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Heart Failure with Preserved ejection Fraction: a haemodynamic explanation of exertional dyspnoea.

Running title: haemodynamics in heart failure

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The study of Y. Saito & al shares an interesting non-invasive exercise evaluation in heart failure with preserved ejection fraction (HFpEF) (1). They compared patients with HFpEF versus controls to shed light on the pulmonary hemodynamics during exercise to explain the exertional dyspnea reported by these patients. They assessed the trend of the pulmonary pressures registered during exercise estimated by echocardiography and its relationship with the associated cardiac output elevation. A retrospective analysis of 345 patients from a single centre tertiary Japanese hospital who were being evaluated for exertional dyspnea were divided into patients defined as having HFpEF (166), and controls (179) who did not reach diagnostic criteria for HFpEF nor pulmonary artery hypertension confirmed by right heart catheterization. The median value of the mean pulmonary arterial pressure (mPAP) over the cardiac output (CO) slope is higher in the HFpEF group (5.2 mmHg/L/min, IQR 3.4-8.0) than in the controls (3.7 mmHg/L/min, IQR 2.4-5.6).

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This cut-off of 5.2 mmHg/L/min has been used by the authors to define the pathophysiological concept of 'disproportionate exercise-induced pulmonary hypertension (DEi-PH) in HFpEF'. With this threshold, the statistical analysis classified half of the group of HFpEF patients as affected by abnormal pulmonary hemodynamic response to exercise. This subgroup experienced impaired exercise capacity (lower peak oxygen consumption, worse ventilatory efficiency), poor left ventricular functional reserve (limited in CO augmentation) and right ventricle dysfunction at peak exercise (impaired RV-PA coupling, increased right-sided congestion)(1).

This work has several strengths. Robust selection criteria thanks to using a combined score to define patients with HFpEF, built on echocardiographic functional and morphological parameters in addition to the natriuretic peptide value (HFA-PEFF score), as recommended by the 2021 European Heart Society guidelines(2, 3). The expired gas analysis confirms the degree of exercise intensity (maximal in all groups with a mean respiratory exchange ratio close to 1.10), which avoids underestimating the maximal oxygen consumption. The authors used the mPAP/CO slope as the main parameter, rather than the mPAP alone, which allows the assessment of disproportionate rise in mPAP to changes in CO, as with rising CO there is a physiological increase in mPAP. Using lung ultrasound to confirm lung congestion during exercising was useful to confirm the findings(4, 5).

To link the pathophysiology with clinical outcomes, the authors then evaluated composite outcomes of all-cause mortality or heart failure events. At a follow-up of six hundred days, there was a significant difference in event free survival in HFpEF patients with DEi-PH compared to controls (*p=0.0003) and those without DEi-PH (†p=0.01)

Regarding limitations, there is a potential underestimation of pulmonary pressures during exercise due to noninvasive measurement. Only a subset of the patients underwent

right heart catheterization during exercise to validate the echocardiographic parameters. Intra- and interobserver correlation coefficients are strong (0.82 to 0.86) but was based on a limited number of exams (n=40). Another challenge is echocardiographic CO estimation, the VTI curve is prone to several errors during exercise, as the sampling volume can be affected by respiration, and the clarity can be impaired. The use of averaged automatic traces using the new echo-machines could be evaluated to validate the assessment during exercise(6). The authors do not give information about the main limiting effort factor (central, peripheral, or mixed) or patient's respiratory threshold value. This would have been interesting in this study where HFpEF patients and control only reach 55 to 60% of the predicted peak oxygen consumption(6). Additional parameters that could have been evaluated include the 6-minutes' walk test distances and the quality-of-life questionnaires that reflect the impact of the disease on these patients (7).

In the statistical analysis, the authors assessed the mPAP/CO slope mean values at peak of the exercise, and the timing of this can be brought into question as we know that diastolic dysfunction appears within the first few minutes of effort when the exercise load is quite weak, and the E and A waves are still distinct, facilitating analysis(2).

Heart failure is an epidemic, with more than 50% being due to HFpEF. HFpEF is not well understood and trials to improve prognosis have so far been disappointing (1) (figure 1). Recent works have tried to subdivide this heterogeneous and aging population in several phenotypes, to try identify therapeutic targets that may differ between subgroups (8-10). The work of Y. Saito & al advanced our understanding of the symptomatology of HFpEF matching symptoms to pathophysiology(1). This complements work by C. Lam et al showing a high prevalence of pulmonary hypertension which may be severe in the HFpEF population(11). They found that pulmonary venous hypertension is one of the main mechanisms, but does not

alone explain the full severity pulmonary hypertension in HFpEF. These results are in favor of an additional role of pulmonary vascular remodeling leading to pulmonary arterial hypertension(11). Trials are underway to assess the role of pulmonary hypertension medications in this group (Cadence, Endeavor...).

With these results suggesting the role of pulmonary vascular remodeling, their findings should be prospectively validated(1). Prospective evaluation and early enrollment may help to understand better why some HFpEF patients develop DEi while others don't. Repeated exercise echocardiography tests may help detect a slight decline of diastolic or right heart function prior to the development of pulmonary hypertension. Other clinical studies would be also useful to validate the threshold of 5.2 mmHg/L/min. This cut-off value differs from to the ones obtained by the sensitivity analysis of this work (3 mmHg/L/min) or from other teams predicting 3-year mortality in patient with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension (4).

The HFpEF patients suffering from disproportionate exercise-induced pulmonary hypertension may benefit from pulmonary arterial hypertension specific therapy, and we are eager to see the results of ongoing studies (12, 13). A better understanding of the syndrome will make the selection of targeted treatments easier(8).

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Figure 1: summary slide about the value of the concept of 'disproportionate exercise-induced pulmonary hypertension in HFpEF'

Heart Failure with preserved Ejection Fraction : A Syndrom

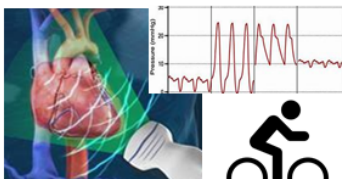
- 1) Clinical assessment
- 2) Biomarkers
- 3) Rest Echocardiography

A matter fo haemodynamic understanding!

Better phenotyping for a more individualized approach of treatments

For a better treatment and management

Disproportionate exercise-induced pulmonary hypertension in HFrEF



Exercise your patient!