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Vascular function

Proportional relations between systolic, diastolic and mean pulmonary artery pressure are explained by vascular properties



**Taco Kind¹, Theo J. C. Faes²
Anton Vonk-Noordegraaf¹, Nico Westerhof^{1,3}**

**Departments of ¹Pulmonary Diseases, ²Physics
and Medical Technology, ³Physiology, Institute for
Cardiovascular Research, VU University Medical
Center, Amsterdam, the Netherlands**

Abstract

Recently, it has been shown that proportional relationships exist between systolic, diastolic and mean pulmonary artery pressure (P_{sys} , P_{dia} and P_{mean}) and that they are maintained under various conditions in both health and disease. An arterial-ventricular interaction model was used to study the contribution of model parameters to the ratios $P_{\text{sys}}/P_{\text{mean}}$, and $P_{\text{dia}}/P_{\text{mean}}$. The heart was modeled by a time-varying elastance function, and the arterial system by a three-element windkessel model consisting of peripheral resistance, R_p , arterial compliance C_a , and pulmonary artery characteristic impedance Z_0 . Baseline model parameters were estimated in control subjects and compared to values estimated in patients with pulmonary hypertension. Results indicate that experimentally derived ratios $P_{\text{sys}}/P_{\text{mean}}$ and $P_{\text{dia}}/P_{\text{mean}}$ could be accurately reproduced using our model (1.59 and 0.61 vs. 1.55 and 0.64, respectively). Sensitivity analysis showed that the (empirical) constancy of $P_{\text{sys}}/P_{\text{mean}}$ and $P_{\text{dia}}/P_{\text{mean}}$ was primarily based on the inverse hyperbolic relation between total vascular resistance (R_T ; calculated as $R_p + Z_0$) and C_a , (i.e. constant $R_T C_a$ product). Of the cardiac parameters, only heart rate affected the pressure ratios, but the contribution was small. Therefore, we conclude that proportional relations between systolic, diastolic and mean pulmonary artery pressure result from the constancy of $R_T C_a$ thus from pulmonary arterial properties, with only little influence of heart rate.

Key Words: pulmonary artery pressure ■ proportional pressure ■ elastance model ■ three-element windkessel model

Introduction

RECENTLY, IT WAS SHOWN that proportional relationships exist between systolic, diastolic and mean pulmonary artery pressure, and that they are preserved under various conditions in both health and disease¹⁻³. Although these empirical relations have shown to be of practical relevance, the physiological mechanism underlying these relations has not yet been elucidated. Since pressure is the result of the interaction between right heart and lung circulation, these proportional relations may, in principle, be explained by ventricular and vascular properties contributing to pulmonary artery pressure.

Recently, Lankhaar et al.^{4,5} showed in a cohort of normal subjects and patients with pulmonary arterial hypertension (PAH) before and after treatment, that pulmonary resistance (R) and compliance (C) are related by an inverse hyperbolic relationship. This inverse relation might, in part, be the underlying mechanism of the proportional relations between the systolic, diastolic and mean pressure.

The aim of this study is to investigate how the proportionality of the pulmonary artery pressure components depends on cardiac and arterial parameters, and, in particular, the inverse relation between R and C , using an interaction model of the pulmonary circulation^{6,7}.

Methods

Mathematical model of the pulmonary circulation

Pulmonary artery pressure $P_a(t)$ was computed using an arterial-ventricular interaction model (Figure 1A)^{6,7}. The arterial bed was modeled using a three-element lumped-parameter windkessel model^{4,8,9} consisting of characteristic impedance of the proximal pulmonary artery (Z_0) and a combination of peripheral pulmonary resistance (R_p) and pulmonary arterial compliance (C_a) (Figure 1A). Right ventricular (RV) function was modeled using a linear time-varying elastance model¹⁰, including a description of the normalized elastance as a function of time as proposed by Senzaki et al.¹¹ (Figure 1A). Although originally introduced for the left ventricle, the elastance model is assumed to be valid for the RV¹².

