Non-invasive intraventricular pressure differences estimated with cardiac MRI in subjects without heart failure and with heart failure with reduced and preserved ejection fraction

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ABSTRACT

Objective Non-invasive assessment of left ventricular (LV) diastolic and systolic function is important to better understand physiological abnormalities in heart failure (HF). The spatiotemporal pattern of LV blood flow velocities during systole and diastole can be used to estimate intraventricular pressure differences (IVPDs). We aimed to demonstrate the feasibility of an MRI-based method to calculate systolic and diastolic IVPDs in subjects without heart failure (No-HF), and with HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).

Methods We studied 159 subjects without HF, 47 subjects with HFrEF and 32 subjects with HFpEF. Diastolic and systolic intraventricular flow was measured using two-dimensional in-plane phase-contrast MRI. The Euler equation was solved to compute IVPDs in diastole (mitral base to apex) and systole (apex to LV outflow tract).

Results Subjects with HFpEF demonstrated a higher magnitude of the early diastolic reversal of IVPDs (−1.30 mm Hg) compared with the No-HF group (−0.78 mm Hg) and the HFrEF group (−0.75 mm Hg; analysis of variance p=0.01). No significant differences in systolic IVPDs were found in adjusted models. IVPD parameters demonstrated only weak correlations with standard Doppler-echocardiographic parameters of diastolic filling and measures of LV structure (No-HF=−0.72; HFrEF=−0.87; HFpEF=−1.52 mm Hg; p=0.006). No significant differences in systolic IVPDs were found in adjusted models. IVPD parameters demonstrated only weak correlations with standard Doppler-echocardiographic parameters.

Conclusions Our findings suggest distinct patterns of systolic and diastolic IVPDs in HFrEF and HFpEF, implying differences in the nature of diastolic dysfunction between the HF subtypes.

INTRODUCTION

The incidence and prevalence of heart failure (HF) is increasing worldwide.1 Clinically, two major subtypes of HF are identified2–4 based on the left ventricular (LV) ejection fraction (EF): HF with reduced (HFrEF) and with preserved EF (HFpEF).2–4 Although LV systolic dysfunction is thought to be the...
key pathophysiological abnormality in HFrEF, diastolic
dysfunction is also present in this condition. Similarly,
whereas diastolic dysfunction is thought to be a key
pathophysiological abnormality in HFrEF, systolic contractile
abnormalities have been also reported in this condition.
Therefore, a better understanding of the nature of physi-
ological abnormalities in HF patients is desirable.

Non-invasive quantitative analysis of intraventricular
flow dynamics can provide important insights into the
processes driving LV ejection and filling. While the anal-
ysis of blood flow velocities (in particular, the transmit-
tral flow velocities) is extensively used in the evaluation
of LV function, much less is known about underlying
pressure differences driving diastolic and systolic intra-
ventricular flow in HFrEF and HFrEF. These pressure
differences can be inferred by solving the Euler equa-
tion, a simplified version of the Navier-Stokes equa-
tions, using information regarding the spatiotemporal
pattern of LV blood flow velocities, which in turn can be
obtained using ultrasound (eg, colour M-mode record-
ings along a transmural scanline) or MRI. The computa-
tion of intraventricular pressure differences (IVPDs) has
been applied in the context of diastolic function analysis
but can also be applied to systole, to interrogate pressure
gradients produced by LV ejection.

The aim of this study is to demonstrate the feasibility of
an MRI-based method to characterise IVPDs throughout
diastole and systole.

METHODS

We prospectively enrolled a sample of patients at the
Corporal Michael J. Crescenz VA Medical Center. The
protocol was approved by the Philadelphia VA Medical
Center Institutional Review Board, and all subjects
provided written informed consent.

