure, pulmonary crackles, and peripheral edema. The European Society of Cardiology also refers to HF as resulting from damage to cardiac structure and functionality that leads to cardiovascular incompetence in maintaining organic homeostasis (BOZKURT et al., 2021).

According to the Japanese Heart Failure Society (2017), HF is a clinical syndrome formed by dyspnea, malaise, swelling, and intolerance to physical activity due to cardiac incompetence, but specifically in the blood ejection pump (BOZKURT et al., 2021).

There is also a subclassification of HF according to left ventricular ejection fraction (LVEF). This classification is based on guidelines and protocols shaped by the clinical practice of many health services. According to the guideline of the American College of Cardiology and the American Heart Association (2022), heart failure can be subdivided into: HF with reduced ejection fraction or HFrEF; CI with improved ejection fraction or HFmEF; CI with intermediate ejection fraction or HFi (some authors also consider it CI with slightly reduced ejection fraction or HFler) and CI with preserved ejection fraction or HFpEF. The classification criteria are based on the capacity of blood ejection through the left ventricle. When LVEF $\leq$ 40%, HFrEF is indicated; Previously LVEF $\leq$ 40% that improved after medical follow-up is called HFmHF; LVEF between 41% and 49% is HFiEF or HFLER and LVEF $\geq$ 50% represents HFp (HEIDENREICH et al., 2022; CORREIA AND MESQUITA, 2022).

PREVALENCE OF HEART FAILURE

With technological improvement and the emergence of new therapeutic approaches, there has been an increase in life expectancy and a reduction in mortality from heart disease. However, there is still a high morbidity and mortality related to HF. LVEF is considered an important evaluator of ventricular disorder, prognosis, and mortality in HF patients. With the advancement of science in recent decades, there has been an improvement in the therapeutic approach to patients with cardiovascular diseases. New drugs have increased the treatment of HF. In addition, several

implantable cardiac devices have been created and new therapeutic guidelines for cardiovascular diseases have been improved, especially HF (WYBRANIEC et al., 2022).

The prevalence of heart failure in the adult world population is approximately 2%. However, in the elderly over 80 years of age, this prevalence can reach 20% of the population. Regardless of its etiology, HF has an unfavorable prognosis, with mortality of approximately 50% of patients in 5 years of disease activity. The morbidity and mortality of HF is high and occurs in all forms of LVEF. Both the HFr and HFRLER and the HFmEFm and HFp. The prognosis of patients with HFrEF tends to be worse than the prognosis of patients with HFler. Comorbidities, such as systemic arterial hypertension, diabetes, dyslipidemia, and obesity are factors that contribute to the worsening of patients' prognosis (CORREIA AND MESQUITA, 2022; WYBRANIEC et al., 2022).

Despite advances in HF therapy over the past few years, there has been little impact on the clinical outcome of patients with HFpEF compared to patients with HFrEF. ICFEm, on the other hand, emerged especially due to advances in the treatment of these patients. That is, many patients migrated from the classification of HFrEF to HFmEF after follow-up and therapeutic success. It is worth noting that with the emergence of this new classification, there was a good reduction in the mortality of these patients. Patients who improved their clinical condition and migrated to HFmEF had approximately a 50% reduction in morbidity and mortality and a decrease in hospitalization, which did not occur with patients with HFrEF and HFp (WYBRANIEC et al., 2022).

NEUROHORMONAL MECHANISMS

When cardiac competence begins to reduce and the patient enters the clinical picture of HF, the body begins to try to readjust its homeostasis with the creation of compensatory mechanisms. Many of these mechanisms are classified as neurohormonal. Among the most well-known mechanisms are the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system. At first, these readjustments established by the body lead to a cascade of adaptations in various organs and systems. Organs such as the heart, lungs, kidneys, and liver acquire new functions to try to maintain homeostasis at adequate levels. However, over time, these new functions end up consuming a lot of the reserves of these organs, leading them to hemodynamic stress and important structural and functional disorders. The prognosis of HF can be inferred through the analysis of the mechanisms of neurohormonal activation. This concept is widely used in the field of pharmacology with a therapeutic scope of HF (HARTUPEE and MANN, 2017).

There are baroreceptors located in blood vessels such as the carotid sinus and the aortic arch. These baroreceptors have the function of evaluating pressure variations and other information. These receptors carry these notifications to the cardiovascular vasomotor centers located in the brainstem. When there is a cardiac disorder with LVEF involvement, the baroreceptors perceive this information

and pass it on to the central nervous system. In addition to these receptors, there are also chemoreceptors and ergoreceptors, which also play a relevant role in the adaptation of cardiovascular homeostasis (COSTANZO LS, 2015; HARTUPEE AND MANN, 2017).

