REVIEW ARTICLE

Endothelial Dysfunction, Inflammation and Heart Failure

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ABSTRACT

Heart failure is one of the leading causes of morbidity and mortality worldwide. Endothelial dysfunction, considered as the primum movens of the atherosclerotic process, is both a marker and maker of heart failure. In this complex clinical scenario, in the last decades inflammation played a pivotal role as the common pathogenetic factor for the appearance and progression of cardio metabolic diseases.

The aim of this narrative review is to examine original articles and reviews published over the past 20 years, focused on the link between inflammation and heart failure, with a particular focus on endothelial dysfunction. The articles and reviews have been searched through PubMed using the following search terms (or combination of terms): "Heart failure," "endothelium or endothelial dysfunction," "oxidative stress," "inflammation," "atherosclerosis," "NLRP3 inflammasome," "Interleukin-1" and "treatment." Only English-language papers were included in the literature search. Additional papers found in the reference list of the retrieved articles were also considered.

Key Words: Endothelial dysfunction; Inflammation; Heart failure; Inflammasome

Abbreviations: ADMA: Asymmetric Dimethyl Arginine; DAMPs: Damage-Associated Molecular Patterns; EF: Ejection Fraction; E-NOS: Endothelial Nitric Oxide Synthase; HF: Heart Failure; HF-pEF: Heart Failure with Preserved Ejection Fraction; HF-rEF: Heart Failure with Reduced Ejection Fraction; IL: Interleukin; NF-kB: Nuclear Factor-Kb; NLRP3: Nucleotide-Binding Oligomerization Domain, Leucine-Rich Repeat Containing Proteins 3; NO: Nitric Oxide; Nrf2: Nuclear Related Factor 2; PRRs: Pattern Recognition Receptors; ROS: Reactive Oxygen Species; TLRs: Toll-Like Receptors

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INTRODUCTION

In recent years, it has been possible to identify many of the pathophysiological mechanisms operating in the onset and progression of chronic-degenerative diseases. In the same way, we have observed an important paradigm shift because the conception of the pathology of the single organ has been abandoned in favor of a broader vision of the morbid process. In addition, it has been possible to observe that very often the same risk factors are shared by different diseases and are interdependent with each other, leading to the introduction, over the years, of the term "global cardiometabolic risk". Interestingly, this definition includes a comprehensive list of classic and emerging factors associated with both cardiovascular and metabolic diseases.

Thus, we examined articles and reviews published in the last 20 years, searched through PubMed using the following search terms or (combination of terms): "heart failure," "endothelium or endothelial dysfunction," "oxidative stress," "inflammation," "atherosclerosis," "NLRP3 inflammasome," "Interleukin-1" and "treatment." Only English-language papers were included in the literature search. Additional papers found in the reference list of the retrieved articles were also considered.

LITERATURE REVIEW

Heart failure

Heart Failure (HF), a multifactorial clinical syndrome with increasing incidence and prevalence worldwide, is one of the most common causes of frequent hospitalization and high rate of mortality, remaining a challenge to be overcome to increase patients' life expectancy and reduce healthcare costs [1]. HF is characterized by a progressive impairment of both myocardial structure and its function with an associated neurohormonal activation that consents to define a specific proinflammatory phenotype; in addition, this neurohormonal activation represents one of the most important pathophysiological mechanisms underlying the progression of cardiac impairment [2,3]. In fact, the massive neurohormonal activation–resulting in an increased secretion of angiotensin II, aldosterone, norepinephrine and epinephrine-by increasing the afterload, reduces cardiac output and activates a vicious circle responsible of the progression to end-stage disease.

Unfortunately, HF incidence is expected to raise further due to the progressive increase in cardio metabolic risk factors such as obesity and type-2 diabetes mellitus which, compared to the past, are the main risk factors for HF [4-6]. In fact, in the 1970s and 1980s, the most frequent causes of HF were high blood pressure and cardiac valvular diseases [7]. The increased efficacy of antihypertensive drugs, together with the growing prevalence of obesity and type-2 diabetes mellitus, contributed to make ischemic heart disease, both acute and chronic, the prevalent cause of HF. Obviously, the ischemic etiology of HF is characterized by a quantitative and/or functional decrease in myocardial tissue that is associated with a progressive decrease in cardiac output.

Current guidelines, on the basis of echocardiographic ejection fraction (EF) value, have defined three main forms of HF including.

- HF with reduced EF (HF-rEF; EF <40%),
- HF with preserved EF (HF-pEF; EF>50%), and
- An intermediate form with an EF ranging from 41% to 49% [8].

