Impaired left ventricular filling due to right-to-left ventricular interaction in patients with pulmonary arterial hypertension


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Gan, C. Tji-Joong, Jan-Willem Lankhaar, J. Tim Marcus, Nico Westerhof, Koen M. Marques, Jean G. F. Bronzwaer, Anco Boonstra, Pieter E. Postmus, and Anton Vonk-Noordegraaf. Impaired left ventricular filling due to right-to-left ventricular interaction in PAH patients compared with control subjects. Stroke volume, right and left ventricular volumes, left ventricular filling rate, and interventricular septum curvature were measured by magnetic resonance imaging and left atrial filling by transesophageal echocardiography. Stroke volume, left ventricular end-diastolic volume, and left ventricular peak filling rate were decreased in PAH patients compared with control subjects: 28 ± 13 vs. 41 ± 10 ml/m² (P < 0.001), 46 ± 14 vs. 61 ± 14 ml/m² (P < 0.001), and 216 ± 90 vs. 541 ± 248 ml/s (P < 0.001), respectively. Among PAH patients, stroke volume did not correlate to right ventricular end-diastolic volume or mean pulmonary arterial pressure but did correlate to left ventricular end-diastolic volume (r = 0.62, P < 0.001). Leftward interventricular septum curvature was correlated to left ventricular filling rate (r = 0.64, P < 0.001) and left ventricular end-diastolic volume (r = 0.65, P < 0.001). In contrast, left atrial filling was normal and not correlated to left ventricular end-diastolic volume. In PAH patients, ventricular interaction mediated by the interventricular septum impairs left ventricular filling, contributing to decreased stroke volume.

ventricular interdependence; stroke volume

In severe pulmonary arterial hypertension (PAH), chronic pressure overload results in right ventricular (RV) hypertrophy and dilatation. Enlargement of the RV might affect the left ventricle (LV), which is intrinsically normal. In patients with chronic RV pressure overload, echocardiographic studies have shown altered LV filling dynamics; i.e., early diastolic filling is impaired and LV filling is redistributed toward late diastole (1, 9, 17, 21, 26). In an earlier study, we reported similar results of impaired LV filling and showed that LV end-diastolic volume (LVEDV) was reduced (23). The phenomenon by which the RV directly influences LV diastolic filling is known as direct ventricular interaction and is mediated by the interventricular septum (6, 13, 15). Direct ventricular interaction has been investigated extensively in animal models (4, 7, 12, 13, 24, 28), and, in patients with chronic RV pressure overload, it has been associated with changes in LV filling dynamics (10, 11, 21, 23). However, the hemodynamic consequence of direct ventricular interaction in PAH patients has not been resolved. We hypothesized that, in PAH patients, direct ventricular interaction impairs LV filling; as a consequence, LVEDV is reduced, and, according to Frank-Starling’s law, stroke volume (SV) is decreased.

The aim of our study was to determine the effect of direct ventricular interaction on SV by magnetic resonance (MR) imaging and echocardiography in a large group of patients with severe PAH.

METHODS

Study population. All 46 PAH patients were referred to our center for evaluation and treatment of PAH. All investigations were part of the patients’ diagnostic workup. The diagnosis of PAH was based on cardiac catheterization data, i.e., mean pulmonary arterial pressure >25 mmHg at rest. Pulmonary hypertension due to lung disease and/or hypoxemia, chronic thrombotic and/or embolic disease, or other possible causes was excluded by further diagnostic workup (ventilation-perfusion scan, chest X-ray, lung function test, high-resolution CT scan, and pulmonary angiography) according to the flowchart of Barst et al. (5). In 11 patients, PAH was associated with systemic sclerosis (CREST syndrome) on the basis of clinical findings and serology. In 35 patients, idiopathic PAH was diagnosed.

The study complies with the Declaration of Helsinki (2) and adheres to Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects of the VU University Medical Center. Written informed consent was obtained from all patients and from the 18 nonsmoking control subjects (39 ± 17 yr of age, 4 men and 14 women, 1.85 ± 0.23 m² body surface area), who had no history of cardiopulmonary disease. None of the patients had been treated for PAH, except with acenocoumarol, at the time of examination.

