Gastrointestinal Changes Associated to Heart Failure

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Abstract

Over the last decade, several studies were conducted on the gastrointestinal changes associated to chronic heart failure. This article presents a literature review on the physiopathology and clinical consequences of pathological digestive changes of heart failure patients. Structural and functional abnormalities of the gastrointestinal tract, such as edema of absorptive mucosa and intestinal bacterial overgrowth, have been leading to serious clinical consequences. Some of these consequences are cardiac cachexia, systemic inflammatory activation and anemia. These conditions, alone or in combination, may lead to worsening of the pre-existing ventricular dysfunction. Although currently there is no therapy specifically earmarked for gastrointestinal changes associated to heart failure, the understanding of digestive abnormalities is germane for the prevention and management of systemic consequences.

Introduction

Heart Failure (HF) may be defined as a complex clinical syndrome that comes from structural and/or functional, acquired or hereditary cardiac abnormalities, and lead to the worsening of the filling capacity and ventricular ejection[1]. It stands as a clinical problem of utmost importance, both due to its high prevalence, and the severity of its clinical manifestations. In Brazil, this is the third cause of hospitalization and the first cause of hospital admission due to cardiovascular disease. According to data of Datasus, in 2003, there were more than 350,000 hospital admissions due to HF countrywide[2].

The most common causes of HF are myocardial ischemia, hypertension, cardiomyopathies and valvopathy. In many cases, however, the etiology is still unknown.

The pioneering studies by Frank, in 1895, and Starling, in 1918, introduced the concept that changes in the heart's relaxation and ejection function are responsible for the development and progression of HF. Nonetheless, over the last decades, the fact that the HF is a much more complex syndrome has been established and, thus, the cardiovascular system is no longer seen as the only to be impacted, but the renal, neuroendocrine, immunological, musculoskeletal, hematologic and gastrointestinal systems as well. Because of this, researches have been performed to elucidate the physiopathology of systemic complications and to propose a treatment capable of improving life quality and expectancy of patients suffering from the disease. They include, *inter alia,* studies about the impairment of the Gastrointestinal Tract (GIT) in HF.

In this review, we will show the structural and functional changes which may occur in the GIT of patients with HF. Subsequently, we will present the manifestations arising out of the GIT impairment, mainly the inappropriate absorption of bacterial constituents. Lastly, we will address the current strategies and those under research to prevent and/or treat GIT changes associated to HF and its systemic consequences.

The GIT impairment in HF has been firstly studied in 1960 by Davidson et al[3] The authors showed that patients undergoing constrictive pericarditis presented protein-losing gastroenteropathy, reversible after surgical correction of cardiac lesion. In spite of the initial studies, only over the last decade the GIT has been more thoroughly evaluated in HF.

Structural gastrointestinal changes associated to HF

Several structural changes have been described in the GIT of patients with HF. Several abnormalities of the gastric mucosa in mosaic pattern were observed in the stomach, including the antral vascular ectasia, mucosal thickening and areas of telangiectasias[4,5].

In the terminal ileum, colon and sigmoid, ultrasound resonance has found increase in the intestinal wall thickness, suggesting the presence of edema of the loops in patients with HF[6]. Although the belief in the existence of intestinal wall edema in patients with important water retention has long existed, this was the first report of change substantiated by imaging examination performed *in vivo*. The sigmoid wall thickness seems to present clinical implications, as their measurements have always been positively related to the blood concentration of leukocytes and ultra-sensitive C-reactive Protein (CRP)[6]. These results suggest that intestinal changes have relevance in the induction of systemic influence, as we will see subsequently. The small intestine wall presents both thickening and increase of the collagen tissue, which is proportional to the severity of HF[7]. To this respect, the distance between the enterocyte basal membrane and the blood capillary is increased[7], possibly due to the said changes 7. Currently, these structural changes are believed to worsen the nutrition of enterocytes and, consequently, to lead to abnormalities in the intestinal Absorption associated to the HF.

