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Obesity and Diastolic Heart Failure: Is Inflammation the Link?

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Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health [1], no worldwide accepted published ranges of body fat percentage for identifying obesity, however, currently exist [2]. As such, the practical definition of obesity is based on the Body Mass Index (BMI), also known as Quetelet's Index, which relates height to weight (weight (kg)/height^2(m^2)) [3]. A BMI greater than or equal to 30 kg/m^2 defines obesity. The use of BMI has, however, many limitations, especially in patients with particular medical conditions where body composition may be altered significantly by changing proportions of fat mass and fat-free mass.

In 2008, more than 1.4 billion adults, 20 years and older, were overweight (BMI ≥ 25 kg/m^2). Of these, over 200 million men and nearly 300 million women were obese [4]. In 2009-2010, the prevalence of obesity was 35.5% among US adult men and 35.8% among adult women [5]. Overweight and obesity are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer [6]. At the same time cardiovascular disease is the leading cause of death in the United States and worldwide [7].

The impact of obesity on cardiovascular disease is likely most evident in the worrisome increase in the incidence of Heart Failure (HF) among middle-age or younger people, especially women. One particular form of HF, known as HF with preserved Ejection Fraction [HFpEF] or diastolic HF, is strongly associated with obesity. This clinical HF syndrome is characterized by symptoms and signs of heart failure, a preserved Left Ventricular Ejection Fraction (LVEF) [hence the name of HFpEF], and abnormal left ventricular diastolic function [hence the name of diastolic HF] [8]. Diastolic HF represents a clinical challenge for the physician due to the lack of universally accepted diagnostic criteria. In 2007, the European Society of Cardiology published a diagnostic algorithm based on the presence of abnormal left ventricular relaxation or stiffness [9], the American Heart Association and the American College of Cardiology have, however, not enforced these criteria, and leave the diagnosis of HFpEF as a diagnosis of exclusion. For the purpose of this Editorial we will refer to the European definition of HFpEF which requires the presence of diastolic dysfunction, and therefore diastolic HF and HFpEF are used interchangeably.

Although the prognosis of HF is related to the degree of reduction in LVEF, HFpEF is not a benign disease, and it has a quite unfavorable prognosis (not much different than HF with reduced LVEF) and a particular resistance to conventional treatments [10].

The fact that obesity and diastolic HF are both on the rise (especially in women) and are both resistant to conventional treatments may not be a coincidence and may indicate that one or more key pathophysiologic mechanisms are not understood.It is likely that the obese patient with diastolic HF may have one or more physiologic impairments that prevent the compensatory release of natriuretic peptides in response to fluid overload [11]. B-type Natriuretic Peptides (BNP) are endogenous diuretic and vasodilatory proteins that are produced in response to increasing ventricular strain and become elevated in most HF patients [12]. In obese patients BNP degradation seems to be paradoxically increased, and BNP synthesis is also reduced (as reflected in lower NT-proBNP levels which are unaffected by degradation or clearance) resulting in low BNP levels.The mechanisms responsible for this BNP paradox in obesity are not clear, paralleling the blurred mechanisms linking morbid obesity and diastolic heart failure [13].

Obesity cannot be viewed as a simple disruption of the energy balance equation, and while a positive caloric balance is necessary for weight gain, it is not sufficient to cause the full spectrum of obesity and obesity-related diseases [14]. Accumulating evidence indicates that chronic low-grade inflammation has a crucial role in the pathogenesis of obesity-related metabolic dysfunction [15-18]. As individuals become obese and their adipocytes enlarge, adipose tissue undergoes molecular and cellular alterations affecting systemic metabolism. Adipocytes are indeed not simply a storage depot for body energy; they are endocrine organs as well, with multiple metabolic roles in regulating whole-body physiology. Recent studies have linked the presence of inflammation within the adipose tissue as a key process in the promotion of altered metabolism (primarily insulin resistance) which characterizes the advanced phases of obesity [15-18]. High fat diet, associated with increase of circulating Free Fatty Acids (FFA) (particularly after a fatty meal) [19], has shown to have powerful pro-inflammatory functions by activating the inflammasome [20-23]. Inflammasome-derived cytokines, Interleukin-1β (IL-1β) and Interleukin-18 (IL-18), promote insulin resistance [24-27]. Accordingly mice deficient in the inflammasome or the IL-1 signaling receptor are, at least in part, protected from the metabolic derangements induced by a high-fat diet [20,28,29].

IL-1β was also described as a myocardial depressant factor in sepsis [30], and it has been recently identified as a target for intervention in heart disease [31,32]. Patients with heart failure have increased circulating levels of IL-1β and related cytokines [30,32]. IL-1β induces changes in contractility and lusitropy (active relaxation), due to changes in calcium currents in the cardiomyocytes [30-32]. Impaired contractility and relaxation are key pathophysiologic processes in heart failure. Two pilot studies of anakinra, an IL-1 blocker, showed improved cardiovascular performance in patients with systolic or diastolic HF [33,34].

