Quantification of right ventricular afterload in patients with and without pulmonary hypertension


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PULMONARY HYPERTENSION (PH) can have a variety of causes (1), but all causes have an increased right ventricular (RV) afterload in common. Because this increased RV afterload may lead to hypertrophy, RV failure, and, ultimately, death, it is important to improve our understanding of the RV afterload. Most often, RV afterload is defined as pulmonary vascular resistance (PVR). Because PVR is the ratio of mean pressure and mean flow, it reflects the arterial load to a steady flow. In reality, however, blood flow is pulsatile. A complete description of RV afterload, therefore, should also include the load to pulsatile flow (38). A decreased arterial compliance, for example, may be of similar importance for RV afterload as an increased PVR (29).

Another determinant of RV afterload that is not reflected by PVR or by arterial compliance is the characteristic impedance of the proximal pulmonary artery (27, 42), which combines both blood inertia and vascular storage properties. The inertial properties play a role in acceleration and deceleration of the blood, and the storage properties arise from the elasticity of the vessel wall (27, 42). In the absence of wave reflection (i.e., if the pulmonary artery were infinitely long and waves would never reach the periphery), the input impedance of the pulmonary arterial system would equal the characteristic impedance (43). Characteristic impedance may be affected, particularly if the large vessels are involved, as is the case in chronic thromboembolic pulmonary hypertension (5).

Differentiating the resistance, compliance, and characteristic impedance in RV afterload thus may provide important diagnostic and prognostic information. The three components can be derived directly from the input impedance spectrum but also by using a physiological model. A model that combines the three components is the three-element windkessel model (42), which is most often represented by an electrical circuit. It is attractive for clinical application because its parameters have a physiological meaning and the number of parameters is limited. The windkessel model has been applied successfully in the analysis of the systemic arterial tree (27), but we do not know studies in the pulmonary circulation, where the model has been used to quantify and differentiate the RV afterload in different forms of PH. Therefore, the aim of the current study was to investigate whether three well-defined and clearly distinct patient groups could be discriminated using the three-element windkessel model and standard clinical measurement techniques.

METHODS

Model and parameter estimation. The three-element windkessel model (Fig. 1) consists of (total) arterial compliance C, pulmonary artery characteristic impedance Z, and peripheral resistance R (42, 43). Resistance of the small arteries and arterioles dominates R, and C is the summation of the total compliance of the pulmonary conduit arteries. Z accounts for the local blood mass and compliance of the proximal pulmonary artery. A single resistor can represent this relation so that the sum of R and Z equals PVR. Note that in the model, R, C, and Z are independent of each other.

Because of the popularity of the three-element windkessel model in different applications, a variety of methods can be found in the literature for estimation of its parameters from pressure and flow data obtained in the aorta or pulmonary artery (2, 9, 40, 42, 43). The energy
The study was approved by the Institutional Review Committee, and all patients gave informed consent.

Measurements. In the NONPH and IPAH patients, pressure was measured via the transfemoral approach with a 6-Fr fluid-filled, single-lumen, multipurpose catheter (Cordis, Miami Lakes, FL). In the CTEPH patients, pressure was measured during pulmonary angiography with a 6-Fr Grollman catheter (Cook, Eindhoven, The Netherlands). The pressure signal and the ECG were digitally recorded at a sampling frequency of 250 Hz using a custom-made LabView application (National Instruments, Austin, TX). During catheterization, cardiac output was measured using Fick’s method. The frequency response of the catheters used in the study was evaluated in vitro using a pressure-step apparatus (33), and the response was analyzed as described by Gardner (10).

