RESEARCH ARTICLE

Increased pulmonary blood volume variation in patients with heart failure compared to healthy controls: a noninvasive, quantitative measure of heart failure

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Increased pulmonary blood volume variation in patients with heart failure compared to healthy controls: a noninvasive, quantitative measure of heart failure. J Appl Physiol 128: 324–337, 2020. First published December 24, 2019; doi:10.1152/japplphysiol.00507.2019.—Variation of the blood content of the pulmonary vascular bed during a heartbeat can be quantified by pulmonary blood volume variation (PBVV) using magnetic resonance imaging (MRI). The aim was to evaluate whether PBVV differs in patients with heart failure compared with healthy controls and investigate the mechanisms behind the PBVV. Forty-six patients and 10 controls underwent MRI. PBVV was calculated from blood flow measurements in the main pulmonary artery and a pulmonary vein, defined as the maximum difference in cumulative PBVV over one heartbeat. PBVV was indexed to stroke volume (SV) in the main pulmonary artery (PBVV_{SV}). Patients displayed higher PBVV_{SV} than controls (58 ± 14 vs. 43 ± 7, P < 0.001). The change in PBVV_{SV} could be explained by left ventricular (LV) longitudinal contribution to SV (R^2 = 0.15, P = 0.02) and the phase shift between in- and outflow (R^2 = 0.31, P < 0.001) in patients. Both variables contributed to the multiple regression analysis model and predicted PBVV_{SV} (R^2 = 0.38); however, the phase shift alone explained ~30% of the variation in PBVV_{SV}. No correlation was found between PBVV_{SV} and large vessel area. In conclusion, PBVV_{SV} was higher in patients compared with controls. Approxiately 40% of the variation of PBVV_{SV} in patients can be explained by the LV longitudinal contribution to SV and the phase shift between pulmonary in- and outflow, where the phase shift alone accounts for ~30%. The remaining variation (60–70%) is suggested to occur on a small vessel level.

Heart failure; magnetic resonance imaging; pulmonary blood volume variation; pulmonary vein; stroke volume

INTRODUCTION

Heart failure (HF) is a clinical syndrome associated with high mortality (26). A cornerstone feature in HF is that cardiac output can only be maintained at increased filling pressures. The most accurate method to estimate left ventricular (LV) filling pressure is by measuring pulmonary arterial wedge pressure from right-heart catheterization (20). However, because of the invasive nature, catheterization is not suitable for serial examinations, and noninvasive alternatives would be preferred. HF has been shown to be associated with alterations in the pulmonary venous flow pattern, related to increased left atrial (LA) and LV filling pressure. This has been shown as decreased pulmonary venous flow during ventricular systole using echocardiography (30) (16). Several aspects of the pulmonary venous velocity patterns as possible surrogate measures of LA pressure have been suggested: the so-called systolic fraction (%venous flow during systole), the systolic velocity-time integral, and peak systolic-to-peak diastolic ratio (18). However, echocardiography is user-dependent, and as much as 20–30% of the patients with HF might be misdiagnosed (4). Therefore, there is a need for a better noninvasive and quantitative method for HF diagnosis.

Such an alternative method could be quantification of the pulmonary blood volume variation (PBVV) using magnetic resonance imaging (MRI) (29). MRI is not as user-dependent as echocardiography and is considered the gold standard for quantifying blood flow noninvasively, even in small vessels (1). PBVV is quantified by measuring the in- and outflow of the pulmonary circulation and reflects the maximum variation in blood volume within the pulmonary vascular bed over one cardiac cycle. PBVV, in contrast to the echocardiographic measures, takes the arterial pulmonary blood flow into consid-
eration in addition to the venous flow (29). This could be of importance, as the right ventricular (RV) propulsion of blood affects the pulmonary venous flow profile (25). Porcine PBVV has previously been shown to substantially decrease after acute myocardial infarction (29). However, PBVV has never been quantified in a clinical setting. Therefore, the aim of the present study was to evaluate whether PBVV differs in patients with HF compared with healthy controls and investigate the mechanisms behind the PBVV.

**Study Population**

The study was approved by the regional ethical review board in Lund, Sweden. Written informed consent was obtained from all subjects. Fifty-four patients with clinically established HF diagnosis [New York Heart Association (NYHA) class I–IV, 65 ± 11 yr, 13 women] were prospectively included between 2013 and 2017 at Skane University Hospital, Lund, Sweden. Ten age- and sex-matched healthy controls (60 ± 7 yr, 4 women) without history of cardiopulmonary disease, diabetes, and cardioactive medication were also included for comparison. Resting electrocardiogram (ECG) was recorded in all subjects. Exclusion criteria for patients were severe kidney failure (glomerular filtration rate <30 mL/min), cardiac device, and atrial fibrillation. The healthy controls had normal cardiac status, including right and left ventricular function on MRI.

For end points, hospital records of the patients were reviewed for unplanned hospitalizations (defined as sudden worsening of HF symptoms leading to hospitalization and death) with a range of 12–51 mo postinclusion.

