The burden of heart failure with preserved ejection fraction (HFpEF) has markedly increased, and despite multiple trials completed over the last few decades, there is currently no proven effective pharmacologic intervention available for the treatment of this condition. A better understanding of the mechanisms that contribute to the pathophysiology of HFpEF is, thus, important. HFpEF is a heterogeneous syndrome, with different degrees of contribution from various pathophysiological processes, which may unfavorably influence average responses to pharmacologic therapies tested in clinical trials. Therefore, the use of noninvasive phenotypes capable of segmenting the HFpEF population into relevant pathophysiological categories represents a promising approach to enhancing our clinical and therapeutic approaches to HFpEF (1).

Myocardial fibrosis (MF) is believed to play an important role in HFpEF. Cardiac magnetic resonance (CMR) imaging has emerged as a powerful tool to assess MF noninvasively. Although the assessment of focal MF with late post-gadolinium enhanced imaging has been available for decades, the more recent development of T1-mapping sequences (particularly modified Look-Locker inversion-recovery [MOLLI] imaging) now allows for quantification of both focal and diffuse MF through computation of the extracellular volume (ECV) fraction. The ECV fraction (often called simply ECV) is the proportion of myocardial tissue that corresponds to the extracellular space, expressed as a percentage. ECV fraction measurements derived from T1-mapping before and after the administration of gadolinium-based contrast agents have rapidly evolved from sequence development and validation to widespread application in clinical research. However, ECV measurements have not yet been broadly adopted for the clinical evaluation of patients with HFpEF.

In this issue of *iJACC*, Kanagala et al. (2) report the results of a prospective observational study in which focal and diffuse MF measured by CMR in individuals with HFpEF (n = 96) were compared with control subjects of similar age and sex (n = 44). The authors also assessed the prognostic value of MF among participants with HFpEF who were followed for the development of death or HF hospitalization during a median time span of ~4.4 years. The authors found that roughly half of the participants with HFpEF exhibited focal fibrosis, and among these, most cases (approximately three-fourths) corresponded to non-ischemic focal fibrosis. The study also demonstrated that indexed ECV (iECV, which is the product of the total left ventricle [LV] wall volume and the ECV fraction indexed for body surface area) was ~25% greater in HFpEF subjects than in control subjects. Interestingly, iECV was a predictor of the composite outcome in various adjusted models, each of which also included a small number of key covariates. Correlates of iECV included left atrial volume, renal dysfunction, and the right ventricular end-diastolic
volume. The authors concluded that HFpEF was associated with both focal and diffuse MF and that iECV was a predictor of adverse outcomes in this population.

This study adds to the growing body of work to determine whether ECV and/or iECV provides clinically relevant information among patients with HFpEF. ECV exhibits desirable characteristics as a biomarker in this condition. First, ECV measurements using MOLLI imaging are precise and reproducible (3) and can be readily acquired during clinical CMR examinations. Second, ECV measurements appear to readily segment the HFpEF population into a subgroup that predominantly exhibits increased LV stiffness and a subgroup that predominantly exhibits slow LV relaxation and hypertensive responses to exercise, presumably due to abnormal vasoactive responses (4). Third, ECV in itself identifies a pathologic process (MF) (5) thought to contribute to HFpEF and to the exercise limitation that characterizes it; as such, it may be suitable for identifying individuals who are more likely to benefit from antifibrotic therapies. Fourth, ECV/iECV may provide useful prognostic information in patients with HFpEF.

Considering the increasing interest in the value of ECV as a potential clinically relevant prognostic factor in HFpEF, it is worth briefly reviewing available data. Duca et al. (5) demonstrated that the ECV fraction was a predictor of cardiac death or hospitalization for HF among 117 patients with HFpEF (5); however, ECV was not independently predictive of outcomes after adjustment for clinical and hemodynamic parameters. In a larger cohort of patients with HFpEF (n = 147) or at risk for HFpEF (n = 263), Schelbert et al. (6) demonstrated that ECV was selected as a predictor of incident death or HF hospitalizations in stepwise Cox regression modeling; the final model also included sex, a history of atrial fibrillation/flutter, and LV end-diastolic volume index. Finally, Roy et al. (7) recently reported a study in 118 HFpEF patients followed for a median of 11 ± 6 months, among whom the ECV fraction predicted death or HF hospitalization after adjustment for diabetes and hemoglobin level. In the study by Kanagala et al. (2), ECV was not an independent predictor of outcomes in a model that adjusted for indices of diastolic function and/or filling pressures, nor in a model that adjusted for prior HF hospitalization, mitral inflow-to-mitral annular early diastolic velocity ratio, and a history of asthma/chronic obstructive pulmonary disease. In contrast, iECV was a more robust predictor in these adjusted models. It is important to note, however, that iECV

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<th>FIGURE 1 Usefulness of ECV Measurements Throughout the Spectrum of Basic, Translational, and Clinical Research in HFpEF</th>
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<tr>
<td><strong>Basic discovery</strong></td>
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<td>• Assessment of MF in animal models of HFpEF</td>
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<td>• Characterization of drug effects in pre-clinical models</td>
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ECV = extracellular volume; HFpEF = heart failure with preserved ejection fraction; MF = myocardial fibrosis.
contains prognostic information derived from measurements of ECV fraction, but also from measurements of LV myocardial wall volume (a linear function of LV mass) through segmentation of LV contours and that the relative contributions of these 2 components in various models need to be further defined in future work.

Although the aforementioned studies are important and exemplary, data demonstrating that ECV or iECV predicts outcomes independent of a comprehensive set of clinical variables in patients with HFpEF are lacking. A frequent limitation of individual studies has been the small number of events due to limited sample sizes, which prevented the inclusion of multiple covariates in order to avoid overfitting of regression models. In this instance, the use of well-validated composite risk scores, such as the MAGGIC (Meta-analysis Global Group in Chronic Heart Failure) risk score calculator (8), could have been useful for avoiding overfitting while testing the independent predictive value of ECV. This remains a goal for future studies. Finally, it is unknown whether ECV or iECV predicts outcomes independently of other imaging phenotypes such as global LV and left atrial strain. Clearly, more research with larger sample sizes and/or subject-level meta-analyses of existing studies would be useful to enhance our understanding regarding the prognostic value of ECV and iECV in HFpEF patients.

Despite some uncertainties, ECV measurements have important applications throughout the spectrum of translational research in HFpEF (Figure 1). In the preclinical Phase, in vivo assessments of ECV in animal models of HFpEF will be extremely valuable. Similarly, ECV will be useful in mechanistic research in humans and in early Phase clinical trials, allowing for targeted enrollment in trials of antifibrotic therapies and better characterizations of the effects of novel drugs on MF, thus better informing the design of Phase III trials. For instance, the randomized placebo-controlled Phase 2 study of the efficacy and safety of pirfenidone in patients with HFpEF (PIROUETTE [Efficacy and Safety of Pirfenidone in Patients With Heart Failure and Preserved Left Ventricular Ejection Fraction]; NCT02932566) is currently using ECV as both a criterion for eligibility and as the primary intermediate endpoint of efficacy. However, the cost and availability of CMR-derived ECV measurements are likely to limit or preclude the use of CMR in global Phase III trials. In this regard, the search for circulating biomarkers of cardiac and extracardiac fibrosis remains an area of active research.

In summary, ECV measurements provide important information for the mechanistic characterization of HFpEF. Kanagala et al. (2) are to be congratulated for providing timely information regarding the prognostic value of iECV in this patient population. Further studies are needed to define the prognostic value of ECV and iECV independent of a comprehensive set of clinical variables and its potential role in the clinical care of patients with HFpEF.

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