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# Comprehensive Echocardiographic and Cardiovascular Magnetic Resonance Evaluation Differentiates Between Patients with Heart Failure with Preserved Ejection Fraction, Hypertensive Patients and Healthy Controls

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**Objectives**

The aim of this study was to investigate the utility of a comprehensive imaging protocol including echocardiography and cardiovascular magnetic resonance (CMR) in the diagnosis and differentiation of hypertensive heart disease and heart failure with preserved ejection fraction (HFpEF).

**Background**

Hypertension is present in up to 90% of patients with HFpEF and is a major etiological component. Despite current recommendations and diagnostic criteria for HFpEF, no non-invasive imaging technique has as yet shown the ability to identify any structural differences between patients with hypertensive heart disease and HFpEF.

**Methods**

We conducted a prospective cross-sectional study of 112 well-characterised patients (62 with HFpEF, 22 with hypertension and 28 healthy controls). All patients underwent cardiopulmonary exercise and biomarker testing and an imaging protocol including echocardiography with speckle tracking analysis and CMR including T1 mapping pre- and post-contrast.

**Results**

Echocardiographic global longitudinal strain (GLS) and extracellular volume (ECV) measured by CMR were the only variables able to independently stratify between the three groups of patients. ECV was the best technique for differentiation between hypertensive heart disease and HFpEF (ECV AUC 0.88; GLS AUC 0.78, $p<0.001$ for

both). Using ECV, an optimal cut-off of 31.2% gave 100% sensitivity and 75% specificity. ECV was significantly higher and GLS was significantly reduced in subjects with reduced exercise capacity (lower peak $VO_2$ and higher $VE/VCO_2$) ($p<0.001$ for both ECV and GLS).

**Conclusions**

Both GLS and ECV are able to independently discriminate between hypertensive heart disease and HFpEF and identify patients with prognostically significant functional limitation. ECV is the best diagnostic discriminatory marker of HFpEF and could be used as a surrogate end-point for therapeutic studies.

**CONDENSED ABSTRACT**

Hypertension is the commonest etiological condition in patients with HFpEF. Development of a non-invasive technique to differentiate between healthy controls, hypertensive and HFpEF patients has yet to be developed. We evaluated 62 HFpEF patients, 22 hypertensive patients and 28 healthy controls with a comprehensive imaging protocol including echocardiographic speckle tracking and CMR T1 mapping. We found that extracellular volume measured by CMR T1 mapping was the best differentiator between the three groups. Both global longitudinal strain and ECV hold promise as a non-invasive marker in HFpEF that may help guide management.

Keywords: heart failure; HFpEF; hypertension; cardiovascular magnetic resonance imaging; speckle-tracking; T1 mapping

Heart failure with preserved ejection fraction (HFpEF) represents 40-50% of all cases of heart failure (HF) and is associated with significant morbidity and mortality.(1) Several randomized control trials have been conducted in search for a useful therapy for HFpEF without success and therefore unfortunately mortality in patients with HFpEF has remained unchanged over the past 20 years.(2) With hindsight, it has become more accepted that the correct identification and selection of HFpEF patients was a major contributing factor to this inability to demonstrate lack of therapeutic benefit.

Initially, HFpEF was simplistically assigned to impaired myocardial relaxation (diastolic dysfunction) but it is now recognised that there are structural and functional changes that occur in this condition.(3) These include changes in both the myocyte (such as changes in titin)(4) and the extracellular matrix (e.g. increased inflammation and fibrosis) and even subclinical left ventricular systolic dysfunction.(5,6) In this work we hypothesized that advanced imaging techniques such as speckle tracking echocardiography and cardiovascular magnetic resonance (CMR) would allow clearer identification of HFpEF cohorts.(6,7)

HFpEF is associated with many comorbidities, including systolic hypertension which is apparent in up to 80-90% of HFpEF patients.(8) Chronic hypertension is also associated with subclinical changes in myocardial structure and function, including in the extracellular matrix.(9) It is conceivable that changes seen in chronic hypertension are a precursor to HFpEF, therefore it is paramount to be able to *non-invasively* identify the threshold that separates hypertensive heart disease and HFpEF, allowing for precise disease phenotyping and targeting of treatment. This is particularly important as the

standard echocardiographic criteria used for diagnosis in HFpEF(10) are often found in patients with hypertensive heart disease.(11)

To the best of our knowledge, no study has previously used a comprehensive multi-parametric imaging protocol to investigate patients with HFpEF and hypertension in such detail. The aim of this study was to use speckle-tracking echocardiography and a comprehensive CMR protocol including T1 mapping and tagging to fully characterise resting myocardial structural and functional changes in patients with cardiopulmonary exercise testing (CPEX)-demonstrated HFpEF compared to patients with asymptomatic hypertension and to healthy controls.