HFrEF was defined as a symptomatic HF in the pres-
ence of a left ventricular ejection fraction (LVEF) <50%.
HFrEF was defined as the presence of all of the following:
(1) New York Heart Association (NYHA) Class II–IV symp-
toms consistent with HF; (2) LV ejection fraction >50%;
(3) Mitral inflow early diastolic (E wave) to annular tissue
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Two-dimensional phase contrast imaging acquisition and
processing
Intraventricular flow velocities were measured with
phase-contrast MRI, using a 1.5T MRI scanner (Avanto
system; Siemens Healthcare; Erlangen, Germany). A
phase contrast gradient echo pulse sequence with in-plane
velocity encoding was applied using retrospective gating
in a plane corresponding to the three-chamber view (LV
outflow tract view) in which both the mitral inflow and
the LV outflow are well visualised. We performed two
consecutive breath-held acquisitions, each with in-plane
velocity encoding in one direction. Both acquisitions
were merged offline to obtain the in-plane two-dimen-
sional-velocity maps. Images were obtained with the
following imaging parameters: TE=2.7 ms, TR=4.8 ms,
temporal resolution=39.8 ms, bandwidth=450 Hz/pixel,
field-of-view=360×360 mm², matrix=152–192×256, spatial
resolution=1.88×1.88 mm², slice thickness=6 mm, flip
angle=20°. Maximal velocity encoding was usually set at
130 cm/s but adjusted during the examination to avoid
aliased velocity measurements.

Image processing and computation of IVPDs
A MATLAB (MathWorks, Natick, Massachusetts, USA)
custom-designed graphi user interface was programmed
to process all phase-contrast MRI sequences. The pres-
sure difference between two points in a plane (the scan-
ing plane) can be calculated from the two-dimensional
planar velocity information as

\[ \text{IVPD} = \sum \left( \left( \frac{\partial P}{\partial x} \right) x + \left( \frac{\partial P}{\partial y} \right) y \right) \]

with pressure derivatives linked through the Euler equation to the two-dimensional-velocity information:

\[ \frac{\partial P}{\partial x} = -\rho \left( \frac{\partial u}{\partial x} + u \frac{\partial u}{\partial x} + \frac{\partial v}{\partial y} \right) \]

with \( u \) the two-dimensional-component vector (\( u_x, u_y \)) of local blood velocity and \( \rho \), blood density (1060 Kg/m³).

The instantaneous pressure difference between any two
points along this streamline (\( \frac{\partial P}{\partial t} \)), is the net result of the change in velocity with time at a given spatial point (\( \text{inertial component}, \left( \frac{\partial u}{\partial t} \right) \)), and the change in velocity with
space at any given time (\( \text{convective component}, \left( \frac{\partial u}{\partial x} \right) \)).

For the assessment of diastolic IVPDs, 2–4 reference
points were placed inside the LV along the inflow direc-
tion at the mitral annulus (Point 1, P1) and the LV
apex (Point 2, P2) (figure 1A, B). For the assessment of systolic IVPDs, 2–4 reference points were placed
along the outflow direction, from the LV apex (P1) to

infiltrative or hypertrophic cardiomyopathy, or extracar-
diagnostic amyloidosis or sarcoidosis.12

Doppler echocardiography
Doppler transthoracic echocardiography was performed
at rest with the patient in supine position using a Vivid E9
device (GE Healthcare, Horten, Norway), equipped with
a cardiac probe.
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Figure 1  Graphical description of the phase-contrast MRI sequence processing to assess diastolic function (left column) and systolic function (right column). (A) and (E) original magnitude images and (B) and (F) calculated velocity vectors images, showing the reference points selection, located at: (left) the mitral annulus (P1) and LV apex (P2); and (right) LV apex (P1) and aortic annulus (P2). (C) and (G) the pseudo colour M-mode image, calculated from the two-dimensional velocity vectors, was used as quality reference of the IVPD curves. Calculated IVPD curves (solid black line); (D) during diastole, showing the (1) E-wave (E-IVPD), (2) reversal E-wave (ER-IVPD) and (3) A-wave (A-IVPD) pressure peaks, and (H) during systole, showing the (1) S-wave (S-IVPD) and (2) reversal S-wave (SR-IVPD) pressure peaks. (C, D) and (G, H) are aligned in time, respectively. Important to REMARK, the colour scale in (B, C, F) and (G) is a visual guidance for the user during the processing, and the linear (two points) and the curvilinear (four points) approximation could be selected by the user for diastolic and/or systolic analysis. IVPD, intraventricular pressure difference.

the aortic annulus (P2) (figure 1E, F). To note, points were: (1) placed using the frame with the best anatomical view of the structures and (2) stationary through the whole cardiac cycle. A pseudo-colour M-mode image was calculated projecting velocity components within the path delimited by the reference points and displayed for processing visual guidance (figure 1C, G).

