Cardiovascular Magnetic Resonance for the assessment of left ventricular filling pressure in heart failure

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The incidence of congestive heart failure (HF) due to both systolic and diastolic dysfunction is increasing worldwide and is expected to rise further over the next decade [1,2]. The reference standard method of diagnosing congestive HF is identification of elevated left ventricular filling pressure (LVFP) [2] or pulmonary capillary wedge pressure (PCWP) during cardiac catheterisation. However, cardiac catherization is an invasive procedure that is reserved for specific clinical conditions, such as patients with suspected pulmonary hypertension. Thus, elevated LVFP is conventionally evaluated non-invasively using multi-parametric echocardiography [3]. Several studies have compared echocardiography-based LVFP assessment against reference standard cardiac catheterisation. The multicentre Euro-filling study [4] demonstrated that the 2016 American Society of Echocardiography (ASE) algorithm for the assessment of filling pressure [3] was able to identify patients with normal and abnormal LVFP[4]. However, there was only weak correlation between single echocardiographic parameters and invasively assessed LVFP. In a more recent study in 204 patients with unexplained dyspnoea and preserved LV ejection fraction, there was also only a weak correlation between echocardiography measures and invasively derived PCWP[5]. Thus, there is a need for more accurate methods of non-invasively estimating LVFP.

Cardiovascular magnetic resonance (CMR) is increasingly used in the diagnostic workflow of patients with HF, providing reference standard assessment of ventricular volumes and function [6], as well as myocardial tissue characterization. Several CMR methods have also been developed to assess diastolic function[7] (and by extension LVFP), although none are routinely used in the clinical environment. These include left atrial size and function (i.e. atrial ejection fraction), myocardial strain (either using tagging or feature-tracking), and phase-contrast CMR derived trans-mitral and pulmonary venous flow [7]. The advantage of CMR metrics is

their accuracy and robustness, which opens the possibility of directly predicting LVFP in patients with HF.

In this issue of European Heart Journal, Garg and colleagues [8] derived a predictive model for estimating LVFP using easily acquired CMR metrics. In this study, right heart catheterisation (RHC) and CMR were performed within 24 hours and increased LVFP was defined as a PCWP of greater than 15 mmHg. Importantly, a significant proportion of the study population (38%) had raised PCWP and the derivation and validation cohorts were large (706 and 127 patients respectively), both of which increase confidence in the validity of the derived model. In their study, Garg et al. demonstrated that several CMR-based metrics correlated with invasively assessed PCWP on univariate analysis. However, only LV mass and left atrial volume were independent predictors of PCWP. The importance of these metrics is not particularly surprising, as the association between left atrial size and LVFP is well recognized and myocardial hypertrophy is a common cause of diastolic dysfunction. The novelty of this study is the subsequent use of these metrics to create a model that estimates PCWP. The authors showed moderate correlation between RHC and CMR PCWP in the derivation cohort ($R = 0.56$) and validation cohorts ($R = 0.55$). It should be noted that the authors did find a strong correlation between RHC and CMR PCWP in patients with HF with mildly reduced ejection fraction. However, this finding should be treated with caution due to the very small number of patients in this group. Conversely, the authors found poorer correlation in patients with HFpEF and increased LV filling pressure, a population in whom accurate measurement is important. Interestingly, the authors chose to use conventional multiple linear regression to create their predictive model, even though more sophisticated methods are now available. One of the main benefits of this approach is that the predictive model is completely transparent and understandable. However, the only moderate correlation and striking proportional error in CMR derived PCWP suggest that more sophisticated modelling may

have been useful. The authors did investigate the use of regularized regressions but showed no improvement in predictive capability. Nevertheless, machine learning techniques that can account for non-linear interactions may enable more accurate estimation of PCWP. Of course, these techniques often lack transparency, and the 'black box' problem is often a barrier to general clinical uptake.

One of the main strengths of this study is the large validation cohort that sets it apart from many previous studies that have developed non-invasive predictors of hemodynamic pressures. The fact that similar correlations between RHC and CMR PCWP were found in both the validation and derivation cohorts demonstrates that model was not overfitted.

Importantly, the CMR derived PCWP exhibited good specificity (92%) and negative predictive value (78%) for binary identification of raised PCWP. Moreover, CMR derived PCWP reclassified 71% of patients from the validation cohort with indeterminate or incorrect findings on echocardiography. Of note, assessment of filling pressure by echocardiography was concordant with RHC-derived PCWP in only 25% of cases. Thus, the main utility of CMR derived PCWP may be the identification of patients with abnormal LVFP, rather than accurate estimation of pressure. Indeed, the authors propose the use of the CMR derived PCWP in patients with discordant clinical and echocardiographic data (i.e. clinical suspicion of HF in patients with normal filling pressures by echocardiography), where the additional role of CMR is expected to be more clinically relevant.

Another area in which CMR derived PCWP may be particularly useful is haemodynamic guidance of HF therapy. In this situation, exact estimation of PCWP is less important than change in response to therapy in individual patients. This could be evaluated using CMR derived PCWP but will require further testing. Interestingly, CMR derived PCWP showed a significant association with mortality on Cox's proportional hazards regression, whereas invasive PCWP did not. This suggests that CMR derived PCWP may 'outperform' invasive

measurement for prediction of outcome, which could be another important use of this method in the clinical environment. Possible reasons for this finding include left atrial size being a measure of average LVFP rather than a snapshot during catheterisation, and the well-recognised association between LV mass and outcome.

The main advantage of the described CMR method of deriving PCWP is its easy applicability, with no need to acquire dedicated CMR sequences or to derive additional parameters, as atrial and ventricular quantification are part of routine CMR scans and of routine CMR reporting. Moreover, being independent of any geometric assumption, CMR is the gold standard for the assessment of LV mass and is highly reproducible [9], making the derived CMR model more robust. In this study, left atrial volumes were measured using the biplane method of disks/area analysis based on 2D images from four- and two-chamber cine views [10], as recommended by the international consensus. However, volume can also be measured directly in the same manner as ventricles, providing a measure without geometric assumptions. This method also enables assessment of left atrial function, by means of its reservoir, conduit and contraction function[7], which might improve the accuracy of the model. In fact, there are several CMR derived measures that might be useful to add to future models to improve accuracy, such as mapping/late enhancement and strain.

The study by Garg et al. [8] is a single centre study and the CMR derived PCWP will need validation in external cohorts. Specifically, future studies are warranted to compare echocardiographic and CMR-derived LVFP in larger cohorts to unequivocally demonstrate the additional benefit of CMR. It would also be interesting and clinically relevant to validate the CMR model in cases where echocardiography cannot be reliably applied to estimate LVFP, such as in patients with valvular heart diseases (mitral stenosis, valvular prosthesis), post

heart transplantation and in patients with arrhythmias (atrio-ventricular block, atrial fibrillation).

The study by Garg et al. [8] further expands the role of CMR as a one-stop-shop technique by providing data on HF aetiology, accurate and highly reproducible assessment of biventricular volumes and function and an accurate estimation of LV filling pressure. Given the good specificity and negative predictive value [8], CMR could be used as a tool to stratify patients for further invasive LVFP assessment. Finally, CMR can be proposed, based on the findings from Garg et al. [8], not only as a diagnostic and prognostic tool in HF assessment, but also as a non-invasive test to monitor response to HF treatment.

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