Magnetic Resonance–Derived 3-Dimensional Blood Flow Patterns in the Main Pulmonary Artery as a Marker of Pulmonary Hypertension and a Measure of Elevated Mean Pulmonary Arterial Pressure

Gert Reiter, PhD*; Ursula Reiter, PhD*; Gabor Kovacs, MD; Bernhard Kainz, MSc; Karin Schmidt, MD; Robert Maier, MD; Horst Olschewski, MD; Rainer Rienmueller, MD

Background—Pulmonary hypertension is a disease characterized by an elevation in pulmonary arterial pressure that is diagnosed invasively via right heart catheterization. Such pathological altered pressures in the pulmonary vascular system should lead to changes in blood flow patterns in the main pulmonary artery.

Methods and Results.—Forty-eight subjects (22 with manifest pulmonary hypertension, 13 with latent pulmonary hypertension, and 13 normal control subjects) underwent time-resolved 3D magnetic resonance phase-contrast imaging of the main pulmonary artery. Velocity fields that resulted from measurements were calculated, visualized, and analyzed with dedicated software. Main findings were as follows: (1) Manifest pulmonary hypertension coincides with the appearance of a vortex of blood flow in the main pulmonary artery (sensitivity and specificity of 1.00, 95% confidence intervals of 0.84 to 1.00 and 0.87 to 1.00, respectively), and (2) the relative period of existence of the vortex correlates significantly with mean pulmonary arterial pressure at rest (correlation coefficient of 0.94). To test the diagnostic performance of the vortex criterion, we furthermore investigated 55 patients in a blinded prospective study (22 with manifest pulmonary hypertension, 32 with latent pulmonary hypertension, and 1 healthy subject), which resulted in a sensitivity of 1.00 and specificity of 0.91 (95% confidence intervals of 0.84 to 1.00 and 0.76 to 0.98, respectively). Comparison of catheter-derived mean pulmonary artery pressure measurements and calculated mean pulmonary artery pressure values resulted in a standard deviation of differences of 3.6 mm Hg.

Conclusions—Vortices of blood flow in the main pulmonary artery enable the identification of manifest pulmonary hypertension. Elevated mean pulmonary arterial pressures can be measured from the period of vortex existence. (Circ Cardiovasc Imaging. 2008;1:23-30.)

Key Words: hypertension, pulmonary ▪ magnetic resonance imaging ▪ blood flow ▪ blood pressure ▪ catheterization

Pulmonary hypertension (PH) is a disease characterized by an elevation in pulmonary arterial pressure that manifests in its early stages during exercise. The diagnosis of PH is established when mean pulmonary artery pressure (mPAP) measured invasively by right heart catheterization exceeds 25 mm Hg at rest (manifest PH) or 30 mm Hg with exercise (latent PH).1

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Noninvasive imaging modalities such as echocardiography and MRI have been used to predict PH. Evaluation of the regurgitant tricuspid jet velocity2-3 and septal bowing4,5 have been used to estimate systolic pulmonary artery pressure, which is related to mPAP,6 the quantity used to define PH. Parameters that directly correlate with mPAP or pulmonary vascular resistance have been related to the shortened acceleration times of blood flow in the right ventricular outflow tract.2,3,7-11 However, the overall applicability and accuracy of the above-described methods are controversial.12-16

Additionally, various authors10,11,17,18 have observed spatially highly inhomogeneous cross-sectional flow profiles and fractions of retrograde flow during systole and diastole in the main pulmonary artery in patients with PH. This was not observed in normal subjects. Even though no correlation between retrograde flow and the degree of PH was found,10,11 these observations suggest PH-caused flow topologies in the
right ventricular outflow tract. Neither echocardiography nor conventional magnetic resonance (MR) through-plane cine phase-contrast imaging appears to be an appropriate technique for a detailed investigation of this assumption, but the MR phase-contrast method can be used to assess time-resolved 3D velocity information of blood flow. Complex cardiovascular flow topologies have been studied with this technique and various adequate visualization tools. The purpose of the present study was to investigate characteristic differences in 3D blood flow patterns in the main pulmonary artery of patients with manifest PH, patients with latent PH, and subjects without PH to determine the blood flow pattern–related measures for mPAP and PH.