Available velocity components were used to calculate pressure gradient fields and differences. Then, interpolated values along the line delimited by P1 and P2 were used to solve equation 1, applying a direct integration method to obtain the IVPD curves (figure 1D, H).

Statistical analysis

Descriptive data are presented as mean±SD or mean (95% CI) for continuous variables or counts (%) for categorical variables. Differences between groups were determined by one-way analysis of variance (ANOVA) and adjusted for potential confounders. Physiological indices were expressed as absolute values as well as absolute differences between measurements (with 95% CIs). A p value <0.05 was considered statistically significant. We presented a model with unadjusted data, and three adjusted models: model 1—adjusted for clinical data (age, sex, African American ethnicity, body mass index (BMI), coronary artery disease, estimated glomerular filtration rate (eGFR) and beta-blocker, ACE-Inhibitor/angiotensin receptor blocker (ARB), loop diuretic and spironolactone use); model 2—model 1 additionally adjusted for echo parameters (Mitral E-wave velocity, E-wave deceleration time, Mitral annular e’ septal); model 3—model 2 additionally adjusted for MRI data (LV mass index and end-diastolic volume index (EDVI)). Statistical analyses were performed using MATLAB statistics and machine learning toolbox (Matlab 2016b, the Mathworks; Natwick, Massachusetts, USA) and SPSS for Mac V.22.

Reproducibility and repeatability assessment

To test the method’s reproducibility (measurements performed by two different operators at least 1 year apart) and repeatability (measurements performed by the same operator at least 1 week apart), 10 cases (included in the study) were assessed, calculating the Pearson r-value squared ($r^2$), the sum of squared error (SSE) and the reproducibility coefficient (RPC).

Echocardiographic/MRI correlation assessment

To evaluate the potential added value of the proposed technique, correlation coefficients were calculated between selected MRI parameters and established Doppler-echocardiographic indices of diastolic function.

RESULTS

General characteristics of the study population are shown in table 1. The mean age of participants with HFrEF, HfPEF and without HF was 65.9, 62.9 and 61.8 years, respectively. The HFrEF group demonstrated a high prevalence of hypertension, diabetes, coronary artery disease and pronounced left atrial enlargement. Consistent with the HfPEF phenotype, subjects in this group were obese and had a high prevalence of hypertension and diabetes. Most subjects with HFrEF and HfPEF were receiving beta blockers, an ACE inhibitor or ARB, and loop diuretics. The study sample was composed predominantly of males, with a high proportion of African-Americans, particularly in the HFrEF group.
Table 1  General characteristics of study subjects

