Targeting the endothelin system: a step towards a precision medicine approach in heart failure with preserved ejection fraction?

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Remarkable achievements have been made in the treatment of patients with cardiovascular disease during the past three decades. These include major therapeutic improvements for patients with acute coronary syndromes, valvular heart disease, cardiac arrhythmias, and heart failure with reduced ejection fraction. One notable exception has been patients with heart failure and preserved ejection fraction (HFpEF), where a number of therapeutic approaches tested in large-scale, multi-centre randomised controlled trials have failed to convincingly document a reduction in the incidence of the primary outcome measure. Several theories have been proposed to explain the failure of these therapeutic strategies in patients with HFpEF, including the heterogeneity of the patient group and the high prevalence and competing risk of comorbidities¹. In addition, the pathophysiological understanding of HFpEF, a prerequisite for targeted, personalized treatment, remains incomplete. Accordingly, rigorous, high-quality studies that further illuminate the pathophysiology of HFpEF are strongly desired.

Endothelin-1 is a 21 amino-acid peptide produced by endothelial cells that causes potent and long-lasting vasoconstriction by paracrine binding to ET_A receptors on vascular smooth muscle cells². Autocrine binding of endothelin-1 to ET_B receptors, on the other hand, causes nitric oxide release and subsequent vasodilation. Soon after its discovery, studies demonstrated that endothelin-1 is produced by other cell types than endothelial cells, including cardiomyocytes, and that endothelin-1 exerts paracrine actions on other organ systems than the vasculature, including inotropic and profibrotic actions in the myocardium and natriuresis in the kidney². Although endothelin-1 exerts its effects predominantly in a paracrine or autocrine fashion, concentrations of endothelin-1 and the biologically inactive fragment of its prohormone can be measured in the circulation. Early clinical studies

demonstrated that circulating endothelin-1 concentrations were elevated in chronic heart failure in proportion to the severity of pulmonary hypertension³ and associated with mortality in patients with acute myocardial infarction⁴. These observations suggested that antagonising the endothelin system might be used to prevent or treat heart failure, but clinical trials of endothelin receptor antagonists in heart failure with reduced ejection fraction (HFrEF) have been disappointing, partly because the treatment leads to fluid retention and congestion via anti-natriuretic and anti-diuretic mechanisms². Another early, seminal discovery was that of increased endothelin-1 expression in vascular endothelial cells in patients with primary pulmonary hypertension⁵. These observations prompted the development of endothelin receptor antagonists that currently are frequently used in the treatment of primary pulmonary hypertension^{2, 6}. In the general population higher concentrations of endothelin-1 have also been linked to pulmonary hypertension in African Americans⁷. The presence of HFpEF has also been associated with activation of the endothelin system, and higher circulating concentrations of endothelin-1 than in control subjects have been observed⁸

In the current issue of the *European Heart Journal*, Obokata and colleagues from the Mayo Clinic present novel and interesting data concerning the neurohormonal basis of pulmonary hypertension in patients with HFpEF⁹. This topic is of considerable interest as it is well established that pulmonary hypertension at rest and during exercise is prevalent and related to symptom severity and clinical outcomes, including mortality, in HFpEF^{10, 11}. Recent data suggest that pulmonary hypertension in HFpEF may not only be due to passive elevation of left-sided filling pressure, but that pulmonary vascular disease also contributes in subgroups of patients¹². Indeed, the combination of HFpEF and pulmonary hypertension at rest or

during exercise exclusively, may represent a specific HFpEF phenotype. Treatment targeted to reduce the degree of pulmonary hypertension at rest and to attenuate the increase in filling pressure seen during exercise may be particularly beneficial in this phenotype. In their study, Obokata and colleagues specifically investigated the potential role the endothelin and the adrenomedullin systems may play for pulmonary hypertension in HFpEF. They measured the circulating concentrations of the C-terminal fragment of pro-endothelin-1 (CT-proET-1) and the mid-regional fragment of the adrenomedullin prohormone (MR-proADM) at rest and during exercise testing and related these concentrations to indices of the severity of pulmonary hypertension, abnormalities of right ventricular-pulmonary artery coupling, exercise capacity, and cardiopulmonary reserve. The findings were intriguing. Circulating levels of CT-proET-1 and MR-proADM were significantly higher in patients with HFpEF than in control subjects. CT-proET-1 and MR-proADM concentrations at baseline correlated closely, suggesting that they reflect the same pathophysiological process. However, concentrations did not change during exercise. Circulating levels of both neurohormones correlated positively with haemodynamic indices such as mean pulmonary artery pressure, pulmonary capillary wedge pressure and inversely with pulmonary artery compliance, with indices of right ventricular diastolic function, as well as with the cardiac output response to exercise and peak oxygen consumption. The authors conclude that patients with HFpEF, compared to control subjects, display activation of the endothelin and adrenomedullin pathways and that the magnitude of activation appears to be associated with exercise capacity, pulmonary hemodynamic derangements, and limitations in right ventricular functional reserve.