Typical risk factors associated with HF-pEF are female gender, essential hypertension and obesity, while ischemic etiology is more associated with HF-rEF [9]. However, increasing evidence support that obesity, with the associated hemodynamic and inflammatory alterations, may also contribute to the development of HF-rEF in some patients [10].

Typical signs and symptoms of HF are the expression of the progressive malfunction of the ventricular myocardium and the compensatory mechanisms that are activated as a result of this. On the other hand, it is important to remember that over the years the etiology of decompensation has profoundly changed. Obviously, all that

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affects both the rapidity of the progression of HF and the sequence of the compensatory mechanisms activated, with clinical important implications from both a therapeutic and preventive point of view. In fact, an early detection and a just as fast correction of these mechanisms could delay the clinical manifestations of HF and the progression to end-stage disease and death. These aspects, which are very important from a prognostic point of view, are very often ignored despite the fact that they can have a heavy impact on mortality [11]. According with this, HF should never be the final diagnosis of a pathogenetic process that is very often ignored in clinical practice. Therefore, in the definition and classification of HF, the identification of the pathogenetic cause should never be avoided, because it can have important implications both on the prognosis and on its overall treatment and prevention.

To better understand the complexity of HF, it is important to remember that it is associated with several cardiovascular and non-cardiovascular comorbidities that contribute to make the prognosis more severe and increase the risk of mortality. In addition, some patients with HF-rEF also have older age, higher prevalence of sarcopenia and cognitive impairment and diminished physical and physiological reserve, all factors that make these patients frailer and at a greater risk of hospitalization and death [12].

Vascular endothelium

The preservation of the anatomical and functional integrity of the endothelium is essential for the physiological activity of the vascular wall. The normal endothelium consists of a monolayer of flat and polygonal cells capable of modulating vascular tone and vascular smooth muscle cells and fibroblasts proliferation, inhibition of monocyte and leukocyte adhesion of platelet aggregation and of the migration and proliferation of vascular smooth muscle cells that are all factors participating to the appearance and progression of atherosclerotic disease [13-18]. The main mediator of all these protective biological actions is the Nitric Oxide (NO), a short-lived molecule, produced from the amino acid L-arginine by the endothelial enzyme NO synthase (e-NOS) [19]. In addition to NO, the endothelium produces and releases other vasoactive substances both vasodilating, such as endothelium-dependent hyperpolarization factor and prostacyclin, and vasoconstrictions as well as endothelin-1, thromboxane A2, angiotensin-II, etc [20]. Due to its characteristics, the endothelium can be considered an autocrine and paracrine organ as it is capable of secreting, in response to a wide variety of signals, numerous chemical mediators that modify the behavior of both the cells that produced them and those nearby [21,22]. The result is a modulation of vessel tone and blood flow in response to nervous, humoral and mechanical stimuli. Blood flow is strictly associated with laminar shear stress, the most important physical stimulator of e-NOS [23-25], while an oscillatory disturbed shear stress promotes the increase in the levels of transcription factors such as Nuclear Factor-kB (NF-kB), that is implicated in pro-inflammatory status due to increased production and reduced scavenging of Reactive Oxygen Species (ROS) or the reduction of other antioxidant pathway such as the Nuclear Related Factor 2 (Nrf2) [26,27]. Therefore, it is not surprising that blood flow, and the associated shear stress, play an important role in the modulation of the endothelium redox state and the inflammatory pathways involved in the atherosclerotic process [24].

Over the time, it has been proved that major and emerging cardiovascular risk factors exert a negative impact on endothelial function by decreasing NO bioavailability [28-41]. This circumstance occurs early in vascular damage and may be produced by different mechanisms as well as reduced NO synthesis, increased NO degradation due to oxidative stress, or to diminished sensitivity to NO [14,15,41,42]. Concerning the first mechanism, it was well demonstrated that different endogenous analogues of L-arginine, such as Asymmetric Di-Methyl Arginine (ADMA), may interfere with e-NOS activity and consequent NO production affecting normal vascular motricity. Interestingly, ADMA has been demonstrated to be augmented in patients with chronic renal diseases, with hypercholesterolemia and in other clinical conditions such as essential hypertension or type-2 diabetes mellitus [43-51].

