Noninvasive assessment of pulmonary arterial hypertension by MR phase-mapping method

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Laffon, Eric, François Laurent, Virginie Bernard, Laurent de Boucaud, Dominique Ducassou, and Roger Marthan. Noninvasive assessment of pulmonary arterial hypertension by MR phase-mapping method. J Appl Physiol 90: 2197–2202, 2001.—We describe a magnetic resonance (MR) imaging method that emphasizes pressure wave velocity to noninvasively assess pulmonary arterial hypertension. Both the blood flow and the corresponding vessel cross-sectional area (CSA) were measured by MR phase mapping in the main pulmonary artery (MPA) in 15 patients. MPA pressures were also measured, in the same patients, by right-side heart catheterization. Two significant relationships were established: 1) between the pressure wave velocity in the MPA and the mean pressure in the MPA (Ppa) writing pressure wave velocity = 9.25 Ppa – 202.51 (r = 0.82) and 2) between the ratio of pressure wave velocity to the systolic blood velocity peak in the MPA (R) and the mean pressure in the MPA writing R = 0.68 Ppa – 4.33 (r = 0.89). Using these relationships, we estimated two pressure values to frame the actual Ppa value in each patient from the present series with a reasonable reliability percentage (87%).

RIGHT-SIDE HEART CATHETERIZATION is the gold standard to measure blood pressure in the main pulmonary artery (MPA) as well as to evaluate its increase in case of pulmonary arterial hypertension (PAH) (17). However, this technique is invasive and, therefore, alternative noninvasive methods would be of great clinical interest. In this connection, different hemodynamic parameters of pulmonary circulation such as mean, systolic, and diastolic pressures in the MPA have been studied by using focused echocardiographic Doppler examination (7, 18). Also, magnetic resonance (MR) imaging method that emphasizes pressure wave velocity to the maximal blood velocity (c) in the tuning of the right cardiovascular system (12). This hemodynamic tuning means that the right cardiovascular system is likely optimized to lower the pressure wave variations (from magnitude images) related to pressure variations and blood flow (from phase images), which then appeared coupled. The coupling optimization, and hence the resonance, of the right cardiovascular system was related to an appropriate timing of the reflected pressure waves that were created at the pulmonary impedance, thereby highlighting the major role of the pressure wave velocity in the system hemodynamics.

The aim of this work was to determine whether the pressure wave velocity (c), or the ratio (R) of the pressure wave velocity to the maximal blood velocity (ΔU), assessed by velocity-encoded imaging within a single slice, could estimate the value of the mean blood pressure in the MPA (Ppa). Patients with right-side heart catheterization were selected, and values of the mean pressure measured in the MPA were compared with those provided by MR phase mapping. The proposed method indicates that the Ppa estimate can be given with a reasonable reliability percentage with two values framing the actual Ppa value.

THEORY

A previous study carried out in healthy volunteers has highlighted the role of the pressure wave velocity (c) in the tuning of the right cardiovascular system (12). It is given by the formula

\[ c = \left(\frac{S}{\rho C}\right)^{1/2} \quad (1) \]

with \( C = \Delta S/\Delta P \) (2)

where \( S \) is the vessel (mean) CSA of the MPA, \( \rho \) is the blood volumic mass (1,060 kg/m³), and \( C \) is the vessel compliance. \( \Delta S \) is the difference between maximal and

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minimal CSA values measured throughout the cardiac cycle, and $\Delta P$ is the pulse pressure, i.e., the difference between the systolic and diastolic pressures in the MPA.

In the present work, it has first been assumed that pressure wave velocity would be of value to assess PAH because it has been shown, in healthy volunteers, that the MR phase-mapping technique could evidence a significant increase in pressure wave velocity with volunteer age (12). Hence, considering that an increase in blood pressure would distend the vessel (increasing $S$) (5) and that this increase would also lower the vessel distensibility (lowering $C$) (16), it was assumed that pressure wave velocity should significantly increase in the case of PAH, according to Eq. 1. However, although pressure wave velocity is related to age (12), neither $C$ nor $S$, which both are involved in the calculation of $c$, were found to be related to age. Consequently, this observation led us to examine alternative parameters, in combination with $c$, that could better assess $Ppa$.