Methods

Subjects

The present study was approved by the local ethics review board, and all subjects gave written informed consent. Subjects with contraindications to MR were not enrolled. Patients with suspected or known PH were sent consecutively to MRI after right heart catheterization and MR investigation within 6.4 days. A total of 42 patients were included in the exploratory study. Thirty-eight patients (Table 1) were investigated by right heart catheterization and MR phase-contrast imaging of the pulmonary artery. Four patients were excluded from evaluation because of air trapping during ergometry (1 patient), missing catheter data during exercise (1 patient), and incomplete MR investigation (2 patients). Patients underwent catheter and MR investigation within 2.8±4.1 days.

In addition, 10 healthy volunteers with no history of cardiovascular or pulmonary disease (Table 1) underwent MR phase-contrast imaging of the pulmonary artery. Conventional ECG-gated cine MRI was used to exclude valvar regurgitations and to confirm normal left and right ventricular function.

Sixty patients were included in the explorative prospective study. Five patients were excluded from evaluation because of missing catheter data during exercise (3 patients) and incomplete MR investigation (2 patients). The remaining 55 patients (Table 2) underwent catheter and MR investigation within 6.4±6.8 days. Generally, no clinically important change in drug treatment or disease state occurred between the 2 examinations.

Right Heart Catheterization and Patient Classification

Right heart catheter examinations were performed with a 7F quadruple-lumen, balloon-tipped, flow-directed Swan-Ganz catheter by the transjugular approach (Baxter Healthcare Corp, Irvine, Calif). Parameters that were obtained included mPAP. Patients with no manifest PH underwent a symptom-limited exercise test on a cycle ergometer in a semisupine position with a right heart catheter in place. A standard protocol with a 25-W increase every 2 minutes was used, and mPAP was measured at each stage of exercise.

On the basis of the results of the catheterization, patients were assigned to 3 groups: manifest PH (clinical classification; see online Data Supplement), latent PH, and subjects without PH. Patients without PH and healthy volunteers were assigned to the control group.

MR Imaging

ECG-gated MR imaging was performed on a 1.5-T field-strength scanner (Magnetom Sonata; Siemens, Erlangen, Germany) with a 6-channel cardiac-array coil. All subjects were investigated in the supine position. Velocity field measurements were part of a comprehensive protocol that included retrospectively ECG-gated cine gradient echo imaging with steady-state free precession in the standard cardiac views (3- and 4-chamber views, right and left ventricular 2-chamber views, right and left ventricular outflow tract, and short-axis planes) to verify in particular the normal cardiac function of healthy volunteers.

To acquire velocity field data, the main pulmonary artery was covered with 3 to 5 gapless slices in the right ventricular outflow tract orientation by 2D, retrospectively ECG-gated, spoiled gradient echo-based phase-contrast sequences with a 4-point velocity encoding scheme. Velocity encoding was set to 90 cm/s in all directions and adapted in the case of aliasing in the main pulmonary artery. Further parameters of the protocol used in the present study were a 234 to 276×340-mm^2 field of view, 96 to 114×192 matrix (interpolated to 192 to 228×384 matrix), 15° flip angle, 89-ms temporal resolution (3 segments, 7.5-ms repetition time), reconstruction of 20 cardiac phases, 4.1-ms echo time, and 451 Hz/pixel bandwidth. GRAPPA (generalized auto-calibrating partially parallel acquisition) with a parallel acquisition factor of 2 and an average of 24 reference lines was used to keep the average imaging time per slice at 22 heartbeats, which allowed the performance of measurements during breath-holds in inspiration. For patients who were not able to hold their breath well, the investigation was performed under free-breathing conditions with 3-fold averaging to suppress breathing artifacts.