In addition, it is important to remember that hemodynamic factors may also be associated with reduced bioavailability of NO; these include the shear stress, the major endogenous physical stimulus of e-NOS activity, the perturbation of which may be considered the most important mechanism responsible for the reduced endothelium-dependent vasodilation in essential hypertension. According with this, shear stress is influenced by vascular wall stiffness or blood viscosity [52,53]. Thus, a dysfunctional endothelium exerts an important pathophysiological role in the development and progression of atherosclerosis disease due to its reduced ability to protect the vascular system. Of interest, some studies have demonstrated that endothelial dysfunction evaluated in both coronary and forearm vasculature provides prognostic information for future clinical events [54-57].

Inflammation

It is well established that some cardiovascular diseases recognize a common pathogenetic mechanism attributable to a pro-inflammatory state due to an increased production of ROS that include both oxygen free radicals (superoxide, hydroxyl and peroxyl radicals) and non-radicals (hydrogen peroxide, hypochlorous acid and ozone) [58-63].

Although basal ROS production is critical for the maintenance of many vital functions, such as defense against pathogenic germs and gene expression, the dysregulation of oxidant signaling is also involved in some pathological events that participate to the appearance and progression of some chronic and degenerative diseases [64-66]. In this process of fine balance between the production of pro-oxidant and antioxidant substances, a key role is played by mitochondria which, together with other systems involved including the endoplasmic reticulum, contribute to intracellular ROS production [58,63,64]. Thus, it is plausible to affirm that the inflammation is an adaptive reaction to aggression from both exogenous and endogenous agents and that a low-grade inflammation is to be considered useful and desirable for cellular homeostasis.

Over the years, the concept of inflammasome an intracellular multiprotein complex has been developed and its pathogenetic role in inflammatory processes that are aimed at protecting the host from external microbial agents or endogenous agents through the production and release of inflammatory cytokines has been well defined [67]. Among the different types of inflammasomes, the nucleotide-binding oligomerization domain, Leucine-Rich Repeat Containing Proteins 3 (NLRP3) is more versatile than the others and is capable of being activated by Damage-Associated Molecular Patterns (DAMPs) that are released by senescent or damaged host cells [67-70]. Interestingly, the canonical pathway of NLRP3 inflammasome activation occurs through the stimulation, by exogenous or endogenous signals, of membrane receptors-called Pattern Recognition Receptors (PRRs)-which also include Toll-Like Receptors (TLRs), specifically TLR4, which induces an up-regulation of both NLRP3 and pro-interleukin (IL)-1b *via* NF-kB pathway [67,71,72]. Therefore, due to its structural characteristics and interaction with other intracellular pathways, the NLRP3 inflammasome may be considered an important and useful cytosolic PRR that, with the subsequent cytokine cascade release and pyroptosis, is efficient to protect the host from external pathogens and clear the body of damaged cells. However, a dysregulated activation of NLRP3 inflammasome by many danger signals such as unsaturated fatty acids, high glucose or cholesterol, b-amyloid aggregates, urate crystal and ceramide induces chronic inflammation participating to the appearance of some chronic and degenerative diseases, including

atherosclerosis, type-2 diabetes mellitus, neurodegenerative diseases, gout and cancers [73-79]. Therefore, consistent with these findings, it should not be surprising that NLPR3 inflammasome is considered as a potential target for the treatment of chronic diseases with underlying inflammation as pathophysiological mechanism [80].

Endothelial dysfunction and mild inflammation in heart failure

It is well established that some cardio metabolic risk factors, by promoting oxidative stress and pro-inflammatory pathways, are associated with endothelial dysfunction characterized by a reduced NO bioavailability, that represents the earlier step in the appearance and progression of atherosclerotic vascular damage [13,14,16-18,20-22,28-33]. In addition, other findings showed that endothelial dysfunction is associated with incident type-2 diabetes mellitus and the progression of subclinical target organ damage, such as atherosclerotic vascular injury, hypertensive cardiac hypertrophy and renal impairment, proving a likely causative effect in the appearance and progression of cardiovascular continuum [52,54-57,81-83].

