A computed method for noninvasive MRI assessment of pulmonary arterial hypertension

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Laffon, Eric, Christophe Vallet, Virginie Bernard, Michel Montaudon, Dominique Ducassou, François Laurent, and Roger Marthin. A computed method for noninvasive MRI assessment of pulmonary arterial hypertension. J Appl Physiol 96: 463–468, 2004. First published August 29, 2003; 10.1152/japplphysiol.00292.2003—The present method enables the noninvasive assessment of mean pulmonary arterial pressure from magnetic resonance phase mapping by computing both physical and biophysical parameters. The physical parameters include the mean blood flow velocity over the cross-sectional area of the main pulmonary artery (MPA) at the systolic and maximal systolic MPA cross-sectional area value, whereas the biophysical parameters are related to each patient, such as height, weight, and heart rate. These parameters have been measured in a series of 31 patients undergoing right-side heart catheterization, and the computed mean pulmonary arterial pressure value (PpaComp) has been compared with the mean pressure value obtained from catheterization (PpaCat) in each patient. A significant correlation was found that did not differ from the identity line PpaComp = PpaCat (r = 0.92). The mean and maximal absolute differences between PpaComp and PpaCat were 5.4 and 11.9 mmHg, respectively. The method was also applied to compute the MPA systolic and diastolic pressures in the same patient series. We conclude that this computed method, which combines physical (whoever the patient) and biophysical parameters (related to each patient), improves the accuracy of MRI to noninvasively estimate pulmonary arterial pressures.

pulmonary arterial hypertension; magnetic resonance phase mapping; computing; pulmonary arterial blood pressures

A VARIETY OF MEDICAL IMAGING methods have been proposed to noninvasively assess pulmonary arterial pressure (Ppa) values (3, 7–9, 17, 18, 20, 21). Among these, our laboratory (15) has recently proposed an MRI method based on the ratio of the pressure wave velocity to the maximal blood flow velocity to assess the mean pressure (Ppa) in the main pulmonary artery (MPA) in patients suffering from pulmonary arterial hypertension (PAH). The aim of the present work was to improve the accuracy of this MRI method to noninvasively estimate Ppa. The present method combines both physical and biophysical parameters. The physical parameters include the mean blood flow velocity over the MPA cross-sectional area (CSA) at the systolic peak (Um) and the maximal systolic MPA CSA value (Smax), whereas the biophysical parameters account for the single type of each patient, such as her or his height, weight, and heart rate (10). The method relies on the fact that any mathematical function involving a particular parameter can be developed in a polynomial series of this parameter. Therefore, a computed program has been implemented to probe different combinations of polynomial series of Um and Smax. The biophysical parameters were introduced to normalize the physical ones, as proposed by Du Bois and Du Bois (4) for the calculation of body surface area.

THEORY

The ratio of the pressure wave velocity (c) to Umax has recently been used to noninvasively assess Ppa, with 87% reliability (15). This ratio is developed in Eq. 1

\[ \frac{c}{U_{\text{max}}} = \frac{1}{U_{\text{max}}} (S_{\text{max}} - S_{\text{min}}) \]

with

\[ S = \frac{S_{\text{max}} + S_{\text{min}}}{2} \]

and

\[ \Delta S = \frac{S_{\text{max}} - S_{\text{min}}}{2} \]

where \( \rho \) is the blood volume mass (1,060 kg/m3); \( S \) is the mean CSA of the MPA; \( \Delta S \) is the difference between maximal and minimal CSA values measured throughout the cardiac cycle; \( \Delta P \) is the pulse pressure, i.e., the difference between the systolic (Psys) and diastolic pressures (Pdiast) in the MPA; and \( S_{\text{min}} \) is minimum systolic MPA CSA assessed at the end-diastolic cardiac phase.

A first limitation of the above-described method is that a relationship between \( \Delta P \) and Ppa is required. Because \( \Delta P \) is unknown, an iterative process has been proposed to overcome this limitation (15). A second limitation is that, whereas the vessel outlining is facilitated for \( S_{\text{max}} \) due to a MRI proton inflow phenomenon, which enhances the systolic blood signal, the outlining is much less reliable for \( S_{\text{min}} \) at the end-diastolic cardiac phase due to a weaker signal of the stationary blood. In particular, Eqs. 1–3 indicate that \( S_{\text{min}} \) measurement uncertainties play a role in the assessment of Ppa assessment. A third limitation is that Eq. 1 does not take into account additional relevant terms related to 1) physical phenomena, such as charge losses or early return of the pressure wave (14), and 2) each type of a patient, such as weight, height, or heart rate.