**Image Acquisition**

*MRI.* All subjects underwent cardiac MRI using a 1.5 Tesla system (Philips Achieva, Philips Medical Systems, Best, the Netherlands, for subjects included before 2015; and Siemens Aera, Erlangen, Germany, for subjects included between 2015 and 2017). The MRI protocol included conventional balanced steady-state free precession short-axis and long-axis cine images during ECG-triggered end-expiratory breath-hold acquisition for cardiac function. Furthermore, two-dimensional flow sequences in a cross-section of the vessels using a nonsegmented phase contrast velocity-encoded gradient echo sequence during retrospective ECG triggering were included in the protocol (28). Phase-contrast MRI averages many cardiac cycles to generate a flow curve for one cardiac cycle. Free-breathing image acquisition of the main pulmonary artery (~170 cardiac cycles) and the ascending aorta was performed in all subjects. The flow in one pulmonary vein was used as a surrogate for flow in all pulmonary veins after validation (see Flow Measurements, PBVV and PBVV SV, and **APPENDIX A**, Part 1). The flow in the pulmonary vein was acquired either during functional residual capacity; that is, at an end-expiratory breath hold (~20 cardiac cycles), in 21 patients or during free breathing (~140 cardiac cycles) in 16 patients. Although a breath-hold sequence is faster than the free-breathing flow sequences, patients with HF may be unable to hold their breath, leading to respiratory motion artifacts. Therefore, in a subset of the patients (n = 9) and healthy controls (n = 5), both breath-hold and free-breathing sequences were used to perform an internal validation to investigate whether there was any difference in calculating PBVV using these sequences. No significant difference was seen (see **APPENDIX A**, Part 2, for details). For the subjects with both flow sequences acquired, the free-breathing flow sequence was used for the results of this study. For each subject, all MRI data were acquired during the same scan. Typical MRI parameters are presented in **APPENDIX B**.

*Echocardiography.* Transthoracic echocardiography was performed on clinical indication. Standard echocardiography was performed using standard imaging systems (Vivid E9/Vivid 7, GE Medical, Horten, Norway or iE33/Epic/CX50, Philips Healthcare, Eindhoven, Netherlands) according to guidelines (23). The median timespan between MRI and echocardiography was 22 days, with an interquartile range of 7–70 days.

**Image Analysis MRI**

All MR image analysis was performed using the freely available software Segment version 2.2 R6901 (Medviso, Lund, Sweden) (11).

**Flow Measurements, PBVV and PBVV SV**

For flow and stroke volume (SV) measurements, a region of interest was manually delineated around the lumen of the aorta (for $\text{SV}_{\text{Aorta}}$), the main pulmonary artery (Fig. 1A), and in the pulmonary veins (Fig. 1B), defining the flow in the specific vessel. The blood flows were quantified using the following formula: vessel area ($\text{cm}^2$) times mean through-plane velocity ($\text{cm/s} = \text{cm/s} = \text{mL/s}$). The calculations were made in the software Segment. A validation on the feasibility of calculating PBVV using the measurement of only one pulmonary vein compared with using all pulmonary veins was made in a subset of healthy controls (n = 9) and patients (n = 4), as described in **APPENDIX A**, Part 1. Intra- and interobserver variability were performed for flow measurements in the main pulmonary artery, the pulmonary vein, and for the calculation of PBVV and PBVV SV in 10 patients with HF (see **APPENDIX C**). The intraobserver variability was performed by observer 1 (M. Al-Mashat and M. Kanski). Interobserver variability was performed by two observers (M. Al-Mashat and M. Kanski).

![Fig. 1. Magnitude and phase images from magnetic resonance imaging examination and the corresponding flow curves in the main pulmonary artery (MPA; A) and pulmonary vein (B) in 1 healthy control. A region of interest was manually delineated (black line) in the lumen of each vessel in the images. The white arrow in the magnitude image (B) points at the pulmonary vein, with the corresponding black arrow in the phase image. Dimensional bars: 1 cm = 10 mm. Ao, aorta.](image-url)
PBVV was computed as previously described (14, 29). The flow in the main pulmonary artery was measured (Fig. 2A). Figure 2B shows the conventional method where the flow in all pulmonary veins was measured and summed. Instead of using all pulmonary veins, only one was used and scaled to match the SV in the main pulmonary artery (Fig. 2C). The difference in arterial (inflow) and venous (outflow) blood flow was integrated over time (Fig. 2D), yielding the cumulative blood volume in the pulmonary circulation (Fig. 2E). Because the heart rate can vary somewhat during the scan and the number of time frames over the cardiac cycle is fixed to 35 frames/cycle, the average of the pulmonary vein and pulmonary artery time-step was used for calculating the cumulative blood volume. The PBVV was defined as the difference between the maximum and the minimum of the cumulative volume variation over the cardiac cycle (Fig. 2E). To adjust for variation in ejected SV from the RV, the PBVV was indexed to the effective SV in the main pulmonary artery (PBVVSV) and presented as a percentage.

The flow profile in the main pulmonary artery from MRI was visually assessed with regard to presence or absence of systolic notch as a sign of pulmonary hypertension (2, 27). Systolic notching was defined as a decrease in deceleration descent of blood flow during mid-to-late ventricular systole (2, 17, 27).

To investigate whether the capacitance of the bigger vessels accounted for PBVV, the relationship between PBVVSV and the area variation of the main pulmonary artery and the pulmonary vein was investigated. The area variation for each vessel was defined as the difference between the maximum and the minimum of the vessel area.

To study the timepoint for when the maximum pulmonary blood volume occurs as a percentage of the cardiac cycle (i.e., the phase shift between the in- and outflow), the cumulative blood volume values were interpolated with a cubic spline using Matlab version R2016b (Math-Works, Natick, MA). The peak value of the smoothed curve was used.

Left and Right Ventricular Volumes and Function

To investigate the cardiac function and its relationship with PBVVSV, end-diastolic volume (EDV) and end-systolic volume (ESV) were measured by manual planimetry in cine short-axis images covering the entire LV and RV, as previously described (5). Planimetric LV SV (SVplan) was defined as EDV−ESV and ejection fraction (EF) as SVplan/EDV × 100. Typical MRI parameters are listed in APPENDIX B.

The LV and RV atrioventricular plane displacement (AVPD) was calculated in 2-, 3- and 4-chamber long-axis cine MRI images. Input points were manually placed in the three long-axis views of the right and left ventricles in end diastole and end systole. LVAVPD was defined as the movement of the atrioventricular plane in the apical-basal direction of the LV.