Image Processing and Analysis in the Exploratory Study

Calculation of velocity fields from the acquired phase images, their visualization, and analysis thereof were performed with dedicated software (4D Flow, Siemens). This software provides visualization of each velocity vector as a color-encoded vector in 3D space: The length and color of the vector indicate the magnitude of velocity, whereas the direction of the vector represents the direction of the

### Table 1. Study Population: Exploratory Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Manifest PH (n=22)</th>
<th>Latent PH (n=13)</th>
<th>Patients Without PH (n=3)</th>
<th>Healthy Volunteers (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female/male), n</td>
<td>10/12</td>
<td>11/2</td>
<td>2/1</td>
<td>6/4</td>
</tr>
<tr>
<td>Age, y</td>
<td>61±10</td>
<td>66±6</td>
<td>55±9</td>
<td>26±7</td>
</tr>
<tr>
<td>mPAP at rest, mm Hg</td>
<td>41±13</td>
<td>16±4</td>
<td>12±2</td>
<td>...</td>
</tr>
<tr>
<td>mPAP during exercise, mm Hg</td>
<td>...</td>
<td>39±6</td>
<td>23±5</td>
<td>...</td>
</tr>
</tbody>
</table>

Values for age and mPAP are given as mean±SD.

### Table 2. Study Population: Blinded Prospective Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Manifest PH (n=22)</th>
<th>Latent PH (n=32)</th>
<th>Patients Without PH (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female/male), n</td>
<td>12/10</td>
<td>27/5</td>
<td>1/0</td>
</tr>
<tr>
<td>Age, y</td>
<td>67±13</td>
<td>56±11</td>
<td>51</td>
</tr>
<tr>
<td>mPAP at rest, mm Hg</td>
<td>39±10</td>
<td>17±3</td>
<td>14</td>
</tr>
<tr>
<td>mPAP during exercise, mm Hg</td>
<td>...</td>
<td>40±6</td>
<td>25</td>
</tr>
</tbody>
</table>

Values for age and mPAP are given as mean±SD.
velocity. Velocity vectors are projected onto (opaque) corresponding anatomic phase-contrast images. The suppression of noisy pixels (by a signal-to-noise threshold in the anatomic phase-contrast images) and an adjustable thinning out of the velocity vector fields enable interpretation of the blood flow patterns within the anatomic context (Figure 1).

In addition to determination of the systolic acceleration time (time difference between maximum and onset of pulmonary outflow), systolic ejection time (time difference between onset and end of pulmonary outflow), maximum blood flow velocity above the pulmonary valve at maximum pulmonary outflow, and maximum velocity above the pulmonary valve at its closure, 3 features of the flow field in the main pulmonary artery were investigated in more detail. First, the existence of vortices in the primary flow direction in the main pulmonary artery was investigated. In general, a vortex is defined as a ring- or spiral-shaped motion of fluid or gas. In terms of the vector field representation of blood flow, this means the formation of concentric ring- or spiral-shaped curves in the main pulmonary artery to which velocity vectors are tangential. A vortex in the primary flow direction in the main pulmonary artery means that there is forward and backward flow through a cross section of the main pulmonary artery through the center of the vortex (Figure 2A). Both the existence of such a vortex and the relative period of existence ($t_{\text{vortex}}$) of a nonvalvular vortex in the main pulmonary artery (number of cardiac phases with vortex divided by the total number of imaged cardiac phases) were determined visually and independently by 2 observers.

The second specific feature investigated was the diastolic streamline of blood flow upward along the anterior wall of the main pulmonary artery. In terms of the vector field representation of blood flow, this means that blood moves continuously up the anterior wall of the main pulmonary artery during diastole (Figure 2B). The relative period of existence of diastolic streamlines ($t_{\text{streamlines}}$; the number of cardiac phases after pulmonary valve closure with streamlines along the main pulmonary artery divided by the total number of imaged cardiac phases) was determined visually and independently by 2 observers.

Third, a location index was introduced to characterize the velocity profile of blood flow above the pulmonary valve in the anterior-posterior direction. Depending on whether the maximum velocity through the cross section of the main pulmonary artery appeared in the anterior, middle, or posterior third of the vessel, the location index was set to +1, 0, or −1, respectively (Figure 2C). In case of equal maximum velocities in multiple sections, the location index was set to the average value of the corresponding thirds (maximum velocities in the section thirds were interpreted as being different if their difference exceeded a typical pixel-by-pixel variation of velocities). The location index was determined in the cardiac phase with maximum pulmonary outflow, as well as in the cardiac phase of pulmonary valve closure.