Cardiac catheterization. Right heart catheterization was performed in all patients, but not in control subjects, with a 7-F Swan-Ganz catheter (model 131HF7, Baxter Healthcare, Irvine, CA) within 2 days of MR imaging and transesophageal echocardiography (TEE) measurements. Cardiac output was calculated by the Fick method, and pulmonary vascular resistance was calculated using the standard formula.

MR imaging measurements. MR imaging was performed on a Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) according to the protocol described earlier (22). SV was measured using MR phase-contrast flow quantification. End diastole and end systole were defined as the maximum and minimum volumes, respectively. EDV, end-systolic volume, ejection fraction, and myocardial mass were calculated using the MR Analytical Software System.
Direct ventricular interaction was quantified by the curvature of the interventricular septum and calculated according to a formula described by Roeleveld et al. (25). A negative value of the curvature corresponds to displacement of the septum toward the LV cavity. LV filling rate was defined as the change in volume over time.

The time of maximum curvature and LV peak filling rate (PFR) were assessed and normalized to the ECG R-R interval for difference in heart rate among individuals. In a random group of five patients and five control subjects, LV filling was measured throughout diastole. Volumetric and geometric measurements were indexed.

Echocardiography. TEE was performed in 20 patients with a 5-MHz 64-element transducer (Hewlett-Packard, Andover, MA) connected to a Hewlett-Packard Sonos 2500 or 5500. The probe was positioned at the level of the left pulmonary vein and mitral valve, and flow velocity patterns were obtained using pulsed Doppler imaging. Mean peak systolic (PVFsyst), diastolic (PVFdia), and atrial reversed (PVFA) flow velocities were obtained from five consecutive beats with patients in sinus rhythm, and mitral early (E) and atrial (A) peak flows were measured. Peak pressure gradients during early diastole (ΔPpv) and atrial contraction (ΔPpa) were calculated using the modified Bernoulli equation: ΔPn = 4 × V2, where ΔPn is peak mitral valve pressure gradient and V is velocity (in m/s).

ECG analysis. The ECG records of all patients were analyzed automatically for complete or incomplete right bundle branch block (RBBB). Complete RBBB was defined as a QRS complex ≥120 ms and incomplete RBBB as a QRS complex ≥100 and ≤120 ms.

Data analysis. The SPSS 11.0 software package was used for statistical analyses, and P < 0.05 was considered statistically significant. Values are presented as means ± SD for descriptive statistics. Student’s paired t-test was performed to compare MR imaging mea-

### Table 1. Patient characteristics and catheterization data

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>No. of patients</th>
<th>iPAH</th>
<th>PHSSc</th>
<th>M/F</th>
<th>Age, yr</th>
<th>Functional status</th>
<th>6-min walk test, m</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>46</td>
<td>35</td>
<td>11</td>
<td>10/36</td>
<td>47±16</td>
<td>III-IV</td>
<td>307±150</td>
</tr>
</tbody>
</table>

Values are means ± SD. iPAH, idiopathic pulmonary arterial hypertension; PHSSc, pulmonary hypertension related to systemic sclerosis; NYHA, New York Heart Association functional classification; Pra, right atrial pressure; sPrv, systolic right ventricular (RV) pressure; dPrv, diastolic RV pressure; sPap, systolic pulmonary arterial pressure; dPap, diastolic pulmonary arterial pressure; mPap, mean pulmonary arterial pressure; Pcapw, pulmonary capillary wedge pressure; SvO2, mixed venous O2 saturation; CO, cardiac output; PVR, pulmonary vascular resistance; HR, heart rate.

![Fig. 1](http://ajpheart.physiology.org/)

**Fig. 1.** Midventricular short-axis MR images of a control subject (A–C) and a patient with severe pulmonary arterial hypertension (PAH, 76 mmHg mean pulmonary arterial pressure; D–F). Images were acquired at end diastole, end systole, and −100 ms after end systole. Temporal frames in A, B, and C are 0, 317, and 421 ms from the ECG R wave, with an R-R interval of 920 ms. Temporal frames in D, E, and F are 0, 250, and 352 ms from the ECG R wave, with an R-R interval of 640 ms. Note right ventricular wall thickening and larger lumen area in PAH patient (D–F). Note maximal leftward ventricular septal bowing in early-diastolic image (F).
Table 2. MR imaging data from control subjects and PAH patients