The systolic volume, defined as the cumulative volume of the venous systolic flow, was calculated using the flow of the pulmonary vein.

Mitrail regurgitation was calculated from MR images using the following formula: (SVplan−SVAorta)/SVplan × 100.

Image Analysis of Echocardiography

Analysis of the echocardiographic images were performed on a dedicated workstation using Echopac software (Echopac BT12, GE Medical, Horten, Norway).

Color doppler over the tricuspid valve with trans-tricuspid valve regurgitant maximum velocity (TRVmax) measured with continuous
Doppler in the view with the largest TRV\textsubscript{max} was used. A TRV\textsubscript{max} value of $\leq 2.8$ m/s was considered normal, and RV systolic pressure (RVSP) was estimated from the modified Bernoulli equation $\Delta P = 4 \times TRV_{\text{max}}^2$ according to international guidelines (9, 23).

Statistical Analysis

GraphPad Prism software version 7.04 (Graph Pad Software, La Jolla, CA) and SPSS version 25.0 (IBM, Armonk, NY) were used for statistical analysis.

Continuous data were expressed as means $\pm$ SD or median and interquartile range [IQR] according to normal distribution tested in histograms. Categorical values were expressed in absolute numbers and percentage. Mann–Whitney’s test was used for comparison between patients with HF and healthy controls with regard to PBVV and PBVV\textsubscript{SV} and to investigate the relationship between PBVV\textsubscript{SV} and NYHA class, systolic notch, left bundle branch block (LBBB), and vessel area variation. Spearman correlation was used for regression analysis. Kaplan–Meier survival analysis with Log-rank (Mantel–Cox) test was used for comparison of HF hospitalizations and death, using the median value of PBVV\textsubscript{SV} as cutoff. Wilcoxon signed test was used for comparison between flow measurements acquired during breath-hold and free-breathing sequences in patients and healthy controls. Wilcoxon signed test was also used for comparison between PBVV calculated using only one pulmonary vein compared with all pulmonary veins. To investigate the diagnostic accuracy of predicting pulmonary hypertension (by estimated RVSP) with PBVV\textsubscript{SV} and the PBVV\textsubscript{SV} versus the phase shift between the in- and outflow, means $\pm 2$ SD were used to define the cut-off value for a normal PBVV\textsubscript{SV}. To investigate which variables could explain the variation in PBVV\textsubscript{SV} in patients with HF, a multiple regression analysis was performed. Variables with $P < 0.10$ entered the multiple regression analysis model. Collinearity existed when two or more dependent variables showed a statistically significant correlation. In such cases, the variable with the lowest $P$ value was chosen to enter the multiple regression analysis model.

Results with $P$ value $< 0.05$ were considered statistically significant.

RESULTS

Fifty-four patients with HF were included for MRI examination. Seven of these were excluded due to inadequate quality of the flow images, and one patient was excluded because flow acquisition in the main pulmonary artery was missing, leaving 46 patients (NYHA class I–IV, 65 $\pm$ 10 yr, 12 women) for statistical analysis. LV and RV volumes were excluded in one patient due to poor image quality. Subject characteristics are presented in Table 1. The lower right pulmonary vein was used in 32 patients and 4 controls, the upper right pulmonary vein was used in 7 patients and 4 controls, the lower left pulmonary vein was used in 3 patients and 2 controls, and the upper left pulmonary vein was used in 4 patients.

PBVV and PBVV\textsubscript{SV} Indexed to Effective Stroke Volume

Patients with HF displayed significantly higher PBVV and PBVV\textsubscript{SV} than healthy controls ($45 \pm 15$ vs. $34 \pm 9$ mL, $P = 0.02$ and $58 \pm 14$ vs. $43 \pm 7\%$, $P < 0.001$ respectively, see Fig. 3).

The intraobserver variability was $-3.88 \pm 4.73$ mL, $R^2 = 0.95$ for the main pulmonary artery (Fig. C1A); $-2.03 \pm 4.07$ mL, $R^2 = 0.81$ for the pulmonary vein (Fig. C1B); $-1.89 \pm 2.53$ mL, $R^2 = 0.99$ for PBVV (Fig. C1C); and $0.48 \pm 2.55\%$, $R^2 = 0.96$ for PBVV\textsubscript{SV} (Fig. C1D). The interobserver variability between observer 1 and observer 2 was $-0.24 \pm 4.61$ mL, $R^2 = 0.96$ for the main pulmonary artery (Fig. C2A); $2.42 \pm 6.39$ mL, $R^2 = 0.57$ for the pulmonary vein (Fig. C2B); $-0.35 \pm 2.60$ mL, $R^2 = 0.99$ for PBVV (Fig. C2C); and $0.04 \pm 2.64\%$, $R^2 = 0.96$ for PBVV\textsubscript{SV} (Fig. C2D).