## METHODS

### Patient Selection

Three groups were studied: 1. HFpEF patients were identified via a large screening programme for HFpEF conducted in primary care. They were diagnosed on the basis of symptoms and signs consistent with HF, elevated BNP at the time of diagnosis (>35 pg/mL), normal left ventricular dimensions with ejection fraction (LVEF) >50%(12) plus evidence of echocardiographic abnormalities such as left ventricular hypertrophy (LVH), left atrial enlargement, or evidence of diastolic dysfunction as per the 2016 European Society of Cardiology guidelines.(12) Determination of diastolic dysfunction required at least 2 of the following to be present: E/e' >13, mean septal and lateral e' velocity <9cm/s or LA volume index >34ml/$m^2$. Finally, all patients underwent CPEX in order to confirm the presence of exercise limitation of cardiac etiology by peak $VO_2$<80% predicted and $VE/VCO_2$ slope>32.(13) All patients underwent a symptom-limited

protocol and were only included in the study if they were able to achieve a respiratory exchange ratio (RER) of ≥1. We excluded any patients with an underlying cardiomyopathy (such as hypertrophic cardiomyopathy, amyloid or ischemic cardiomyopathy). Significant underlying ischemia was excluded by a combination of clinical history and either non-invasive ischemia testing or invasive coronary angiography if indicated. Additionally, any patient with late gadolinium enhancement on CMR consistent with prior myocardial infarction was excluded. We excluded people with predominant lung disease such as chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis (with an $FEV_1$<1.5) and patients with anemia (hemoglobin <110g/L). 2. Non-consecutive patients with a history of chronic arterial hypertension were recruited from the Aberdeen Royal Infirmary hypertension database. Patients were required to have a documented history of essential hypertension (systolic BP >140mmHg) for greater than 6 months and to be on at least one treatment agent. We excluded any patients with overt cardiac disease (such as prior myocardial infarction or any valve disease classified as worse than mild) and any patient with secondary hypertension. All hypertensive patients were self-declared asymptomatic at the time of evaluation. Patients were required to have no previous documented cardiovascular disease other than hypertension. To match for co-morbidity distribution between groups, we excluded patients with significant underlying pulmonary disease and anemia. 3. Healthy volunteers were recruited from public advertising. Volunteers had no self-declared past medical history and were not taking any medication at the time of recruitment. Additionally, we performed a case record review to ensure there was no significant past medical history, a resting ECG, echocardiogram and BNP. Volunteers

were only recruited if all of these were normal. The study was approved by the North of Scotland research ethics committee and all subjects provided informed consent.

**Imaging Protocol**

**Echocardiography:** All patients underwent a comprehensive 2-dimensional echocardiographic protocol using a Vingmed E9 system (GE Healthcare, Norway) with a 2.5-MHz probe. Standard views were taken in the parasternal, apical and subcostal windows.

**Cardiovascular Magnetic Resonance** (CMR): All patients then underwent a full CMR protocol on a 3 Tesla (Achieva, Phillips, The Netherlands). The full CMR protocol has been described previously.(14,15) Briefly, following localizers, cine images were acquired in 2, 3 and 4-chamber views, and a full left ventricular short-axis stack taken. Following this, a native T1 mapping sequence was performed using a modified Look Locker Inversion recovery sequence (MOLLI, 3(3)3(3)5 scheme) in 2 short-axis slices corresponding to mid-ventricular level. Then, tagged magnetic resonance imaging sequences were performed in short axis at the base, mid-cavity and apical levels. Gadolinium contrast was given and late gadolinium enhancement (LGE) imaging performed in the full short-axis stack and the 3 long-axis views. Finally, 2 post-contrast MOLLI (5(3)) slices were performed at exactly 15 minutes post-contrast at the same mid-cavity level. A blood sample was taken at the time of CMR scanning for measurement of haematocrit.

**Image Analysis**

Both echocardiographic and CMR images were each analysed independently by 2 experienced operators. Echo images were analysed offline using EchoPac (GE Healthcare, Norway). CMR images were analysed offline using CVI42 (Circle Cardiovascular Imaging, Calgary, Canada) for assessment of left ventricular mass, volumes, T1 mapping and LGE. Tagged CMR images was analysed using HARP (Diagnosoft, Palo Alto, California). Extracellular volume as a percentage of the myocardium (ECV) was calculated using the formula ECV = (1−hematocrit) × (ΔR1myocardium/Δ R1blood), where R1 = 1/T1.

**Statistical Analysis**

Statistical analysis was performed using SPSS v.22.0 (IBM, Armonk, NY, USA). Continuous data are reported as mean ± standard deviation while categorical data are reported as number with percentage in brackets. Comparisons between the three groups were made using a one-way ANOVA with an independent t-test with post-hoc Bonferroni correction for between group comparisons for continuous variables with normal distribution, Kruskal-Wallis test for non-normally distributed continuous variables and a chi-square test for categorical variables. Correlations were assessed using Pearson's (for parametric data) or Spearman's (for non-parametric data) correlation. Optimal cut-offs for significant variables of interest were calculated using Youden's index (sensitivity + (1-specificity)). Receiver-operator characteristic curves were then plotted using the optimal cut-off in order to assess the area under the curve. Logistic regression analysis was performed to determine the relationship between significant echocardiographic and CMR variables and the diagnosis of HFpEF. Statistical

significance was indicated by $p<0.05$. Both intra- and inter-observer variabilities were calculated as mean ± SD between 2 independently measured variables.

## RESULTS

### Baseline Characteristics

In total we included 112 patients; 62 with HFpEF, 22 with hypertension and 28 healthy controls. Baseline characteristics are shown in **Table 1**. There was no significant difference in age between the three groups however there were more male hypertensive patients. 18 of the hypertensive patients (82%) were taking at least 2 anti-hypertensive medications, however no patients in this study were taking mineralocorticoid receptor antagonists. HFpEF patients were overweight compared to the other two groups and had significantly higher BNP levels than both hypertensive patients and healthy controls. There were significant differences in CPEX parameters with HFpEF patients demonstrating significant cardiac limitation on exercise compared to both hypertensive patients and controls – HFpEF patients had a significantly lower $VO_2$ and higher $VE/VCO_2$ compared to hypertensive patients and controls (both $p<0.001$). HFpEF patients had a significantly lower heart rate at peak exercise compared to hypertensive patients and controls.(16) No CPEX tests were terminated early due to blood pressure response.