In patients who do not have HF, the baroreceptors located in the carotid sinus and the aortic arch, together with the mechanoreceptors located in the heart and lungs, carry information to the central nervous system related to blood pressure and blood flow. This exchange of information occurs in a physiological way. In HF patients, there are disturbances in blood pumping, with consequent alteration of blood flow. It is worth remembering that mechanoreceptors can be subdivided into Pacini corpuscles (responsible for vibration and percussion), Meissner corpuscles (responsible for velocity), Ruffini corpuscles (responsible for pressure) and Merkel disks (responsible for localization) (COSTANZO LS, 2015; HARTUPEE AND MANN, 2017).

Patients with the onset of heart failure have several compensatory mechanisms, such as: sympathetic nervous system (SNS) and renin-angiotensin-aldosterone (RAAS). In addition to these and other mechanisms, occasional cardiac remodeling and repair occur in the body of these patients guided by inflammatory mediators. These and other actions aimed at maintaining homeostasis are classified as neurohormonal activation. Among the most well-known neurohormones, norepinephrines and angiotensin II, produced by various tissues, including the myocardium, stand out. However, the constant demand for these compensatory mechanisms and inflammatory mediators can lead to deleterious actions in the body. This constant damage can also be considered one of the etiologies of HF (HARTUPEE and MANN, 2017).

The renin-angiotensin-aldosterone system is a compensatory mechanism that has several receptors. Two relevant angiotensin II receptors are: AT1R and AT2R. The first receptor is responsible for several cardiovascular outcomes. Among them: arterial and venous vasoconstriction, sodium retention and potassium release, aldosterone release, cardiovascular repair and hypertrophy, and inflammatory mediation. The second receptor, AT2R, has an uncertain function, however, many authors have already proven its inhibitory activity in relation to AT1R. AT1R and AT2R are known to be G-protein-adhered transmembrane receptors. While AT1R is abundant in the human body, AT2R is found in small amounts. However, this second receptor can increase greatly in specific pathological conditions, such as: arterial hypertension, acute myocardial infarction and atherosclerosis (FARIA-COSTA et al., 2014).

HF sufferers develop high chemosensitivity to hypoxia and hypercapnia. In addition, these patients have intense sensory disturbance related to muscle metabolism during physical activity. Intense neurohormonal activation, deficit in functional capacity, and increased morbidity and mortality are directly related to increased chemosensitivity. This short-term neurohormonal activation helps maintain cardiovascular homeostasis. However, in the long term, this neurohormonal attempt to

maintain cardiac output in normal patterns leads to destruction of cardiac tissues and irreversible cardiovascular disorders (HARTUPEE AND MANN, 2017).

It is important to emphasize that the current therapeutic approach is based on studies of neurohormonal mechanisms and their developments. Pharmacology has developed a lot in recent years and with it the understanding of the relevance of the antagonism of neurohormonal systems as a therapeutic basis and improvement of the prognosis of heart failure. Very high levels of neurohormones in patients with long-term HF cause structural and functional damage to the heart, much of it irreversible. Due to advances in the treatment of HF, many patients with HFrEF achieve clinical improvement and are later considered patients with HFmEF (HARTUPEE AND MANN, 2017).

HOSPITAL PROGNOSIS OF HEART FAILURE

Heart failure has a relevant impact on the world economy, being responsible for a high consumption of public coffers. This syndromic finding has a high rate of demand and morbidity and mortality in the global health system. In addition, HF increases the length of hospital stay and is directly responsible for the increase in demand for hospital care and readmission. Many authors have already proven in several studies the impact that HF has on the follow-up and prognosis of hospitalized patients (DAVISON et al., 2016).

In a study carried out in 17 countries (USA, Canada, Israel, Belgium, France, Germany, Italy, Netherlands, Sweden, United Kingdom, Czech Republic, Hungary, Poland, Romania, Ukraine, Argentina and Russia) Davison et al. (2016), analyzed 1849 patients within 30 days of hospitalization with hospital discharge and 1902 patients within 90 days after hospital discharge with death outcome. In the study, of 1849 patients hospitalized within an interval of up to 30 days, with hospital discharge, 372 were readmitted to hospital services. Of these, 182 patients were hospitalized for complications directly related to HF. Of the 1849 patients, 45 died during the study. Regarding the 1902 patients discharged from hospital, 153 had a death outcome within 90 days of discharge. The most common risk factors for increased mortality rates were advanced age, obesity, hypertension, diabetes, leukocytosis, reduced sodium and bicarbonate, among others (DAVISON et al., 2016).

SURGICAL APPROACH IN HEART FAILURE

According to Falls and Kolodziej (2019), HF accounts for approximately 3% of the budget foreseen for health in the United States. Many pharmacological treatments have been developed in recent years for the management of HF. However, the eventual need for surgical approach in patients was seen as a complementary treatment for this pathology.