<table>
<thead>
<tr>
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<th>Control (n = 18)</th>
<th>PAH (n = 46)</th>
<th>P</th>
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<tr>
<td>SVI, ml/m²</td>
<td>41 ± 10</td>
<td>28 ± 13</td>
<td>&lt;0.001</td>
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<tr>
<td>HR, beats/min</td>
<td>71 ± 10</td>
<td>81 ± 16</td>
<td>&lt;0.05</td>
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<td>CI, 1 min⁻¹/m²</td>
<td>3.0 ± 0.7</td>
<td>2.0 ± 0.9</td>
<td>&lt;0.01</td>
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</tbody>
</table>

Right ventricle

- EDVI, ml/m²: 72 ± 22 vs. 96 ± 27 (P < 0.001)
- ESVI, ml/m²: 35 ± 14 vs. 70 ± 27 (P < 0.001)
- EF, %: 48 ± 10 vs. 29 ± 11 (P < 0.001)
- MI, g/m²: 22 ± 5 vs. 50 ± 13 (P < 0.001)

Left ventricle

- EDVI, ml/m²: 61 ± 14 vs. 46 ± 14 (P < 0.01)
- ESVI, ml/m²: 20 ± 6 vs. 20 ± 10 (NS)
- EF, %: 67 ± 7 vs. 56 ± 13 (P < 0.001)
- MI, g/m²: 62 ± 13 vs. 73 ± 12 (P < 0.001)
- Curvature, cm⁻¹: 0.35 ± 0.08 vs. −0.13 ± 0.15 (P < 0.001)
- PFR, ml/s: 541 ± 248 vs. 216 ± 90 (P < 0.001)
- PFR/EDVI, s⁻¹: 4.5 ± 1.5 vs. 2.7 ± 1.1 (P < 0.001)
- TPR: 0.55 ± 0.08 vs. 0.59 ± 0.11 (NS)

Values are means ± SD. SVI, stroke volume index; CI, cardiac index; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; MI, myocardial mass index; curvature, interventricular septum curvature [negative value indicates curvature towards left ventricular (LV) cavity]; PFR, LV peak filling rate; PFR/EDVI, LV PFR normalized for LV end-diastolic volume; TPR, time to LV PFR normalized to R-R interval; NS, not significant.

Measurements of the PAH group with those of the control group. Linear regression analyses were performed to assess the correlations between catheterization, MR imaging, and TEE data.

RESULTS

Patient characteristics and hemodynamic variables are shown in Table 1. With respect to cardiac catheterization and MR imaging measurements, there were no statistically significant differences between patients diagnosed as idiopathic PAH and PAH related to systemic sclerosis. In five patients, the ECG could not be analyzed. The PAH group had a mean pulmonary arterial pressure of 55 ± 16 mmHg, a normal pulmonary capillary wedge pressure (7 ± 5 mmHg), and elevated right atrial pressure (10 ± 5 mmHg). There was no significant difference in heart rate during cardiac catheterization (81 ± 16 beats/min), MR image acquisition (82 ± 15 beats/min), and TEE (88 ± 16 beats/min). All patients were in sinus rhythm during the investigations.

MR imaging measurements. Midventricular end-diastolic, end-systolic, and early diastolic short-axis cine MR images for individuals matched for age (35 yr), gender (female), and body surface area (1.8 m²) are shown in Fig. 1. The images of the PAH patient show distinct RV wall thickening and a larger RV lumen area in end diastole and end systole than the images of the control subject. End-diastolic and end-systolic LV lumen area are smaller in the PAH patient than in the control subject. The interventricular septum bends toward the LV during contraction and is maximal in early diastole (at 352-ms trigger delay from the R wave of the ECG).

The parameters measured with MR imaging are summarized in Table 2. SV was decreased in PAH patients compared with control subjects. Although heart rate was increased, cardiac index was lower. Furthermore, PAH patients had, on average, a dilated hypertrophied RV accompanied by a decrease in RV ejection fraction. For the LV, EDV was decreased in PAH patients compared with control subjects, end-systolic volume was within the normal range, and ejection fraction was lower in PAH patients than in control subjects. In all control subjects and four PAH patients, the position of the interventricular septum remained unaltered during the cardiac cycle, and in two PAH patients, the septum flattened during diastole.