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Therefore, the present proposed method only involves $U_{\text{max}}$ and $S_{\text{max}}$. The principle of the method is based on an expression of $P_{\text{pa}}$ as a combination of powers of $U_{\text{max}}$ and $S_{\text{max}}$. These combinations are determined by computing. Furthermore, the method also allows us to take into account biophysical parameters in a manner similar to that proposed by Du Bois and Du Bois (4) for the calculation of body surface area. When applied to the present issue, this manner is equivalent to normalize $U_{\text{max}}$ ($U_n$) and $S_{\text{max}}$ ($S_n$)

$$
U_n = U_{\text{max}}^{\beta_{\text{height}} \cdot \beta_{\text{weight}} \cdot \beta_{\text{HR}}} \quad (4)
$$

$$
S_n = S_{\text{max}}^{\beta_{\text{height}} \cdot \beta_{\text{weight}} \cdot \beta_{\text{HR}}} \quad (5)
$$

where $HR$ is heart rate (10). Consequently, according to this normalization, the aim of the work was to compute polynomial series of $U_n$ and $S_n$.

### MATERIALS AND METHODS

The procedures used in the present work have been described previously (14, 15).

**Patients.** MRI and right-side heart catheterization were performed in 31 patients, 14 women and 17 men, aged 24–83 yr (mean 63 yr). Right-side heart catheterization was performed for the following indications: lung transplantation ($n = 4$), primary PAH ($n = 5$), secondary PAH due to chronic thromboembolic disease ($n = 4$), cardiac valvular disease ($n = 7$), and myocardial disease ($n = 11$).

The investigation conforms with the principles outlined in the Declaration of Helsinki. An institutional ethics committee approved the study, and informed consent was obtained for both the right catheterization and MRI, after the nature of the procedures had been explained. The time interval between the two techniques was usually 2 days, but anyway <1 wk. Patients’ height, weight, and heart rate ranged between 1.80 and 1.50 m, 113 and 54 kg, and 100 and 56 beats/min (mean 1.67 m, 77 kg, 77.5 beats/min, respectively). The catheterization provided the values of the $P_{\text{sys}}$, $P_{\text{max}}$, and mean $P_{\text{pa}}$ in the MPA, which ranged between 115 and 13, 66 and 2, and 84 and 6 mmHg (mean 44.0, 18.1, 28.3 mmHg), respectively.

**Magnetic resonance phase mapping.** Experiments were performed with a 1-T Magnetom Expert Imager (Siemens, Erlangen, Germany). The flow quantification software provided by the manufacturer, previously validated (16), was used. For each patient, CSA and blood flow values were measured throughout a complete cardiac cycle (14, 15). We manually outlined the MPA CSA in each magnitude image of a patient frame (Fig. 1). 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. $U_{\text{max}}$ was obtained from the flow pattern at the systolic peak by averaging two consecutive points. $S_{\text{max}}$ was obtained from the CSA pattern by averaging two or three consecutive points, because the CSA peaked was less sharp than the flow pattern (14, 15).

**Computing.** A computed program was implemented from a Microsoft Excel software to test 1) different possibilities of power indexes, as expressed in Eqs. 4 and 5, and 2) different combinations of polynomial series of $U_n$ and $S_n$, $p_1 (U_n)$ and $p_2 (S_n)$, respectively. A first mandatory condition was the following. In the $P_{\text{pa}}$ range of interest, if $U_1 > U_2$, then $p_1 (U_1) > p_1 (U_2)$, and if $S_1 > S_2$, then $p_2 (S_1) > p_2 (S_2)$. Furthermore, when considering the graph $P_{\text{pa}}$ obtained from catheterization ($P_{\text{pa}}$) vs. $P_{\text{pa}}$ obtained by computing ($P_{\text{pa}}$), a second mandatory condition was to obtain the highest correlation coefficient. This correlation coefficient is indicated for a linear regression, the equation of which is the identity line. Indeed, the computing procedure allows us to set the constants involved in the expression of $P_{\text{pa}}$ to obtain such a fit.