Image Processing and Analysis in the Blinded Prospective Study

After analogous postprocessing of MR data, the existence of a vortex and its relative period of existence ($t_{\text{vortex}}$) were determined by a single observer blinded to the catheter results.

Statistical Analysis

Statistical analysis was performed with NCSS (J. Hintze, NCSS, LLC, Kaysville, Utah). Mean values are given together with standard deviations (SDs). Group means of the manifest PH, latent PH, and control groups were compared via 1-way analysis of variance and Tukey-Kramer multiple-comparison test. We generally set the significance level to 0.05. For $t_{\text{vortex}}$, we additionally performed an analysis of covariance with age as the covariate.

A $\chi^2$-coefficient was calculated to specify the interrater agreement with respect to the existence of a vortex. To characterize the diagnostic accuracy of predicting manifest PH via vortex formation,
sensitivity and specificity were determined together with their 95% confidence intervals.

Interobserver variability in the determination of relative periods of the existence of vortices and streamlines was specified by within-subject SDs (calculated by variance component analysis) and intra-class correlation coefficients. Mean values of the data of the 2 observers were used to study differences between group means and to analyze the relationship between periods of existence of vortices and mPAP by correlation and regression analysis. For the blinded prospective study, comparison of mPAP values measured by catheter and calculated by the regression equation obtained in the exploratory study was performed by Bland-Altman analysis.

The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Description of Flow Patterns

During systolic acceleration of blood flow through the pulmonary valve, the flow patterns in the manifest PH, latent PH, and control groups were similar. Blood flow velocities were uniformly distributed across the cross section of the main pulmonary artery. Their primary direction was parallel to the vessel wall. Velocities increased from one cardiac phase to the next until a maximum was reached (Figure 1A through 1C). Although mean maximal peak velocities did not differ significantly between the groups (79±21 cm/s in manifest PH, 74±11 cm/s in latent PH, and 77±11 cm/s in the controls), the mean acceleration time was significantly shorter in the manifest PH group and was not significantly different between the latent PH and control groups (mean acceleration times of 107±25 ms in manifest PH, 133±24 ms in latent PH, and 141±26 ms in the control group; P=0.0006 for F test).

After maximum outflow, blood flow velocities gradually decreased until the pulmonary valve closed. No significant differences in total ejection times were observed (374±54 ms in manifest PH, 365±64 ms in latent PH, and 392±60 ms in controls). During the deceleration period, the flow profiles changed from rather homogeneous velocity distributions across the cross section of the main pulmonary artery to profiles with higher velocities at the anterior wall (Figure 1D through 1F): Although the position indexes for velocity profiles above the pulmonary valve were 0.1±0.5, 0.2±0.3, and 0.1±0.3 at maximal outflow, they were 1.0±0.1, 1.0±0.0, and 1.0±0.0 at valvular closure in the manifest PH, latent PH, and control groups, respectively.

There was, however, a structure that occurred only in the patients with manifest PH: A vortex in the primary flow direction was formed, typically below the right pulmonary artery at the posterior wall of the main pulmonary artery (Figure 1D). In 2 patients with high mPAP, vortex formation had already begun in the acceleration phase. The rotational direction of the vortex was always more distal from the right ventricle from anterior to posterior and more proximal to the right ventricle from posterior to anterior (as drawn in Figure 2A and visible in Figure 1D and 1G). During deceleration of blood flow through the pulmonary valve, the region covered by the vortical motion typically increased, and the center of the vortex moved in the main pulmonary artery.