Keywords

Heart failure/complications, cachexia, abnormalities of the digestive system, intestinal absorption, anemia

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Functional gastrointestinal changes associated to HF

In physiological conditions, the splanchnic circulation received nearly 25% of the cardiac output, leading the intestine to be one of the organs more intensely perfused in rest[8]. The splanchnic circulation is richly supplied with sympathetic nerves. Consequently, the increase in the sympathetic nervous system activities triggers the constriction of pre-capillary resistance vessels and post-capillary capacitance vessels, entailing reduction of blood perfusion. The intestinal vascular changes may precede changes in heart rate or blood pressure[9]. On account of this, even discrete reductions of the cardiac output may lead to different degrees of intestinal ischemia. In patients with advanced HF, Krack et al[10] observed intramucosal acidosis in the stomach induced by light physical activity, evidencing, however, the occurrence of hypoperfusion of GIT.

The functional changes involve abnormalities of intestinal permeability. The Intestinal Absorption happens through transcellular routes, in which the food constituents are absorbed to the interior of the enterocyte and, subsequently, to the blood capillary and, through paracellular route, in which they are passively absorbed while passing between enterocytes[5]. The paracellular absorption route may be evaluated by sugar administration tests and subsequent analyses of its concentration in urine[6]. Both in the small intestine and in colons, the independent paracellular absorption of transfer proteins is increased in HF, suggesting rupture of the intestinal barrier[5,6]. In its turn, the passive transfer mediated by transfer proteins of the small intestine is reduced in HF, suggesting deficit of ATP for microcirculation[6].

In 1996, King et al[11] observed that patients with HF and cachexia presented reduction of the intestinal absorption of fats compared to patients who did not undergo cachexia or healthy individuals. The decrease of intestinal absorption was well documented in a recent work, in which the higher loss of proteins and fats was found in the feces of patients with HF in functional classes III and IV than in those in classes I and II[7]. Additionally, the reduction of intestinal absorption was more evident in patients with cardiac cachexia. This, evidence suggest that changes in intestinal absorption may be involved in the etiology of cachexia associated to HF[12].

In addition to the changes in absorption, patients with HF present high level of intestinal bacterial colonization. Adopting the FISH (Fluorescence In Situ Hybridization) technique, one could evidence that the bacterial concentration in mucosal biofilm and the extent of bacterial adhesion to the sigmoid wall are increased in the HF[6]. Currently, the increase of intestinal bacterial colonization is believed to be the result of GIT structural and functional changes, probably jointly with immunological abnormalities associated to HF.

One of the main consequences of gastrointestinal changes is the inappropriate absorption of bacterial constituents, especially endotoxins, also known as lipopolysaccharides[5]. Endotoxins are important toxic and immune components of Gram-negative bacteria. In spite of the difficulties for dosing endotoxins, Niebauer et al[13] showed that patients with HF and edema present increase in the plasma concentration of endoxins compared to those without edema. Additionally, after therapy with diuretics, there was normalization of the serum concentration of endotoxins[13]. This study was important to underscore the current hypothesis that the intestinal wall edema would be involved in the change of intestinal permeability and inappropriate absorptions of bacterial constituents. The intestinal edema and its systemic consequences seem to characterize the main difference, relating to GIT impairment, between chronic and stable HF and the decompensated HF.

Currently, the lipopolysaccharides are considered one of the most powerful inducers of the tumor necrosis factor (TNF)-α and other pro-inflammatory substances.

The importance of TNF-α in HF was primarily described by Levine et al[14] in 1990. The authors observed that patients with HF presented high serum levels of TNF-α especially higher in those with cachexia. The findings were capital for the understanding of the HF physiopathology and its complications and have influenced the performance of a significant amount of research in this area[15,16]. Soon, the assumption that TNF-α is a good marker of severity in HF has been substantiated, and correlating to the survival, the HF functional class, the cardiac performance and the serum concentration of brain natriuretic peptides[17-20]. In experimental studies, the increase of TNF-α, induced by exogenous administration or by the increase of gene expression, leads to the HF phenotype, characterized by ventricular remodeling and reduction of survival[21,22]. These findings allowed to conclude that TNF-α is not only a marker of severity, but also an inducer of HF and worsening of the ventricular dysfunction picture. Later on, researchers have found that, in addition to TNF-α, other cytokines also increase in the HF.