**Statistical analysis.** In addition to the linear regression for $P_{\text{pa}}$ and $P_{\text{pa}}$, the Bland and Altman method was used to compare the two parameters (1). Intra- and interobserver variability of $U_{\text{max}}$ and $S_{\text{max}}$ were also assessed by using the same method. The mean and maximal absolute differences between $P_{\text{sys}}$, $P_{\text{max}}$, and $P_{\text{pa}}$ obtained from catheterization and computing, respectively, were also calculated. $P_{\text{pa}}$ measurement uncertainty related to uncertainty ($e$) in any parameter used in the calculation (e.g., $U_{\text{max}}$, $S_{\text{max}}$, patient weight, height, or heart rate) was assessed by considering the mean absolute difference $P_{\text{pa}} - P_{\text{pa}} (+e)$, from the whole patient series.

### RESULTS

Among the different tested combinations of parameters, the selected computed result for $P_{\text{pa}}$ was as follows

$$
P_{\text{paComp}} = p_1 (U_n) + p_2 (S_n) \quad (6)
$$

with

$$
p_1 (U_n) = -0.0017 \, \bar{v}^2 + 1.1534 \, \bar{y} - 2.6239 \quad (7)
$$

and

$$
y = 114.90 \, U_n^{-3} - 526.45 \, U_n^{-2} + 801.41 \, U_n^{-1} - 381.98 \quad (8)
$$

$$
p_2 (S_n) = 0.0104 \, \bar{z}^2 + 0.9650 \, \bar{z} - 0.0977 \quad (9)
$$

and

$$
\bar{z} = -0.0556 \, \bar{v}^2 + 1.3475 \, \bar{v} + 0.6691 \quad (10)
$$

and

$$
\bar{v} = 5 \times 10^{-12} \, S_n^2 - 2 \times 10^{-6} \, S_n - 2.33 \quad (11)
$$

$$
U_n = U_{\text{max}}^{0.50} \cdot \text{height}^{-0.63} \cdot \text{weight}^{0.30} \cdot \text{HR}^{0.14} \quad (12)
$$

$$
S_n = S_{\text{max}}^{1.50} \cdot \text{height}^{-4.30} \cdot \text{weight}^{2.30} \cdot \text{HR}^{0.60} \quad (13)
$$

where $U_{\text{max}}$, $S_{\text{max}}$, height, weight, and HR are expressed in cm/s, cm², m, kg, and beats/min, respectively.
The plot $P_{pca} \text{Cat}$ vs. $P_{pca} \text{Comp}$ is presented in Fig. 2. Equation of the linear regression was the identity line, i.e., $P_{pca} \text{Cat} = P_{pca} \text{Comp}$ ($r = 0.92$). The comparison between the two parameters by means of the Bland and Altman method leads to the following: $P_{pca} \text{Cat} - P_{pca} \text{Comp} = 0 \pm 2.37 \text{ mmHg}$ (95% reliability; graph not shown). When $P_{pca} \text{Comp}$ was calculated by using only $p_1$ (Un) or a computed polynomial series of $U_{\text{max}}$, the correlation coefficient of the linear regression was then 0.90 and 0.85, respectively (graphs not shown). We also examined the role of patient age as a possible fourth biophysical parameter after the normalization was done with patient height, weight, and heart rate and found that it did not improve the correlation coefficient. It should also be noted that no significant correlation was found between $P_{pca} \text{Cat}$ and patient’s height ($r = 0.15$), weight ($r = 0.13$), or heart rate ($r < 0.01$).

Intra- and interobserver variability for $U_{\text{max}}$ and $S_{\text{max}}$ are presented in Figs. 3, A and B, and 4, A and B, respectively. The range of values were 16.68–98.95 and 16.97–99.70 cm/s for $U_{\text{max}}$ and 3.74–13.17 and 3.80–13.26 cm$^2$ for $S_{\text{max}}$, respectively. This variability was not significantly different one from the other. In contrast, significant differences were found in the $S_{\text{min}}$ intra- and interobserver variability: the mean differences and 95% reliability domains were $-0.17 \pm 0.16$ and $-0.22 \pm 0.10$ cm$^2$, respectively (graphs not shown). The standard deviation of intra- and interobserver variability was 1.93 and 2.07 cm/s for $U_{\text{max}}$ and 0.48 and 0.38 cm$^2$ for $S_{\text{max}}$, respectively. Therefore, when $U_{\text{max}}$ and $S_{\text{max}}$ measurement uncertainties were taken equal to 1 SD from the intraobserver variability, $P_{pca} \text{Comp}$ uncertainty was found equal to 3.6 and 0.6 mmHg, respectively. Measurement uncertainty for patients’ height, weight, and heart rate was estimated to be 1 cm, 1 kg, and 10% of the patient heart rate value, respectively, leading to $P_{pca} \text{Comp}$ uncertainty equal to 0.6, 0.4, and 1.6 mmHg, respectively. The sum of all of the uncertainty was then equal to 6.8 mmHg. In addition, the $P_{pca} \text{Cat}$ measurement uncertainty was estimated to be 1 mmHg. These values should be compared with the mean and maximal absolute differences between $P_{pca} \text{Cat}$ and $P_{pca} \text{Comp}$, 5.4 and 11.9 mmHg, respectively.