Elastance is parameterized by end-systolic elastance (E_{es}), end-diastolic elastance (E_{ed}), intercept volume (V_0) of the pressure-volume relationship, heart rate (HR), time to reach end-systolic elastance (t_{es}). Diastolic filling of the ventricle is described with a venous filling pressure of the RV (P_v), and a small venous resistance (R_v) over which filling takes place. The tricuspid and pulmonary valves were assumed sufficient. Left atrial pressure (P_{la}) was neglected in the model (set at zero). The model directly yields pulmonary arterial and ventricular pressure (Figure 1D).

Model parameters and simulations

Model parameters were estimated from data measured in a group of 11 control subjects (Group 1; see paragraph patient selection) and then averaged to obtain a single set of baseline parameters. Arterial parameters, Z_0 , R_p and C_a , were estimated from measured pressure and flow using a prediction-error minimization method. Instead of averaging C_a , baseline C_a was determined by averaging $1/C_a$ followed by calculating the reciprocal. This procedure was performed because of the inverse relation between resistance and compliance. Elastance parameters were obtained as follows (see also Figure 1C). End-systolic elastance was calculated as $E_{es} = (P_{\max} - P_{es}) / V_s$, with P_{\max} maximum isovolumic pressure, P_{es} end-systolic pulmonary artery pressure, and V_s stroke volume. P_{\max} was computed using a single-beat estimation method¹³⁻¹⁵; P_{es} was determined at end-systole, t_{es} , obtained from pulmonary artery flow $F_a(t)$ at zero flow. Note that P_{es} is lower than the pressure at the left top corner in a pressure-volume loop and, therefore, E_{es} is also lower than elastance that would be determined from a pressure-volume loop.

The $F_a(t)$ tracings were also used to derive stroke volume, V_s . Subsequently, an approximation of V_0 was made using the $E_{es} = P_{es} / (V_{es} - V_0)$, where V_{es} was derived from MRI data (see paragraph patient selection and measurements). Diastolic pressure of the RV was assumed to be equal to pulmonary venous pressure (P_v) and E_{ed} was estimated by $P_v / (V_{ed} - V_0)$, where V_{ed} was derived from MRI data. The ‘venous’ resistance (R_v) was arbitrarily set at 0.1 mmHg·s/ml⁷.

Numerical integration was performed using the MATLAB ordinary differential equations solver ODE15S (R14SP1), supporting stiff differential equations and a variable order method. For each simulation run, 25 heartbeats were simulated to obtain a steady state, and only the last beat was taken to obtain a single pulmonary artery pressure curve (figure 1D).

Data analysis

Proportional pressure relations

Previously, proportional relations have been reported between systolic (P_{sys}) and mean (P_{mean}) pressure^{1,3}, and between diastolic (P_{dia}) and P_{mean} ¹. The reported intercepts of these linear relations were very small (i.e. ranging -0.22 to 2 mmHg for P_{sys} and P_{mean} ¹⁻³ and -0.66 for P_{dia} and P_{mean} ¹) in comparison to the range of systolic and diastolic pressures. Thus, these numerically insignificant intercepts can be neglected in a first order approximation, and pressure components can therefore be considered not only linearly related, but also proportionally related.

In this study, the proportionalities are expressed by the ratios $K_{\text{sys}} = P_{\text{sys}} / P_{\text{mean}}$ and $K_{\text{dia}} = P_{\text{dia}} / P_{\text{mean}}$ and were tested in both our measured and simulated data and, moreover, were compared to data reported in literature.