The progressive aging of the population, together with the increase of incidence of both obesity and diabetes, continue to increase the burden and medical costs of cardiovascular diseases, despite a lot of preventive strategies. Thus, as consequence of the worldwide increase of these factors, both atherosclerotic coronary disease and type-2 diabetes mellitus represent the major underlying pathogenetic mechanism involved in the incident HF. Therefore, given the close association between cardio metabolic risk factors and endothelial dysfunction, it is likely that the latter also contributes to the pathogenesis of HF with different mechanisms, such as the reduction of vasoreactivity of epicardial and small coronary vessels, the after-load increase, myocardial oxidative stress and fibrotic process [84,85]. On the other hand, there are other data showing that failing patients, regardless of EF, have endothelial dysfunction [85-88]. According with this, it is possible to affirm that HF-related endothelial dysfunction is, at the same time, marker and maker for HF. In addition, recent findings demonstrated that chronic mild inflammation has a crucial role in the HF development, particularly in patients with HF-rEF, confirmatory of the strong interplaying between endothelial dysfunction and inflammation itself [89-91]. According with this, we recently published data from prospective studies demonstrating that endothelial dysfunction, in association with C-reactive protein or insulin resistance, is a strong and independent predictor of incident HF in a group of hypertensive patients allowing to affirm its causative role in the cardiovascular continuum, from risk factors to clinical events [92,93]. Therefore, altogether, these data allow concluding that endothelial dysfunction not only is present in failing patients, but it also participates to the pathogenesis of HF.

For all the above, it is plausible that pathogenetic mechanisms underlying this association may be recognizable in an excessive production of ROS that lowers the NO bioavailability, activates the neurohormonal cascade with associated release of inflammatory cytokines, and produces alterations of local shear stress due to low cardiac output [84]. Confirmatory of this, there are recent data regarding the role of coronary microvascular dysfunction that, modifying metabolic apart of the myocardium, plays an important role of myocardial diseases, including HF-pEF [94]. However, it is important to also remark the adjunctive role of pre-existing traditional cardiovascular risk factors that participate, increasing oxidative stress too, to the vascular motricity impairment, whose association with endothelial function impairment has well established from long time [28-36]. In fact, it is well demonstrated that blunted endothelium-dependent vasodilation is detectable in different clinical conditions, such as diabetes, high blood pressure, and chronic kidney disease, thus offering a biological explanation of the involvement of endothelial dysfunction in HF development.

Furthermore, augmented arterial stiffness is another important pathogenetic mechanism relating endothelial dysfunction to the HF appearance, particularly HF-pEF. In fact, it is well recognized that the aortic stiffening produces the augmentation of left ventricular systolic workload, due to central systolic blood pressure increase. These hemodynamic alterations reverberate negatively both in the left ventricle, by promoting cardiac hypertrophy and consequent diastolic dysfunction, and in the coronary circulation decreasing coronary perfusion pressure [95,96]. Similar data were also observed by us, demonstrating that endothelial dysfunction in hypertensive patients is inversely related to pulse pressure, a surrogate marker of vascular aging and arterial stiffness [52]. Moreover, endothelial dysfunction is associated with other proliferative mechanisms involved in cardiac hypertrophy such as the modification of both matrix metalloproteinases affecting cell migration and the redox-sensitive pathway either in response to chronic pressure overload or neurohumoral stimuli as proved by experimental findings [97-99]. Specifically, pro-oxidant mediators contribute to cardiac hypertrophy by activating certain mitogenic protein kinases and the transcription factor NF-kB. The proliferative role of these pro-oxidant factors is confirmed by some *in vivo* evidence demonstrating the antioxidant effect in reducing the development of experimental cardiac hypertrophy due to blood pressure overload in mice or guinea pigs [97,100]. In addition, oxidative stress may increase cardiac interstitial fibrosis that represents an important harmful aspect of both left ventricular hypertrophy and following HF progression [97,101]. According with this, we previously reported, in hypertensive patients, that endothelial dysfunction parallels the increase of cardiac mass as well as that the preserved endothelial function predicts regression of cardiac mass, independently of traditional cardiovascular risk factors and antihypertensive therapy [82,102]. These two conditions acquire an important prognostic significance since the co-existence of both endothelial dysfunction and cardiac hypertrophy significantly increases the risk of subsequent cardiovascular outcomes, confirming the importance of better stratifying the cardiovascular risk of the hypertensive patients [103].

CONCLUSION

In conclusion, it is plausible to affirm that endothelial dysfunction and its associated inflammation, operate in the development of incident HF, thus allowing hypothesizing its causative role in the cardiovascular continuum. In addition, given the association of endothelial dysfunction with diabetes mellitus and/or coronary artery disease, it is plausible that these two clinical conditions, that are well recognized determinant of both structural and functional cardiac alterations, also contribute to the progression from endothelial dysfunction to HF. These data support what is already known about the progression from hypertension to HF, retaining diabetic cardiomyopathy and ischemic cardiac dysfunction as intermediate steps in this continuum. Obviously, since endothelial dysfunction is also associated, in a bidirectional manner, with diabetes and ischemic heart disease it is possible to affirm that a dysfunctional endothelium concurs to HF development with multiple pathogenetic mechanisms.

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