Table 1. Characteristics of the included subjects

|                      | Healthy Controls | Patients with HF | P Value |
|----------------------|------------------|------------------|---------|
| Gender (Women/Men)   | 4 (40%)/6 (60%)  | 12 (33%)/34 (67%)|         |
| Age, yr              | 60 $\pm$ 7       | 65 $\pm$ 10      | 0.15    |
| Length, cm           | 173 $\pm$ 9      | 173 $\pm$ 9      |         |
| Weight, kg           | 71 $\pm$ 14      | 80 $\pm$ 16      |         |
| Clinical             |                  |                  |         |
| Diabetes             | 0                | 5/46 (11%)       |         |
| LBBB                 | 0                | 21/46 (46%)      |         |
| NT pro-BNP, ng/L     |                  |                  |         |
| Systolic blood pressure, mmHg* | 1328 [537–2097]  | | |
| Diastolic blood pressure, mmHg* | 135 [120–148]  | | |
| NYHA class†         |                  |                  |         |
| I                    | 8/36 (22%)       |                  |         |
| II                   | 18/36 (50%)      |                  |         |
| III                  | 8/36 (22%)       |                  |         |
| IV                   | 2/36 (16%)       |                  |         |
| MRI                  |                  |                  |         |
| LVEF, %              | 59 $\pm$ 5       | 34 $\pm$ 13      | $< 0.001$ |
| LVSV, mL             | 97 $\pm$ 25      | 95 $\pm$ 25      | 0.66    |
| LVEDV, mL            | 163 $\pm$ 36     | 104 $\pm$ 104    | $< 0.001$ |
| LVESV, mL            | 65 $\pm$ 13      | 209 $\pm$ 109    | $< 0.00$ |
| RV EF, %             | 55 $\pm$ 6       | 47 $\pm$ 11      | 0.04    |
| RVSV, mL             | 89 $\pm$ 21      | 88 $\pm$ 24      | 0.86    |
| RVEDV, mL            | 162 $\pm$ 33     | 193 $\pm$ 58     | 0.07    |
| RVESV, mL            | 73 $\pm$ 16      | 105 $\pm$ 48     | 0.02    |
| HR, beats/min        | 65 $\pm$ 12      | 62 $\pm$ 13      | 0.34    |
| CO, L/min            | 6.2 $\pm$ 1.8    | 5.8 $\pm$ 1.7    | 0.57    |
| CI, L·min$^{-1}$·m$^{-2}$ | 3.4 $\pm$ 0.9   | 3.0 $\pm$ 0.8   | 0.37    |
| Effective SV (MPA), mL | 78 $\pm$ 16     | 81 $\pm$ 24      |         |
| LVAPVD, mm           | 14.2 $\pm$ 1.9   | 8.5 $\pm$ 3.7    | $< 0.001$ |
| RVAPVD, mm           | 19.1 $\pm$ 2.7   | 14.4 $\pm$ 4.8   | 0.003   |
| Mitral regurgitation, % | 21 [14–30]     | |         |
| Medication           |                  |                  |         |
| Beta blockers        | 38/46 (83%)      |                  |         |
| ACEI/ARB             | 42/46 (91%)      |                  |         |
| Statins              | 20/46 (43%)      |                  |         |
| Antithrombotic drugs | 30/46 (65%)      |                  |         |
| Diuretics            | 30/46 (65%)      |                  |         |
| Etiology             |                  |                  |         |
| Ischemic cardiomyopathy | 26/46 (57%)     |                  |         |
| Nonischemic cardiomyopathy | 10/46 (22%) | | |
| Unknown/other        | 10/46 (22%)      |                  |         |

PBVV$\textsubscript{SV}$ Versus Systolic Cardiac Function

In patients with HF ($n = 45$), the change in PBVV$\textsubscript{SV}$ could be explained by EF, being more pronounced on the right side ($R^2 = 0.30$, $P < 0.001$, Fig. 4A) than on the left side of the heart ($R^2 = 0.15$, $P = 0.01$, Fig. 4B). No such relationship was observed in the healthy controls (RVEF: $R^2 = 0.13$, $P = 0.32$).
and LVEF: \( R^2 = 0.23, P = 0.16 \). The LVAVPD was lower in patients with HF compared with healthy controls \((8.5 \pm 3.7 \text{ vs. } 14.2 \pm 1.9 \text{ mm, } P < 0.001)\). Furthermore, the change in the product of LV area times LVAVPD could be determined by the volume entering the left atrium through the pulmonary veins in systole in healthy controls \( (R^2 = 0.80, P < 0.001, n = 10, \text{Fig. 5A}) \) and patients with HF \( (R^2 = 0.59, P < 0.001, n = 45, \text{Fig. 5B}) \). Additionally, the change in PBVVSV could be determined by LV area times LVAVPD as a percentage of the SV in the main pulmonary artery (LV longitudinal contribution to SV) in patients with HF \( (R^2 = 0.15, P = 0.02, n = 36, \text{Fig. 5D}) \) but not in healthy controls \( (R^2 < 0.01, P = 0.92, n = 8, \text{Fig. 5C}) \).

The change in PBVVSV could be determined by LVEDV indexed to body surface area (BSA) (as measure of ventricular dilation) in patients with HF \( n = 36 (R^2 = 0.10, P = 0.06) \). \( R^2 \) for determining PBVVSV by RVEDV/BSA was 0.13 \( (P = 0.03) \).

There was no significant difference in PBVVSV between patients with LBBB on ECG compared with patients without LBBB \( (54 \pm 10 \text{ vs. } 57 \pm 21\% , P = 0.42) \).

**PBVVSV Versus Systolic Notch and Estimated Right Ventricular Systolic Pressure**

In 7 of 46 patients, a systolic notch was seen in the main pulmonary artery flow profile. Patients with a systolic notch displayed significantly higher PBVVSV compared with patients without a systolic notch \( (71 \pm 18 \text{ vs. } 56 \pm 12\% , P = 0.01, \text{Fig. 3B}) \). The change in PBVVSV could to some extent be determined by estimated RVSP from transthoracic echocardiography \( (R^2 = 0.13, P = 0.05, n = 30/46) \). In 6 of the 7 patients with a systolic notch, both PBVVSV and elevated estimated RVSP \( (>31 \text{ mmHg}) \) were higher than in patients without systolic notch. The remaining patient with systolic notch had a PBVVSV of 35\%, and estimated RVSP was normal \( (25 \text{ mmHg}) \). The sensitivity and specificity for the diagnostic accuracy of predicting pulmonary hypertension (by estimated RVSP) with PBVVSV using the cutoff of 57\% were 88\% and 64\%, respectively. The corresponding sensitivity and specificity using systolic notch were 75\% and 63\%, respectively.

