Myocardial adiposity in heart failure with preserved ejection fraction: the plot thickens

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For many years, adipose tissue was considered merely as a useful tissue for energy storage and supply for metabolic needs. However, in recent years it has become increasingly clear that an increase in fat, or ‘adiposity’, may actually contribute to the development of cardiovascular diseases via local and systemic inflammatory pathways. For instance, the presence of obesity doubles the risk for new-onset heart failure (HF) compared to those with normal body mass index (BMI). In addition, obesity is highly prevalent in HF patients and it has been postulated that a specific subtype of obesity-induced HF exists within the population of HF with preserved ejection fraction (HFrEF). Gaining insight in the mechanisms underlying the association between obesity and HFrEF is of paramount importance, since it may help to develop novel effective therapeutic pathways for HFrEF. This is essential, as there are currently no evidence-based treatment strategies for HFrEF.

The study by Wu et al. in this issue of the Journal is therefore timely, and may provide interesting new evidence suggesting that intramyocardial accumulation of fat may contribute to the pathophysiology of HFrEF. The authors conducted a comprehensive non-invasive Magnetic Resonance Spectroscopy ($^1$H-MRS) study of the myocardium to quantify myocardial lipid content in a large population of patients with HFrEF, HFrEF and matched controls. $^1$H-MRS is a well-established technique that is employed in several clinical diseases such as the differentiation of neurological tumors. For cardiac analysis a section of the interventricular septum is typically analyzed to overcome motion artifacts. Nevertheless, one measurement can be performed within a single heartbeat and the quality of the analysis and the signal to noise ratio is typically high. $^1$H-MRS is capable of quantifying myocardial lipid content accurately and reproducibly, in addition to a number of other metabolites such as creatine. More importantly, $^1$H-MRS is a technique that is available on most modern MR scanners, and would therefore offer the opportunity for large scale implementation. Despite this, very little is known about myocardial fat content in patients with HF. The authors should therefore be congratulated for this meticulous study in arguably the largest population of HF patients studied with $^1$H-MRS to date.

The study provides several intriguing and novel insights. First, the authors demonstrated that myocardial lipid content is 50% higher in HFrEF patients than in healthy controls, whereas this increase was not apparent in patients with HFrEF. Second, higher concentrations of intramyocardial fat were positively associated with the severity of diastolic dysfunction in patients with HFrEF, while this association was not present in patients with HFrEF or in controls. Third, in HFrEF patients the myocardial lipid content was significantly higher in women than in men and the association between myocardial lipids and diastolic dysfunction was most pronounced in women. The present data therefore add substantial support to the hypothesis that adipose tissue is involved in the pathophysiology of HFrEF. Moreover, it suggests that intramyocardial lipid...
accumulation may represent a pathophysiological phenomenon that is specific to HFpEF syndrome and could be amendable to therapeutic interventions. Furthermore, the data suggest that it represents a sex-specific mechanism that could partially explain the high prevalence of HFpEF among women.

Many patients with HFpEF are obese, and increasing evidence suggests that adipose tissue and the associated inflammation are involved in the pathophysiology of HF.2,6 Recently, it has been shown that body fat distribution (visceral fat vs. peripheral fat), rather than obesity per se, is associated with increased mortality in HF patients.7 Moreover, patients with HFpEF showed increased volumes of the visceral fat adjacent to the heart (e.g. epicardial fat) compared to controls, a finding which has been confirmed in the current study.8 This is particularly interesting, since epicardial fat and the underlying myocardium share a common, contiguous microcirculation, with no basal layer separating the two tissues.9 It is therefore plausible that the increase in intramyocardial fat in HFpEF patients, as shown by Wu et al, may be related to the epicardial fat expansion and infiltration to the underlying myocardium. However, the main limitation is that the measurement of intramyocardial fat in this study was performed in the septal myocardium, therefore this hypothesis could not be tested with the current study. However, histological studies suggest that epicardial fat may indeed infiltrate the myocardium.10 Another possibility is that lipid accumulates in the extracellular space and could thereby influence myocardial stiffness or induce local inflammation. This hypothesis is supported by the independent association between extracellular volume and myocardial lipid content observed in the current manuscript. Finally, the increased myocardial lipid content could also be explained by an intracellular accumulation of lipids as a consequence of altered myocardial metabolism.11 Fat accumulation in the extracellular matrix or intracellular compartment could affect myocardial mechanics and stiffness by local inflammation caused by pro-inflammatory adipokines, which are known to be abundant in adipose tissue.12 Indeed, myocardial fat seems to be related to diastolic dysfunction, an observation that is confirmed by the current study.13 These potential pathophysiological pathways of increased intramyocardial adipose tissue are displayed in Figure 1. These hypotheses are, however, speculative and warrant further investigation.
Another intriguing observation is the fact that the lipid accumulation appears to be more prominent in women than in men. Earlier studies have shown that men and women have essentially different body fat distributions.\textsuperscript{5} For instance, men are more prone to store fat around the organs (e.g. visceral fat), whereas women are more likely to store fat subcutaneously.\textsuperscript{7} Therefore, the finding that intramyocardial fat is increased in HFpEF women is surprising, especially since BMI, the prevalence of type II diabetes mellitus and the amount of epicardial fat did not differ between HFpEF men and women. The difference in myocardial lipid content between men and women therefore seems to be unrelated to traditional risk factors for adiposity, and opens up new avenues for pathophysiological hypotheses for HFpEF.

In conclusion, the study performed by Wu and colleagues adds novel and important data to the hypothesis that adipose tissue, especially in- and around the heart, is involved in the pathophysiology of HFpEF. However, several important and inherent limitations that come with $^1$H-MR spectroscopy imaging should be addressed, which includes the fact that measuring triglycerid content using $^1$H-MR spectroscopy does not distinguish whether the triglycerid is actually inside the myocardial cell (infiltration of adipose tissue), or in the interstitial matrix. Recent animal studies support the
first hypothesis, namely that adipose tissue infiltrates the myocardial cell, making it steatotic.\textsuperscript{14} Also, the total myocardial lipid content is approximated using a single voxel in the ventricular septum. Therefore, this imaging technique might overlook regional differences in myocardial lipid content.

What should we expect from future studies concerning myocardial adiposity and HF? First, although the evidence that myocardial adiposity negatively impacts the myocardium is getting more robust, more studies are needed to provide precise pathophysiological insights into how it may affect cardiac function and structure. As depicted above; it is currently unknown whether myocardial fat accumulation is preceded by epicardial fat accumulation, and whether the myocardial fat is stored intra- or extracellular. Therefore, future studies should focus on further unraveling the exact relationship between intramyocardial adipose tissue and HF. The use of relatively new non-invasive imaging techniques, such as MR imaging and MR spectroscopy, may greatly aid in this quest. Second, according to the current study, intramyocardial fat seems to particularly affect HFpEF women. This observation should be further investigated, as sex differences are increasingly recognized in HF and intramyocardial fat accumulation may be a specific pathophysiological pathway that is mainly applicable for women. Third, studies investigating novel lipid-lowering therapies are of interest in the context of treating HFpEF. Drug therapies, such as sodium-glucose co-transporter 2 (SGLT2) inhibitors are promising in the treatment of HF, as they appear to improve myocardial metabolism and reduce the secretion of pro-inflammatory adipokines.\textsuperscript{15} However, if SGLT2 inhibitors also influence myocardial triglyceride content remains to be demonstrated.

In summary, the plot around the true impact of adipose tissue on the myocardium appears to be thickening. Uncovering specific pathways of its effect, as reported by Wu et al. is paramount to get to the heart of the problem.
REFERENCES