Among those, the ratio ($R$) of pressure wave velocity in the MPA to $\Delta U$ at the systolic peak

$$ R = \frac{c}{\Delta U} \quad (3) $$

was retained for the following reason: in case of PAH, pressure wave velocity is likely to increase, whereas $\Delta U$ is likely to decrease (because of an increase in $S$).

**MATERIALS AND METHODS**

**Ppa estimation method.** The principle of the method is to use an experimental graph that significantly correlates pressure wave velocity or $R$ with $Ppa$. The first step of the work was to establish such graphs. In each patient, pressure wave velocity and $R$ were obtained from both MR imaging data and right-side heart catheterization, whereas $Ppa$ was obtained from right-side heart catheterization. The second step was to show that PAH could be assessed by estimating $R$ (or $c$), using only MR imaging data to graphically estimate $Ppa$. The method is subsequently described using $R$, although pressure wave velocity could have been used as well. The $\Delta U$ can be obtained from the flow pattern provided by the phase-mapping technique. The pressure wave velocity can also be assessed when $S$ and $\Delta S$ are measured in the magnitude images of a volunteer frame provided that $\Delta P$ is known. However, like $Ppa$, $\Delta P$ is unknown from MR imaging data, and, hence, a relationship between $Ppa$ and $\Delta P$ is needed to overcome this problem. Therefore, we have established an experimental plot of $\Delta P$ vs. $Ppa$ using values provided by right-side heart catheterizations in a large series of patients (see below). However, it should be kept in mind that, at this stage, $Ppa$ and $\Delta P$ are correlated but still unknown for a given patient in the absence of right-side heart catheterization data.

The procedure was, first, to calculate pressure wave velocity with MR imaging measurements of $S$ and $\Delta S$ using an arbitrary value of $\Delta P$ that was initially chosen equal to 15 mmHg (with 1 mmHg = 136 Pa), the value given for healthy volunteers (3). The calculation then allowed us to obtain a first estimate of $R$ and hence of $Ppa$ by means of the R-$Ppa$ graph. The plot of $\Delta P$ vs. $Ppa$ was then used with the first estimate of $Ppa$ to get a more accurate value of $\Delta P$. This altered value of $\Delta P$ was then used for a second estimation of $R$ and hence of $Ppa$. A series of iterations was subsequently performed until two successive estimates of $Ppa$ were only separated by $\pm 1\%$.

However, because of the scatter of the data in the R-$Ppa$ graph, we considered uncertainties in the final $Ppa$ estimate. We thus drew two lines that delimited a cone that contained most of the points of the graph. Two iterative procedures as described above were performed using each of the two lines that provided final minimal and maximal estimates of $Ppa$, respectively. Consequently, for each patient, the result of the $Ppa$ estimation is given with two values framing the actual value, with a percentage of reliability, because the cone in the R-$Ppa$ graph did not involve all of the data points.

**Patients.** MR imaging and right-side heart catheterization were performed in 15 patients, 8 women and 7 men, aged 24–78 yr (mean of 52 yr). After the nature of the procedures was explained, informed consent was obtained for both the right catheterization and MR imaging. The time interval between the two techniques was as short as possible, usually within 1 wk, except for one patient. This latter patient, however, did not show clinical changes between the two examinations. This stability was confirmed by the consistency in the parameters derived from two successive catheterizations performed in this patient, separated by 6 mo, which framed MR imaging. Indications for the right-side heart catheterization were as follows: lung transplantation ($n = 5$), primary PAH ($n = 4$), secondary PAH due to chronic thromboembolic disease ($n = 4$), left-side cardiac valvular disease ($n = 1$), and myocardial disease ($n = 1$). The catheterization provided the value of the pulse pressure in MPA ($\Delta P$) and the value of the mean MPA pressure ($Ppa$).