**Vessel Area Variation and the Phase Shift Between the In- and Outflow**

The change in PBVVSV could not be explained by the area variation of the main pulmonary artery (controls: \( R^2 = 0.05, P = 0.60, n = 8 \); patients: \( R^2 = 0.10, P = 0.07, n = 36, \text{Fig. 6, A and B}) \), nor by the area variation of the pulmonary vein (controls: \( R^2 = 0.38, P = 0.10 \); patients: \( R^2 < 0.01, P = 0.74, \text{Fig. 6, C and D}) \).

The change in PBVVSV could not be explained by the phase shift between the in- and outflow in healthy controls \( (R^2 = 0.04, P = 0.65, n = 8, \text{Fig. 7A}) \). However, in patients with HF, the change in PBVVSV could be explained by the phase shift \( (R^2 = 0.31, P < 0.001, n = 36, \text{Fig. 7B}) \). There was no difference between patients with or without LBBB in when the phase shift between the in- and outflow occurred (Fig. 7B). A significant difference in this phase shift was found between patients with \( \text{PBVVSV} \leq 57\% \) and patients with \( \text{PBVVSV} > 57\% \) \( (29 \pm 6 \text{ vs. } 40 \pm 9\% , P < 0.001, n = 36, \text{Fig. 7C}) \).

**Multiple Regression Analysis**

The univariate regression analysis of all the variables with the correlation with PBVVSV was studied. Variables that showed colinearity were removed from the multiple regression analysis. This resulted in the LV longitudinal contribution to SV and the
phase shift between the in- and outflow entering the multiple regression analysis (Table 2). These variables contributed to the model and predicted together PBVVSV with an $R^2$ value of 0.38; however, the LV longitudinal contribution to SV did not contribute statistically significantly to the model ($P = 0.06$). The phase shift alone predicted the model with an $R^2$ value of 0.31.

**PBVV SV Versus Major Adverse Cardiac Events and NYHA**

During the follow up (median: 21 mo, range: 12–51 mo), 2 of 46 patients died and there were 8 unplanned hospitalizations for HF in total. Using the median value of PBVVSV (55%) as cutoff, comparisons between the two groups above and below
the median were performed. The number of the composite end point of hospitalizations and deaths did not differ between patients with PBVVSV $\leq 55\%$ (total number of hospitalizations $= 6, 1$ death) and patients with PBVVSV $> 55\%$ (total number of hospitalizations $= 2, 1$ death, $P = 0.56$).

There was no significant difference in PBVVSV between patients with NYHA class I-II ($n = 26$) and patients with NYHA class III-IV ($n = 10$) ($56 \pm 15\%$ vs. $61 \pm 9\%$, $P = 0.15$).

**DISCUSSION**

This is the first study to investigate PBVVSV using MRI in patients with HF and show that PBVVSV was higher in patients with HF compared with healthy controls. We found that $\sim 40\%$ of the variation in PBVVSV in patients with HF can be attributed to the LV longitudinal contribution to SV and on the phase shift between the pulmonary in- and outflow. However, the LV longitudinal contribution to SV did not contribute significantly to the model; the phase shift alone predicted the model and accounts for $\sim 30\%$ of the variation. Because the lack of large vessel distensibility cannot be the cause, the remaining variation (100–40% = 60% and 100–30% = 70%; 60–70%) is suggested to occur on the small vessel level.

**PBVV in Relation to Previous Work**

In the current study, PBVV was higher in patients with HF compared with healthy controls (Fig. 3). PBVV has previously been quantified in pigs and decreased following acute experimentally induced myocardial infarction (29). The mechanism behind this decrease is not fully understood, but it could be due to sympathetic activation and increased serum concentration of vasoconstrictors such as endothelin, which leads to vasoconstriction of the pulmonary arteries after acute myocardial infarction. However, the patients included in the current study were patients with chronic HF under medication with beta blockers and angiotensin inhibitors. Furthermore, the pigs in the previous work were young and healthy, and therefore had unscathed physiological compensatory mechanisms. Also, after the experimentally induced infarction, the coronary flow is fully restored. In contrast, patients with ischemic heart disease have chronically diseased vessels. Backward failure causes increased pressure in the pulmonary vasculature (with vasoconstriction and sympathetic activation). Another difference can be differences in LA pressure. LA pressure is usually elevated in patients with left-sided HF (10). An increased LA pressure in patients with HF has been shown to affect the pulmonary venous flow pattern, which in turn results in a decreased systolic pulmonary venous flow (30) that in theory should lead to an elevated PBVV. Increased LA pressure could therefore influence the PBVV to a higher degree than the mechanisms of increased serum levels of vasoconstrictors and potential remodeling of the pulmonary vessels. However, after acute experimentally induced infarction in pigs, the LA pressure remained unchanged (29), which at least in part could

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Table 2. Predictors of pulmonary blood volume variation indexed to effective stroke volume in patients with heart failure

| Predictors | $R^2$ Value | $\beta$ Value | $P$ Value |
|------------|-------------|---------------|------------|
| PBVV SV    |             |               |            |
| LV longitudinal contribution to SV | 0.38 | $-0.27$ | 0.06 |
| Phase shift between in- and outflow | 0.50 | 0.0001 |            |

Predictors of the dependent variable pulmonary blood volume variation indexed to effective stroke volume (PBVV SV) and the results from multiple regression analysis. Note that the left ventricular (LV) longitudinal contribution to the stroke volume (SV) and the phase shift between the pulmonary in- and outflow predict the mechanism and variation behind the PBVV SV with an $R^2$ value of 0.38.
explain why the PBVV decreased. Another possible mechanism for the difference in PBVV\textsubscript{SV} in patients with HF compared with healthy controls is the effects of the sympathetic nervous system on the cardiovascular system. In patients with HF, the sympathetic nervous system and several physiological processes are impaired with aging (24). Aging might therefore lead to an increased vessel stiffness, which could affect the flow patterns and a theoretical lower PBVV. Stiffer vessels would allow a lower variation in the pulmonary blood volume over the cardiac cycle. However, the PBVV in the current study was higher in patients with HF compared with age-matched controls. Furthermore, diabetes could also play a role on the effect of the cardiovascular system (22) because it is one of many causes behind changes in the sympathetic nervous system. In our study, however, only 5 of 46 (11%) patients had diabetes. The presence of diabetes or prediabetes in patients with HF is ~30–40% (8); therefore, our patient cohort may not be representative for patients with diabetes.