| Variable                        | No-HF (n=159) | HFrEF (n=47) | HFpEF (n=32) | P value |
|---------------------------------|---------------|--------------|--------------|---------|
| Age (years)                     | 61.8±11.5     | 65.9±10.7    | 62.9±8.6     | 0.09    |
| Male                            | 145 (91)      | 46 (98)      | 28 (88)      | 0.18    |
| Race                            |               |              |              |         |
| African-American                | 72 (45)       | 31 (66)      | 16 (50)      | 0.04*   |
| Caucasian                       | 74 (47)       | 15 (32)      | 15 (47)      | 0.20    |
| BMI (kg/m²)                     | 29.5 (25.7, 33.1) | 27.9 (24.2, 32.9) | 35 (29.3, 41.7) | 0.0007†‡ |
| Heart rate (bpm)                | 68.9±13       | 69±11.9      | 67.4±11.9    | 0.84    |
| Ejection duration (ms)          | 319±30        | 311±47       | 325±33       | 0.27    |
| Current smoker                  | 43 (28)       | 15 (33)      | 8 (25)       | 0.73    |
| Hypertension                    | 118 (75)      | 41 (89)      | 29 (91)      | 0.03    |
| Diabetes                        | 64 (41)       | 27 (59)      | 18 (56)      | 0.04*   |
| Coronary artery disease         | 47 (30)       | 24 (51)      | 11 (34)      | 0.03*   |
| Drug therapy                    |               |              |              |         |
| Beta blocker                    | 74 (47)       | 43 (91)      | 24 (75)      | <0.0001†‡ |
| ACE-inhibitor/ARB               | 80 (51)       | 37 (79)      | 26 (81)      | <0.0001†‡ |
| Calcium-channel blocker         | 41 (26)       | 12 (26)      | 13 (41)      | 0.23    |
| Spironolactone                  | 3 (2)         | 6 (13)       | 4 (13)       | 0.002*† |
| Statin                          | 103 (65)      | 36 (77)      | 21 (66)      | 0.33    |
| Aspirin                         | 84 (53)       | 37 (79)      | 19 (59)      | 0.007*  |
| Thiazide                        | 34 (22)       | 11 (23)      | 5 (16)       | 0.74    |
| Loop diuretics                  | 2 (1)         | 35 (74)      | 23 (72)      | <0.0001†‡ |
| eGFR (mL/min/1.73m²)§            | 86 (65, 98.8) | 74 (56.5, 92.3) | 84 (63, 99) | 0.056* |
| LV EF (%)                       | 59.6 (52.2, 65.6) | 36.6 (23.7, 42.5) | 61.4 (58, 70.3) | <0.0001†‡ |
| LA volume index (mL/m²)          | 30.7 (23.8, 39.5) | 46.1 (35.7, 65.3) | 36.6 (26.4, 49.9) | <0.0001* |
| LV EDVI (mL/m²)                 | 69.9 (58.4, 82.4) | 102.7 (85.8, 141.4) | 69.1 (56.7, 79.5) | <0.0001†‡ |
| LV mass index BSA (g/m²)        | 64.5 (56.9, 76.5) | 88.6 (77.9, 107.1) | 72 (59.3, 83.2) | <0.0001†‡ |
| Mitral E-wave velocity (cm/s)   | 69.5 (58.1, 85.5) | 74.3 (54.7, 93.6) | 69.6 (60.5, 92.7) | 0.54    |
| Mitral E-wave deceleration time (ms) | 210 (170, 240) | 180 (140, 220) | 220 (170, 270) | 0.06    |
| Mitral A-wave velocity (cm/s)   | 74.6±21.7     | 62.3±22.3    | 74.7±19.6    | 0.008*  |
| Mitral annular e¹, septal (cm/s) | 7.58 (5.9, 9.65) | 5.61 (4.12, 7.9) | 6.77 (5.24, 8.19) | 0.0007* |

Values are mean±SD or mean (95% CI), or counts (percentages).

*p<0.05 for No-HF vs HFrEF.
†p<0.05 for No-HF vs HFpEF.
‡p<0.05 for HFrEF vs HFpEF.
§eGFR was calculated using the Modification of Diet in Renal Disease Study equation.
ACE, angiotensin convertase enzyme; ARB, angiotensin receptor blocker; BSA, body surface area; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HFrEF, HF with reduced ejection fraction; HFpEF, HF with preserved ejection fraction; LV, left ventricular.

In all three groups (No-HF, HFrEF and HFpEF), subjects exhibited, in general, consistent IVPD patterns described previously using colour M-mode Doppler echocardiography14–17 or cardiac MRI13 18 19 (figure 1D, H). The diastolic period of the calculated IVPD waveforms was typically characterised by (1) a large early diastolic forward positive difference (E-IVPD) during ventricular relaxation, associated with early diastolic rapid filling; (2) an early diastolic negative peak associated with the deceleration of the early filling (ER-IVPD); (3) a second, late diastolic, positive peak (A-IVPD) associated with atrial contraction (see figure 1D). The systolic period was characterised by a typical biphasic configuration with (1) a large forward positive peak (S-IVPD) associated with ventricular systole (rapid ejection) followed by (2) a negative peak (SR-IVPD) associated with its deceleration (slow ejection phase) (see figure 1H). Selected IVPD parameters are shown and compared in table 2, and figures 2 and 3.
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### Table 2  Comparison of diastolic and systolic intraventricular pressure difference parameters between the groups