Because the procedure described in the present paper requires the use of an experimental relationship between the two hemodynamics parameters ($\Delta P$ and $Ppa$) to be as reliable as possible, the results derived from catheterization performed in 15 additional patients (although without MR imaging) were included.

**MR phase mapping.** Experiments were performed, as previously described (12), with a 1-T Magnetom Expert Imager (Siemens, Erlangen, Germany) employing a gradient system capable of generating 20 mTm/s. We used the Flow Quantification software developed by the manufacturer, previously validated (13). A turboFLASH sequence with a dark-blood preparatory scheme was used to obtain an oblique sagittal slice in which the MPA appeared in its total length. Then, a slice was selected at mid-MPA perpendicularly to the vessel axis. The repetition time (ms), the echo time (ms), and the flip angle (degrees) were 30, 6, and 30, respectively. The field of view was 338 × 450 mm (192 × 256 pixels), the slice thickness was 10 mm, and the encoding velocity was 150 or 75 cm/s. The number of phases was 40 (40 consecutive measurements separated by 30 or 28 ms, respectively, depending on the encoding velocity), starting directly after detection of an electrocardiogram trigger, to record a complete cardiac cycle, whatever the patient cardiac frequency. The time of acquisition was ~5 min. The software displayed both the magnitude and phase images (Fig. 1, A and B, respectively). An area of reference, chosen at the level of the vertebral body that appeared in the slice, served as a null velocity (13).

**Quantitative analysis at MR imaging.** For each patient, all CSA and blood flow values were measured throughout a complete cardiac cycle. We manually outlined the MPA CSA in each magnitude image of a patient frame. This procedure was repeated two to three times to obtain an averaged CSA value and an averaged blood velocity value for each point of the CSA and flow patterns, respectively. The maximal mean velocity was obtained from the flow pattern at the systolic peak (Fig. 2A) by averaging one or two consecutive points.
The maximal and minimal CSA values and the difference were obtained from the CSA pattern (Fig. 2B) by averaging two or three consecutive points. The minimal CSA value was estimated at the end of the cycle. The mean CSA (S) was the mean of the maximal and minimal CSA averaged values.

**Statistical analysis.** To construct the relationship between $\Delta P$ and $P_{pa}$, different types of fit, i.e., linear, polynomial, exponential, and power, were probed. The coefficient of correlation ($r$) given by fitting was used to determine the best fit and to assess the significance of a relationship between these two parameters.

The relationships between MPA (mean) CSA and $P_{pa}$ as well as that between pressure wave velocity and $P_{pa}$ and between R and $P_{pa}$ were assumed to be linear.

The reliability of the proposed method was tested by means of a one-tailed sign test, which was applied to the comparison of the framing $P_{pa}$ values with the actual $P_{pa}$ values.

**RESULTS**

Table 1 presents, for each patient, the values of $P_{pa}$ and $\Delta P$ (provided by right catheterization) as well as $S$, $\Delta S$, $c$, and $R$ (provided by MR imaging).

Figure 1 shows the magnitude image (A) and the corresponding phase image (B) provided by velocity-encoded MR imaging in one patient. CSA pattern was established by outlining the magnitude image.

As indicated above, Fig. 2 shows the time curve of the mean blood velocity over the CSA (A) and the time curve of the CSA values (B) throughout a complete cardiac cycle in one patient. The curve shown in Fig. 2A is not representative of the series. Flow patterns were different in 11 patients whose $P_{pa}$ was $\geq 25$ mmHg (Table 1). Moreover, in 3 of these 11 patients, we did not observe a negative end-systolic flow peak, nor did we observe a reasonably identified diastolic flow peak. Nevertheless, the CSA pattern illustrated in Fig. 2B was roughly similar in all of the patients with PAH. In particular, the decrease in the CSA between the systolic and the diastolic peaks never fell below the value of the end-diastolic (minimal) CSA, as described under physiological conditions (12). Moreover, in one of four patients whose $P_{pa}$ was $< 25$ mmHg (Table 1), the CSA pattern presented one systolic peak with a smooth exponential-like fall. It should be noted that 1) the end-diastolic part of the CSA pattern was always noisy because of measurement uncertainties and 2) the values of the two first points were often greater than those of the minimal end-diastolic values. Furthermore,