### Echocardiographic Parameters

Echocardiographic data are summarised in **Table 2**. There were no significant differences between groups in LVEF, transmitral velocities or E/E'. HFpEF patients had significantly lower eGLS than both hypertensive patients ($p=0.004$) and controls

(p<0.001) but similar eGCS to hypertensive patients. Controls had significantly higher eGCS than both HFpEF patients (p<0.001) and hypertensive patients (p=0.002). Left ventricular torsion was significantly reduced in both HFpEF patients and hypertensive patients compared to controls (p<0.001 for both groups) but there was no significant difference between the two patients groups. Global circumferential systolic strain *rate* was significantly lower in hypertensive patients compared to controls (p=0.019). Reproducibility of echocardiographic speckle tracking was as follows: (global longitudinal strain (GLS): inter-observer 5±2% intra-observer: 4±2%; global circumferential strain (GCS) both inter- and intra-observer variability were 4±1%).

**Cardiovascular Magnetic Resonance Parameters**

CMR data are summarised in **Table 3**. There were no significant differences in indexed LV volumes or LVEF between all 3 groups. None of the patients had late gadolinium enhancement present. Hypertensive patients had a significantly higher indexed LV mass compared to both HFpEF patients (p<0.001) and controls (p<0.001). Controls also had significantly lower indexed LV mass than HFpEF patients (p<0.001). HFpEF patients had a significantly lower GCS measured by CMR (cGCS) compared to controls (p=0.039). HFpEF patients had a trend towards a higher native T1 than both hypertensive patients and controls. ECV was significantly higher in both HFpEF patients (35.9% ± 5.0) and hypertensive patients (31.9% ± 5.2) versus controls (27.0% ± 4.3; p<0.001 and p=0.04 respectively). ECV was also significantly higher in HFpEF patients vs. hypertensives (p=0.04). Representative examples of the speckle tracking and T1 mapping analysis are shown in **Figure 1.** Our inter- and intra-observer variability for all

T1 mapping analysis were 2.7±1.5% and 1.5±0.5%. Reproducibility for CMR tagging has been previously reported.(14)

**Differentiation Between HFpEF, Hypertension and Controls**

eGLS and CMR-derived ECV were the only 2 parameters that were significantly different between HFpEF and hypertensive patients. Both were independently associated with the diagnosis of HFpEF (GLS: OR 1.50; 95% CI 1.08-2.08, p=0.016; ECV: OR 1.21; 95% CI 1.02-1.42, p=0.025). Using ROC analysis, ECV was an excellent discriminator between HFpEF and hypertension (AUC: 0.88; 95% CI 0.70-1.00, p=0.005) while eGLS was also a good discriminator between the two patient groups (AUC: 0.78; 95% CI 0.57-0.99, p=0.037). The optimal cut-off for differentiation between HFpEF and hypertension using ECV was 31.2% which gave a sensitivity of 100% and specificity of 75%. The optimal cut-off using GLS was -17.8% which gave a sensitivity of 83.3% and a specificity of 62.5% (**Figure 2**). In a multivariable analysis with these two variables, only ECV remained significantly associated with a diagnosis of HFpEF (GLS: OR 2.68 per 1% increase in GLS; 95% CI 0.86-8.34, p=0.09; ECV: OR 1.99 per 1% increase in ECV; 95% CI 1.06-3.72, p=0.032).

ECV, torsion and eGCS were able to differentiate between hypertensive patients and controls. All 3 variables were significantly correlated ($p < 0.01$) and were associated with diagnosis of hypertensive heart disease (ECV: OR 1.31; 95% CI 1.02-1.69, p=0.038; LV torsion: OR 0.54; 95% CI 0.34-0.86, p=0.01; GCS: OR 1.47; 95% CI 1.11-1.95, p=0.007) however in multivariable stepwise analysis none of these variables remained significant.

### Correlation of ECV and GLS with Structural and Functional Parameters

As the best novel parameters identified, differences in ECV and GLS were examined based on the severity of structural and functional characteristics of patients. There was a strong correlation between GLS and peak $VO_2$ (r=-0.54, p=0.002) and GLS and $VE/VCO_2$ (r=0.47, p<0.001), however there were no significant correlations between GLS and BNP (r=-0.004, p=0.98) or E/E' (r=0.10, p=0.46). There were significant correlations between ECV and peak $VO_2$ (r=-0.41, p=0.001), $VE/VCO_2$ (r=0.28, p=0.024) and BNP (r=0.32, p=0.026). There was no correlation between ECV and E/E' (r=-0.008, p=0.95).

There were significant differences in ECV and GLS in patients with more severe functional limitation on CPEX. Patients with peak $VO_2$ less than the median (17.5 ml/kg/min) had significantly higher ECV and GLS than those with $VO_2$ greater than the median (ECV: 35.9% vs 30.5%, p<0.001; GLS: -16.18% vs. -19.08%, p<0.001). Patients with $VE/VCO_2$ greater than the median (34.06) had significantly higher ECV and GLS than those with $VE/VCO_2$ less than the median (ECV: 35.6% vs 30.5%, p<0.001; GLS: -16.05% vs. -19.15%, p<0.001). There was no significant difference in ECV or GLS based on E/E' or median BNP **(Figure 3)**.