HF can occur at the systolic and/or diastolic level. Systolic heart failure can lead to irreversible myocardial disorders. This diagnostic identity can lead to symptoms refractory to drug therapy, increased intolerance to physical exercise, and increased demand for care in health units. In these cases, the surgical approach, such as heart transplantation or insertion of mechanical circulatory support devices may be more effective measures (FALLS and KOLODZIEJ, 2019).

In the scientific literature, many findings corroborate the idea that congestive exacerbation is closely associated with intense demand for health services. Therefore, congestion management in these patients, i.e., preload management, is one of the therapeutic goals targeted by healthcare professionals. Afterload is also evaluated and treated in HF patients through some classes of antihypertensive drugs. Drugs such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, angiotensin/neprilysin receptor inhibitors (INRA) are drugs recommended by the American Heart Association, with a class I recommendation grade. heart transplantation (FALLS and KOLODZIEJ, 2019).

HEART TRANSPLANT

This therapeutic measure is adopted after failure in the face of the use of drugs recommended by international guidelines and protocols. Studies have shown that after 5 years of follow-up of HF in patients with advanced clinical conditions, 80% of patients die. This corroborates the need for a surgical approach in some cases. One of the surgical approaches is heart transplantation. This is considered the gold standard in the treatment of HF at an advanced stage. It is worth remembering that in the United States, 4,111 heart transplants were performed in 2022, 3,818 in 2021, 3,658 heart transplants in 2020 and 3,552 in 2019. The survival rate of heart transplantation in the first year is greater than 80% and after 5 years it is greater than 70% (FALLS and KOLODZIEJ, 2019; UNOS, 2023; WILHELM, 2015).

INDICATIONS FOR HEART TRANSPLANTATION

Before seeking heart transplantation, some therapeutic measures may be intended. Despite drug therapy or the use of other cardiac surgeries, if there is still therapeutic failure, heart transplantation can be used, taking into account some indications. Among these indications, the following can be highlighted: patients using beta-blockers with oxygen consumption less than or equal to 12ml/kg/min or 14ml/kg/min without using this medication; patients with ischemic disease and angina refractory to medical therapies where revascularization is not recommended; patients with advanced heart failure without drug improvement; patients with advanced HF without improvement with insertion of mechanical circulatory support devices; patients in functional class III or IV; patients in a 6-minute walk test of less than 300 meters (MANGINI et al., 2015).

CONTRAINDICATIONS TO HEART TRANSPLANTATION

Given the need for heart transplantation, it is necessary to evaluate the possible risks of surgery. There are some factors that contraindicate the surgical approach. Some conditions or comorbidities are impediments to this therapy. Among them, it is worth highlighting: severe lung disease, severe cerebrovascular diseases, severe peripheral arterial obstructive diseases, pulmonary arterial hypertension, severe psychiatric disorders, severe liver disease, psychoactive drug abuse, failure to adhere to treatment, and incompatibility between the recipient and the organ donor (MANGINI et al., 2015).

COMPLICATIONS IN CARDIAC SURGERIES

There are complications that can arise in heart surgery. Approximately 30% of patients may develop atrial fibrillation (AF) in the postoperative period of these procedures. When this occurs, it is important to keep in mind the therapeutic need of this event. In postoperative AF, the therapeutic goal becomes the control of heart rate and rhythm. AF has a relevant impact on patients with heart failure. Thus, many protocols recommend heart rhythm control in patients who have both comorbidities: AF and HF. According to Yang et al. (2021), in a randomized study with a therapeutic approach to postoperative AF in cardiac surgeries, where heart rate and rhythm control was managed, the need for therapeutic association with other treatment strategies was perceived in a large number of patients. In view of these findings, great relevance was perceived in the continued medical evaluation of hospitalized patients. It was also possible to notice the impact on the reduction of medical prescription of anticoagulants at hospital discharge. Patients with HF who were initially approached for heart rhythm control required a shorter time to achieve sinus heart rhythm, and were discharged from the hospital in better conditions (YANG et al., 2021).

Heart failure often predisposes its patients to atrial fibrillation due to a number of factors intrinsically associated with the two pathologies. Among the shared mechanisms and the specific pathophysiology of each one, the following can be listed: chronotropic incompetence; neurohormonal activation system; tachycardia-induced cardiomyopathy; inflammation at a systemic level; endothelial dysfunction; feeding of the renin-angiotensin-aldosterone system; attriventricular remodeling with gradual mitral and tricuspid regurgitation and natriuretic peptide circulation disorders. There are also risk factors common to both diagnostic identities: systemic arterial hypertension; obesity, aging, diabetes, dyslipidemia, and obstructive sleep apnea syndrome (KOTECHA et al., 2016; YANG et al., 2021).

