PERSPECTIVES

A horse of a different colour: distinct mechanisms of HFpEF and HFrEF

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The past 20 years have seen a remarkable re-thinking of heart failure classification and diagnosis. This has included the realization that approximately half of patients suffer primarily from impaired ventricular relaxation; individuals who are now defined as exhibiting heart failure with preserved ejection fraction (HFpEF). These patients contrast with those diagnosed with HF with reduced ejection fraction (HFrEF), who present with compromised ventricular contraction. Unfortunately, although significant progress has been made over the last decades in treating HFrEF, this has not been replicated for HFpEF management. Thus, there is an urgent need to investigate the pathophysiological mechanisms that distinguish these two diseases, to enable the development of better-targeted therapies.

In the current issue of *The Journal of Physiology*, Kilfoil et al. (2020) have done exactly that. In an elegantly performed study, the authors directly compared remodelling of cardiomyocyte substructure and function in rat models of HFpEF and HFrEF. They observed that expected disruption of t-tubule structure and Ca^{2+} release observed in HFrEF did not occur in HFpEF myocytes. Rather, they report maintained t-tubule structure and an augmentation of the Ca^{2+} transient linked to increased L-type Ca^{2+} current. Thus, while impaired contractility in HFrEF can be traced to reduced systolic function of individual myocytes, generally preserved systolic function observed in HFpEF also appears to have a myocyte-level parallel.

Why would these two forms of heart failure exhibit such divergent types of cellular remodelling? Differences in workload are likely to be key. Our own recent findings have shown that the high workload, and specifically the elevated wall stress, that accompany HFrEF directly trigger t-tubule remodelling (Frisk *et al.* 2016). HFpEF, on the other hand, is associated with concentric hypertrophy and maintained wall stress across the left ventricle. Thus, a central driver of subcellular remodelling is absent. This difference may explain why therapies which mechanically unload the heart, including left ventricular assist devices and inhibitors of the renin-angiotensin system, have proven to be effective in treating HFrEF but have not shown benefit in HFpEF.

While Kilfoil and colleagues report that t-tubule structure and Ca^{2+} release are preserved in HFpEF, they note important irregularities in diastolic Ca^{2+} homeostasis. They observed that under baseline conditions, Ca^{2+} decay rates were similar to values in healthy cells, but that there was a desynchronization of Ca^{2+} removal and significant elevation of resting Ca^{2+} levels. Furthermore, upon treatment with isoprenaline (isoproterenol), an additional deficit in diastolic Ca^{2+} homeostasis emerged, as the expected acceleration of Ca^{2+} decline was significantly blunted. This slowed and incomplete removal of Ca^{2+} is expected to increase 'active' stiffness in the heart, as curtailed detachment of myofilament cross-bridges compromises relaxation. Importantly, the fact that this burden becomes more apparent during stress may partly explain why HFpEF patients describe a worsening of symptoms during exertion.

These exciting findings, which support an active stiffening of the myocardium in HFpEF, add to compelling evidence from others that there is also a marked increase in *passive* stiffness in this condition. A body of work has indicated that this occurs at the level of the extracellular matrix, due to collage deposition, but also within cardiomyocytes due to a stiffening of the giant elastic protein titin (Gladden *et al.* 2014). These passive mechanisms of diastolic dysfunction have been linked to endothelial dysfunction and the inflammatory milieu of HFpEF, and thus are quite distinct from the mechanical overload signals that are centrally involved in triggering HFrEF. Whether deficits in diastolic Ca^{2+} homeostasis are similarly triggered by endothelial dysfunction and inflammation remains unclear. The precise nature of the impairment also requires further investigation, to determine whether decreased Ca^{2+} removal stems from reduced Ca^{2+} reuptake by SERCA, slowed removal from the cell by the Na^{+}-Ca^{2+} exchanger, or even compromised uptake into mitochondria.

One issue not experimentally addressed in the present work is that HFpEF encompasses a very diverse patient group which, in keeping with the metaphor, might be better compared with an array of horses of several different colours. While some of these patients develop the disease in conjunction with hypertension – a condition presently modelled by the use of Dahl salt-sensitive rats – many HFpEF patients suffer from obesity, diabetes and other comorbidities. It is as yet unclear whether the cellular mechanisms for diastolic dysfunction are shared between these different disease aetiologies. Diabetes, for example, is associated with increased activity of the Na^{+}-glucose co-transporter-1 (SGLT-1), which is believed to drive cytosolic Na^{+} accumulation, and thereby slowed Ca^{2+} removal by the Na^{+}-Ca^{2+} exchanger (Lambert *et al.* 2015). SERCA expression and activity are also reported to be reduced in diabetic patients; a deficit that has been linked to hyperglycaemia, oxidative stress and post-translational modifications of the pump. Based on these findings, one might expect that decreased Ca^{2+} removal from the cytosol may play a more marked role in impairing relaxation in diabetic HFpEF than in patients with different comorbidities. If true, such findings would indicate that development of heart failure therapies could benefit from refinement according to disease aetiology. Indeed, perhaps the disappointing progress in treating HFpEF to date reflects the examination of a 'mixed bag' of patients in clinical studies, while therapeutic benefits might have become apparent if the patients included in the study had been more homogeneous (Roh *et al.* 2017). This angle should

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also be taken with future investigations of HFpEF pathophysiology, using approaches such as those expertly employed by Kilfoil *et al.* (2020), but with comparisons made not only between HFpEF and HFrEF, but between HFpEF aetiologies.

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Additional information

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calcium regulation, cardiomyocyte, heart failure, HFpEF, HFrEF