## DISCUSSION

In this study we identified several important findings. First, an advanced imaging protocol including echocardiographic speckle tracking and T1 mapping can differentiate between patients with comprehensively CPEX-characterised HFpEF, hypertensive heart disease and controls. Both hypertensive heart disease and HFpEF are associated with

a reduction in LV torsion and in eGCS. Additionally, both GLS and ECV are able to completely separate the 3 phenotypes (HFpEF, hypertensive heart disease and normal) and ECV is the strongest imaging diagnostic marker for independently differentiating between hypertensive heart disease and HFpEF. Finally, we have also showed, for the first time that both GLS and ECV correlate strongly and are significantly different in patients with objective functional limitation based on peak $VO_2$ and $VE/VCO_2$, which are established markers of prognosis in HFpEF.

The diagnosis of HFpEF remains challenging. Although echocardiographic criteria(12) are clear, these abnormalities are often found in hypertensive patients without HFpEF. Additionally, although CPEX is an extremely valuable diagnostic tool for identifying those who are limited on exercise, a majority of patients with HFpEF are unable to exercise, hence, a further technique to clarify the diagnosis would be desirable.

Echocardiographic determination of diastolic dysfunction is primarily via the use of tissue Doppler imaging, particularly the E/E' ratio, however this is not completely reliable as it can still be normal in patients with HF, and conversely, be abnormal in hypertensive heart disease.(11,17) Recently, speckle-tracking echocardiography has been used to identify subclinical LV dysfunction with HFpEF patients being shown to have reduced GLS.(6) Additionally, reduced GLS has also been shown to be an independent marker of adverse prognosis in patients with HFpEF.(18) Our findings are in keeping with those of the PARAMOUNT echocardiographic substudy, which showed that reduced GLS was also present in HFpEF patients compared to both controls and hypertensive patients.(6) Underlining the importance of subclinical LV dysfunction in the pathophysiology of HFpEF, a further recent study by Kosmala et al. also showed that

subclinical systolic dysfunction measured by reduced GLS was the best discriminator between HFpEF patients with exercise limitation and those without.(19)

In our comprehensive imaging study, we have also shown that while both ECV and echocardiographic GLS are able to identify HFpEF patients, ECV measured non-invasively by T1 mapping is the best technique for independently differentiating between HFpEF and hypertensive patients. In our study, the presence of an ECV greater than 31.2% had 100% sensitivity for diagnosis of HFpEF. This highlights the potential diagnostic utility of ECV in HFpEF patients. We speculate that an increase in ECV is one of the earliest pathophysiological changes seen in both HFpEF and hypertension, and that as the progression from hypertensive heart disease to HFpEF is perhaps reflected (or caused) by the increase in ECV. In our study we also measured ECV in our control group, confirming the normalcy limits. We postulate that this increase in ECV reflects underlying changes such as fibrosis, collagen expansion and increased collagen cross-linking that lead to alterations in myocardial function.(5) Our findings are also in keeping with the recent study by Rommel et al. in which the authors evaluated 24 patients with HFpEF, finding that these patients had a significantly higher ECV than controls and that ECV was correlated with invasive measures of ventricular stiffness.(22)

We also identified that GCS and LV torsion were all significantly different in controls compared to both patient groups. When present, fibrosis in hypertension particularly seems to involve the myocardial midwall which contains circumferential shortening fibres and might lead to GCS being affected before longitudinal shortening.(23) The fact that GCS is reduced in both hypertensive patients and in HFpEF whereas only GLS is

reduced in HFPEF might reflect the underlying disease process, and might explain why GLS seems to be a more powerful predictor of prognosis in both hypertension and HFpEF than GCS.(18,24) As the circumferential fibres also contribute to LV torsion, it therefore follows that LV torsion is reduced in HFpEF and hypertension.

The utility of left ventricular torsion as a diagnostic marker in HFpEF is not clear – this is in contrast to HFrEF where LV torsion is almost always decreased.(25) In contrast, studies in HFpEF have had conflicting results. Similar to our study, Yip et al. found that LV torsion was significantly reduced in both HFpEF and HFrEF patients compared to controls.(26) This replicated results from a study by Tan et al, who also found that as well as a reduction in GLS in HFpEF patients compared to controls, there was also a significant reduction in LV torsion in HFpEF patients.(27) A recent analysis in the MESA study found that increased mass at baseline (often associated with hypertension) was associated with a reduction in torsion, although there was an increase in torsion noted in patients with progressive age-related left ventricular remodelling in a further study from this group, suggesting that the relationship is still unclear.(28,29)

These findings could have important clinical diagnostic and therapeutic implications. While undoubtedly echocardiography remains the mainstay of diagnosis and management of HF patients, where available, CMR could become an important tool for further characterisation of patients, particularly in difficult clinical cases. If ECV also proves to be a non-invasive marker of disease activity, this could help investigation of novel therapeutic options.

Both peak $VO_2$ and $VE/VCO_2$ are established markers of functional limitation and prognosis in HFpEF.(30) We found that both GLS and ECV were correlated with

functional limitation as measured using CPEX. This perhaps supports our hypothesis that the development of subclinical dysfunction measured by GLS and the development of structural changes shown by an increase in ECV are precursors to the development of clinical HF**.** Recent work has suggested that GLS does correlate well with exercise capacity in HFpEF,(31) and we have added to this by showing a similar relation with ECV measured by T1 mapping. While both speckle-tracking echocardiography and CMR T1 mapping are not yet routine in general clinical practice, we believe that our study, in line with others, has clearly demonstrated the utility of these techniques in diagnosing HFpEF in a more reliable manner than previously available.

