**CLINICAL PERSPECTIVE**

Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome without proven treatments. The underlying phenotypic heterogeneity of HFpEF may in fact be responsible for its dismal record in clinical trials, which have potentially included patients with widely differing disease pathophysiology and therapeutic responsiveness. Problems of inherent heterogeneity exist in many fields outside of medicine, and in such cases machine learning approaches, namely the application of computer algorithms to seek useful patterns in data, have been successfully applied. The primary reason for such success is that computers can detect far subtler patterns such as the covariation of dozens or even hundreds of variables, while the human mind is only able to construct much simpler classifications, such as HFpEF with/without diabetes or HFpEF with/without pulmonary hypertension. We applied a form of machine learning known as unsupervised learning to find inherent patterns in HFpEF patient data that could be the basis for a revised clinical classification. Starting with a detailed characterization based on quantitative clinical, laboratory, electrocardiographic, and echocardiographic phenotypes, we applied model-based cluster analysis to derive 3 distinct disease classes that differed markedly in clinical characteristics, cardiac structure/function, invasive hemodynamics, and clinical outcome. Importantly, these distinctions, including the ability to stratify risk above and beyond current metrics, were replicated in an independent, prospective validation cohort, suggesting robustness of our results. In the future, applying machine learning approaches to dense phenotypic data in the context of clinical trials may prove invaluable in precisely redefining heterogeneous cardiovascular disease conditions—such as HFpEF—according to therapeutic responsiveness.