In all patients, volumetric flow in the pulmonary artery was measured with MRI using phase-contrast velocity quantification within 7 days after right heart catheterization. It was assumed that despite the delay in the pressure and flow measurement, the patient was in the same hemodynamic steady state. On a 1.5-T scanner (Magnetom Sonata; Siemens Medical Solutions, Erlangen, Germany), images of the main pulmonary artery cross section were acquired with velocity encoding perpendicular to the imaging plane. The slice location and orientation were determined as described previously (25). A two-dimensional spoiled gradient-echo pulse sequence was applied with an excitation angle of 15°, a TE of 4.8 ms, a TR of 11 ms, and a receiver bandwidth of 170 Hz per pixel. Velocity sensitivity was set to 150 cm/s, but, if appropriate, was adjusted to lower or higher values in individual cases. The velocity encoding was interleaved, resulting in a temporal resolution of 22 ms. The field of view was set to 260 × 320 mm, and the matrix size was set to 208 × 256. No k-space segmentation was applied, and acquisitions were not averaged. Acquisitions were prospectively triggered to the ECG, and during the acquisition the patients breathed freely. The ECG was recorded during the acquisition. In the image reconstruction, concomitant gradient terms were removed. Phase offset errors were removed using a time-varying variant of the method described by Lankhaar et al. (18).

Volumetric flow as a function of time was obtained from the MRI phase images after analysis with Medis Flow (Medis, Leiden, The Netherlands). Contours were drawn semiautomatically around the pulmonary artery cross section in the MRI magnitude images. The average velocity within the contour of each image was multiplied with its area. Analysis of a complete cine resulted in a volumetric flow curve with a sampling period of 22 ms. The flow curve is an average of ~200 heartbeats.

Data preprocessing. Pressure resulted from a continuous recording, whereas flow was an average of many cardiac cycles. The sampling

| Table 1. Patient characteristics and hemodynamic data |
|-------------|----------------|----------------|----------------|
| n | NONPH | CTEPH | IPAH |
| Age, yr | 54±16 | 61±13 | 51±16 |
| Male/female | 2/8 | 3/7 | 2/7 |
| mPAP, mmHg | 18±4 | 45±14* | 58±14* |
| sPAP, mmHg | 28±7 | 74±19* | 91±22* |
| dPAP, mmHg | 10±3 | 30±13* | 36±8* |
| Right atrium pressure, mmHg | 4±1 | 10±4* | 7±4 |
| Heart rate, beats/min | 73±11 | 82±14 | 89±15 |
| Cardiac index, l/min-1m-2 | 3.9±1.4 | 2.2±0.7* | 3.1±1.6 |
| Total pulmonary vascular resistance, dyn·cm-5 | 150±101 | 854±360* | 978±390* |
| SV02, % | 73±7 | 59±12* | 61±10* |

Data are means ± SD. mPAP, sPAP, and dPAP, mean, systolic, and diastolic pulmonary artery pressure; SV02, mixed venous oxygen saturation; NONPH, no pulmonary hypertension (control); CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension. *P < 0.05, significantly different from NONPH.
frequency of the pressure signal was higher (250 Hz) than that of the flow signal (45 Hz). Furthermore, differences in heart rate were found in both signals because measurements were not conducted simultaneously. Therefore, pressure and flow had to be preprocessed before analysis.

From the pressure signal, an interval of ~20 s during which the pressure is stationary (no large variations in systolic, diastolic, and mean pressure) was selected. Underdamping artifacts were removed by zero-phase filtering (25a) with a fifth-order Butterworth filter (cutoff frequency 10 Hz). The cycles in the selection were ensemble averaged. The influence of beat-to-beat variations due to breathing was reduced by setting the average of each individual cardiac cycle to the overall average of the selected interval.

The flow curve was resampled to the sampling frequency of the pressure curve by using zero padding in the frequency domain (25a). Subsequently, the start of diastole was identified (first zero crossing after its minimum). Because valvular leakage could be excluded in all patients, it was assumed that diastolic flow equals zero. Therefore, all diastolic samples were set equal to zero, and the period length of the resulting flow curve was adjusted to match the period length of the ensemble-averaged pressure by adding or deleting zero samples in diastole. Finally, to ensure a periodic flow, the last five samples (after interpolation) of flow were linearly interpolated to the first sample of flow.