**Study Limitations**

Our study has some limitations. First, it was a single-centre study with relatively small numbers, although it is still one of the largest studies in the area. Additionally, we performed a comprehensive characterisation of patients with CPEX, echocardiography and CMR. Second, post-contrast T1 mapping was performed only at one time point (15 minutes). The optimal time-point has yet to be confirmed. Third, we did not perform exercise echocardiography, which might provide some further differentiation in HFpEF patients.(19) Fourth, we were unfortunately unable to completely match the cohorts for gender due to the inability to recruit enough female participants, a well-recognized shortfall with many studies. In addition, although we excluded significant underlying coronary artery disease where clinically indicated and excluded patients with an ischemic pattern of LGE on CMR or exercise-induced ischaemia, as we did not perform invasive coronary angiography we accept that the presence of any subclinical CAD may have affected the results. Finally, as the patients studied were not recruited from a

single presenting group, it is possible that the diagnostic performance of ECV and GLS may differ in other groups of patients, hence these techniques should be validated in other cohorts.

## CONCLUSIONS

Using a comprehensive imaging protocol including echocardiography and CMR, both speckle tracking and T1 mapping were able to identify underlying myocardial structural differences and differentiate between functionally-limited HFpEF patients, those with hypertensive heart disease and healthy controls. ECV measured by CMR T1 mapping was the best independent predictor of the diagnosis of HFpEF, with an optimal cut-off of ECV greater than 31.2% having 100% specificity and 75% sensitivity. ECV could be considered the first non-invasive imaging biomarker of HFpEF, providing improved diagnostic clarity and potentially serving as a surrogate end-point in clinical trials.

## PERSPECTIVES

### Competency in Medical Knowledge

Differentiation of HFpEF, hypertensive heart disease and healthy subjects can be difficult using current non-invasive imaging techniques. T1 mapping using CMR can be used to specifically identify each of the three groups of patients with its assessment of extracellular volume.

### Translational Outlook

ECV measured by T1 mapping could be used as both a therapeutic and prognostic marker in HFpEF and could potentially be used to predict which patients with hypertensive heart disease are at higher risk of developing heart failure.

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**Figure Legend**

1. Representative examples.

   Representative examples of echocardiographic global longitudinal strain (eGLS) (top row - ED – end-diastole; ES – end-systole) and pre- and post-contrast T1 mapping (middle and bottom rows respectively). Column A shows a male healthy volunteer with an eGLS of -22.1%. Mean native T1 was 1212.7ms, post-contrast T1 was 586.1ms. ECV was calculated at 24.9%. Column B shows a hypertensive male with an eGLS of -18.2%. Mean native T1 was 1169.0ms, post-contrast T1 was 593.5ms. ECV was calculated at 31.2%. Column C shows a male with HFpEF (LVEF with an eGLS of -15.0%. Mean native T1 was 1265.0ms, post-contrast T1 was 484.8ms. ECV was calculated at 36.3%.

2. ROC Curves.

   Sensitivity and specificity for differentiation of HFpEF and hypertensive patients. ECV (blue) gave an area under the curve of 0.88 (95% CI 0.70-1.00, p=0.005) while eGLS (red) gave an area under the curve of 0.78 (95% CI 0.57-0.99, p=0.037).

3. ECV and GLS Compared to Structural and Functional Parameters.

   The relationship between structural and functional parameters compared to ECV (left) and GLS (right). Patients with functional limitation measured by CPEX (peak $VO_2$ less than the median and $VE/VCO_2$ greater than the median) had significantly increased ECV and reduced GLS. Data is shown as mean ± SD.

Figure 1.