| Variable   | No-HF (n=159) | HFrEF (n=47) | HFP EF (n=32) | P value |
|------------|---------------|--------------|---------------|---------|
| **Unadjusted model** |               |              |               |         |
| E-IVPD (mm Hg)   | 0.76 (0.68, 0.84) | 0.83 (0.67, 0.98) | 0.83 (0.64, 1.02) | 0.63    |
| ER-IVPD (mm Hg)  | −0.78 (−0.93, −0.63) | −0.75 (−1.02, −0.47) | −1.30 (−1.60, −0.99) | 0.01†   |
| A-IVPD (mm Hg)   | 0.93 (0.85, 1.02) | 0.72 (0.56, 0.88) | 0.92 (0.73, 1.11) | 0.07    |
| S-IVPD (mm Hg)   | 1.7 (1.56, 1.84)  | 1.41 (1.16, 1.65) | 1.99 (1.65, 2.34) | 0.01†   |
| SR-IVPD (mm Hg)  | −1.15 (−1.28, −1.02) | −0.90 (−1.17, −0.64) | −1.37 (−1.64, −1.10) | 0.04†   |
| **Adjusted model 1** |               |              |               |         |
| E-IVPD (mm Hg)   | 0.75 (0.65, 0.85) | 0.86 (0.64, 1.08) | 0.85 (0.61, 1.08) | 0.70    |
| ER-IVPD (mm Hg)  | −0.76 (−0.95, −0.56) | −0.85 (−1.23, −0.47) | −1.35 (−1.72, −0.97) | 0.02*   |
| A-IVPD (mm Hg)   | 0.94 (0.83, 1.05) | 0.71 (0.49, 0.92) | 0.94 (0.70, 1.17) | 0.15    |
| S-IVPD (mm Hg)   | 1.7 (1.52, 1.89)  | 1.49 (1.14, 1.84) | 1.89 (1.47, 2.33) | 0.16    |
| SR-IVPD (mm Hg)  | −1.15 (−1.32, −0.98) | −0.94 (−1.30, −0.58) | −1.34 (−1.67, −1) | 0.14    |
| **Adjusted model 2** |               |              |               |         |
| E-IVPD (mm Hg)   | 0.84 (0.71, 0.97) | 0.93 (0.67, 1.19) | 0.79 (0.54, 1.04) | 0.62    |
| ER-IVPD (mm Hg)  | −0.68 (−0.92, −0.45) | −0.99 (−1.41, −0.56) | −1.48 (−1.87, −1.08) | 0.009*  |
| A-IVPD (mm Hg)   | 0.97 (0.84, 1.11) | 0.75 (0.50, 1.00) | 0.97 (0.72, 1.22) | 0.27    |
| S-IVPD (mm Hg)   | 1.72 (1.49, 1.96)  | 1.46 (1.03, 1.89) | 1.86 (1.39, 2.33) | 0.25    |
| SR-IVPD (mm Hg)  | −1.17 (−1.34, −0.99) | −0.83 (−1.21, −0.46) | −1.32 (−1.64, −1.01) | 0.04†   |
| **Adjusted model 3** |               |              |               |         |
| E-IVPD (mm Hg)   | 0.85 (0.72, 0.99) | 0.91 (0.63, 1.20) | 0.79 (0.54, 1.05) | 0.76    |
| ER-IVPD (mm Hg)  | −0.72 (−0.96, −0.49) | −0.87 (−1.34, −0.40) | −1.52 (−1.92, −1.13) | 0.006†  |
| A-IVPD (mm Hg)   | 0.98 (0.85, 1.12) | 0.73 (0.46, 1.00) | 0.99 (0.73, 1.24) | 0.24    |
| S-IVPD (mm Hg)   | 1.74 (1.51, 1.98)  | 1.47 (1.01, 1.92) | 1.86 (1.37, 2.34) | 0.34    |
| SR-IVPD (mm Hg)  | −1.17 (−1.35, −0.99) | −0.86 (−1.25, −0.47) | −1.31 (−1.64, −0.99) | 0.11    |

Data are presented as mean (95% CI).

Unadjusted model; adjusted model 1: adjusted for clinical data (age, sex, African American ethnicity, BMI, coronary artery disease, eGFR and beta blocker, ACE-inhibitor, ARB, loop diuretic, and spironolactone use); adjusted model 2: model 1 additionally adjusted for echo parameters (Mitral E-wave velocity, E wave deceleration time, Mitral annular e’ septal); adjusted model 3: model 2 additionally adjusted for MRI data (LV mass index and EDVI).

* p<0.05 for No-HF vs HFP EF.
† p<0.05 for HFrEF vs HFP EF.
‡ p<0.05 for No-HF vs HFrEF.

EDVI, end-diastolic volume index; eGFR, estimated glomerular filtration rate; HF, heart failure; HFP EF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; IVPD, intraventricular pressure difference; LV, left ventricular.