**Mechanisms Behind the PBVV\textsubscript{SV}**

We found that ~40% of the variation in PBVV\textsubscript{SV} in patients can be explained by LV longitudinal contribution to SV and the phase shift between the in- and outflow. However, the phase shift alone accounts for ~30% of the variation.

**Longitudinal shortening.** In the current study, the systolic longitudinal shortening of the LV was highly correlated with LA inflow during systole, in line with an earlier study (6) (Figs. 5 and 8). It is known that the pulmonary venous flow profile is affected by the AV-plane movement (25). The descending systolic AV-plane cause a decreased pressure in the atrium that sucks blood from the pulmonary veins into the atrium (6), resulting in a high PBVV\textsubscript{SV}. This also explains the correlation between PBVV\textsubscript{SV} and LVEF (Fig. 4B) because patients with decreased LVEF also have lower AVPD.

**Phase shift.** The phase shift between the in- and outflow and PBVV\textsubscript{SV} seen in patients with HF (Figs. 7 and 8) means that the later the PBV maximum occurs, the higher the PBVV\textsubscript{SV}. This phase shift could in part be a result of a dyssynchronous and dyssynergic LV, leading to an offset in the timing for when blood starts to flow into the left atrium during systole (19) and thus a greater accumulation of blood in the pulmonary circulation. Contradictory to this alternative explanation, there was no difference between patients with LBBB and those without. Simply having a difference in timing between ejection of blood

![Diagram of the mechanisms behind PBVVSV](image-url)
into the pulmonary circulation and suction into the left atrium does not seem to affect PBVVSV. Therefore, this phase shift may instead reflect total blood volume status (the more intravascular blood volume, the more distended vessels) and differences in vascular distensibility (due to remodeling).

**Vessel distensibility.** In the current study, no correlation was found between PBVVSV and the large vessel area variation (Fig. 6). The reason could be that the patients included in the current study have remodeling and stiffening of the large vessels secondary to the chronic HF (7); however, no correlation was found between PBVVSV and area variation in healthy controls either. If the entire pulmonary circulation would be completely stiff, the inflow and outflow profiles would be identical and in phase, as blood is incompressible. Therefore, this lack of correlation at the large vessel level (main pulmonary artery and pulmonary vein) suggests that the PBVV occurs on a small vessel level (arterioles and venules), including the capillaries (when the pulmonary arterial pressure exceeds the alveolar pressure). Previous studies estimating pulmonary capillary blood volume using the Roughton and Forster method have not shown any statistically significant increase in patients with HF compared with healthy controls (3, 21). Therefore, the variation in PBVV is likely to occur in the arterioles and venules. Although these compartments cannot be studied in detail using the data presented in this work, previous work by Karatzas and Lee (15) has shown by nitrous oxide body plethysmography that a considerable amount of the SV (average ~60%) is stored in the small arteries and capillaries during systole, which is in agreement with the numbers found in the present study (60–70%). Previous studies have shown that this increase in pulmonary volume during systole benefits gas exchange in acute respiratory distress syndrome (12) (13). It has also been shown that patients with HF have a decreased gas exchange to the lungs (21). Therefore, the increase in PBVV seen in patients with chronic HF might in part be a compensatory mechanism to maintain an adequate gas exchange.

**PBVV and Signs of Pulmonary Hypertension**

In this study, a positive correlation was found between PBVVSV and the pressure gradient between the right atrium and RV from echocardiography (estimated RVSP) in patients with HF. This means that an increased PBVVSV could be a sign of pulmonary hypertension (9) and therefore a measure of RV function. Additionally, 6 of the 7 patients with systolic notch were among the patients presenting with the highest PBVVSV values, and the estimated RVSP was also elevated in these patients. In the one remaining patient with systolic notch (1/7), the PBVVSV value was low and estimated RVSP was normal. Therefore, these results showed that PBVVSV could be a sensitive marker of increased pulmonary artery pressure, and further studies are needed with more patients with systolic notch to investigate the use of PBVVSV in the diagnosis of pulmonary hypertension. In this study, the correlation between PBVVSV and EF was more pronounced on the right side than on the left side of the heart (Fig. 4A). Thus, lower global RV function is associated with higher PBVVSV. This could also be related to the fact that PBVVSV is higher in patients with signs of pulmonary hypertension. PBVVSV might therefore be an indirect measure of RV function.

**Limitations**

This study lacks invasive measurements. Instead, echocardiography was used for pressure estimations. This measure is sensitive to angular error and may therefore underestimate the pressure. Because MRI and echocardiography were not performed during the same day, changes in filling pressures could affect the results of the study. Furthermore, there was no difference in major adverse cardiac events in this study, possibly due to the relatively short follow-up period. In the current study, a validation was performed to investigate whether there is a difference in using one or all pulmonary veins in the calculation of PBVV. The results were comparable and showed that PBVV can be calculated using only one pulmonary vein, significantly shortening the scan time (see APPENDIX A, Part 1). Furthermore, the pulmonary venous flows were acquired either during breath hold or during free breathing. Therefore, a validation was also performed to investigate whether there is a difference in calculating PBVV and PBVVSV using breath-hold or free-breathing flow sequences. The results showed that there was no difference; see APPENDIX A, Part 2, for more details.