Preprocessing thus yielded an average pressure and an average flow wave of the same length, sampled at the same frequency. Although $t = 0$ of both signals coincided with the R wave of the ECG, synchronization was still necessary. With the windkessel model, this was done as follows. Flow was used to predict pressure with the windkessel model. Flow was then shifted in time (i.e., samples at the end of the cardiac cycle were cyclically rotated to the beginning of the cycle), and the windkessel parameters were estimated again from pressure and the shifted flow. With the use of these new parameters, the pressure was predicted and compared with the measured pressure. Shifting of flow was repeated until the difference between predicted and measured pressure (i.e., the sum of squared residuals) was minimal. Data processing, simulation, and parameter estimation were conducted using MATLAB (version 7.0.0.19920, R14; The MathWorks, Natick, MA).

Accuracy of the energy balance method and pressure measurement. A simulation model was used to assess the accuracy of the energy balance method in the presence of distortions due to the transfer characteristics of a fluid-filled catheter. Both a pressure and a flow wave were simulated with the ventricle-vascular bed model described by Stergiopulos et al. (41). In this model, the vascular bed is modeled as a three-element windkessel model and the ventricle as a time-varying elastance. Three sets of model parameters were chosen such that the pressure and flow waves generated by the model were representative of the three patient groups used in this study. The simulated pressure wave was used as input to a second-order differential equation model of the fluid-filled catheter (10, 14). Depending on the damping and natural frequency chosen for this model, an under- or overdamped catheter could be simulated. Subsequently, the distorted pressure wave resulting from this catheter model was filtered with the Butterworth filter as described above. Both the filtered and unfiltered distorted pressure wave and the simulated flow wave were used to estimate the windkessel parameters using the energy balance method. The estimated parameters were compared with the true parameters (as initially set in the simulation). This procedure was repeated for different combinations of natural frequencies and damping coefficients.

Statistical methods. The group averages of the basic hemodynamic data and the estimated windkessel parameters of the patients were compared using one-way analysis of variance with a least significant difference (LSD) post hoc test that compares all pairs of patient groups. Differences with $P < 0.05$ were regarded as significant. Values are presented as means ± SD. Statistical analysis was conducted with SPSS 12.0.1 for Windows (SPSS, Chicago, IL).

RESULTS

Basic hemodynamic characteristics of patient groups. The characteristics of the study population are shown in Table 1. Note that although the pulmonary artery pressure seems to be lower in the CTEPH group than in the IPAH group, the difference is not statistically significant ($P = 0.083$). Also, there is no difference in PVR (calculated from mean pressure and Fick’s cardiac output, $P > 0.5$), right atrium pressure ($P = 0.39$), and mixed venous saturation ($P > 0.5$). Thus severity of the PH is comparable in both groups.

Model parameters of patient groups. An example of a preprocessed pressure-flow pair from each patient group is shown in Fig. 2. The estimated windkessel model parameters of the three patient groups are shown in Fig. 3. The NONPH group differed significantly from the CTEPH and IPAH groups.
in terms of $R$, $C$ (estimated with the energy balance method), and $Z$ ($P < 0.01$ vs. CTEPH, $P < 0.001$ vs. IPAH). As to the difference between the two groups with PH, there was a significant difference in terms of $Z$ and $R$ ($P < 0.05$) but not in terms of $C$ (Fig. 3). Thus RV afterload in terms of peripheral resistance and characteristic impedance is different in CTEPH from the RV afterload in IPAH but not in terms of pulmonary arterial compliance. All three compliance estimation methods resulted in the same significance levels for the differences in compliance among the patient groups (Fig. 3, middle).