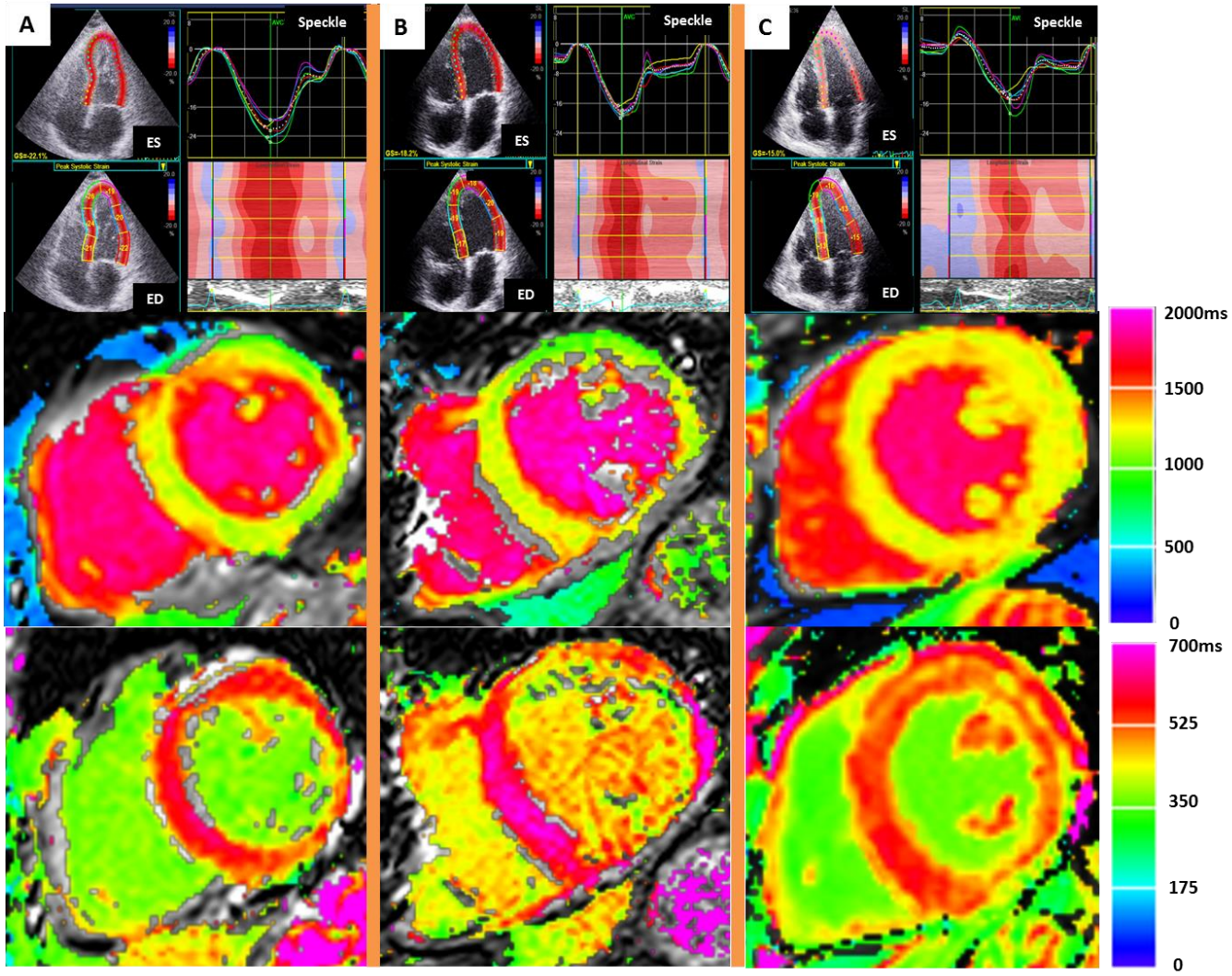
A
Speckle
ES
ED
B
Speckle
ES
ED
C
Speckle
ES
ED
2000ms
1500
1000
500
0
700ms
525
350
175
0

Figure 2.

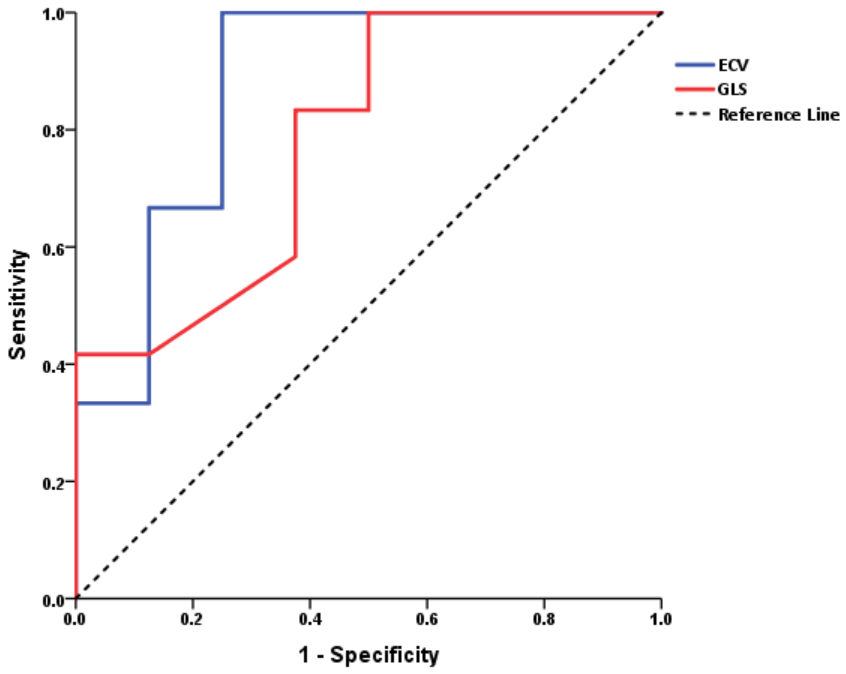
1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity
ECV
GLS
Reference Line

Figure 3.