After closure of the pulmonary valve, blood flow in the main pulmonary artery did not stop immediately. Mean maximum velocities above the pulmonary valve were 28±9 cm/s in manifest PH, 21±6 cm/s in latent PH, and 18±5 cm/s in controls, and the differences between manifest PH and both latent PH and controls were significant (P=0.0012 for F test). In all subjects, blood flow was observed spatially continuously up the anterior wall of the main pulmonary artery after pulmonary valve closure; in the case of manifest PH, this flow was accompanied by the rotational flow of the vortex (Figure 1G through 1I). The mean relative periods of the existence of these streamlines (tstreamlines) were 0.42±0.15 in manifest PH, 0.29±0.07 in latent PH, and 0.15±0.05 in controls (Figure 3) and differed significantly between all
groups ($P<0.0001$ for F test). Age dependence was not significant ($P=0.10$ in analysis of covariance). Interobserver variability of the measurement of $t_{\text{streamlines}}$ was 0.04, and the intraclass correlation coefficient was 0.93.

**Vortices and mPAP**

For all 22 patients in the manifest PH group, the described vortex was found, whereas this flow pattern was not detected in any of the subjects without manifest PH ($\kappa$-index for evaluating twice the existence of vortices was 1.00). The use of the existence of vortices in the primary flow direction in the main pulmonary artery as a diagnostic criterion for the presence of manifest PH resulted in a sensitivity of 1.00 and a specificity of 1.00, with 95% confidence intervals of 0.84 to 1.00 and 0.87 to 1.00, respectively.

The correlation coefficient between $t_{\text{vortex}}$ and mPAP of patients with manifest PH was 0.94 (95% confidence interval 0.85 to 0.97). The corresponding linear regression equation was mPAP (in millimeters mercury) $= 16.7 + 58.0 \cdot t_{\text{vortex}}$, with an SD of 4.8 mm Hg from the regression line (Figure 4A). Interobserver variability of the measurement of the relative period of existence of the vortex ($t_{\text{vortex}}$) in the primary flow direction was 0.03, and the intraclass correlation coefficient was 0.97.

In the blinded prospective study, all 22 patients with manifest PH had a vortex of blood flow in the main pulmonary artery, whereas 30 patients without manifest PH had none. In 3 patients with latent PH, a vortex was detected (mPAP at rest of 21, 21, and 23 mm Hg with $t_{\text{vortex}}$ of 0.05, 0.05, and 0.25, respectively). Consequently, the vortex criterion for the presence of manifest PH led to the same sensitivity as the exploratory study. Specificity obtained was 0.91 (95% confidence interval 0.76 to 0.98). The comparison of mPAP measured by catheter and mPAP calculated by the regression equation resulted in a nonsignificant bias of −0.2 mm Hg, an SD of differences of 3.6 mm Hg, and 95% limits of agreement of −7.3 and 6.9 mm Hg, respectively (Figure 4B).

**Discussion**

The main findings of the exploratory study were as follows: (1) Manifest PH coincides with the appearance of a vortex of blood flow in the main pulmonary artery; (2) the relative period of existence of the vortex ($t_{\text{vortex}}$) correlates with mPAP at rest, with a high correlation coefficient of 0.94 in patients with manifest PH; and (3) the relative period ($t_{\text{streamlines}}$) of continuous diastolic flow upward along the anterior wall of the main pulmonary artery differed significantly between patients with manifest PH, those with latent PH, and controls.

**Vortex Formation**

Elevated mPAP in manifest PH is accompanied by an anomalous time course of pulse pressure,2,24 and the pressure gradient between the right ventricle and the pulmonary artery becomes zero and positive earlier during systole.25,26 This fact explains the reduced acceleration time in patients with manifest PH, which is the rationale for attempts to assess mPAP and PH directly by noninvasive methods.2,3,7–11 We also observed reduced acceleration times in patients with manifest PH.

Other features of the anomalous time course of the pulse pressure of patients with manifest PH are consistent with the observed vortex formation: The results for the position index
and mPAP, but a larger group of patients with manifest PH would be needed to compare different model equations statistically.