The sources producing cytokines are not yet fully clear. The very myocardium, if structurally damaged, may express and produce higher levels of inflammatory mediators, such as adhesion molecules, TNF-α and IL-6. Circulating leukocytes, platelets, endothelial cells, and lung and liver cells may also be involved in the production of cytokines. To this respect, the inflammatory response does not depend on the HF etiology, happening as the common final pathway in patients with HF, irrespective of the cause of the disease[23]. The mechanisms proposed in the genesis of the production of cytokines include the hemodynamic overcharge, neuro-hormonal activation, presence of tissue hypoxemia and hypoperfusion, oxidation of low-density lipoprotein, presence of autoantibodies and immune stimulation caused by microbial agents, mainly the endotoxins[23].

Currently, one of the main stimuli for the cytokines in HF is believed to the absorption of endotoxins coming from the GIT[23]. The reduction of intracellular production of cytokines after selective intestinal decontamination with antibiotic underpins the assumption[13,24]. Endotoxins may be deactivated by serum cholesterol, which forms micellas in its surrounding, trapping them in its interior. This fact has been used to explain why patients with HF and high cholesterol have better survival than those with reduced cholesterol. According to the theory, higher serum concentrations of cholesterol imply higher neutralization of endotoxins[25,26]. More recently, the increase in the serum concentration of TNF-α was observed to induce further changes in the intestinal epithelial barrier[9,12]. Thus, there is a vicious cycle in which the increase

of serum concentration of a cytokine facilitates the absorption of endotoxins which, in their turn, induce the production of several cytokines.

Therefore, we may conclude that the HF induces structural and functional abnormalities in GIT. One of the most important consequences of the GIT impairment is the change of intestinal absorption, leading to the impairment of the nutritional status and the immune activation[9,12].

Consequences of the gastrointestinal changes associated to HF

Anemia

In a recently published meta-analysis, including more than 153,000 patients with HF, the prevalence of anemia was 37.2%[27]. Several factors may be involved in the etiology of anemia, such as the decrease of the food intake, reduction of intestinal absorption, blood losses by GIT, abnormalities in the production of red blood cells, worsening of kidney function, chronic inflammation, blood dilution and the use of drugs[28]. Subsequently, we will briefly address the etiological factors involved in the genesis of anemia associated to HF which are the partial result of GIT abnormalities.

The "needful" component seems to play an important role in the development of anemia. This would arise of the triad of changes commonly found in HF: reduction of food intake, decrease of intestinal absorption and blood losses by the GIT[28]. As in other chronic diseases, in HF there is activation of mechanisms involved in the reduction of the iron absorption. The lipopolysaccharides, such as the IL-6, induce the liver production of hepcidin, acute-phase protein which reduces the gastrointestinal iron absorption, leading to decrease in serum iron, a condition referred to as actual iron deficiency. Additionally, hepcidin reduces the release of iron in the stocks of macrophages and hepatocytes, also contributing to the reduction of serum iron, in this case referred to as iron functional deficiency[29]. Another factor which may induce anemia is the blood loss by GIT. Many patients with HF use antiplatelet agents, such as acetylsalicylic acid and/or anticoagulants. These drugs may both cause mucosa lesions in several parts of the GIT, and facilitate the blood loss by the digestive tube[28].

Iron deficiency, in addition to inhibiting erythropoiesis, may induce additional heart abnormalities, as it is associated with the activation of the sympathetic nervous system, ventricular dilatation, cardiac mitochondrial changes and thrombocytosis. The abnormalities associated to iron deficiency may be reversible with the iron administration. There are reports that the replacement of iron may even inhibit the production of TNF-α[30,31].

Although it has not been systematically evaluated in large studies, iron deficiency was reported in 1% to 44% of the cases, depending on the severity of HF and the population studied[32,33]. In patients with severe HF, iron deficiency was the most frequent cause of anemia, accounting for 73% of the cases[34]. Nonetheless, many authors believe that, after correction of the iron deficiency, patients may develop the inflammatory component of the disease which causes anemia.

Cachexia

Other system consequence arising out at least partially of GIT changes and the immune activation during HF is cachexia. Currently, cachexia is considered a predictive factor of the reduced survival of patients with HF, irrespective of important variables, such as age, functional class of HF or ejection fraction[35].