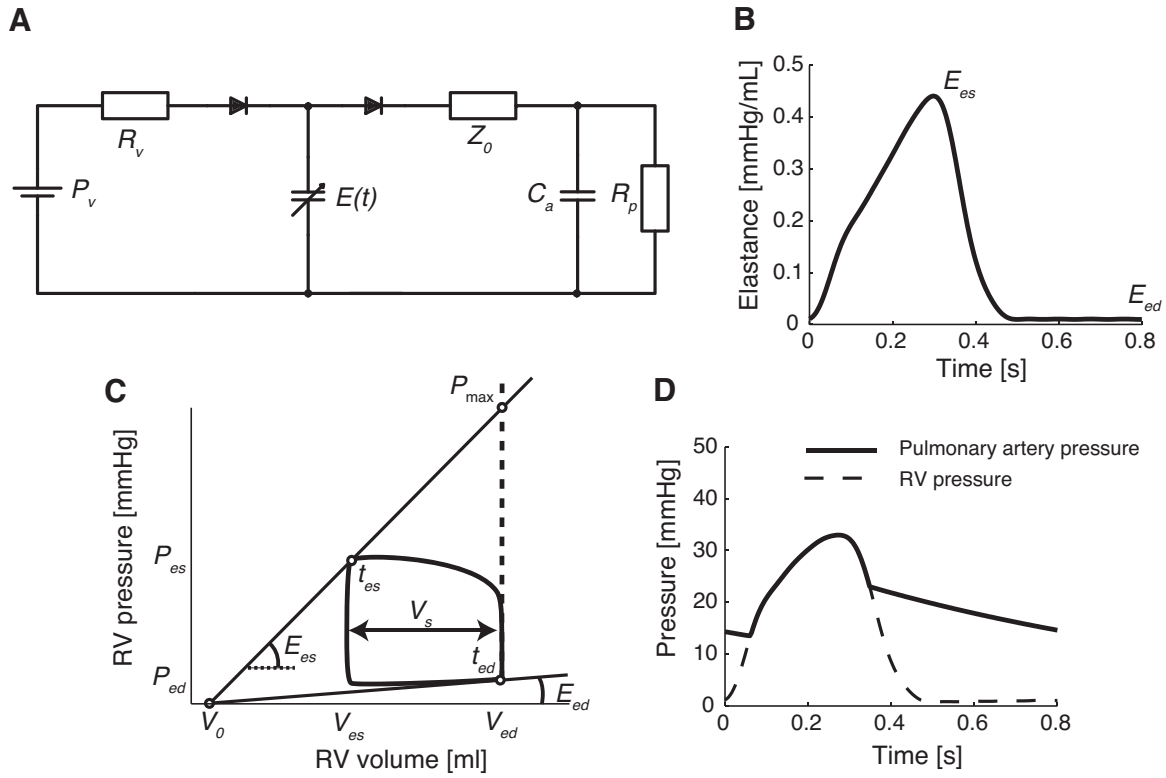


Figure 1 - (A) Arterial-ventricular interaction model. The arterial system is modeled by a three-element windkessel model, consisting of characteristic impedance (Z_0), peripheral vascular resistance (R_p) and arterial compliance (C_a). The heart is modeled using a time-varying elastance model, with elastance function constructed using a normalized elastance curve¹¹ as depicted in (B). A Pressure-Volume loop with the major ventricular parameters is shown in (C). Examples of simulated pulmonary artery pressure $P_a(t)$ and right ventricular pressure $P_{RV}(t)$ are shown in (D). E_{es} = end-systolic elastance; E_{ed} = end-diastolic elastance; V_0 = intercept volume; P_v = venous filling pressure; R_v = venous resistance; t_{es} = time to reach end-systolic elastance; t_{ed} = time to reach end-diastolic elastance; V_s = stroke volume; P_{max} = maximum isovolumic pressure.

Definition of the RC-time

To assess the hypothesized association between the inverse proportional RC-relation (i.e. constant RC-time)^{4,5,16,17} and the pressure proportionalities, the definition of RC-time requires some attention.

The three-element windkessel model consists of two resistive components, peripheral resistance (R_p) and characteristic impedance, which is also modeled as a resistance (Z_0), thus total pulmonary vascular resistance (R_T) equals the summation of these components. The constant product not only holds for R_p and C_a ⁴, but also for R_T and C_a ^{5,18,19}. The product R_p times C_a determines diastolic pressure decay, whereas the product R_T times C_a also determines systolic pressure loading. Moreover, Z_0 primarily affects P_{sys} , while R_p both affects P_{mean} , P_{sys} and P_{dia} . In this study we considered the product of total resistance and compliance (i.e. R_T times C_a).

A drawback of the three-element windkessel model is that the characteristic impedance is not an Ohmic resistance but an impedance not existing for mean pressure and flow. In this model the magnitude (modulus) is constant with value $|Z_0|$ for all frequencies. Thus, for low frequencies total impedance of the arterial system is described less accurate. In the physiological range, however, the errors in systolic and diastolic pressure are small as has been shown by Stergiopoulos et al.⁷. Moreover, being a lumped model, it does not contain spatial information and therefore cannot describe wave reflection phenomena⁷.