**Comparison of compliance estimation methods.** Compliance estimated with the pulse pressure method ($C_{PPM}$) and with the ratio stroke volume over pulse pressure ($SVPP$, ratio of stroke volume over pulse pressure) correlated well with the compliance estimated with the energy balance method ($C_{EBM}$) (overall correlations: $\rho = 0.83, P < 0.0001$, $C_{EBM}$ vs. $C_{PPM}$, and $\rho = 0.85, P < 0.0001$, $C_{EBM}$ vs. $SVPP$). Also, $C_{PPM}$ and $C_{SVPP}$ correlated well overall ($\rho = 0.99, P < 0.0001$). Analyzed for each patient group separately, all three methods showed good correlations ($\rho > 0.82, P < 0.01$), except for the NONPH group. In the latter group, $C_{EBM}$ correlated weakly with $C_{PPM}$ ($\rho = 0.50, P = 0.14$) and with $C_{SVPP}$ ($\rho = 0.58, P = 0.08$). $C_{EBM}$ and $C_{SVPP}$ showed no bias with respect to each other, whereas they were consistently greater than $C_{PPM}$.

**Accuracy of pressure measurement and energy balance method.** The damping $\zeta$ and natural frequency $f_n$ of the used catheters as determined using the pressure-step apparatus (33) were $\zeta = 0.37 \pm 0.10$ and $f_n = 15.2 \pm 4.0$ Hz for the multipurpose catheter, $\zeta = 0.41 \pm 0.10$ and $f_n = 14.3 \pm 0.4$ Hz for the Swan-Ganz catheter, and $\zeta = 0.43 \pm 0.10$ and $f_n = 19.6 \pm 0.7$ Hz for the Grollman catheter. In all tests, the frequency response was adequate, as defined by Gardner (10). For the simulation model, the accuracy of the energy balance method was tested using $(\zeta, f_n)$ combinations in the ranges $\zeta = 0.25–0.55$ and $f_n = 13–21$ Hz. These ranges included all frequency responses found in the in vitro test of the catheters. A cutoff frequency of 10 Hz for the Butterworth filter was used. From the simulations it followed that without filtering, the maximum error in $Z$ and $C$ was <12% in all cases. Filtering reduced the error in the estimated parameters to \(\leqslant 9\%\), except for $C$ in the simulated NONPH case (error 3% before and 12% after filtering).

**Relationship between $R$ and $C$.** The parameters $R$ and $C$ ($C_{EBM}$) of all patients showed a strong inverse relationship, independent of the patient group to which they belonged (Fig. 4). Fitting $C = \tau/R$ to the data resulted in $\tau = 0.75$ s ($R^2 = 0.77$). This relationship implies that the product $RC$ equals 0.75 s in all patients. Indeed, the average product of $R$ and $C$ was not significantly different among the three groups (0.79 ± 0.31 in NONPH, 0.74 ± 0.37 in CTEPH, and 0.69 ± 0.22 s in IPAH). The same holds for the $RC$ times as determined from $C_{PPM}$ and $C_{SVPP}$, although the former resulted in a smaller $RC$ time (overall average 0.48 ± 0.17 s). Thus, on average, the RC time is not altered in PH.

**Relationship between $P$ and $C$.** The mean pulmonary artery pressure $P$ and $C$ ($C_{EBM}$) of all patients also showed a relationship (Fig. 5). Fitting an exponential model (19, 43) to the data,

$$C(P) = ae^{-bP}$$

resulted in $a = 6.5$ ml/mmHg and $b = 0.037$ mmHg$^{-1}$ ($R^2 = -0.62$, absolute sum of squares = 72.5), whereas fitting an inverse model,

$$C(P) = b/P$$

resulted in $b = 69.7$ ml ($R^2 = -0.16$, absolute sum of squares = 69.3). Comparison of both models with Akaike’s information criterion (21) showed that despite its better fit, the exponential model (higher $R^2$) is less likely than the inverse model (evidence ratio 6.82, corresponding to a 13% chance...
that the exponential model is most likely compared with an 87% chance that the inverse model is most likely). Similar results were found for P vs. C_dip and C_dv (both with a 96% chance that the inverse model is most likely).