The plots of the $P_{\text{dias}}$ and $P_{\text{sys}}$ measured by catheterization ($P_{\text{dias Cat}}$ and $P_{\text{sys Cat}}$, respectively) vs. the computed ones ($P_{\text{dias Comp}}$ and $P_{\text{sys Comp}}$, respectively) are presented in Fig. 5. The equation of the linear regression was again that of the identity line: $P_{\text{dias Cat}} = P_{\text{dias Comp}}$ ($r = 0.93$) and $P_{\text{sys Cat}} = P_{\text{sys Comp}}$ ($r = 0.86$), respectively. The mean and maximal absolute differences between $P_{\text{dias Cat}}$ and $P_{\text{dias Comp}}$ were 3.6 and 9.2 mmHg, respectively. The mean and maximal absolute differences between $P_{\text{sys Cat}}$ and $P_{\text{sys Comp}}$ were 10.6 and 28.7 mmHg, respectively.

**DISCUSSION**

The present study indicates that estimation of the mean blood pressure in the MPA using noninvasive MRI measurements of the maximal systolic blood velocity and vessel CSA...
can be more accurate than previously reported (15). A first improvement is to select relevant physical parameters, with low intra- and interobserver variability (Eq. 1, Figs. 3 and 4) and to take into account biophysical parameters that may play a role in the pressure estimation. A second improvement is 1) to compute the best normalization of the physical parameters by means of the biophysical ones, in a manner similar to that used for body surface area calculations (4), and 2) to select the combination of polynomial series of the normalized physical parameters leading to the best correlation with the pressure value given by invasive right-side catheterization. Using this method in a series of 31 patients, over a wide range of pressure values, we found mean and maximal absolute differences in Ppa between values given by catheterization and the computation equal to 5.4 and 11.9 mmHg, respectively.

The present method is a development of the former one (15), which estimated maximal and minimal Ppa values to frame the actual Ppa value. The comparison with right-side catheterization showed that PpaCat was framed by the two values in 13 of 15 patients of the series (87% reliability). Moreover, the difference between the framing values ranged between 9 and 52 mmHg for the patient series. The present MRI method should also be compared with ultrasound methods. Stevenson (21) compared several echographic methods against catheterization in a selected pediatric series (50 patients), under nearly ideal circumstances and with an experienced physician. The best correlation coefficient and mean absolute difference between pressure estimates and values from catheterization for Ppa, Pdias, and Psys were r = 0.94 and 7.7 mmHg, r = 0.96 and 4.5 mmHg, and r = 0.97 and 5.4 mmHg, respectively. However, it should be noted that 1) the best echographic method used in each of the above-mentioned assessment was successful in 98, 98, and 89% of patients, respectively; 2) the regression was not the identity line; and 3) in the particular case of Ppa assessment, the maximal difference between the estimate and the value from catheterization was 27 mmHg. Nevertheless these figures can be compared with ours: r = 0.92 and 5.4 mmHg (maximal difference = 11.9 mmHg), r = 0.93 and 3.6

![Fig. 4. Intra- (A) and interobserver (B) variability for maximal systolic main pulmonary artery cross-sectional area (Smax), according to Bland and Altman's presentation (1). The mean differences (solid lines) and 95% reliability (dashed lines) domains were 0.03 ± 0.18 and −0.14 ± 0.14 cm², respectively.](image-url)

![Fig. 5. Plot of diastolic and systolic pressure measured from catheterization (PdiasCat and PsysCat) vs. those assessed from computing (PdiasComp and PsysComp). A: PdiasCat vs. PdiasComp. Equation of the regression line is the identity line PdiasCat = PdiasComp (r = 0.93). B: PsysCat vs. PsysComp. Equation of the regression line is the identity line PsysCat = PsysComp (r = 0.86).](image-url)
mmHg, and \( r = 0.86 \) and 10.6 mmHg for \( \text{P}_{\text{pa}} \), \( \text{P}_{\text{dia}} \), and \( \text{P}_{\text{sys}} \), respectively. In agreement with Stevenson’s work, we suggest that the availability of a variety of noninvasive methods to assess pulmonary pressure is of value and that these different methods should be considered complementary rather than competitive. A much larger study than the present one is, however, warranted to compare these MRI and ultrasound methods in adults.