**Diastolic IVPDs**

Unadjusted comparisons demonstrated no significant differences in E-IVPD (No-HF=0.76; HFrEF=0.83; HFP EF=0.83 mm Hg; p=0.63) and A-IVPD (No-HF=0.93; HFrEF=0.97; HFP EF=0.92 mm Hg; p=0.07) between the groups (table 2 and figure 2). In contrast, ER-IVPD was significantly different between the groups (ANOVA p=0.01), consistent with a more pronounced reversal of the early diastolic IVPD in HFP EF (−1.30 mm Hg) compared with the No-HF group (−0.78 mm Hg) and the HFrEF group (−0.75 mm Hg). After adjustment for age, sex, African American ethnicity, BMI, coronary artery disease, eGFR and medication use (adjusted model 1), these differences persisted (No-HF=−0.76; HFrEF=−0.85; HFP EF=−1.35 mm Hg; p=0.02). Similarly, these differences were present after further adjustment for Doppler-echo cardiographic parameters (adjusted model 2: No-HF=−0.68; HFrEF=−0.99; HFP EF=−1.48 mm Hg; p=0.009) and LV structure (adjusted model 3: No-HF=−0.72; HFrEF=−0.87; HFP EF=−1.52 mm Hg; p=0.006).

**Systolic IVPDs**

In unadjusted analyses (table 2 and figure 2), there were significant differences between groups in S-IVPD (No-HF=1.7; HFrEF=1.41; HFP EF=1.99 mm Hg; p=0.01) and SR-IVPD (No-HF=−1.15; HFrEF=−0.90; HFP EF=−1.37 mm Hg; p=0.04), with more pronounced IVPDs in the HFP EF group compared with the HFrEF group. Between-group differences in SR-IVPD were also present after adjustment for general clinical...
Figure 2  Comparison of IVPDs between groups for the unadjusted model. Computed parameters from diastole (left) and systole (right) are shown. Error bars represent 95% CIs. ANOVA, analysis of variance; HF, heart failure; HFrEF, HF with reduced ejection fraction; HFpEF, HF with preserved ejection fraction; IVPD, intraventricular pressure difference.

Figure 3  Selected IVPD parameters (ER and SR—wave peak pressures) with statistically significant differences between groups for adjusted models: (top) adjusted model 1; (middle) adjusted model 2; (bottom) adjusted model 3. Computed parameters from diastole (left) and systole (right) are shown. Error bars represent 95% CIs. ANOVA, analysis of covariance. HF, heart failure; HFrEF, HF with reduced ejection fraction; HFpEF, HF with preserved ejection fraction; IVPD, intraventricular pressure difference.

characteristics and Doppler-echocardiographic parameters (adjusted model 2; table 2 and figure 3), but no significant differences in systolic IVPDs were found between the groups after further adjustment for LV structure (adjusted model 3; table 2 and figure 3).

Reproducibility and repeatability assessment
Higher reproducibility was demonstrated for diastolic E-IVPD and ER-IVPD parameters ($r^2\geq0.70$; SSE$\leq0.58$; RPC$\leq0.55$) in comparison with A-IVPD ($r^2=0.56$; SSE$=0.98$; RPC$=0.65$) and systolic parameters (S-IVPD: $r^2=0.04$; SSE$=5.3$; RPC$=1.6$; SR-IVPD: $r^2=0.47$; SSE$=1.3$; RPC$=0.76$). This trend was maintained for the repeatability assessment, although altogether higher indexes were found in this case (diastolic parameters: $r^2\geq0.92$; SSE$\leq0.21$; RPC$\leq0.32$; systolic parameters: $r^2\geq0.71$; SSE$\leq1.6$; RPC$\leq0.87$).
to characterise cardiac performance. However, the assessment and interpretation of intraventricular pressure gradients in clinical practice remains complicated by its dependency on a large number of factors and interactions. Furthermore, flow occurs in multiple and rapidly changing directions, forming complex vortex patterns. The complexity of intraventricular flow and technical limitations of ultrasound imaging, the standard method in cardiovascular assessment, make it difficult to relate intraventricular flow patterns and derived IVPDs to LV myocardial function in a quantitative manner.