To investigate the influence of LVEDV, RVEDV, and RV afterload on SV, a correlation analysis was performed. Within the PAH patient group, SV was related to LVEDV (r = 0.62, P < 0.001), but not to RVEDV (Fig. 2). Furthermore, SV was not correlated to mean pulmonary arterial pressure (r = −0.24, P = not significant).

LV PFR was decreased in PAH patients compared with control subjects (Fig. 3). The LV volume curve shows that PAH patients start LV filling with approximately the same LVEDV fraction as control subjects. However, in PAH patients, early filling is slower: they reach 75% of LVEDV in ~80% of the R-R interval, whereas control subjects reach 75% of LVEDV only in 60% of the R-R interval. In PAH patients, LV filling is a more gradual process; in control subjects, after initial rapid filling, a plateau is reached in mid-diastole (70–85% of the R-R interval). The same phenomena are more explicitly shown in Fig. 3B: PFR in PAH patients is about two-thirds of that in control subjects. However, in mid-diastole (70–85% of the R-R interval), LV filling rate is greater in PAH patients than in control subjects. In PAH patients, the time onset of PFR occurred after the time of maximal leftward septum curvature. For the total patient group, the time of maximal curvature was 389 ± 92 ms after the R wave of the ECG, whereas the time to PFR was 425 ± 78 ms (P < 0.01). The filling rate at the time of maximal septum curvature (142 ± 98 ml/s) was correlated...
to septum curvature \( (r = 0.64, P < 0.01) \) and to LVEDV \( (r = 0.65, P < 0.001) \).

In a subset of five PAH patients and five control subjects, LV filling was measured throughout diastole, thus including the last part of diastole until the next heartbeat. From these data, the relative contribution of the atrial contraction can be quantified more explicitly. Figure 4 presents the diastolic LV volume curve and the corresponding time derivative, LV filling rate. In PAH patients, LV filling was slow and gradual (Fig. 4A). In control subjects, LV volume increased rapidly in early diastole, reached a plateau in middiastole, and finally increased rapidly because of atrial contraction. Figure 4B shows the slow and gradual filling in early and middiastole in PAH patients. However, in the late-diastolic phase (80–100% of the R-R interval), the filling rate of PAH patients exceeds that of control subjects, and the contribution of the atrial contraction is more important in the LV filling process.

**TEE measurements.** TEE measurements were performed in 20 PAH patients to assess left atrial filling. The ratio of early mitral peak flow \( (E = 54 \pm 15 \text{ cm/s}) \) to atrial mitral peak flow \( (A = 67 \pm 15 \text{ cm/s}) \) was reversed \( (E/A = 0.81 \pm 1.01) \). The calculated pressure gradient during early mitral peak flow \( (\Delta P_E) \) was 1.16 \( \pm 0.10 \) and 1.77 \( \pm 0.09 \) mmHg during atrial peak flow \( (\Delta P_A) \). Compared with the literature \((16, 18)\), PVF_{syst} (59 \pm 16 \text{ cm/s}), PVF_{dia} (42 \pm 10 \text{ cm/s}), and PVF_{syst/dia} (1.5 \pm 0.5) showed no abnormalities. Peak PVF_{syst} (35 \pm 10 \text{ cm/s}) was increased. Linear regression analysis showed that PVF_{syst} was not related to SV or mean pulmonary arterial pressure, and there was no significant correlation between PVF_{dia} and PFR. Furthermore, PVF_{syst} and PVF_{dia} were not related to LVEDV.

**DISCUSSION**

The contribution of the LV to heart failure in PAH patients is unclear and controversial. In this study, we have demonstrated that the reduction of SV in PAH patients is related to the filling state of the LV at end diastole, which is reduced because of an abnormal filling pattern. The main mechanism of LV underfilling was leftward interventricular septum displacement.

