Multilayer myocardial strain improves the diagnosis of heart failure with preserved ejection fraction

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Abstract

Aims The diagnostic and treatment of patients with heart failure with preserved ejection fraction (HFpEF) are both hampered by an incomplete understanding of the pathophysiology of the disease. Novel imaging tools to adequately identify these patients from individuals with a normal cardiac function and respectively patients with HF with reduced EF are warranted. Computing multilayer myocardial strain with feature tracking is a fast and accurate method to assess cardiac deformation. Our purpose was to assess the HFpEF diagnostic ability of multilayer strain parameters and compare their sensitivity and specificity with other established parameters.

Methods and results We included 20 patients with a diagnosis of HFpEF and, respectively, 20 matched controls. We assessed using feature-tracking cardiac magnetic resonance longitudinal and circumferential myocardial strain at three distinct layers of the myocardium: subendocardial (Endo-), mid-myocardial (Myo-), and subepicardial (Epi-). Comparatively, we additionally assessed various others clinical, imaging, and biochemical parameters with a putative role in HFpEF diagnostic: left ventricular end-diastolic volume (LVEDV), left ventricular mass (LVM), interventricular septum (IVS) wall thickness and free wall thickness, left atrial volume and strain, septal and lateral mitral annular early diastolic velocity (e’), E/e’ ratio, and plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP). Global longitudinal strain (GLS) is significantly impaired at Endo (−20.8 ± 4.0 vs. −23.2 ± 3.4, P = 0.046), Myo- (−18.0 ± 3.0 vs. −21.0 ± 2.5, P = 0.002), and Epi- (−12.2 ± 2.0 vs. −16.2 ± 2.5, P < 0.001) levels. Compared with any other imaging parameter, an Epi-GLS lower than 4% shows the highest ability to detect patients with HFpEF [area under the curve (AUC) = 0.90 (0.81–1), P < 0.001] and in tandem with NT-proBNP can diagnose with maximal sensibility (93%) and specificity (100%), patients with HFpEF from normal, composed variable [AUC = 0.98 (0.95–1), P < 0.001]. In a logistic regression model, a composite predictive variable taking into account both GLS Epi and NT-proBNP values in each individual subject reached a sensitivity of 89% and a specificity of 100% with an AUC of 0.98 (0.95–1), P < 0.001, to detect HFpEF.

Conclusions Epi-GLS is a promising new imaging parameter to be considered in the clinical assessment of HFpEF patients. Given its excellent specificity, in tandem with a highly sensitive parameter such as NT-proBNP, Epi-GLS holds the potential to greatly improve the current diagnostic algorithms.

Keywords Multilayer myocardial strain; Heart failure with preserved ejection fraction; NT-proBNP; Cardiac magnetic resonance; Feature tracking

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Background

Approximately half of the patients diagnosed with heart failure (HF) maintain a normal ejection fraction (HFP EF) despite increased left ventricular (LV) filling pressure and lusitropic stiffness. In contrast with HF with reduced EF (HFrEF), in HFP EF, elevated inflammation levels determining microvascular disease, reconfiguration of structural proteins such as titin and interstitial collagen deposition, are the main pathophysiological effectors. Such heterogeneity in pathophysiology is putatively responsible for the difficulty of finding a unifying and accessible imaging marker of disease severity. EF is ipso facto within the normal range, and global longitudinal strain (GLS), a powerful and robust prognostic factor in HFrEF, is only inconstantly decreased in HFP EF patients. Echocardiography-derived indexes of severity of diastolic dysfunction such as E/e’ correlate only moderately with LV filling pressure, and even, so, up to one-third of patients diagnosed with HFP EF have a normal diastolic function.

Aims

We hypothesized that benefiting from a superior spatial resolution and complete 3D coverage of the myocardial volume provided by the cine sequences, cardiac magnetic resonance (CMR) feature tracking (FT) can assess longitudinal and circumferential myocardial strain at multiple layer level and potentially augment the accuracy to detect deformation abnormalities in patients with HFP EF.

Methods

To establish this, we included 20 patients with a diagnosis of HFP EF and, respectively, 20 age-matched and gender-matched controls. Diagnosis of HF should have been older than 30 days, the patients were required to be in a stable state with no changes in their HF medication and no HF hospitalization within the previous 7 days, HFP EF was defined in agreement with recent ESC guidelines, as presence of signs and symptoms of HF and LVEF ≥50% at the time of study inclusion plus the existence of one of the following echocardiographic criteria: left atrial volume index > 34 mL/m², E/e’ > 13 (medial or lateral mitral anulus), LV hypertrophy: septal wall thickness or posterior wall thickness ≥ 13 mm. Exclusion criteria were as follows: atrial fibrillation, symptomatic significant coronary artery disease, co-existence of any inherited cardiomyopathy or amyloidosis, myocardiitis, pulmonary disease, and anaemia. Demographic and baseline characteristics of the study population are presented in Table 1. Table 1. Global longitudinal strain is significantly impaired at Endo- (−20.8 ± 4.0 vs. −23.2 ± 3.4, P = 0.046), Myo- (−18.0 ± 3.0 vs. −21.0 ± 2.5, P = 0.002), and Epi- (−12.2 ± 2.0 vs. −16.2 ± 2.5, P < 0.001) levels (Figure 1B). In contrast, in keeping with previously published meta-analysis, GCS was similar at any level of myocardium in HFP EF patients (Table S1). In a comparative receiver operating characteristic analysis, GLS Epi has the best ability to detect between HFP EF with an area under the curve (AUC) of 0.90 (0.81–1), P < 0.001, compared with 0.80 (0.66–0.94), P = 0.002, for GLS Myo and 0.69 (0.53–0.86), P = 0.046, for GLS Endo (Figure 2C). Additionally, this performance is higher than of any other parameter included in our analysis, excepting only NT-proBNP that is borderline better with an AUC of 0.91 (0.79–1), P < 0.001 (Figure 2C). In particular, a threshold value of Epi-GLS < −13.0% demonstrated an excellent diagnostic specificity (100%) for HFP EF. According to our data, a complementary threshold value for NT-proBNP > 203 ng/mL was able to detect all but two HFP EF patients, showing very good

