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Up Next: The Dawn of Systems Biology in HFpEF Research

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Dear Editor,

Heart failure with preserved ejection fraction (HFpEF) is a complex clinical syndrome with heterogeneous pathophysiology and presentation[1]. Despite this, on tissue and cellular level, common pathogenetic substrates have emerged as critical in the development and progression of HFpEF: e.g., systemic (meta)-inflammation, abnormal myocardial energetics, tissue fibrosis, vascular dysfunction and dysregulated signaling pathways in cardiomyocytes [2, 3].

The limited availability of animal models represented a major obstacle in conducting mechanistic studies elucidating the pathophysiology of this syndrome[4]. For years, researchers have gone through great efforts to develop novel animal models of HFpEF by reproducing risk factors commonly associated with this syndrome in patients. Arterial hypertension and pressure overload (aortic banding), metabolic dysfunction (diabetes, obesity, dyslipidemia), renal wrapping and aging each in isolation have not been successful in reproducing in experimental animals all the clinical characteristics of HFpEF[5]. More recently, a new generation of animal models employing combinatory approaches in terms of predisposing alterations and displaying a variety of pathophysiological features have proven particularly robust in reproducing clinically relevant HFpEF phenotype(s)[6, 7]. Animal models of diseases are powerful tools for translational research, but their development is limited to the available knowledge of the pathological condition in study. Arguably, using exclusively this approach, the identification of the unknown underlying mechanisms of complex clinical syndromes such as HFpEF will be missed.

Considering the heterogenous nature of HFpEF and the corresponding complexity of the biological networks occurring in a large number of tissues and cell types, HFpEF conundrum cannot be fully addressed – and resolved – by traditional reductionist approaches. One drawback of relying solely on this type of research is evident: the failure of the near totality of therapeutic approaches in HFpEF. Hence, we believe that a more comprehensive, “holistic” view in HFpEF research is needed. In this sense, systems biology – the study of complex interactions in biological systems and the emergent properties that arise from such interactions – represents a powerful approach in HFpEF. Over the last decade, systems biology has been enriched by sophisticated tools. Indeed, current rapid technological advances now enable high-throughput and systematic profiling of cellular genome, transcriptome, proteome, metabolome, to name a few. Together with clinical information, these -omics data will be fundamental for establishing integrated and predictive HFpEF models.

Disease-centered systems biology approaches feed on the availability of human bio-samples. In HFpEF, multi-omics analyses of plasma samples have contributed to a better classification and identification of different HFpEF endotypes. For example, analysis of circulating biomarkers from patients enrolled in large HFpEF trials coupled with their clinical characteristics, has allowed to identify several HFpEF phenotypic clusters related to metabolism, tissue remodeling, inflammation and renal dysfunction which are predictive of mortality and major cardiovascular outcomes [8]. Despite informative, plasma samples often do not allow to infer about cardiac molecular alterations and mechanisms of HFpEF pathogenesis in cardiomyocytes. To this end, the availability of human myocardial samples represents a powerful and indispensable resource for cardiac-targeted systems biology approaches. Strikingly, in contrast with the abundance of studies employing -omics approaches in myocardial tissue from patients with heart failure with reduced ejection fraction (HFrEF), until now only one study has conducted (bulk) transcriptomic analysis of human HFpEF hearts[9].

Cardiac HFrEF -omics studies rely mostly on samples from explanted hearts at the time of transplant or from myocardial tissue removal during left ventricular assist device (LVAD) implantation, guaranteeing a large amount of tissue for multiple analyses. Differently from HFrEF, there are several challenges in procuring high-quality myocardial tissue samples from HFpEF patients. Frist and foremost, ultimate diagnosis of HFpEF is complex. It typically requires a vast array of diagnostic tools which might delay the HFpEF diagnosis itself and its proper clinical identification. Second, sampling myocardial tissue in "real" HFpEF patients must rely on collecting endomyocardial biopsies (EMBs) rather than samples from as open-chest procedures. In high-volume centers, obtaining EMBs is generally considered a safe procedure. Reported complications rates in teaching hospitals range between 1.5 to 4%, generally being non-lethal such as minor pericardial effusion. However, it should be noted that complication rates in low-volume hospitals are significantly more frequent, underlying the importance of this procedure being conducted by experienced interventionalists and, overall, limiting the availability of EMBs samples in HFpEF[10]. Another important point is the choice of "control" myocardial tissue samples. Often, control samples are autoptic specimens. Despite cadaveric myocardial tissue represents a precious resource, for their use in HFpEF research caution is warranted. In principle, the choice of this type of controls poses some issues which might limit the interpretations of the results (i.e., comparison with EMBs samples from living patients). Investigating HFpEF pathogenetic signature in human myocardium will greatly help the definition of HFpEF sub-populations further improving the classification of this syndrome. In this context, EMBs represent a powerful tool of next-generation precision medicine. Too little is known about specific molecular alterations occurring in the myocardium of HFpEF patients and their identifications may overcome the current "one-size-fits-all" therapeutic approaches.

The paucity of tissue(s) availability from HFpEF subjects is not limited to the heart. HFpEF is a systemic condition and accumulating evidence suggests that other, primarily non-cardiac alterations might contribute to this syndrome (i.e., non-alcoholic fatty liver disease and chronic kidney disease). Therefore, a successful systems biology approach in HFpEF should involve the collection and analysis of human myocardial tissue as well as other – and perhaps more easily accessible – tissue samples (e.g., liver/kidney biopsies).

In the context of the increasing worldwide effort to reach in-depth clinical phenotyping of HFpEF, it goes without saying that fruitful biobanking of human HFpEF tissues samples should be exploited for mechanistic research. To effectively implement this, we propose an ideal way of operation in which samples from patients with HFpEF should be rigorously biobanked and made available to the entire research community fostering the integration and exchange of multi-omics data. We advocate the necessity of increasing the number of high-volume, highly specialized, "comprehensive" HFpEF centers around the world. These centers should be an integral part of the clinical/basic/translational research facilities in an ideal – and hopefully realistic – effort to collect clinical data and tissue samples for HFpEF research providing, at same time, the best available standard of care for the patients.

In summary, we submit that there is a critical need for human myocardial and other tissue samples from thoroughly phenotyped HFpEF patients to promote modern systems biology approaches in order to gather large scale -omics data in HFpEF. This will accelerate translational research studies, establish eligible patient populations for novel and established cardiovascular therapeutics, and lay the ground for future precision medicine approaches. The dawn of HFpEF systems biology is upon us!

Disclosures

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