There are some aspects of technical source errors that should be taken into consideration. To minimize the effect of background phase offsets, the vessel of interest was centered in the image for the flow images. Additionally, if the background phase residual errors had been significant, the flow ratio between the main pulmonary artery and the aorta (QP/QS) would have been abnormal, which was not the case in this study (see QP/QS data in APPENDIX C). This was therefore a strength of the study. Loss of precision could be introduced if using a suboptimal velocity encoding (VENC) parameter. This was considered in the current study by using a higher VENC (200 cm/s) for flow measurement in the main pulmonary artery and a lower VENC (80 cm/s) for the pulmonary vein (see Table B1 in APPENDIX B).

An example of the physiological aspects of source errors is that the intrathoracic pressures are different when acquiring flow images during breath hold and free breathing, which could affect flow patterns. In this study, however, flow measurements were acquired during both breath hold and free breathing in a subset of patients and controls (see APPENDIX A, Part 2). These measurements showed that there was no difference in the calculation of PBVV and PBVVSV between these two methods, which is a strength of the study. A physiologic beat-to-beat variation could also be a potential source of error. However, the flow acquisitions used for PBVV calculation were averaged over several beats, thus adjusting for a beat-to-beat variability.

A final potential source of error is observer variability. The intra- and interobserver variability of the delineations of calculation of PBVV and PBVVSV showed an inconspicuous bias, demonstrating the power of this method. See APPENDIX C for more details.

**Conclusions**

The pulmonary blood volume variation indexed to effective stroke volume is higher in patients with HF compared with healthy controls. Approximately 40% of the variation of PBVVSV in patients with HF can be explained by the LV longitudinal contribution to SV and the phase shift between the pulmonary...
in- and outflow, where the phase shift alone accounts for \(~30\%\) of the variation. Because the large vessel distensibility does not differ, the remaining variation (60–70\%) is suggested to occur on the small vessel level. Future studies are needed to show the clinical added value of PBVVSV in comparison to invasive measurements of the LA pressure.

**APPENDIX A**

**PART 1: PULMONARY BLOOD VOLUME VARIATION (PBVV) CALCULATION USING ONE VERSUS ALL PULMONARY VEINS**

**Method**

A validation on the feasibility of calculating PBVV using only one pulmonary vein compared with using all pulmonary veins was made in healthy controls and patients with heart failure (HF). The measured flow in one pulmonary vein was scaled to match the flow over one cardiac cycle in the main pulmonary artery (Fig. 2C).

**Results and Interpretation**

In 9 of the 10 healthy controls and 4 of the 46 patients, the flow in all pulmonary veins was measured for the head-to-head comparison between PBVV calculated using one pulmonary vein versus using all pulmonary veins.

There was no statistically significant difference in PBVV calculated using all pulmonary veins compared with only one pulmonary vein (35 ± 9 vs. 35 ± 8 mL, \(P = 0.07, 1.7 ± 4.6\%\) difference, bias = −1.8 ± 4.7 mL, Fig. A1). This means that the PBVV can be calculated using only one pulmonary vein and yields comparable results, which leads to shorter scan time.

**PART 2: ACQUISITION; PULMONARY VEIN FLOW AT BREATH HOLD VERSUS FREE BREATHING**

**Method**

The flow in the main pulmonary artery was acquired during free breathing for all subjects. The flow in the pulmonary vein was acquired either during breath hold (21 patients with HF) or during free breathing (16 patients with HF). A breath-hold sequence is faster than the free-breathing flow sequences, but patients with HF may be unable to hold their breath. Therefore, in a subset of patients \((n = 9)\) and healthy controls \((n = 5)\), both breath-hold and free-breathing sequences were acquired to perform an internal validation to investigate potential differences between breath-hold and free-breathing sequences for calculating the PBVV.

**Results and Interpretation**

The flow in the pulmonary vein was acquired either during breath hold (32 patients and 5 controls) or during free breathing (26 patients and 10 controls). Fourteen subjects (9 patients and 5 controls) underwent flow acquisitions with both breath hold and free breathing. The results from the comparison for the 14 subjects are presented in Table A1. There was no difference in flow measurement of the main pulmonary artery, pulmonary vein, PBVV, or PBVV indexed to effective stroke volume (PBVVSV) during breath hold (BH) and free breathing in 14 subjects (both healthy controls \(n = 5\) and patients with heart failure \(n = 9\)).

**APPENDIX B**

Magnetic resonance imaging parameters for flow (Table B1) and cine-short axis (Table B2) images for the Philips Achieva and Siemens Aera scanners are presented.

**APPENDIX C**

The QP/QS in healthy controls and intra- and interobserver variability in patients with HF.

**METHODS**

The fraction between the flow in the main pulmonary artery and the flow in the aorta (QP/QS) was calculated in 10 healthy controls. Intra- and interobserver variability was performed on 10 randomly selected patients with HF for the delineations of the main pulmonary artery, pulmonary vein, and the calculation of PBVV and PBVVSV.