**Series vs. direct ventricular interaction.** Impaired LV filling in RV pressure overload might be the result of two mechanisms: series and direct interaction \((4, 6, 13)\). Under normal conditions, series interaction, i.e., increased RV afterload leading to a decrease in RV output and, thus, to a decrease in left atrial and LV filling, is the dominant physiological mechanism. In direct interaction, substantial RV dilatation and hypertrophy might compress the LV, thereby impairing LV filling. Either mechanism results in a reduced LVEDV and SV. In PAH patients, series and direct interaction might occur concomitantly. Although our results cannot distinguish between these two mechanisms completely, the data provide several arguments that direct ventricular interaction contributes significantly to LV filling impairment: 1) In PAH patients, early diastolic filling rate at the time of maximal septum curvature was closely related to interventricular septum curvature. 2) Early diastolic filling rate at the time of maximal septum curvature was correlated to LVEDV. Argument 2 opposed the hypothesis that early diastolic filling is less important, because early filling impairment could be compensated toward end diastole. 3) Left atrial filling was normal and not related to LVEDV and, thus, could not explain the impaired filling or underfilling of the LV.

**Mechanisms of direct ventricular interaction.** Two mechanisms of direct ventricular interaction have been identified from previous research: 1) direct ventricular interaction mediated by the pericardium and 2) interventricular asynchrony. Because both ventricles are enclosed within a relatively nondistensible pericardium, increases in RV volume may occur at the expense of LV volume \((6)\). A reduction of RV volume...
paradoxically increases LV volume (3). Interventricular asynchrony describes the effect of a slow, prolonged decay of RV pressure, causing higher pressure in the RV than in the LV in early diastole (27).

**Pericardium.** Animal studies by Elzinga et al. (13) provided early evidence that the pericardium plays an important role in right-to-left ventricular interaction. Recently, by constricting the main pulmonary artery, Baker and Belenkie and their co-workers (4, 7) studied the effect of acute RV pressure overload on LV output in dog hearts in situ. Opening of the pericardium in the animal models facilitated LV filling, leading to an increase of LVEDV and, consequently, cardiac output. However, in contrast with the animal studies, RV pressure overload in the PAH patients developed gradually and was chronic, rather than acute. Pericardiotosmes performed by Blanchard and Dittrich (8) in patients with chronic RV pressure overload due to pulmonary emboli showed that the pericardium has little influence on cardiac and interventricular septum deformations, and it was concluded that the human pericardium is capable of adapting over time to cardiac geometry alterations. For this reason, it is unclear whether pericardial constraint plays a significant role in mediating direct ventricular interaction in PAH patients.

**Ventricular asynchrony.** Evidence that interventricular asynchrony might play a role in PAH can be obtained from the ECG, which frequently showed an complete or incomplete RBBB configuration in PAH. Furthermore, research on the LV in heart failure patients showed interventricular asynchrony in a substantial proportion of these patients, regardless of the QRS duration (14). However, in only a limited number of studies was evidence found for mechanical interventricular asynchrony in PAH.

Stojnic et al. (27) showed that, in addition to a reduction of early LV diastolic filling velocity and an increase in LV filling velocity during atrial contraction, the time of pressure decline was prolonged in the RV compared with the LV. They concluded that diastolic LV filling impairment is mediated by deformation of the interventricular septum toward the LV cavity and is caused by a right-to-left ventricular asynchrony. Invasive data from our own group showed right-to-left ventricular asynchrony (25) in PAH patients. Synchronous RV and LV pressure measurements in PAH patients showed a significant right-to-left transseptal pressure gradient at the time of maximal leftward septal displacement measured by MR imaging. Recently, tissue Doppler imaging in patients with pulmonary hypertension provided circumstantial evidence of mechanical asynchronous between the RV free wall and the interventricular septum and between the RV and LV free wall (19, 20). These data suggest that ventricular mechanical asynchrony might play a role in mediating direct ventricular interaction in PAH patients.

**Study limitations.** The major limitation of this study is that although we found evidence that direct ventricular interaction contributes significantly to the hemodynamic deterioration of PAH patients, the separate contribution of series and direct interaction to LV filling could not be quantified. Furthermore, we were not able to measure pulmonary venous flow and LV filling simultaneously. However, neither MR imaging nor TEE is able to measure pulmonary venous flow and LV filling simultaneously.

In conclusion, in PAH, direct ventricular interaction mediated by the interventricular septum impairs LV diastolic filling, which results in an underfilling of the LV. The close relation between LVEDV and SV in the absence of such a relation for RVEDV provides evidence that underfilling of the LV contributes to a decrease in SV.

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