An important limitation of the previous method was the broad variability of \( S_{\min} \) measurements (Eq. 1), leading, now only, to the consideration of \( U_{\max} \) and \( S_{\max} \) as relevant physical parameters. The relative intra- and interobserver variability of \( U_{\max} \) and \( S_{\max} \) was found to be 0.8 and 1.5 and 0.4% and 1.8%, on average, respectively (Figs. 3 and 4, respectively). We previously observed (15) that the value of the vessel CSA is not significantly correlated with \( \text{P}_{\text{pa}} \). The present study has confirmed this finding, because the contribution of \( U_{\max} \) in the \( \text{P}_{\text{pa}} \) estimation was much greater than that of \( S_{\max} \). This is supported by the high-correlation coefficient calculated when \( p_{1} \) (Un) or a computed polynomial series of \( U_{\max} \) is used to estimate \( \text{P}_{\text{pa}} \): \( r = 0.90 \) and \( r = 0.85 \), respectively, compared with \( r = 0.92 \) when both Un and Sn are used. This also explains why \( \text{P}_{\text{pa}} \) measurement uncertainty is mainly related to that of \( U_{\max} \), 6.8 and 3.6 mmHg, respectively. We suggest that the following hypothesis might explain the relevance of \( U_{\max} \) to the assessment of \( \text{P}_{\text{pa}} \): when pulmonary vascular resistance increases, \( \text{P}_{\text{pa}} \) also increases to maintain the pulmonary blood flow, but the greater the pulmonary vascular resistance, the less efficient this adaptation. Hence, under these conditions, the blood flow tends to diminish. This assumption is coherent with the strongly nonlinear relationship between \( 1/U_{\max} \) and \( \text{P}_{\text{pa}} \) and the secondary role of the vessel CSA in the assessment.

Further improvement in the present method may be expected. First, the reliability of each physical parameter could benefit from forthcoming improvement in imaging, such as motion-adapted cine phase-contrast images (12) and use of an automatic delineation of the vessel (11, 13). Second, the principle of the method allows us to introduce additional parameters, both physical and biophysical, to improve its accuracy. Indeed, although the contribution to the final pressure estimate of such additional parameters may be relatively less and less important, they can, nevertheless, improve its accuracy. For example, if \( S_{\min} \) measurement becomes more reliable due to improvement in imaging (see above), it will be possible to compute further combinations of polynomial series of \( U_{\max}, S_{\max}, \) and \( S_{\min} \) (or \( \Delta S \) as well; Eq. 3). Also, it has been shown that respiratory motion produces periodical variations in the mean \( \text{P}_{\text{pa}} \) (6). Therefore, respiratory frequency could be introduced in the physical parameter normalization as an additional biophysical parameter along with patient height, weight, and heart rate (Eqs. 4 and 5). However, introduction of this parameter obviously requires a specific recording. Alternatively, lowering the image acquisition time could be considered to perform measurements within a breath hold, as done for pressure measurements during catheterization. Finally, it should be kept in mind that some phenomena occurring in \( \text{P}_{\text{pa}} \) assessment are difficult to avoid or measure. In particular, in patients with primary pulmonary hypertension, pulmonary vasomotor waves induce rythmic oscillations in pulmonary arterial blood pressure (6). Also, the influence of the sedative prescription before the right-side catheterization that has been shown to be efficient (21) is difficult to assess.

We have also tested the method by the additional computed estimation of \( \text{P}_{\text{dia}} \) and \( \text{P}_{\text{sys}} \) in the same series of patients. The correlation coefficient for \( \text{P}_{\text{dia}} \) (\( r = 0.93 \)) was higher than that for \( \text{P}_{\text{sys}} \) estimation (\( r = 0.86 \)) and close to that for \( \text{P}_{\text{pa}} \) assessment (\( r = 0.92 \)).

In conclusion, we suggest that the present noninvasive method, with a mean and maximal absolute uncertainty of 5.4 and 11.9 mmHg, respectively, could be helpful to screen patients to decide whether the catheterization should be performed and for the follow-up of hemodynamic changes associated with medical therapies, such as long-term vasodilator treatment in patients with PAH (2, 5).

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