The study has been performed by leaders in the field of haemodynamic function in HFpEF, using an impressive investigational set-up with comprehensive and detailed haemodynamic recordings at rest and during exercise. Still, the study design merits some comments. Notably, the cross-sectional study design precludes conclusions to be drawn concerning the direction of the observed associations. It is therefore unclear whether activation of the endothelin and adrenomedullin systems is causing or is caused by the haemodynamic derangements observed. Moreover, the generalisability of the results depends on the characteristics of the patients and the control group studied. The study included patients with haemodynamically confirmed HFpEF and a small control group with exertional dyspnoea without cardiac pathology or signs of heart failure. As widespread and complex neurohormonal activation is characteristic for HFpEF and elevation of endothelin and adrenomedullin has been documented previously, it is not surprising that CT-proET-1 and MR-proADM were found to be higher in HFpEF patients than in control subjects. The same would likely be the case for many other neurohormones and cardiac biomarkers. Indeed, the authors have recently published data showing that cardiac troponin T, a marker of chronic myocardial injury, is higher in HFpEF patients than in the control group¹³. The theory that endothelin plays a particularly important role in the pathophysiology of pulmonary hypertension in HFpEF would have been further strengthened by data showing that the association with endothelin is substantially stronger than the activation of other neurohormones. In other words, even though the findings of Obokata and colleagues are compatible with activation of the endothelin system in HFpEF, it remains somewhat unclear whether this activation is specific for endothelin or just part of the general neurohormonal activation observed in heart failure. As such, the study illustrates the limitations of a hypothesis-based versus an unbiased approach to biomarker research, i.e. the importance of

the neurohormone(s) tested relative to those not measured remains unknown in the hypothesis-based approach. The authors argue that patients with HFpEF and supramedian CT-proET-1 levels had higher pulmonary artery pressure and worse pulmonary artery compliance than those with infra-median values and make inferences from longitudinal, experimental animal studies where the activation of the endothelin system precedes the development of pulmonary hypertension. Still, randomised controlled trials using endothelin-1 receptor antagonists will be required to firmly establish that the endothelin system actually plays an important pathophysiological role in the development of pulmonary hypertension in HFpEF. Similarly, the therapeutic efficacy of augmenting the adrenomedullin system must await the results of randomized controlled trials. Administration of the adrecizumab, a humanized, monoclonal, non-neutralising antibody directed at the N-terminus of adrenomedullin leads to a dose-dependent increase in adrenomedullin and a randomized clinical trial in patients with acute heart failure and elevated adrenomedullin is being planned.¹⁴ Such a therapeutic approach is also conceivable in patients with HFpEF and pulmonary hypertension.

Major efforts have been made to identify effective therapies for patients with HFpEF, but so far results have been disappointing. The study of Obokata and colleagues illuminates the potential pathophysiological significance of two targetable neurohormonal systems in patients with HFpEF and pulmonary hypertension, the endothelin system and the adrenomedullin system. The findings of Obakata and colleagues are encouraging in that they not only suggest that the endothelin may play an important role in the pathophysiology of pulmonary hypertension in HFpEF, but also that measurement of CT-proET-1 may provide a means to phenotypically characterize and identify those patients most likely to benefit from

interventions targeted to inhibit the endothelin system. The results of past randomised intervention trials of endothelin receptor antagonists in the setting of HFpEF and pulmonary hypertension, however, are humbling. For instance, a pilot study that included patients with HFpEF and pulmonary hypertension showed no signal of benefit of bosentan in an unplanned interim analysis and the trial was stopped prematurely.¹⁵ However, prior studies have been small and the ongoing SERENADE trial (NCT03153111), a phase 2b multi-centre trial of macitentan versus placebo in patients with HFpEF and pulmonary vascular disease or right ventricular dysfunction may provide more robust effect estimates. The study of Obakata and colleagues raises the exciting possibility that specific phenotyping using neurohormonal measurements may permit more precise targeting of therapeutic approaches in HFpEF that ultimately could lead to improved care for this important patient group.

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