ISCHEMIC CARDIOMYOPATHY AND HEART FAILURE

Heart failure is intrinsically related to ischemic cardiomyopathy. HF acts leading to long-term left ventricular diastolic dysfunction. In the onset of coronary artery disease (CAD), ischemic cardiomyopathy can lead to HF if not properly managed. Scenarios of myocardial weakening, cardiac tissue necrosis, or loss of cardiac contractility competence can lead to disturbances of left ventricular functionality. Despite the clinical picture of ischemic cardiomyopathy, patients with this diagnostic identity may have several signs and symptoms of HF. Despite the therapeutic advance in cardiovascular diseases, HF still presents several challenges to be overcome by the scientific community (DEL BUONO at al., 2022).

According to Del Buono et al. (2022), ischemic cardiomyopathy is the most common cause of heart failure in the population. The correct therapeutic management of ischemic cardiomyopathy helps to reestablish blood support to the cardiac tissue and, consequently, reduces the eventuality of HFrEF. With the updating of therapeutic measures, new approaches have been established, including the inflammatory modulation of patients with ischemic cardiomyopathy. However, there is still a great lack of information regarding the best conduct to advance the prognosis and quality of life in these patients.

INTERLEUKIN sST2 RECEPTORS - 1β

Among the most relevant markers in HF, interleukins 1 beta (IL-1β) stand out. These ILs are generated by macrophages as protein molecules that mediate relevant inflammatory processes in the cardiovascular system. There are IL alpha and beta with several important biological activities. IL-1β are cytokines initially generated in their non-activated forms. These ILs are subsequently activated by caspases

1 (CAPS1 / interleukin-converting enzymes 1) in its pro-inflammatory protein forms. In addition to inflammatory activity, there is also a relationship between these cytokines and cell growth, cell development, and apoptosis. An effective treatment currently carried out occurs with the programmed inhibition of these inflammatory cytokines. This inhibition occurs with the use of receptor antagonists for these ILs. An example is the use of Anakinra, a drug that antagonists inflammatory activity at the cardiovascular level that helps reduce cardiac disorders, reduce hospital admissions, decrease cardiac remodeling after ischemic events, improve physical fitness and cardiorespiratory fitness (BAYES-GENISet al., 2022).

Many heart cells, including cardiomyocytes and cardiac fibroblasts, produce cytokines in response to any damage caused to heart tissue. An important cytokine, interleukin 1 plays an important role in this process. This interleukin has a type 1 receptor known as ST2 or Tumorigenicity Suppression 2 which has several subgroups such as soluble ST2 (sST2) and ligand ST2 (ST2L).

These receptors are formed as a result of a series of damages to the cardiovascular system (BAYES-GENISet al., 2022; VILLACORTA and MAISEL, 2016).

In patients with heart failure, both soluble ST2 and IL-1 binding ST2 act actively, and the relationship of these receptors in cardiac remodeling and ventricular dysfunction has been proven. Many scholars have already proven the association between high concentrations of sST2 with fibrosis and cardiovascular stress. In other words, sST2 is an excellent predictor of cardiovascular outcomes in both chronic and acute HF, being a recent biomarker for use in medical practice. Interleukin 33 (IL-33), belonging to the interleukin 1 family, is also a ligand for ST2. This interleukin is not only expressed in the cardiovascular system, but also in other systems. sST2 works as a receptor with high affinity for IL-33. Thus, large amounts of sST2 influence the deleterious prognosis at the cardiovascular level (BAYES-GENIS et al., 2022; VILLACORTA and MAISEL, 2016).

In agreement with Villacorta and Maisel (2016), biomarkers are very useful in HF. It is already known that B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are references in the diagnosis of heart failure, and are considered gold standard tests. However, these tests have no relevant prognostic value and cannot define the best therapeutic strategy alone.

Acute myocardial infarction (AMI) is also related to the elevation of cardiac biomarkers. Therefore, the increase in these markers alone is not enough to make a diagnosis of HF. Another cause of elevation of many cardiac biomarkers is recurrent physical stress. Therefore, the patient's anamnesis and clinical condition are always mandatory for diagnostic accuracy (MORAIS MENEGASSI et al. 2019).

CONCLUSION

Heart failure is a syndromic pathology caused by a series of different etiological diagnoses. It is not yet possible to determine this syndrome as a disease arising from a single pathophysiological finding. However, with technological advances, much has been achieved in the diagnostic and therapeutic management of this pathology. Patients facing the onset of HF have several compensatory mechanisms, in addition to eventual cardiac remodeling and repair guided by inflammatory mediators. These and other actions are classified as neurohormonal activation. Biomarkers, on the other hand, have been widely studied in recent years, play an important role in this study. Among the most important markers are interleukins 1 beta (IL-1β), created by macrophages as mediators of inflammatory processes in the cardiovascular system. Biomarkers are very useful, being a reference in the diagnosis of HF and important aids in its therapeutic management.

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