Although the pathophysiology of cachexia associated to HF is not completely understood, several factors have been blamed for its development, such as decreased food intake, reduced intestinal absorption of nutrients, increased baseline energy expenditure and immune and neuroendocrine changes[36,37].

The cachexia is associated to several systemic complications, including the heart and skeletal muscle changes. Evaluating the impairment specifically of cachexia on o the heart is difficult, once it occurs in connection with the chronic inflammatory disease and, as already said, the immune activation leads to important deleterious effects in the heart[12]. In our laboratory, we evaluated the isolated effects of the restricted food intake on normotensive and hypertensive rats' hearts. The reduced body weight led to the diminishing of the cardiac muscle mass, which was followed by important morphological and ultrastructural changes, albeit with discrete functional changes in normal hearts[38-41]. In turn, in the hypertrophied heart of rats spontaneously hypertensive, the restricted food intake induced, in addition to morphological changes, the worsening of ventricular and myocardial function[42-45]. This data show that the development of cachexia may lead to additional heart changes and worsening of pre-existing HF picture.

Lastly, in HF, the combination of cachexia and immune activation may induce abnormalities in skeletal muscles, entailing reduction of the capacity to perform physical efforts and the worsening of life quality. The physical inactivity, in its turn, results in loss of muscle mass and worsening of the cachexia picture[9,12,16,46,47].

Treatment of the GIT changes associated to HF

We will now address the possible therapeutic targets to prevent or reduce gastrointestinal changes associated to HF and its systemic consequences. Insofar as the GIT changes induce reduction in intestinal absorption of nutrients, administering nutritional therapy early on is important, to prevent the development of cachexia and, if necessary, to treat it aggressively. The nutrition therapy in HF is complex and is not the object of our review.

As discussed previously, the edema of the intestinal loops leads to change in intestinal permeability and absorption of endotoxins. Thus, maintaining patients with the possible lower edema level is important. In addition to the diuretic therapy, the neuro-hormonal blockade should be performed according to the current guidelines, aiming to improve the HF picture.

The iron deficiency should be routinely tested and treated with the iron administration orally or intravenously. In spite of the experimental studies which have been showing reduction of intestinal shift with antibiotic therapy, there is no definition about the fact that modulation of intestinal microflora is useful to control the systemic inflammatory process. On account of this, the selective intestinal decontamination is not indicated for HF[9,12].

As there is difficulty preventing inappropriate absorption of bacterial constituents, their systemic effects may be blocked. Over the last decade, several clinical trials have been evaluating the effects of several immunomodulator agents[48]. The drugs with anti-TNF-α activity include the etanercept and the infliximab. In large clinical trials, these agents have insignificant results or worsened the evolution of HF, and are currently contraindicated[49,50]. Another immunomodulator evaluated in HF was pentoxifylline. Its possible actions include the inhibition of the synthesis of cytokines, mainly the TNF-α. Pentoxifylline was testes only in small studies, which had favorable or insignificant results[51]. Thalidomide, evaluated in small studies, presented divergent results[48]. Finally, preliminary studies with the administration of immunoglobulin showed positive results, such as the improvement in ejection fraction[48]. Currently, several potential immunomodulatory agents are under experimental investigation, such as inhibitors of T cells activation, antagonists of specific chemokines, IL-10, antagonists of IL-1 receptors, TACE inhibition, inhibition of p38 MAP kinase, methotrexate and n-acetylcysteine[23,52]. Lastly, physical exercises are believed to play an important role in the modulation of the increased inflammatory response in HF[53,54]. As a matter of fact, Adamopoulos et al[55] showed that regular physical exercises may reduce the serum concentration of TNF-α and IL-6.

In sum, there are structural and functional changes of the gastrointestinal tract in heart failure. Its clinical consequences include worsening of the nutritional status, systemic inflammatory activation and anemia. These conditions, either isolated or in combination, induce heart changes and worsening of pre-existing ventricular dysfunction. As for now, there is no definite therapeutic modality for preventing or reducing gastrointestinal changes associated to heart failure and its systemic consequences.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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