![Fig. 1. Typical magnitude image (A) and corresponding phase image (B) provided by velocity-encoded magnetic resonance (MR) imaging in 1 patient.](image)

![Fig. 2. Blood velocity over the main pulmonary artery (MPA; A) and corresponding cross-sectional area (CSA) values (B) vs. time throughout a complete cardiac cycle in 1 volunteer. Note that data points in A are not representative of the series (see RESULTS). In contrast, the CSA pattern illustrated in B was roughly similar in all of the patients with pulmonary arterial hypertension.](image)
there was no significant correlation between S and Ppa (not shown).

*Relationships between hemodynamics and MR imaging data.* The plots of pressure wave velocity and R vs. Ppa are presented in Figs. 3 and 4, respectively. Equations of the linear regression were pressure wave velocity $c = 9.25 Ppa - 202.51$ ($r = 0.82$), and $R = 0.68 Ppa - 4.33$ ($r = 0.89$, $n = 15$, $P < 0.01$), respectively. The equations of the two lines of the cone sketched in the figure were $y = 0.91x - 6.32$ and $y = 0.65x - 10$, respectively. According to the cone limits, the following typical ranges of Ppa estimation could be identified: 14–25, 40–61, and 60–90 mmHg.

**Estimation of Ppa from MR imaging data.** Figure 5 shows the experimental plot of DP vs. Ppa, provided by right-side catheterization in 30 patients. Both linear and power fits were very close, with the best coefficient of correlation being found with the power fit ($r = 0.82$ and $r = 0.86$, respectively). Consequently, at each step of the iterative procedure, the relationship $DP = 0.76 Ppa^{0.998}$ was used.

Figure 6 shows, for each of the 15 patients, the minimal and maximal estimates of Ppa given by the method, according to the cone limits defined in Fig. 4 vs. the actual Ppa derived from right-side catheterization. Once the iterations of the minimal and maximal DP estimates were done, the values of the nearest lower and nearest greater integer, respectively, were used to draw the estimation frame. For the minimal
estimate, iterations were stopped when the value was 15 mmHg. In 13 of 15 patients (87%), the actual value of \( \Delta P \) was framed by the estimates, indicating a strong significance of the proposed method \( (P < 0.01) \).

The method also provided minimal and maximal estimates of the pulse pressure in the MPA \( (\Delta P; \text{not shown}) \). In 5 of 15 patients, these estimates did not frame the actual value provided by the right catheterization. The \( \Delta P \) estimation reliability was less than that of Ppa (67% vs. 87%).

**DISCUSSION**

The present study indicates that the mean blood pressure in the MPA can be noninvasively estimated by using velocity-encoded MR imaging. The estimate is given with two values framing the actual value. In this work, these limit values were based on the limits of the cone sketched in the R-Ppa graph (Fig. 4). Under these conditions, the reliability percentage to find the actual Ppa value within the framing values was 87%. The same method could be implemented with the c-Ppa graph (Fig. 3).

A further validation of the method is warranted with a much larger number of patients to determine which of the two graphs is the most suitable. However, we believe that the choice might depend on the expected value of Ppa. Indeed, comparison of Fig. 3 and 4 indicates that the c-Ppa graph might be more relevant to assess weak PAH, whereas the R-Ppa graph might be more relevant to assess severe PAH. Whatever the correlation graph used, it is noteworthy that the limits of the cone are arbitrarily set by the physician, hence the framing values and the percentage of reliability. In the present series, when the equation of the second line is \( y = 0.65x - 13 \) (instead of \( y = 0.65x - 10 \)), the reliability percentage becomes 93%. The validation should also include a large variety of diseases. In the present series, the worst Ppa estimate was obtained in the only patient (patient 12) suffering from left-side cardiac valvular disease.