**Diastolic Streamlines**

Apart from the vortex pattern in the main pulmonary artery, the study showed significant differences in diastolic streamlines of blood flow in the manifest PH, latent PH, and control groups. Given the interpretation of the vortex as a “reservoir of kinetic energy,” the difference between manifest PH and the other groups is not surprising. It is, however, surprising that the relative period of \( t_{\text{streamlines}} \) of continuous diastolic flow upward along the anterior wall of the main pulmonary artery differed significantly in an investigation at rest between patients with latent PH and controls and therefore allows identifying latent PH. In accordance with the explanation of the phenomenon for manifest PH, the prolonged \( t_{\text{streamlines}} \) reflects changes in pulmonary vascular resistance and compliance of the pulmonary vasculature that are too small to lead to vortex formation, as in manifest PH. A possible limitation of the study is that a portion of the \( t_{\text{streamlines}} \) difference between patients with latent PH and control subjects may be attributed to the different age distributions in these groups, although age was not significant as a covariate: Although normal mPAP does not depend significantly on age, normal pulmonary vascular resistance \(^{31}\) and compliance \(^{28}\) do.

**Retrograde Flow**

In contrast to previous studies that used MR phase-contrast measurements to study PH, \(^9\) - \(^{11}\) we acquired time-resolved 3D flow information in the main pulmonary artery to analyze flow topology–related quantities. For patients with manifest PH, increased retrograde flow at the posterior wall of the main pulmonary artery \(^ {10,11,17,18}\) can be explained immediately by the existence of a vortex. We could not define a general rule for the motion of the vortex throughout the cardiac cycles which explains why no relation between the retrograde through-plane velocities and mPAP was found in previous studies.\(^ {10,11}\)
Error Estimate and Verification by the Blinded Prospective Study

As mentioned, part of the SD of 4.8 mm Hg in the linear regression determination of mPAP via t_{vortex} resulted from the MR sequence technique and the method of vortex determination: We used a moderate time resolution to keep the imaging time short and interpolated the retrospectively acquired data to images of 20 cardiac phases. Consequently, a difference of 1 cardiac phase in the determination of t_{vortex} or t_{realtime} corresponded to at least 5% of the RR interval, and the minimal difference in mPAP that could be resolved with this time resolution was 2.9 mm Hg.

The color-encoded vector field representation of measured velocity fields was appropriate for the interpretation of blood flow patterns. The existence of vortices and streamlines was determined visually with excellent interobserver agreement, which might decrease if catheter results are unknown to the observers. However, the variability of 3% of the RR interval resulting from the catheter measurements could be explained fully.

To validate the findings with regard to vortices of blood flow, a blinded prospective study was performed. Within confidence limits, this study reproduced the results of the exploratory study. Nevertheless, the appearance of vortices in 3 patients with latent PH should be discussed. Whereas the large deviation of measured and calculated mPAP for 1 patient was probably due to physiological variability (~8.2 mm Hg, Figure 4B), 2 patients with a t_{vortex} of 0.05 illustrate a problem associated with the moderate time resolution of MR measurements: Short-living vortices might be missed, and these vortices might correspond to mPAP values slightly below 25 mm Hg according to the linear regression equation (calculated for mPAP values above 25 mm Hg; Figure 4A).

In summary, 3D visualization of blood flow patterns in the main pulmonary artery via MR phase-contrast measurements is a promising tool for noninvasive detection and understanding of PH. It allows the identification of manifest and latent PH. Elevated mPAP can be determined with physical accuracy by measuring the period of existence of the vortex associated with PH.

Disclosures

Dr Gert Reiter is employed by Siemens Medical Solutions. The remaining authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Pulmonary hypertension is associated with a poor prognosis. Currently, the only established method to diagnose pulmonary hypertension is to directly measure pulmonary arterial pressure on right heart catheterization. We present a new method to measure elevated mean pulmonary arterial pressure noninvasively by magnetic resonance velocity imaging. Our findings suggest that (1) manifest pulmonary hypertension coincides with the appearance of a vortex of blood flow in the main pulmonary artery; (2) the relative period of existence of this vortex correlates in a highly significantly manner with mean pulmonary arterial pressure; and (3) the relative period of continuous antegrade diastolic flow along the anterior wall of the main pulmonary artery is significantly prolonged in patients with latent pulmonary hypertension compared with controls. These findings suggest that flow patterns in the main pulmonary artery allow not only the identification of manifest and latent pulmonary hypertension but also the measurement of elevated mean pulmonary arterial pressures.
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