The increasing availability of cardiovascular MRI has made it an advantageous alternative from a technical point of view due to its high image quality, reproducibility, repeatability, plane of view flexibility, sufficient spatial and temporal resolution and reduced operator dependency. Furthermore, MRI-based IVPD calculations allow for a more flexible definition and alignment of the operator’s ‘scan line’, which could be relevant when the blood flow exhibits a curved trajectory. Additionally, two-dimensional-velocity information from phase contrast MRI improves the accuracy of IVPDs even if the temporal resolution, a critical parameter to calculate IVPDs, is lower in comparison with ultrasound. In fact, Thompson and McVeigh reported that a minimum temporal resolution of 44 ms may avoid significant underestimation of the local acceleration contribution to the total intracardiac pressure differences. Previously, making use of computational fluid dynamics simulations, we assessed the impact of temporal resolution in IVPD calculations, showing that the temporal resolution of phase contrast MRI is, at least in theory, sufficient to resolve IVPDs. Furthermore, we also showed that IVPDs estimated by a one-dimensional method as colour-Doppler ultrasound are larger in magnitude than when the two-dimensional velocity information was used, but the estimates based on two-dimensional velocity information are more accurate, especially in extreme scan line misalignments, which could be particularly sensible after mid and late diastole due to formation of vortices. We speculate that this explains, at least partly, some of the difference between values reported here and in other studies.

There were no significant differences in E-IVPD and A-IVPD between the groups. This may be a consequence of early filling pseudonormalisation due to greater filling pressures. Additionally, in HFrEF patients, pronounced diastolic abnormalities can often be elicited only during physiological perturbations, such as exercise or dobutamine infusions, as subjects with HFrEF exhaust their reserve. Nonetheless, our results demonstrate that HFrEF is associated with a greater magnitude of the ER-IVPD. Although, the slope of mitral inflow deceleration temporally coincides with ER-IVPD, it is interesting to note that we did not find significant differences in the deceleration time between the groups, and that ER-IVPD was not strongly related to the deceleration time.

**DISCUSSION**

We compared diastolic and systolic IVPDs between subjects with HFrEF, HfPEF or No-HF. We found physiologically expected patterns of IVPD in all three groups, with significant differences in diastolic IVPDs. Specifically, subjects with HfPEF exhibited more pronounced reversal peak of early diastolic IVPDs, which was independent of clinical parameters, echocardiographic parameters of LV filling, and LV structure assessed by MRI. Subjects with HFrEF demonstrated a non-significant trend of increasing E-IVPD and decreasing A-IVPD, S-IVPD and SR-IVPD. Our findings suggest distinct patterns of systolic and diastolic IVPDs and differences in the nature of both diastolic and systolic dysfunction between HF subtypes. IVPD parameters demonstrated only weak correlations with standard Doppler-echocardiographic parameters.

Previous studies have shown that, despite being small in magnitude, IVPDs have a significant role in efficient filling and emptying of the LV and could be used to characterise cardiac performance. However, the assessment and interpretation of intraventricular pressure gradients in clinical practice remains complicated by its dependency on a large number of factors and interactions. Furthermore, flow occurs in multiple and rapidly changing directions, forming complex vortex patterns. The complexity of intraventricular flow and technical limitations of ultrasound imaging, the standard method in cardiovascular assessment, make it difficult to relate intraventricular flow patterns and derived IVPDs to LV myocardial function in a quantitative manner.

The increasing availability of cardiovascular MRI has made it an advantageous alternative from a technical point of view due to its high image quality, reproducibility, repeatability, plane of view flexibility, sufficient spatial and temporal resolution and reduced operator dependency. Furthermore, MRI-based IVPD calculations allow for a more flexible definition and alignment of the operator’s ‘scan line’, which could be relevant when the blood flow exhibits a curved trajectory. Additionally, two-dimensional-velocity information from phase contrast MRI improves the accuracy of IVPDs even if the temporal resolution, a critical parameter to calculate IVPDs, is lower in comparison with ultrasound. In fact, Thompson and McVeigh reported that a minimum temporal resolution of 44 ms may avoid significant underestimation of the local acceleration contribution to the total intracardiac pressure differences. Previously, making use of computational fluid dynamics simulations, we assessed the impact of temporal resolution in IVPD calculations, showing that the temporal resolution of phase contrast MRI is, at least in theory, sufficient to resolve IVPDs. Furthermore, we also showed that IVPDs estimated by a one-dimensional method as colour-Doppler ultrasound are larger in magnitude than when the two-dimensional velocity information was used, but the estimates based on two-dimensional velocity information are more accurate, especially in extreme scan line misalignments, which could be particularly sensible after mid and late diastole due to formation of vortices. We speculate that this explains, at least partly, some of the difference between values reported here and in other studies.

