Myocardial adiposity in heart failure with preserved ejection fraction

van Woerden, Gijs; van Veldhuisen, Dirk J.; Rienstra, Michiel; Westenbrink, B. Daan

Published in:
European Journal of Heart Failure

DOI:
10.1002/ejhf.1653

Publication date:
2019

ESC European Society of Cardiology

European Journal of Heart Failure (2020) **22**, 455–457
doi:10.1002/ejhf.1653

EDITORIAL COMMENT

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

Gijs van Woerden, Dirk J. van Veldhuisen, Michiel Rienstra, and B. Daan Westenbrink*

Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

This article refers to 'Myocardial adipose deposition and the development of heart failure with preserved ejection fraction' by C.K. Wu *et al.*, published in this issue on pages 445–454.

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.[1] 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 (HFpEF).[2] Gaining insight in the mechanisms underlying the association between obesity and HFpEF is of paramount importance, since it may help to develop novel effective therapeutic pathways for HFpEF. This is essential, as there are currently no evidence-based treatment strategies for HFpEF.[3]

The study by Wu *et al.*[4] 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 HFpEF. 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 HFpEF or HF with reduced ejection fraction (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 tumours. For cardiac analysis, a section of the interventricular septum is typically analysed to overcome motion artefacts. 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.[5] ^{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 magnetic resonance 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 HFpEF 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 HFpEF, while this association was not present in patients with HFrEF or in controls. Third, in HFpEF 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 HFpEF. 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,[8] a finding which has been confirmed in the current study. 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

The opinions expressed in this article are not necessarily those of the Editors of the *European Journal of Heart Failure* or of the European Society of Cardiology. doi: 10.1002/ejhf.1617

*Corresponding author. Department of Cardiology, University Medical Center Groningen, AB 31, PO Box 30.001, 9700 RB Groningen, The Netherlands. Tel: +31 50 3612355, Fax: +31 50 3614391, Email: b.d.westenbrink@umcg.nl

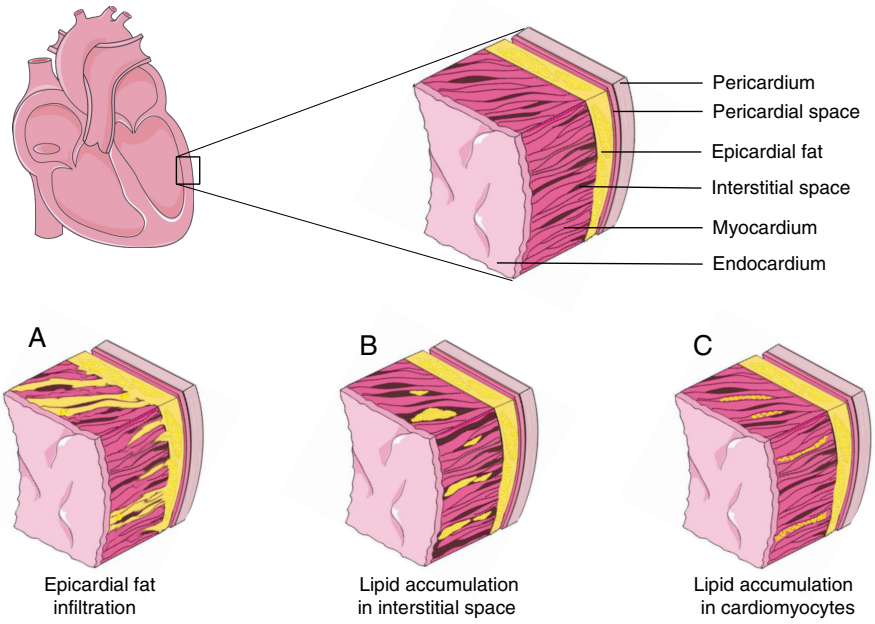

Figure 1 Potential pathophysiological pathways (scenarios A, B and C) of increased intramyocardial adipose tissue. Adapted from Servier Medical Art licensed under CC BY 3.0.

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,[13] an observation that is confirmed by the current study. 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 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.[6] 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.[7] Therefore, the finding that intramyocardial fat is increased in HFpEF women is surprising, especially since body mass index, 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-MRS imaging should be addressed, which includes the fact that measuring triglyceride content using ^{1}H-MRS does not distinguish whether the triglyceride 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.[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 myocardial fat is stored intra- or extracellularly. Therefore, future studies should focus on further unravelling the exact relationship between intramyocardial adipose tissue and HF. The

use of relatively new non-invasive imaging techniques, such as magnetic resonance imaging and MRS, 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.[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.

Conflict of interest: none declared.

References

1. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med* 2002;**347**:305–313.
2. Obokata M, Reddy YN, Pislaru SV, Melenovsky V, Borlaug BA. Evidence supporting the existence of a distinct obese phenotype of heart failure with preserved ejection fraction. *Circulation* 2017;**136**:6–19.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
4. Wu CK, Lee JK, Hsu JC, Su MY, Wu YF, Lin TT, Lan CW, Hwang JJ, Ly L. Myocardial adipose deposition and the development of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020;**22**:445–454.
5. Booij HG, Koning AM, van Goor H, de Boer RA, Westenbrink BD. Selecting heart failure patients for metabolic interventions. *Expert Rev Mol Diagn* 2017;**17**:141–152.
6. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;**62**:263–271.
7. Streng KW, Voors AA, Hillege HL, Anker SD, Cleland JG, Dickstein K, Filippatos G, Metra M, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Zannad F, Damman K, van der Meer P, Lang CC. Waist-to-hip ratio and mortality in heart failure. *Eur J Heart Fail* 2018;**20**:1269–1277.
8. van Woerden G, Gorter TM, Westenbrink BD, Willems TP, van Veldhuisen DJ, Rienstra M. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. *Eur J Heart Fail* 2018;**20**:1559–1566.
9. Packer M. Epicardial adipose tissue may mediate deleterious effects of obesity and inflammation on the myocardium. *J Am Coll Cardiol* 2018;**71**:2360–2372.
10. Tansey DK, Aly Z, Sheppard MN. Fat in the right ventricle of the normal heart. *Histopathology* 2005;**46**:98–104.
11. Sharma S, Adrogue JV, Golfman L, Uray I, Lemm J, Youker K, Noon GP, Frazier OH, Taegtmeyer H. Intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart. *FASEB J* 2004;**18**:1692–1700.
12. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, Sarov-Blat L, O'Brien S, Keiper EA, Johnson AG, Martin J, Goldstein BJ, Shi Y. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003;**108**:2460–2466.
13. Rayner JJ, Banerjee R, Holloway CJ, Lewis AJ, Peterzan MA, Francis JM, Neubauer S, Rider OJ. The relative contribution of metabolic and structural abnormalities to diastolic dysfunction in obesity. *Int J Obes (Lond)* 2018;**42**:441–447.
14. Holloway GP, Snook LA, Harris RJ, Glatz JF, Luiken JJ, Bonen A. In obese Zucker rats, lipids accumulate in the heart despite normal mitochondrial content, morphology and long-chain fatty acid oxidation. *J Physiol* 2011;**589**:169–180.
15. Yurista SR, Sillje HH, Oberdorf-Maass SU, Schouten EM, Pavez Giani MG, Hillebrands JL, van Goor H, van Veldhuisen DJ, de Boer RA, Westenbrink BD. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. *Eur J Heart Fail* 2019;**21**:862–873.