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Underestimation of congestion in very obese heart failure with preserved ejection fraction patients: EAT your heart out...!?! 

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This article refers to ‘Uncoupling between intravascular and distending pressures leads to underestimation of circulatory congestion in obesity’ by M. Obokata et al., published in this issue on pages 353–361.

Obesity, which commonly is defined as a body mass index (BMI) >30 kg/m², is a global health burden that has grown to pandemic proportions, associated with substantial morbidity and mortality. Obesity is commonly present in patients with heart failure (HF) with preserved ejection fraction (HFpEF) and may even represent a risk factor for HFpEF development. We and others have previously demonstrated that obesity also affects plasma levels of cardiac biomarkers, and that higher BMI is associated with lower plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. Despite this inverse relationship, prognostic value for NT-proBNP remains intact throughout different BMI categories except for severely obese (BMI >40 kg/m²) individuals. This suggests that, despite lower plasma levels, these biomarkers may still reflect ongoing cardiac disease in obese individuals and that assessment of cardiac biomarkers can be helpful to diagnose HF in obese individuals.

In this issue of the Journal, Obokata et al. underline the challenge of HF diagnosis in patients with obesity. In their study they demonstrate that current strategies of evaluation of biomarkers and echocardiographic data may result in underestimation of HFpEF in very obese patients. Obokata and colleagues studied the relationship between multiple plasma and echocardiographic biomarkers on central haemodynamics in obese (BMI <35 kg/m²) and in very obese subjects (BMI ≥35 kg/m²). Using heart catheterization and echocardiography, they evaluated 212 subjects with unexplained dyspnoea, and obtained additional blood samples in 58 of 212 subjects. The authors showed that obesity is associated with higher intracardiac pressures and that traditional biomarkers (e.g., NT-proBNP and troponin T) or echocardiographic parameters (e.g., E/e') in very obese patients may not accurately reflect circulatory congestion assessed by invasive measurement. They postulate that this finding indicates uncoupling of cardiac wall stress from intravascular pressures. In obese patients with a BMI <35 kg/m², the traditional biomarkers and echocardiographic biomarkers exhibited a better correlation with central haemodynamics and uncoupling was not seen. This suggests that the diagnosis of HFpEF is more difficult in the very obese, and may be missed more often than currently assumed.

There are several considerations in interpretation of the data. First, in their study, BMI was used as a surrogate for obesity and adipose tissue, and those patients with higher BMI were considered to have more adipose tissue than those with lower BMI. BMI, however, does not reflect adipose tissue distribution and although BMI is widely used to assess obesity, there is consensus that other parameters of obesity, such as waist circumference and relative fat mass more accurately predict new onset HF. Second, obese individuals are very likely to experience dyspnoea on exertion, and this is the case in both obese patient populations as well as in otherwise healthy obese individuals. The increased prevalence of dyspnoea on exertion may cause inclusion bias with relative over inclusion of obese individuals, as compared to leaner individuals, as they experience higher symptom burden and may therefore be referred at earlier stages of disease. Finally, the authors did not study the mechanisms that are responsible for this uncoupling, but it is reasonable to assume that this may be explained by increased volume of adipose tissue. The authors support this potential explanation and postulate that ‘Obesity is associated with an increase in external pressure applied on the heart. This may be mediated by increases in heart size due to hypertrophy, chamber dilatation, and plasma volume retention as well as increases in pericardial and intrathoracic fat’. Therefore, they suggest that lower biomarker levels in obese patients are not only the result of obesity-induced paracrine changes, but may also reflect enhanced pericardial restraint due to increased adipose tissue in the epicardium.

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.2377

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Adipose tissue, or fat, is not a simple storage organ, but rather an organ with complex function, present at various sites throughout the body. Epicardial adipose tissue (EAT) refers to the layer of fat that is located between the myocardium and the visceral pericardium. It typically accounts for 20% of total heart mass, and is involved in energy homeostasis, coronary protection through formation of a mechanical boundary and inhibition of atherosclerosis by providing anti-atherogenic and anti-inflammatory adipokines. The amount of EAT increases once total visceral adipose tissue volume increases, and obesity can therefore be regarded as a risk factor for higher EAT volumes. Higher EAT volumes are associated with a pro-inflammatory state and increased cardiac fibrosis, and higher total EAT volumes are found in patients with HF in comparison to healthy subjects, even independently of obesity. In obese individuals with HFpEF, increased EAT is associated with higher intracardial pressures and significantly lower peak oxygen consumption as compared to those without increased EAT volumes. The amount of EAT is best visualized by cardiac magnetic resonance imaging (MRI). Unfortunately, the current study by Obokata et al. did not include cardiac MRI scanning to further bolster their findings. Recent cardiac MRI studies in patients with HFpEF have already demonstrated that the site of EAT accumulation is associated with structural changes that induce haemodynamic and electrical changes, and that in these patients higher EAT volume is associated with worse outcomes, including all-cause mortality and HF hospitalizations.

We therefore hypothesize that, apart from local pro-inflammatory and pro-fibrotic changes due to increased EAT volumes, build-up of EAT itself may also act as an important disease modifier that increasing volumes of EAT may form a dense and compact layer around the myocardium that prevents the heart from passive filling, resulting in higher intracardiac pressures and lower natriuretic peptide levels due to limited left ventricular (and right ventricular) stretch, and thus uncoupling of intracavitary and intravascular pressures. This phenomenon somewhat resembles the clinical features of cardiac tamponade albeit to increased amount of fat and not fluid (Figure 1). Although no specifics on fat tissue or EAT volumes were determined in the study by Obokata et al., their results are highly suggestive that pseudo-cardiac tamponade is directly associated with BMI and adipose tissue volume, and is present at BMI > 35 kg/m². Future studies are essential to validate and bolster this hypothesis and to evaluate if targeting EAT may represent an important treatment strategy to improve cardiac filling in obese patients, especially those with BMI > 35 kg/m² to restore central haemodynamics and improve signs and symptoms.

The relationship between cardiac biomarkers in obesity may also be modified by sex: in women, lower NT-proBNP levels are typically observed with increasing BMI, body weight and waist circumference, while this relationship was more complex in males. In addition, in women with HFpEF, every 100 cm² increase in visceral adipose tissue was associated with a 4.0 mmHg increase in post-capillary wedge pressure, and this did not happen in men. Besides a potential mechanistic effect of increased fat mass, we have previously suggested that these sex-specific observations could be a result of sex-specific properties of the fat tissue itself. Interestingly, in this study, no sex effect was observed and circulatory congestion was underestimated in men and women to a similar extent. Although this interesting finding warrants further research, it suggests that once individuals become very obese, sex-specific
differences in fat accumulation site or adipocyte properties become less relevant and do not have to be taken into account as such.

It may be clear that obesity is a vast and complex problem without a simple ‘one-strategy-fits-all’ solution. The combination of obesity and HFpEF is common, but renders a complicated combination that deserves full attention. Besides the potential malicious local effects of excessive adipose tissue, fat accumulation itself may also be part of deteriorating cardiac state. Pseudo-cardiac tamponade may be responsible for uncoupling of cardiac and intravascular pressures that may result in underdiagnosis and potential suboptimal treatment of obese HFpEF patients. Increasing attention is being paid to reduction of EAT via pharmacological or surgical routines, and results are eagerly awaited. Until then, the most straightforward option for patients is to lose weight. The range of BMI in this study is very disturbing. Further, on longer term, early detection and recognition of those HFpEF patients with high EAT volumes may be helpful to optimize treatment strategy and improve quality of life of obese HFpEF patients with unexplained dyspnoea. **Conflict of interest:** none declared.

References