Contribution of arterial and cardiac changes to K_{sys} and K_{dia}

Sensitivity analysis was performed to study the effect of isolated alterations in arterial parameters (R_T and C_a) and ventricular parameters (HR, E_{es} , E_{ed} , V_0 , t_{es} , P_v) on $P_a(t)$, (including K_{sys} and K_{dia}). In these analyses, parameter values were varied from 50% to 250% of baseline values as determined from mean values of the control group (Group 1; see paragraph patient selection)

For the arterial parameters, two scenarios were simulated, namely with and without the constraint of a constant RC-time. The rationale of this approach is that experimental data shows constant K_{sys} and K_{dia} with obvious large mutual differences in R_T and C_a but constant $R_T \cdot C_a$, and sensitivity analysis using the model should reproduce this constancy. In the first scenario, it was assumed that no proportional relation exists between R_T and C_a . Thus, the individual effect of varying R_T or C_a on K_{sys} and K_{dia} were determined. For the second data set, it was assumed that $R_T \cdot C_a$ is constant. Hence, an increase in R_T is accompanied by a proportional decrease in C_a (or vice versa) and the combined effect on K_{sys} and K_{dia} was studied.

Patient selection and measurements

The institutional ethics committee approved the study and all patients gave informed consent. Included were 11 patients suspected of pulmonary hypertension at echocardiography but in whom the diagnosis could not be established. These patients served as control subjects and were used to compute baseline model parameters (Group 1). We also included 98 patients (Group 2) diagnosed with PAH. In 19 of these patients the complete set of model parameters was computed for comparison purposes (Group 2a). In the remainder of patients (Group 2b), we only determined P_{sys} , P_{dia} , P_{mean} , the ratios K_{sys} and K_{dia} and heart rate.

All patients were evaluated according to a standard diagnostic protocol. Pressure was measured with a 6-Fr fluid-filled, single-lumen, multipurpose catheter (Cordis, Miami Lakes, FL) in the main pulmonary artery and in the right ventricle. All measurements were carried out after careful flushing and use of heparin to prevent catheter artifacts.

Pressure tracings of non-PH patients and subset of PAH patients were digitally stored using an AD instruments PowerLab acquisition system. These patients also underwent cardiac MR imaging for flow and volume measurements within 1 day before or after right heart catheterization. Despite this time difference in the measurements, it was assumed that the patient was in the same hemodynamic steady state. MR examination was performed on a 1.5-T Siemens Avanto MRI system (Siemens Medical Solutions, Germany), equipped with a 6-element phased-array coil. Main pulmonary artery flow was measured using phase-contrast velocity quantification. 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 initially set to 150 cm/s, but adjusted to lower or higher values in individual cases. Velocity encoding was interleaved resulting in a temporal resolution of 22 ms. Field of view was set to 260x320 mm, and the matrix size was set to 208x256. Pulmonary flow was obtained using Medis Flow software package (Medis, Leiden, The Netherlands). Contours around the pulmonary artery cross section were semi-automatically drawn in the MRI magnitude images. The average velocity within each contour was multiplied with its area to obtain a volumetric flow curve as a function of time.

End-diastolic volume was obtained from a stack of short-axis slices with a typical slice thickness of 5 mm and an interslice gap of 5 mm, fully covering both ventricles from base to apex. Endocardial surfaces, excluding trabeculae and papillary muscles, were manually traced using Mass (Medis, Leiden, The Netherlands) to obtain end-diastolic and end-systolic volumes.

Data pre-processing

Due to the time-delay between pressure and flow measurements and the different sampling rates (250 Hz versus 45 Hz, respectively) the data were pre-processed. This was performed in a similar manner as in⁴. Briefly, a stationary pressure interval of about 25 seconds with no underdamping artifacts was selected. The selection was filtered using a fifth-order Butterworth (cut-off frequency was 10 Hz). Subsequently, end-diastole was identified using the R wave of the ECG and the cardiac cycles were ensemble averaged. The flow curve was resampled to the sampling rate of pressure.