DISCUSSION

In this study, a hemodynamic model of the pulmonary vascular bed was used to quantify RV afterload in three distinct patient groups. By combining standard clinical measurements of the pulmonary artery pressure and flow wave in individual patients, a difference was shown in peripheral resistance of the pulmonary artery pressure and flow wave in individual patient groups. By combining standard clinical measurements, the vascular bed was used to quantify RV afterload in three distinct groups were different from those of the NONPH group. Fitting an exponential model to the data, the model of Fung (43) showed that the term in the denominator is negligible. Thus, for comparison of the RV afterload in groups of patients, the compliance estimation method appears not to be of great importance.

Constant RC time. The RC time characterizes the exponential decay of pulmonary artery pressure during diastole (27, 35), although R and C also are important determinants of RV afterload during systole. In the past, it has been shown that there is an inverse relation between pulmonary arterial compliance and vascular resistance under normal and a wide variety of experimental conditions in both humans and dogs (27, 35). An inverse relation corresponds with a constant RC time. In our study, an inverse relationship was indeed found, but there was a difference between the value of 0.75 s that we found and the average of 0.33 s reported by Reuben (35). The correlation may be attributed to the difference in estimation methods: Reuben used the exponential decay of the pulmonary artery pressure wave in diastole from which left atrial pressure was subtracted and used PVR (=R + Z), whereas used the energy balance method (2) and used R instead of PVR.

Pressure-dependent compliance. Pressure dependence of vascular compliance agrees with earlier findings on the pulmonary artery (7, 16) and the aorta (17, 19, 22). Several models to describe the relationship between pressure and compliance have been proposed in the literature (16, 17, 19, 22), most of them being exponential. When fitted to the data, the model of Fung (43) showed that the term in the denominator is negligible, and thus the inverse model presented above suffices. Neglecting the term has the advantage that the following equation holds:

\[ RC = (P/F) \times (\beta/P) = \beta/F \]  

where F is the cardiac output. If the mean cardiac output F = 5.3 l/min = 88.9 ml/s and \( \beta = 62.6 \) ml are substituted, an RC time of 0.70 s results. This agrees very well with the RC time of 0.75 s we found.

The remarkable consistency and similarity in all patients, whether with or without PH, in both RC time and pressure-dependent compliance suggests that there are little or no structural changes in the elastic properties of the pulmonary artery in PH. The pulmonary circulation seems to keep RC time constant by the mechanism that was suggested by Sniderman et al. (38): an increased resistance R leads to an increased pressure (Ohm’s law), which in turn leads to a decrease in compliance C by a shift in position on the pressure-volume relationship of the large pulmonary artery.
Clinical value of model. It has been shown that PVR is a poor predictor of prognosis in PH (38). This may be explained in part by the fact that PVR does not reflect the entire RV afterload. In the pulmonary circulation, the pulsatile components of pressure and flow constitute as much as one-third to one-half of the total hydraulic power that is transferred from the RV to the pulmonary vascular bed (28). As a consequence, pulsatility plays a more important role in the pulmonary than in the systemic circulation. Piene and Sund (34) showed that the RV and its load are matched (i.e., pump efficiency is maximal) by the characteristic impedance of the pulmonary vascular bed, and they even suggested that pulsatility is transferred throughout the whole pulmonary vascular bed to assist the left atrium. Pulsatility and mismatching of the RV to its afterload may therefore better explain signs of clinical worsening than quantities related to steady flow only, such as PVR and mean pulmonary artery pressure (38). Thus, identifying the different components that constitute RV afterload is a prerequisite for understanding the mechanisms that lead to RV failure. Optimal insight in RV afterload would be obtained by an input impedance spectrum (26), but because input impedance spectra are difficult to interpret, a simpler model is preferable for clinical practice. It has been shown that the input impedance of the pulmonary circulation can be represented by the three-element windkessel model (11, 42). This model has the advantage that it is easy to interpret and that it is, as our findings show, sensitive enough to characterize differences in physical properties of the pulmonary vascular bed in different patient groups.