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sensitivity (Figure 1D). All numerical data are included in Supporting Information Table S1. In a logistic regression model, a composite predictive variable taking into account both GLS Epi and NT-proBNP values in each individual subject reached a sensitivity of 89% and a specificity of 100% with an AUC of 0.98 (0.95–1), \( P < 0.001 \), to detect HFpEF (Figures 1C and S1).

Additionally, we showed that, measured selectively at the level of the subepicardial layer, GLS has an increased potential to diagnose HFpEF and discriminate early phases of contractile impairment.

These results may be surprising. It has been previously proposed that a more pronounced vulnerability to ischaemia of subendocardial small-calibre vasculature irrigating predominantly longitudinally distributed fibres found at this level is responsible for a significant decrease in long-axis contraction. However, so far, there are no clear clinical evidences to substantiate this assumption and such a model is theoretically flawed.\(^\text{11}\) In contrast, several possible explanations for the increased sensitivity of FT Epi-GLS could be proposed:

### Discussion

In line with previous studies, our findings confirmed a decrease of longitudinal strain in patients with HFpEF.\(^\text{10}\)
Pericardium is a rigid membrane that contains the movements of the heart towards exterior, and thus, the confounding effect of shear strain is absent at this level. Also due to pericardial containment, subepicardial deformation is in a tighter connection with a long axis descend of the mitral valve plane showed also to be an additional index of severity in HFpEF. Left ventricular hypertrophy, observed in up to one-half of patients with HFpEF, leads to a decrease EDV and thus a false positive increase in strain assessment. Feature tracking relies on adequate contour identification and tracking over the cardiac cycle phases, subepicardial longitudinal benefits from a high contrast difference between T1 values of myocardium, pericardium, and surrounding extracardiac space.

In contrast with GLS, and confirming previous studies, GCS is not different at any level of the myocardium between HFpEF and controls. NT-proBNP has been recently proposed by the most recent guidelines as a major diagnostic criteria for HFpEF. Our findings confirmed that NT-proBNP is generically a good discriminator of HFpEF from control subjects. However, NT-proBNP exponentially increase in the restrictive phase of diastolic dysfunction; thus, it might be particularly inefficient in identifying HFpEF patients without or with an earlier stage of diastolic dysfunction. Additionally, NT-proBNP is not efficient to separate HFpEF from HFrEF. In contrast, we showed previously an excellent specificity for Endo-GCS, which is normal in HFpEF patients but significantly decreased in HFrEF, to separate HFpEF from HFrEF with various degrees of severity. With this current study, we brought new evidence that Epi-GLS is specifically decreased in HFpEF patients compared with control and thus, in tandem with Endo-GCS, constitutes an excellent diagnostic tool to optimally identify patients with HFpEF from both healthy individuals and patients with HFrEF.
Heart failure with preserved ejection fraction is particularly difficult to treat; important therapeutic tools such as β blockers, angiotensin-converting enzyme inhibitors or angiotensin-receptor antagonists, and mineralocorticoid-receptor antagonist, efficient in improving morbidity and mortality in HFrEF patients, all failed to show any benefits in HfPEF. In these conditions, prompt diagnostic and progression monitoring are key factors to direct a salvaging adjuvant therapy such as decreasing an excessive preload or symptoms control. Our study suggests that recent advances in image processing such as multilayer CMR FT potentially increase the diagnostic accuracy in patients suspected of having HfPEF.

Conflicts of Interest

Sebastian Kelle is supported by a grant from Philips Healthcare and received lecture honoraria from Medis. Sebastian Kelle and Burkert Pieske received funding from the DZHK (German Centre for Cardiovascular Research) and by the BMBF (German Ministry of Education and Research). Burkert Pieske reports having received consultancy and lecture honoraria from Bayer Daiichi Sankyo, MSD, Novartis, sanofi-aventis, Stealth Peptides, and Vifor Pharma and editor honoraria from the Journal of the American College of Cardiology. Radu Tanacli and the other co-authors report no conflict of interest.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. ROC Analysis: Multilayer Myocardial Strain and other parameters to detect patients with HfPEF. GLS – global longitudinal strain, GCS – global circumferential strain, LVM – left ventricular mass, LVEDV – left ventricular end-diastolic volume, LA – left atrium, e’ septal, lateral – peak early diastolic velocity at the septal and lateral mitral annular sites, E/e’ – ration between early trans-mitral flow velocity and average peak early diastolic velocity, NT-proBNP – N-terminal prohormone of brain natriuretic peptide. P < 0.05 (for all the comparisons a P value < 0.05 was considered statistically significant)

Figure S1. ROC Analysis to detect patients with heart failure with preserved ejection fraction (HfPEF) from control: GLS Epi – subepicardial global longitudinal strain, NT-proBNP – N-terminal prohormone of brain natriuretic peptide, Combined – logistic regression composite predictor to detect HfPEF. AUCs were respectively: 0.90 (0.81–1), P < 0.001 for GLS Epi, 0.91(0.79–1), P < 0.001 for NT-proBNP, 0.98 (0.95–1), P < 0.001 for Combined. For all the comparisons a P value < 0.05 was considered statistically significant.
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