The proposed method has the following limits. First, as already mentioned (12), outlining is facilitated by the known proton inflow phenomenon, which enhances the blood signal within the vessel in MR imaging magnitude images. Therefore, the outlining method has limitations when the flow is weak, as in the end-diastolic part of the cardiac cycle, especially in the case of PAH (14). Moreover, it has been shown (13) that physiological cardiac period variations, occurring during the phase-mapping acquisition, could disturb the recording of the end-diastolic cardiac phase. We believe that these are the reasons why the final points of the cycle were not accurately measured, as shown in Fig. 2B. Furthermore, it should be noted that magnitude images provided by a phase-mapping software are not optimized for an accurate vessel outlining, although averaging cautions (as described in MATERIALS AND METHODS) can reduce the measurement uncertainties. It is suggested that sequences different from those of the MR phase-mapping sequence could be implemented, such as cine-MR imaging sequences, to better delineate the vessel wall. Second, the selection of the measurement slice is also critical. The slice must be set perpendicularly to the MPA axis, although the actual shape of the MPA is curved. Moreover, the slice must be set between the beginning of a right pulmonary artery on the right-hand side and the heart valve on the left-hand side to avoid erroneous measurements. As previously reported (12), in some patients the MPA CSA position can significantly move in the slice plane during the cardiac period. This movement is likely due to heart contraction as well as to individual MPA curved anatomy. However, it has recently been shown in the aorta (9) that motion-adapted cine phase-contrast flow measurements could be implemented, which would overcome this problem in the MPA. Third, as already indicated, a much larger number of patients are required to better assess the method to take into account interexamination variability and intra- and interobserver variabilities. However, because the present method might benefit from the use of an automatic delineation of the vessel, such variability could be limited (9, 11).

The value of S was not significantly correlated with Ppa in our series. Although the distending effect of an increase in Ppa on the vessel wall has already been evoked (1, 10), the results of the present study suggest that the value of the PAH cannot be satisfactorily assessed by means of measurements of MPA CSA. In this connection, if the proposed MRI method was used as a primary test to indicate catheterization, patient 15, whose presented CSA value was high, in the absence of PAH, would have avoided the catheterization.

It has been demonstrated (7, 14) that the systolic flow pattern is modified in the case of PAH. In the present series, analysis of the flow patterns over the complete cardiac cycle revealed that they were qualitatively different from those described in healthy volunteers. In particular, the diastolic flow peak observed in healthy volunteers could not be identified in all the patients of the series. On the basis of our previous work (12), we believe that this observation might qualitatively reflect the loss of the tuning of the right cardiovascular system in case of PAH, hence a rise in right ventricular work.

The CSA patterns in PAH were modified compared with those of healthy volunteers (Fig. 2B), showing that the decrease in the CSA between the systolic and the diastolic peaks never fell below the value of the end-diastolic (minimal) CSA. This finding can be explained by a windkessel effect, which can be neglected in healthy volunteers (12). Such is not the case when the blood pressure is increased as in PAH. In other words, the CSA pattern of the MPA in case of PAH resembles that of the aorta (6).

A variety of ultrasound methods have been described to noninvasively estimate pulmonary artery pressures (18). For example, the mean pressure can be estimated by acceleration time divided by the ejection time from wave forms (7). However, Stevenson (18) observed, in a selected pediatric series, that this method was more
accurate from the right ventricle outflow pattern than from the MPA flow pattern. Stevenson also showed that ultrasound methods provided accurate estimations of systolic and diastolic pressures from peak tricuspid regurgitation velocity and end-diastolic pulmonary regurgitation velocity, respectively (18).

The MR method also provided an estimate of the pulse pressure in the MPA, $\Delta P$. In this series, it was less reliable than the Ppa estimate. This comparison suggests that the accuracy of the Ppa estimation could be improved if the $\Delta P$-Ppa relationship in the MR method were better characterized. Alternatively, an accurate $\Delta P$ estimate provided by ultrasound examination may be of value. Therefore, a method combining MR and ultrasound should be evaluated.

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REFERENCES