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What is Actually Preserved in HFpEF? Focus on Myocyte Calcium Handling Remodelling

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What is Actually Preserved in HFpEF? Focus on Myocyte Calcium Handling Remodelling

Dear Editor,

One of the hallmarks of heart failure with reduced ejection fraction (HFrEF) is ultrastructural remodelling of the t-tubular system and of the dyadic structure found in ventricular cardiomyocytes which would normally ensure tight control and regulation of excitation-contraction coupling. Remodelling of these specific microdomains, and more specifically Ca^{2+} cycling in these areas, are thought to contribute to the arrhythmogenic phenotype seen in many HFrEF patients (1,2). However, we note that according to recent epidemiological studies, more than half of patients suffering with HF in the community have heart failure with preserved ejection fraction (HFpEF), (3). Treatment options for HFpEF remain limited with standard therapy used in HFrEF, such as β-blockers and angiotensin-converting enzyme having minimal effects on prolongation of life in these patients.(4) Sudden death is the most common cause of death in this population, for example in the recently published EMPEROR-Preserved trial, between 3.3 and 3.8% of participants died from sudden cardiac death (5). Although speculative, it is more than likely that at least some, if not the majority, of these deaths were due to sudden cardiac arrhythmias.

Despite these facts, there is currently a paucity of information available with regards to arrhythmogenic remodelling in ventricular myocytes isolated from HFpEF patients. The majority of the information that is available has been obtained from animal models of HFpEF which may or may not recapitulate all the characteristics of this multifaceted disease as recently reviewed by van Ham *et al*. (6). Recent work from the Louch lab has shown that in myocytes isolated from HFpEF patients the t-tubule density is actually increased, due to proliferation and/or broadening of these structures. These findings are in contrast to what is seen in HFrEF, where t-tubules in both the transverse and axial plane appear to be lost. Interestingly, these data were also dependent on the etiology of disease when animal models were utilised, indicating that multiple mechanisms are at play in HFpEF with abnormal diastolic Ca^{2+} homeostasis contributing to the phenotype under certain conditions (7). Similar findings had previously been shown by Kilfoil *et al*.(8) where, using a rat model of HFpEF, cardiomyocytes isolated from HFpEF hearts showed saturated excitation-contraction coupling with greater synchronicity in Ca^{2+} release, whilst t-tubule structures remained intact. In this model, β-adrenergic stimulation did not lead to an increase in Ca^{2+} transients nor Ca^{2+} current, indicating some blunting of the sympathetic pathways that would be present in healthy myocytes. Recent work in HFrEF myocytes has shown distinct remodelling of β-adrenergic receptors including relocation of β-2 adrenergic receptors and their respective signalling pathways away from the t-tubular membrane, which has dramatic effects on compartmentalised responses to sympathetic stimulation (9). Whether this is also true in HFpEF remains to be investigated and may yield some novel targets for treatment of HFpEF. Synchronicity of Ca^{2+} release in the myocytes is due in part to coupling of L-type Ca^{2+} channels and ryanodine receptors. Ryanodine receptors on the membrane of the sarcoplasmic reticulum react quickly to the Ca^{2+} entering via the Ca^{2+} channel, leading to Ca^{2+} induced Ca^{2+}

release. However, not all ryanodine receptors are coupled to Ca^{2+} channels. Work using porcine models of myocardial infarction and utilising human isolated myocytes have shown that in both HFrEF and after myocardial infarction, spontaneous Ca^{2+} release at non-coupled sites becomes more apparent and is under the control of CaMKII and mitochondrial ROS production (10). It is thought that these spontaneous calcium release events contribute to arrhythmia generation, either by directly leading to triggered beats due to DAD formation, or potentially through increased heterogeneity of action potential durations and beat-to-beat variability of repolarization. To our knowledge, no such studies have been carried out in cardiomyocytes from HFpEF patients nor in animal models of HFpEF.

Clinical evidence also demonstrates sex specific differences in HFpEF epidemiology. Women are more likely to have HFpEF than men, despite worse symptoms, greater congestion and lower quality of life. Nevertheless, remarkably, their risk of sudden death is half that of men with better survival rates overall. Studies into sex specific differences of mechanisms of HFpEF development and progression, concentrating on potential differences in Ca^{2+} handling, are therefore also warranted.

Over the last years much progress has been made in understanding arrhythmogenesis in HFrEF. Although newer data is starting to be generated in the HFpEF field, as partially noted above, there is still much work to be done in this area to really understand what exactly is preserved in the HFpEF myocyte. Such studies should lead to the development on novel drugs specifically targeting elements that are altered in HFpEF which we can add to our therapeutic arsenal against HF.

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Disclosures

None

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