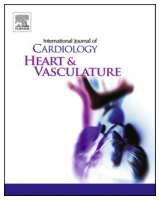
IJC Heart & Vasculature 54 (2024) 101485

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature



Editorial

Epicardial adipose tissue and exercise intolerance in HFpEF

This article refers to 'Association of epicardial fat with cardiac structure and function and exercise capacity in heart failure with preserved ejection fraction: a systematic review and meta-analysis' by Fukuta *et al.,* published in this issue on pages XXX [1].

Although heart failure (HF) with preserved ejection fraction (HFpEF) is increasingly becoming the dominant form of HF, there is still a need for a better understanding of the underlying pathophysiological mechanisms [2]. Patients with HFpEF most often complain of exercise intolerance, impairing functional capacity and limiting their quality of life [3]. When quantified by the objective measurement of peak VO_2, patients with HFpEF exhibit a mean peak VO_2 that is inadequate to perform the physical activities necessary for activities of daily living [4,5]. Hence, especially better understanding of the causes of exercise intolerance is crucial to improve morbidity in patients with HFpEF. It has been demonstrated that there is a correlation between obesity, particularly visceral adiposity, and exercise intolerance [6,7]. Visceral fat depots, including abdominal visceral adipose tissue (VAT) and epicardial adipose tissue (EAT) have been linked to myocardial dysfunction and elevated filling pressures [8], all measurements known to be associated with exercise intolerance. Therefore, it can be suggested that EAT may in part contribute to the onset and/or maintenance of exercise intolerance. In light of these suggestions, it is crucial to gain further insights into the effects of EAT on exercise capacity.

In the present issue of the *Journal*, Fukuta *et al.* conducted a meta-analysis examining the effects of EAT in patients with HFpEF, including the association between exercise intolerance and EAT [1]. A total of eleven studies were included using two different methodologies to measure EAT: echocardiography and cardiac magnetic resonance (CMR) imaging. To evaluate the association between exercise capacity and EAT, a meta-analysis was conducted incorporating three studies that used peak VO_2 and echo-based measurement of EAT thickness. No study investigated the association between CMR-quantified EAT and peak VO2. In their analysis, a significant negative correlation between peak VO_2 and EAT was observed, with a pooled correlation coefficient of -0.37 ($p = 0.000$, $I^2 = 0$ %). Fukuta *et al.* concluded that these findings indicate that increased EAT is thus associated with exercise intolerance.

A meta-analysis is inherently dependent on the quality and power of the included studies. In this meta-analysis, all the included studies were cross-sectional, which introduces potential biases and limits the ability to draw causal conclusions. Additionally, there was substantial variability in the measures assessed, with only two or three studies available for each measurement, limiting the strength of the findings. The calculated I^2 values may also be influenced by the fact that the meta-analysis is based on relatively small studies, each with limited power. Still, the overview of the available literature in this meta-analysis is of interest as it substantiates the necessity for further research to reinforce the debate concerning the role of EAT in the pathophysiological mechanisms of exercise intolerance.

The pathophysiological mechanisms underlying exercise intolerance are complex and often involve a combination of several intra- and extracardiac mechanisms, including limited cardiac and peripheral vascular reserve during exercise, limited mechanical ventilation and gas exchange with reduced pulmonary vascular reserve, skeletal muscle dysfunction and anemia [9]. Given the high degree of heterogeneity and diversity of phenotypes, determining the exact causality is often challenging, leading to unclear treatment targets and consequently limits patients' quality of life.

Patients with HFpEF often have multiple comorbidities, each of which can also have an impact on exercise capacity through various mechanisms [10]. One of the most-common comorbidity in patients with HFpEF is obesity or visceral adiposity. The link between obesity and exercise intolerance is well established, with both central and peripheral mechanisms being considered, such as increased LV filling pressure, lung vasculopathy and increased pulmonary pressures, all leading to myocardial structural and functional changes [11]. In addition, in obese patients, excess adipose tissue accumulation in skeletal muscles correlates with muscle weakness, mitochondrial pathway disruption and therefore exercise intolerance [7]. Compared to other adipose tissue depots, EAT is thought to be particularly important in the underlying mechanisms of exercise intolerance, given its unique characteristics and its proximity to the myocardium. The pathophysiological mechanisms underlying EAT that could contribute to myocardial dysfunction are an inflammatory imbalance due to pro-inflammatory paracrine effects of adipose tissue, lipid infiltration in the myocardium and mechanical impairment due to pericardial constraint [8,12,13]. Regarding exercise intolerance, the constrictive effect of EAT on the heart is of particular interest, as this effect becomes more pronounced during physical exertion. The existence of EAT within the pericardium can potentially lead to pericardial constraint and ventricular interdependence when the heart dilates in response to increased venous return in response to exercise. This hypothesis was underlined by the association between increased EAT thickness and invasive haemodynamic signs of pericardial constraint in patients with HFpEF [14]. Nevertheless, it is important to acknowledge that the precise causal relationship between EAT and myocardial dysfunction remains unclear. It is also a possibility that adipose tissue accumulation may be a consequence of myocardial dysfunction itself.

If EAT plays a significant role in the pathophysiology of exercise intolerance and the clinical outcomes of patients, then therapies specifically focused on reducing the amount of EAT may yield potential

https://doi.org/10.1016/j.ijcha.2024.101485
Received 30 July 2024; Received in revised form 2 August 2024; Accepted 2 August 2024
Available online 11 September 2024

benefits. However, before the focus can be shifted to potential treatments aimed at reducing EAT, it is crucial to further investigate the hemodynamic and functional effects of EAT. For this purpose, the utilization of exercise CMR could be beneficial. Bicycle exercise stress testing during CMR has been shown to be a feasible and reliable instrument in the evaluation of myocardial impairments [15]. As the haemodynamic changes that lead to mechanical impairment are typically only visible during exercise, exercise CMR could provide further insights into the pathophysiological link between EAT and exercise intolerance. A subanalysis of the HFpEF-Stress trial showed that patients with diastolic dysfunction and increased EAT had more pronounced signs of diastolic functional failure and adverse structural remodelling [12]. Further findings from studies utilising exercise CMR to examine the impact of EAT on cardiac function in patients with HFpEF, among other outcomes from the EXPOSURE study [NCT06514820], are currently awaited.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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