**RESULTS AND INTERPRETATION**

In healthy controls, the QP/QS was 1.06 ± 0.1. This means that the background phase residual errors in the flow measurements are acceptable. The intraobserver variability was \(-3.88 ± 4.73\ mL, R^2 = 0.95\) for the main pulmonary artery (Fig. C1A); \(-2.03 ± 4.07\ mL, R^2 = 0.81\) for the pulmonary vein (Fig. C1B); \(-1.89 ± 2.53\ mL, R^2 = 0.95\) for the pulmonary vein (Fig. C1B). The values are presented as means ± SD. Flow in the main pulmonary artery, one pulmonary vein, pulmonary blood volume variation (PBVV), and PBVV indexed to effective stroke volume (PBVVSV) during breath hold (BH) and free breathing in 14 subjects (both healthy controls \(n = 5\) and patients with heart failure \(n = 9\)).
Table B1. Magnetic resonance imaging parameters for flow images

| Parameters          | Philips Achieva | Siemens Aera |
|---------------------|-----------------|--------------|
| Flow images         | Free Breathing  | Free Breathing |
|                     | Breath Hold     | Breath Hold  |
| Slice thickness, mm | 5               | 5            |
| Reconstructed frames per cardiac cycle | 35               | 30           |
| TR/TE, ms           | 8.7/6.4         | 9.8/2.7      |
| Flip angle, °       | 15              | 20           |
| Pixel size, mm      | 1.2 × 1.2       | 1.5 × 1.5    |
| Velocity encoding gradient (arterial flow), cm/s | 200              | 200          |
| Velocity encoding gradient (venous flow), cm/s | 80               | 80           |

Magnetic resonance imaging parameters for flow for the Philips Achieva and the Siemens Aera scanners. TE, echo time; TR, repetition time.

R² = 0.99 for PBVV (Fig. C1C); and 0.48 ± 2.55%, R² = 0.96 for PBVVSV (Fig. C1D). The interobserver variability between observer 1 and observer 2 was −0.24 ± 4.61 mL, R² = 0.96 for the main pulmonary artery (Fig. C2A); 2.42 ± 6.39 mL, R² = 0.57 for the pulmonary vein (Fig. C2B); −0.35 ± 2.60 mL, R² = 0.99 for PBVV (Fig. C2C); and 0.04 ± 2.64%, R² = 0.96 for PBVVSV (Fig. C2D). Table C1 summarizes the intra- and interobserver variability. The results of both intra- and interobserver variability showed that there was a bias in the delineations of the pulmonary vein. A missing part of the pulmonary vein will result in a lower flow in that vein. However, our data show that this is of minor importance when calculating the PBVV, as long as the representative flow profile is captured. In the case of an underestimated total flow in the vein, this will render a larger factor that the venous flow profile is multiplied with (arterial flow/venous flow), leading to a similar PBVV volume (note the small bias in calculated PBVV and PBVVSV). The delineations of the main pulmonary artery and the calculation of PBVV and PBVVSV could be reproduced with very small bias, suggesting that the PBVV is relatively observer independent.

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Table B2. Magnetic resonance imaging parameters for cine-short axis images

| Parameters          | Philips Achieva | Siemens Aera |
|---------------------|-----------------|--------------|
| Cine-short axis images (acquired during breath hold) |                 |              |
| Slice thickness, mm | 8               | 6            |
| Slice gap, mm       | 0               | 0            |
| TR/TE, ms           | 2.6/1.5         | 2.6/1.2      |
| Flip angle, °       | 60              | 59           |
| Pixel size (reconstructed, mm) | 1.5 × 1.5       | 1.0 × 1.0    |

Magnetic resonance imaging parameters for cine-short axis images for the Philips Achieva and the Siemens Aera scanners. TE, echo time; TR, repetition time.

DISCLOSURES

Erasmus Bachus has been an employee of AstraZeneca Denmark since January 2, 2019. None of the other authors has any conflicts of interest, financial or otherwise, to declare.

AUTHOR CONTRIBUTIONS

M.A.-M., H.A., and M.K. conceived and designed research; M.A.-M., M.C., and M.K. performed experiments; M.A.-M. and M.K. analyzed data; M.A.-M. and M.K. interpreted results of experiments; M.A.-M. and M.K. prepared figures; M.A.-M. and M.K. drafted manuscript; M.A.-M., J.J., M.C., R.B., E.O., M.M., E.B., G.R., H.A., and M.K. edited and revised manuscript; M.A.-M., J.J., M.C., R.B., E.O., M.M., E.B., G.R., H.A., and M.K. approved final version of manuscript.

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PBVV AS A MEASURE OF HEART FAILURE

Fig. C1. Intraobserver variability. Scatterplot of the delineations of the main pulmonary artery (A), pulmonary vein (B), calculation of the pulmonary blood volume variation (PBVV; C) and PBVV indexed to stroke volume (PBVVsv; D) performed by observer 1 the first and second time and the corresponding Bland–Altman plots. Solid lines in the scatterplots represent the fitted regression line, and dashed lines represent the line of identity. Bland–Altman plots present the average difference between the first and second delineations and calculations.
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Fig. C2. Interobserver variability. Scatterplot of the delineations of the main pulmonary artery (A), pulmonary vein (B), calculation of the pulmonary blood volume variation (PBVV; C), and PBVV indexed to stroke volume (PBVVsv; D) performed by observer 1 and observer 2 and the corresponding Bland-Altman plots. Solid lines in the scatterplots represent the fitted regression line, and dashed lines represent the line of identity. Bland–Altman plots present the average difference between observer 1 and observer 2 performing the same delineations and calculations.
Table C1. Intra- and interobserver variability

|                          | Intraobserver Variability | Interobserver Variability |
|--------------------------|---------------------------|---------------------------|
|                          | Bias                      | $R^2$                     | Bias                      | $R^2$                     |
| Main pulmonary artery, mL| -3.88 ± 4.73              | 0.95                      | -0.24 ± 4.61              | 0.96                      |
| Pulmonary vein, mL       | -2.03 ± 4.07              | 0.81                      | 2.42 ± 6.39               | 0.57                      |
| PBVV, mL                 | -1.89 ± 2.53              | 0.99                      | -0.35 ± 2.60              | 0.99                      |
| PBVV SV, %               | 0.48 ± 2.55               | 0.96                      | 0.04 ± 2.64               | 0.96                      |

The results of intra- and interobserver variability for the main pulmonary artery, pulmonary vein, pulmonary blood volume variation (PBVV), and PBVV indexed to stroke volume (PBVV SV) in 10 patients with heart failure.

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