Relaxing from dyspnoea

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This editorial refers to ‘Serelaxin in acute heart failure patients with preserved left ventricular ejection fraction: results from the RELAX-AHF trial’$^1$, by G. Filipatos et al., on page 1041

Breathing differs from other vital functions in that it is regulated not only by automatic centres located in the brainstem but also by voluntary signals initiated in the cortex.$^1$ Dyspnoea is the most prevalent symptom in heart failure and it is experienced in different ways and reported with several qualitative expressions. It seems as though dyspnoea associated with heart failure is different from the dyspnoea associated with pulmonary disease and is felt as being more suffocating than in other conditions.$^1,2$

The pathophysiology behind dyspnoea is complex and incompletely understood. The mechanisms include haemodynamic, pulmonary, muscular, and factors in the central nervous system.$^1,3,4$ The most simplistic approach in heart failure is that dyspnoea is a direct expression of elevated pulmonary intracapillary pressures and the ensuing increased intrapulmonary water.$^5$

Dyspnoea can be assessed by a number of instruments including visual analogue scales and Likert scales. In chronic stable heart failure, the simple assessment of dyspnoea by a 5-grade Likert scale could predict a significant independent risk of death over 5 years in the COMET study when adjusted for all baseline variables.$^6$ In acute heart failure (AHF), relief of the dyspnoea discomfort is an important objective for treatment. For a long time, furosemide and nitrates have been used to target dyspnoea in AHF. The rationale for the administration of these agents has been to relieve pulmonary congestion and/or reduce elevated left ventricular (LV) filling pressure, thus also reducing the intracapillary pressure.$^7$ The reduction in dyspnoea in association with these agents is observed in most patients over minutes or hours, and there is a relationship between reduction in filling pressures and relief of dyspnoea.$^8$ However, it is not always obvious how much congestion is present just by measuring dyspnoea.$^7$ There have been several attempts to reduce the time to a certain level of improvement of dyspnoea above that obtained with nitrates. The VMAC trial did show an improvement in dyspnoea after infusion of the brain natriuretic peptide neseritide above that achieved with i.v. nitroglycerine.$^9$ This finding led to the approval of nesiritide in the USA for the treatment of AHF. However, even though a slight improvement in dyspnoea by nesiritide was observed in the large ASCEND trial, it did not reach the pre-specified significant level or translate into improved outcomes.$^10$ In this trial, ~20% of the patients had an LV ejection fraction (EF) of ≥40%. There was no interaction in the effects of nesiritide by LVEF split at this value. In a subsequent analysis, early dyspnoea relief was associated with improved 30-day survival.$^11$

As stated above, dyspnoea is a condition which is influenced by many factors and is not simply explained by fluid congestion and elevated LV filling pressures. Dyspnoea is not associated with LVEF, at least as assessed in trials or registries.$^4$ It can be associated with LV diastolic properties translated into LV filling pressures which illustrate the difficulty in trying to express symptoms of HF by LVEF. The findings from COMET indicate that the causes of dyspnoea include more than a simple haemodynamic explanation or congestion. There are probably additional vascular and/or muscular factors that also influence dyspnoea in addition to various experiences by the patient. These mechanisms are poorly understood. A way forward would be to describe dyspnoea better, e.g. by adding a qualitative aspect in addition to the quantitative assessment we use today.

Filipatos and co-authors report the effects of the vasodilating recombinant human peptide serelaxin in AHF from the previously presented RELAX-AHF trial$^{12}$ now analysed by baseline LVEF.$^{13}$ The primary endpoint in RELAX-AHF was dyspnoea, and they also present findings on the secondary outcomes. The present analyses have used a higher LVEF of 50% for comparison while in the original report on LVEF a cut-off of 40% was used.$^{13}$ This alteration was done to comply with the recommended definition of heart failure with preserved EF (HfPEF) in the recent European Society of Cardiology (ESC) guidelines.$^{14}$ The findings show that the results from the main study are consistent across reduced and preserved LVEF. If anything, the improvement of dyspnoea is more pronounced in patients with preserved LVEF as there were more patients who were markedly or moderately improved on the dyspnoea Likert scale in this group compared with those patients who had reduced LVEF. The effects on outcomes showed no interaction by LVEF.
These findings are also most interesting as RELAX-AHF showed an improvement in 180-day all-cause mortality. This outcome was a pre-specified safety outcome but not an efficacy outcome and needs to be interpreted with caution. However, the findings are very interesting, and the lack of interaction by LVEF in this analysis is a promising result in the HFpEF cohort as very few effects from other interventions on long-term outcomes have previously been reported in this group of patients with heart failure, including the recent TOPCAT results.15

The results illustrate the complexity of assessing and understanding the mechanisms behind dyspnea in heart failure. It is clear from RELAX-AHF that the intensity of dyspnea showed no relationship to LV systolic function. The quality of dyspnea was not assessed in this study. Accordingly, the translation of pathophysiology and organ dysfunction to symptoms remains to be better understood. There is more than just haemodynamic alterations behind the symptom expression and, in heart failure, the involvement of pulmonary function is probably also important. In addition, there is a need for better instruments for the assessment of dyspnea in heart failure. A combination of qualitative and quantitative scales should be developed and validated for better understanding of the syndrome of dyspnea. By these efforts we might be able to develop the treatment of AHF and reduce the burden of dyspnea.

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References