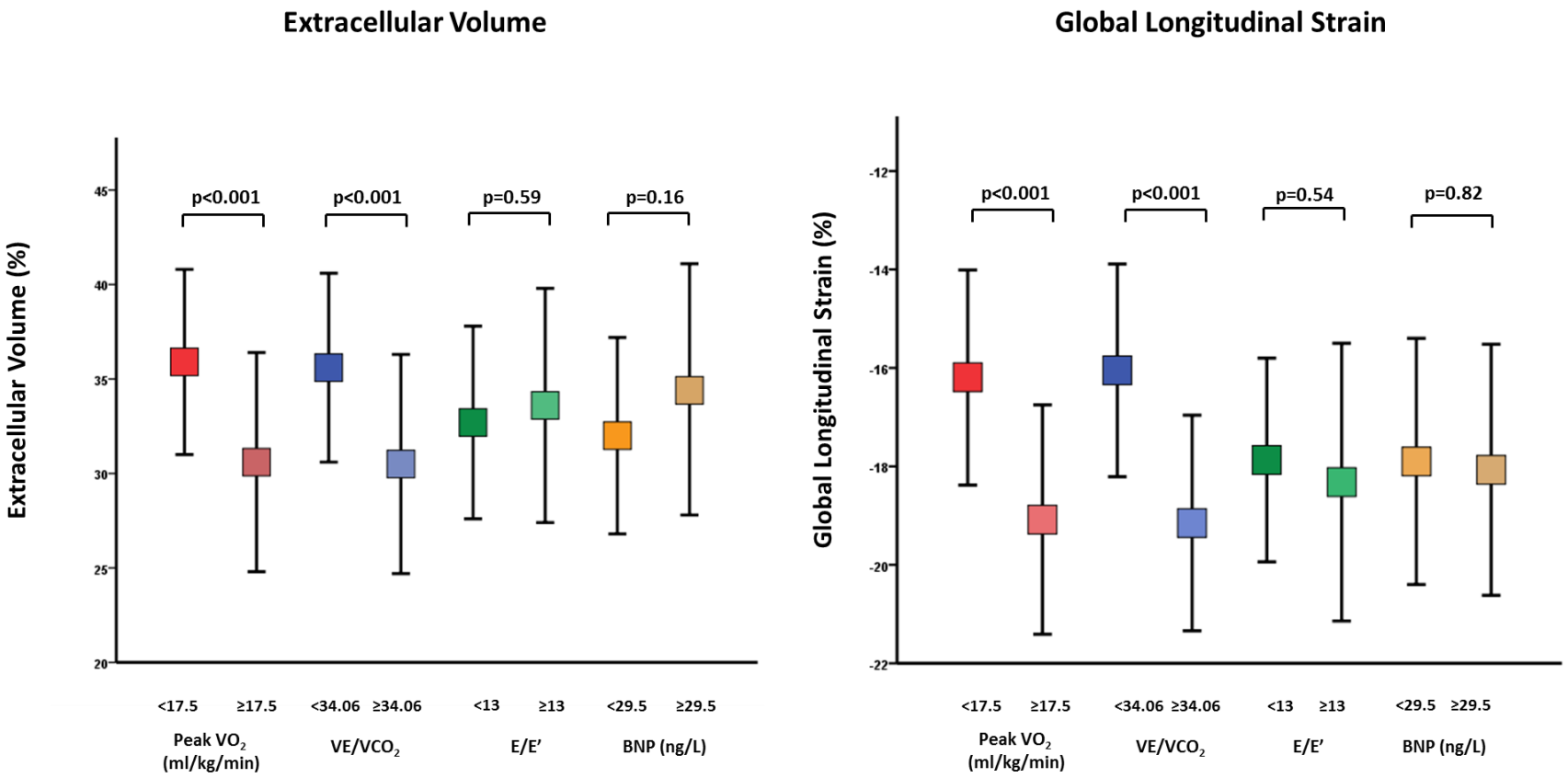
Extracellular Volume
Extracellular Volume (%)
45
40
35
30
25
20
p<0.001
p<0.001
p=0.59
p=0.16
<17.5
≥17.5
<34.06
≥34.06
<13
≥13
<29.5
≥29.5
Peak VO2 (ml/kg/min)
VE/VCO2
E/E'
BNP (ng/L)
Global Longitudinal Strain
Global Longitudinal Strain (%)
-12
-14
-16
-18
-20
-22
p<0.001
p<0.001
p=0.54
p=0.82
<17.5
≥17.5
<34.06
≥34.06
<13
≥13
<29.5
≥29.5
Peak VO2 (ml/kg/min)
VE/VCO2
E/E'
BNP (ng/L)

Table 1. Baseline Characteristics

| | **HFpEF (n=62)** | **Hypertensives (n=22)** | **Controls (n=28)** |
|---|---|---|---|
| Age | 70.8 ± 7.6 | 66.9 ± 5.2 | 67.7 ± 11.2 |
| Male | 20 (32.3) | 17 (77.2) | 14 (50.0) |
| BMI (kg/m$^2$) | 29.2 ± 3.5* | 26.7 ± 2.9 | 25.6 ± 2.7 |
| Hypertension | 47 (75.8) | 22 (100) | 0 (0) |
| Mean Time Since Diagnosis (years) | 2.7 ± 0.9* | 7.3 ± 2.4$^+$ | - |
| Diabetes | 6 (9.7) | 3 (14) | 0 (0) |
| Beta-Blocker | 22 (35.5) | 0 (0) | 0 (0) |
| ACEI/ARB | 31 (50) | 15 (68) | 0 (0) |
| Statin | 36 (58.1) | 10 (46) | 0 (0) |
| CCB | 21 (33.9) | 12 (55) | 0 (0) |
| Loop Diuretic | 30 (48.4) | 8 (36) | 0 (0) |
| Median BNP | 52.1 (17-87)* | 11.9 (1-23) | 28.8 (8-40) |
| Hemoglobin (g/L) | 137.1 ± 11.6 | 142.3 ± 9.3 | 140.5 ± 10.2 |
| Creatinine (μmol/L) | 79.5 ± 24.6 | 77.1 ± 13.9 | 75.8 ± 11.3 |
| Rest Heart Rate (bpm) | 79.4 ± 18.9 | 78.4 ± 14.1 | 70.8 ± 11.1 |
| Rest SBP (mmHg) | 146.6 ± 23.7$^+$ | 147.2 ± 7.2$^+$ | 135.4 ± 16.0 |
| Rest DBP (mmHg) | 82.1 ± 12.4 | 82.0 ± 12.0 | 81.6 ± 12.1 |