While systolic and diastolic HF share many of the presenting clinical symptoms and some pathophysiologic features (i.e. impaired relaxation), the 2 syndromes (commonly referred to HF with reduced EF [HFrEF] or preserved EF [HFpEF]) are clearly distinct [8-10]. As mentioned earlier, while obesity is a risk factor for cardiac disease, obesity is much more closely linked to HFpEF (diastolic HF) than

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HFrEF, especially in younger or middle-aged adults, so that it is unlikely to have HFpEF without obesity. HFpEF in the elderly has different pathophysiologic mechanisms and it is not as strongly associated with obesity [35,36]. What causes HFpEF in obese individuals is still poorly understood. HFpEF is characterized by increased cardiac stiffness (mainly at a cardiomyocyte level), reduced contractility reserve, impaired vascular response (endothelial dysfunction) and impaired natriuretic peptide response [36]. While the increased stiffness, reduced contractile reserve, and endothelial dysfunction are common to HFpEF and HFrEF, the impaired natriuretic peptide response (BNP paradox) appears to be preferentially linked to obese HFpEF. While it is not established, it is reasonable to suggest that impaired natriuretic peptide response may be causing or contributing to the heart failure syndrome, suggesting that obesity is not only a risk factor for HF, but rather obesity itself, through the endocrine functions of the adipose tissue, may be causing or accentuating the heart failure syndrome by impairing the activity of the natriuretic peptides that represent an endogenous protective mechanism. In fact, there is evidence that shows that weight loss after surgery leads to restored BNP concentrations [37] and resolution of heart failure syndrome. Accordingly, patients with HFpEF had low protein kinase G activity in the heart (downstream signaling of BNP), and this was associated with increased cardiomyocyte stiffness [38]. Reduced natriuretic peptide signaling in obese HFpEF may reflect reduced synthesis, impaired processing to mature peptides by corin, impaired release, increased clearance by the type C receptor or increased degradation by endopeptidates [39]. Neprilysin is an endopeptidase that cleaves active peptides (as BNP) into inactive peptides [39]. A recent clinical trial found favorable effects of a neprilysin inhibitor (LCZ696) in patients (mostly obese) with HFpEF [40]. Neprilysin is expressed in a wide range of cell types, including adipocytes [39]. Obesity is associated with a marked increase in neprilysin levels and activity [41]. Increased neprilysin activity in obese HFpEF may therefore represent a key mechanism in the BNP paradox. Indeed, neprilysin inhibitors also restored also insulin sensitivity in animal models of obesity [41]. The mechanisms involved in increased neprilysin activity in obesity are also not clear, yet the finding of increased activity with IL-1 stimulation [42,43] suggests that inflammation (IL-1β) may explain the increased neprilysin and BNP paradox in obese HFpEF Figure 1. Adipocytes, however, also have a higher expression of the natriuretic peptide receptor C which functions as a clearance receptor. Whether increased clearance occurs with increased obesity is not known and evidence suggest that obesity is linked to impaired BNP synthesis or release, as obesity is associated with reduced NT-proBNP levels (which are not affected by neprilysin) [44,45]. Moreover, obesity is associated with changes in active myocardial relaxation (lusitropy) due to changes in L-type calcium channel function [46], as well as changes in myocardial stiffness related to changes in phosphorylation and/or isoform shifts in the large protein, titin, that functions as a molecular spring necessary for the passive elasticity (recoil) of the myocardium [47]. Although alterations in titin have recently been shown to be sufficient to cause HFpEF [48], altered collagen deposition should not be ignored as a contributor to myocardial stiffness, particularly in the context of pressure overload, metabolic derangements and altered natriuretic peptide activity [49]. In particular, BNP decreases collagen synthesis via cGMP/PKG regulation of MMPs, negative feedback on fibroblasts, also TGF-B/inflammation involvement, and therefore impaired BNP activity may promote collagen deposition [50-52].

In conclusion, the association between obesity andHFpEF remains poorly understood. Systemic inflammation appears to be causally linked to both obesity and heart failure, and may be also linked to a reduction in natriuretic peptide activity (BNP paradox) which is almost exclusively seen in the obese HFpEF. There is an urgent need to advance our understanding in this area as there is a growing epidemic of both obesity and HFpEF, especially among middle-aged women. A better understanding may lead to testing new therapies, with the aim to determine whether amelioration of obesity or its consequences will halt the HFpEF epidemic. The list of potential interventions to improve outcomes in these obese-diastolic HF patients is long, including dietary restrictions, exercise programs, natriuretic peptide signaling agonists, anti-inflammatory therapies, and bariatric surgery.

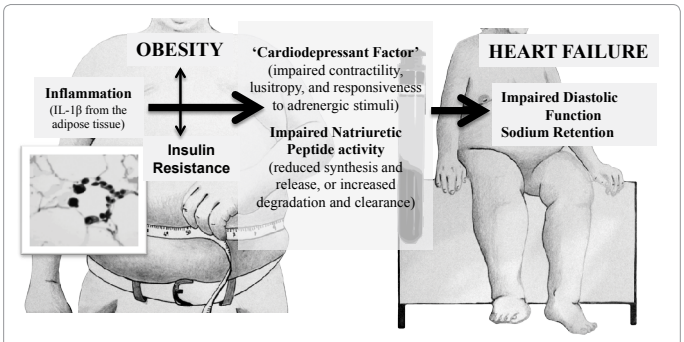

Figure 1:Schematic representation of the proposed link between obesity and heart failure. Inflammation in the adipose tissue induces to a systemic IL-1-dependent low-grade inflammatory response leading to impaired cardiac function and natriuretic peptide activity and hence to worsening of the heart failure syndrome.

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