There were no significant differences in E-IVPD and A-IVPD between the groups. This may be a consequence of early filling pseudonormalisation due to greater filling pressures. Additionally, in HfPEF patients, pronounced diastolic abnormalities can often be elicited only during physiological perturbations, such as exercise or dobutamine infusions, as subjects with HfPEF exhaust their reserve to preserve the diastolic suction force at rest, limiting their ability for adaptation to stress. Nonetheless, our results demonstrate that HFrEF is associated with a greater magnitude of the ER-IVPD. Although, the slope of mitral inflow deceleration temporally coincides with ER-IVPD, it is interesting to note that we did not find significant differences in the deceleration time between the groups, and that ER-IVPD was not strongly related to the deceleration time.
Therefore, our data suggests that ER-IVPD may be a more sensitive marker of diastolic function in HFpEF.

We also examined systolic IVPDs. A typical biphasic IVPD pattern was observed in systole, with a positive peak immediately followed by a negative one. HFrEF individuals exhibited lower values, whereas the HFpEF group presented an overall higher total magnitude of S-IVPD and SR-IVPD, suggesting differences in systolic flow dynamics between groups. These differences could be related to the unsteady nature of ejective flow, abnormalities in chamber geometry, and/or the sequence of regional contraction.20

Our reproducibility and repeatability assessments suggest a general adequate inter and intra-operator variability for early diastolic IVPD parameters. Reproducibility and repeatability were lower for A-IVPD, probably due to a more complex flow after mid and late diastole.8,14

Systolic parameters evidenced a need to refine the standardisation of the method, particularly for S-IVPD. The overall correlation between IVPD parameters and echocardiographic indexes was weak or non-existent. In fact, previous publications have pointed out a weak correlation between Doppler echocardiographic estimates of LV filling pressure with invasive filling pressure measurements and the necessity to include further analysis of non-invasive measures.27 28 In contrast, echocardiographic16 17 and MRI15 based IVPD parameters have shown good agreement against invasive intraventricular measurements, adding potentially relevant information for cardiovascular assessments.

The reported data should be interpreted considering the strengths and limitations of the study. Strengths of this study are the inclusion of patients with HFrEF and HFpEF, and the assessment of IVPDs with phase-contrast MRI, which overcomes a number of assumptions made with colour M-mode echocardiography and allows for a more consistent interrogation of intraventricular flow. Our study also has limitations. We did not perform invasive catheter-based measures of distensibility which would have been unfeasible in the absence of a clinical indication for LV catheterisation. From a technical point of view, the MRI acquisition requires relative long breathholds (~20s) and has limited temporal and plane spatial resolution, while the processing could be affected by the image alignment and assumptions made about the nature of flow from the three chambers view. On computation of the IVPDs, viscous forces are neglected and it is assumed that inflow and outflow is laminar.3 17 25 On average, our HFpEF subjects did not have marked left atrial enlargement, suggesting the presence of mild HFpEF. This may have led to underestimations of true underlying differences. Our population was a clinical sample referred for a cardiac MRI study, which may not fully represent population-based trends. Moreover, complementary myocardial mechanic studies could be included to improve the analysis.29

In conclusion, we demonstrated the feasibility to assess IVPDs throughout the cardiac cycle using phase-contrast MRI and compared IVPDs between subjects without HF and subjects with HFrEF and HFpEF. Our findings suggest distinct patterns of diastolic IVPDs in HFpEF, implying differences in the nature of diastolic dysfunction between the HF subtypes. Further research is warranted to exploit MRI analysis thoroughly to assess the significance of these novel indices regarding risk stratification and response to therapy.

**Contributors**

Design: FL-H, PS and JAC; oversight and funding: PS and JAC; manuscript drafting: FL-H; critical review of the manuscript: all authors; data collection: 60, MKJ, KJ, RM, IV and SA; image analyses: ZH, RB, AT and WW.

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