| | | | |
|---|---|---|---|
| Peak Heart Rate (bpm) | 125.9 ± 25.0* | 158.6 ± 13.7 | 149.6 ± 12.6 |
| Peak SBP (mmHg) | 170.5 ± 28.2 | 190.7 ± 18.7$^{+}$ | 167.1 ± 27.0 |
| Peak DBP (mmHg) | 77.0 ± 15.2 | 88.1 ± 30.3 | 85.8 ± 12.3 |
| Peak $VO_2$ | 12.6 ± 3.5* | 27.0 ± 5.9 | 31.4 ± 7.5 |
| $VE/VCO_2$ | 40.4 ± 6.3* | 28.2 ± 2.7 | 27.6 ± 5.3 |

BMI – body mass index; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin II receptor blocker; CCB – calcium channel blocker; BNP – B-type natriuretic peptide; SBP – systolic blood pressure; DBP – diastolic blood pressure

* $p<0.05$ vs. controls and hypertensive patients; + $p<0.05$ vs. controls

Table 2. Echocardiographic Data

| | HFpEF (n=62) | Hypertensives (n=22) | Controls (n=28) | p value |
|---|---|---|---|---|
| **LVEF (%)** | 65.1 ± 8.2 | 65.4 ± 8.4 | 64.2 ± 6.4 | 0.85 |
| **E** | 0.74 ± 0.25 | 0.72 ± 0.21 | 0.75 ± 0.16 | 0.89 |
| **A** | 0.90 ± 0.24 | 0.83 ± 0.16 | 0.80 ± 0.18 | 0.07 |
| **E/A** | 0.85 ± 0.24 | 0.86 ± 0.18 | 0.98 ± 0.27 | 0.06 |
| **E' (septal)** | 6.3 ± 1.8 | 6.8 ± 1.8 | 7.6 ± 1.8* | **0.007** |
| **E' (lateral)** | 9.5 ± 2.7 | 8.4 ± 2.9 | 10.2 ± 2.7 | 0.76 |
| **E/E' (septal)** | 12.65 ± 5.64 | 11.29 ± 4.34 | 10.40 ± 3.21 | 0.12 |
| **E/E' (lateral)** | 9.60 ± 3.82 | 9.40 ± 3.58 | 7.71 ± 1.90 | 0.06 |
| **E/E' (average)** | 11.12 ± 4.41 | 10.34 ± 3.20 | 9.04 ± 2.06 | 0.07 |
| ***Number of patients E/E' ≥13*** | *17 (27.4)* | *6 (27.3)* | *2 (7.7)* | *0.11* |
| ***Estimated PASP*** | *30.0 ± 4.5* | *27.3 ± 4.7* | *25.6 ± 4.2* | *0.12* |
| **eGCS** | -12.74 ± 3.50 | -14.03 ± 4.26 | -18.08 ± 2.61*$^{+}$ | **<0.001** |
| **eGLS** | -16.05 ± 2.16$^{+}$ | -18.58 ± 2.84* | -19.59 ± 1.49* | **<0.001** |
| **GCS Rate** | -0.95 ± 0.26 | -0.73 ± 0.57 | -1.05 ± 0.18$^{+}$ | **0.023** |
| **GLS Rate** | -0.87 ± 0.17 | -0.99 ± 0.18 | -0.93 ± 0.16 | 0.13 |
| **LV Torsion** | 13.39 ± 6.00 | 13.52 ± 5.41 | 22.86 ± 4.88*$^{+}$ | **<0.001** |

LVEF – left ventricular ejection fraction; PASP – pulmonary artery systolic pressure; eGCS – echocardiographic global circumferential strain; eGLS – echocardiographic global longitudinal strain

*p<0.05 vs HFpEF patients; +p<0.05 vs hypertensives

Table 3. CMR Data

| | HFpEF (n=62) | Hypertensives (n=22) | Controls (n=28) | p value |
|---|---|---|---|---|
| **LVEF (%)** | 66.7 ± 9.3 | 65.6 ± 6.7 | 64.3 ± 4.3 | 0.42 |
| **LVEDVi** | 67.8 ± 17.5 | 64.8 ± 11.7 | 60.6 ± 23.3 | 0.06 |
| **LVESVi** | 23.2 ± 12.1 | 17.5 ± 7.7 | 23.1 ± 11.9 | 0.82 |
| **LVMi** | 70.8 ± 20.2$^{+}$ | 107.2 ± 23.1* | 69.2 ± 23.2$^{+}$ | **<0.001** |
| **cGCS (%)** | -15.10 ± 2.62 | -16.23 ± 3.81 | -18.50 ± 1.21* | **0.045** |
| **Native T1 (ms)** | 1218 ± 78 | 1185 ± 58. | 1194 ± 29 | 0.06 |
| **ECV (%)** | 35.9 ± 5.0$^{+}$ | 31.9 ± 5.2* | 27.0 ± 4.3*$^{+}$ | **<0.001** |

LVEF – left ventricular ejection fraction; LVEDVi – indexed left ventricular end-diastolic volume; LVESVi – indexed left ventricular end-systolic volume; LVMo – indexed left ventricular mass; cGCS – CMR global circumferential strain; ECV – extracellular volume

*p<0.05 vs HFpEF patients; +p<0.05 vs hypertensives