At first sight, a windkessel model may not seem to be a good representation of the pulmonary circulation. Being a lumped model, it does not contain spatial information and therefore cannot describe wave reflection phenomena, which play an important role in the pulmonary circulation. However, in this study we were interested in the arterial load on the heart and not in aspects of wave traveling and reflection. To this end, a windkessel model is adequate (42).

Clinical implications. The similar \( RC \) time in all patients may explain why changes in PVR often do not reflect clinical changes in PH patients. If it is assumed that the \( RC \) time remains constant under all circumstances, an equal decrease in PVR (e.g., due to therapy) will have a much larger impact on the compliance in patients with a low PVR than in patients with a high PVR. Thus patients with a low PVR will improve in both steady and pulsatile RV afterload, whereas patients with a high PVR only improve in steady afterload. This is illustrated in Fig. 6. Both patients have an equal improvement in PVR, but the resulting improvement in compliance of patient A is much larger than that of patient B. Changes in compliance, on the other hand, may better reflect clinical changes in PH patients, because this has recently been shown to be a strong and independent predictor of survival in IPAH (24). It still remains to be studied whether changes in compliance also better reflect clinical changes and whether the \( RC \) time remains the same during treatment. If so, the \( RC \) time may be used to retrospectively estimate compliance from resistance.

Limitations. The NONPH group consisted of patients with unexplained complaints that led to the suspicion of PH. Therefore, they may not be completely normal. The NONPH group has a mean pulmonary artery pressure of 18 mmHg, which is slightly elevated compared with the normal value of 12 mmHg given in literature (12, 23). However, because a catheterization is required, it has been acceptable practice to use such a control group (30). Furthermore, all patients were screened extensively before inclusion in the study according to the clinical guidelines for the management of PH (1). IPAH patients reactive to NO were excluded. Therefore, no conclusions can be drawn on compliance changes in response to NO or on reactive IPAH.

The measurements of pressure and flow were not conducted simultaneously but were treated as if they had been. Simultaneous measurement of pressure and flow in the human pulmonary artery is difficult due to the anatomic position of the artery. Several methods have been used in the past (15, 28, 30, 31), but most of them cannot be applied routinely in the clinic because they require either high operator skills (with observer variability as a consequence) or expensive devices. The feasibility study of Muthurangu et al. (31) bears most resemblance with the current study. Their setup with MR-guided catheterization would be preferable, but in most clinics (as in ours) it is not available. Although nonsimultaneity may lead to errors in the parameter estimations due to variations in the state of the patient, we assume that it will not affect accuracy to a great extent. Because parameters are estimated from averaged signals, short-term variations will average out. The remaining signals reflect the long-term state of the pulmonary vascular bed. For stable patients, it may be safely assumed that this will not change within a week.

Pulmonary artery pressure was measured using fluid-filled catheters. As pointed out by numerous authors (4, 13, 20, 27), pressure waves measured with a fluid-filled catheter have to be interpreted cautiously, because the pressure waveform may be distorted by the dynamic response of the catheter. By taking care of a properly flushed catheter system, we optimized the catheter response. Remaining underdamping artifacts were filtered out. Furthermore, we concluded from a sensitivity test on the parameter estimation method that the energy balance method was robust in the presence of distortions.

In conclusion, this study has shown that it is possible to detect differences in RV afterload in distinct patient groups by using a three-element windkessel model. The windkessel parameters were shown to be different in patients with NONPH, CTEPH, and IPAH. Furthermore, it was shown that a strong relationship exists between resistance and compliance and between pres-
sure and compliance, which indicates that the elastic properties of the large pulmonary arteries remain unaltered in PH.

REFERENCES