Synchronization was performed using the following approach. The measured flow and pressure curves were used to estimate a three-element windkessel model and to predict pressure. The error between measured and predicted pressure was determined (i.e., the sum of squared residuals). Flow was then shifted in time and the windkessel model was estimated again to predict pressure. Shifting of the flow curve was repeated until the difference between predicted and measured pressure was minimal.

Table 1 - Hemodynamics and model parameters in control subjects and PAH patients

| Parameter | Group 1 Controls (n=11) | 2a PAH (n=19) | 2b PAH (n=79) |
|---|----------------------------------|---------------------|---------------------|
| Systolic PA pressure (P_{sys}), mmHg | 32 ± 6 | 86 ± 18* | 81 ± 22* |
| Diastolic PA pressure (P_{dia}), mmHg | 13 ± 4 | 36 ± 9* | 30 ± 10* |
| Mean PA pressure (P_{mean}), mmHg | 21 ± 4 | 55 ± 11* | 50 ± 13* |
| Ratio K_{sys} ($P_{\text{sys}}/P_{\text{mean}}$) | 1.52 ± 0.15 | 1.57 ± 0.13 | 1.59 ± 0.16 |
| Ratio K_{dia} ($P_{\text{dia}}/P_{\text{mean}}$) | 0.58 ± 0.10 | 0.65 ± 0.07 | 0.59 ± 0.09 |
| Characteristic impedance (Z_0), mmHg·s/ml | 0.05 ± 0.01 | 0.11 ± 0.05* | not determined |
| Peripheral resistance (R_p), mmHg·s/ml | 0.30 ± 0.08 | 0.90 ± 0.37* | not determined |
| Total vascular resistance (R_T), mmHg·s/ml | 0.32 ± 0.09 | 1.01 ± 0.39* | not determined |
| Arterial compliance (C_a), ml/mmHg | 5.85 ± 2.71 | 0.98 ± 0.53 * | not determined |
| Inverse arterial compliance ($1/C_a$), mmHg/ml | 0.35 ± 0.13 | 1.37 ± 0.77* | not determined |
| $R_T C_a$ -time, seconds | 0.82 ± 0.24 | 0.76 ± 0.29 | not determined |
| End-systolic elastance (E_{es}), ml/mmHg | 0.44 ± 0.41 | 1.51 ± 0.87* | not determined |
| End-diastolic elastance (E_{ed}), ml/mmHg | 0.01 ± 0.03 | 0.06 ± 0.06 | not determined |
| Intercept volume (V_0), ml | -50 ± 106 | 71 ± 87* | not determined |
| Time to reach E_{es} (t_{es}), seconds | 0.33 ± 0.04 | 0.35 ± 0.07 | not determined |
| Heart rate (HR), beats/minute | 77 ± 13 | 83 ± 15 | 80 ± 16 |
| Filling pressure (P_v), mmHg | 6.5 ± 7.0 | 7.9 ± 6.0* | not determined |
| End-diastolic volume (V_{ed}), ml | 103 ± 64 | 173 ± 63* | not determined |
| Peak isovolumic pressure (P_{max}), mmHg | 48 ± 14 | 124 ± 47* | not determined |
| Stroke volume (V_s), ml | 68 ± 17 | 46 ± 18* | not determined |

Values are mean ± SD (ranges in parentheses), with the average over all cardiac cycles. Results are shown for original time and for normalized time. V_0 = constant intercept volume; $V_0(t)$ = time-varying intercept volume; E_{es} = end-systolic elastance. *Values of V_0 are equal for both original and normalized time, since these are computed using the end-systolic pressure-volume relationship in both situations. $^{\dagger}E_{\text{es}}$ is equal for the formulation with V_0 constant and for $V_0(t)$ time-varying, if time is normalized since the end-systolic pressure-volume relationship is equal in both formulations.

Results

Patient hemodynamics and model parameters

Hemodynamic data and model parameters are summarized in Table 1. Figure 1D shows a simulated pulmonary arterial pressure curve using the arterial-ventricular interaction model with average parameter values of the control group (Group 1) in table 1.

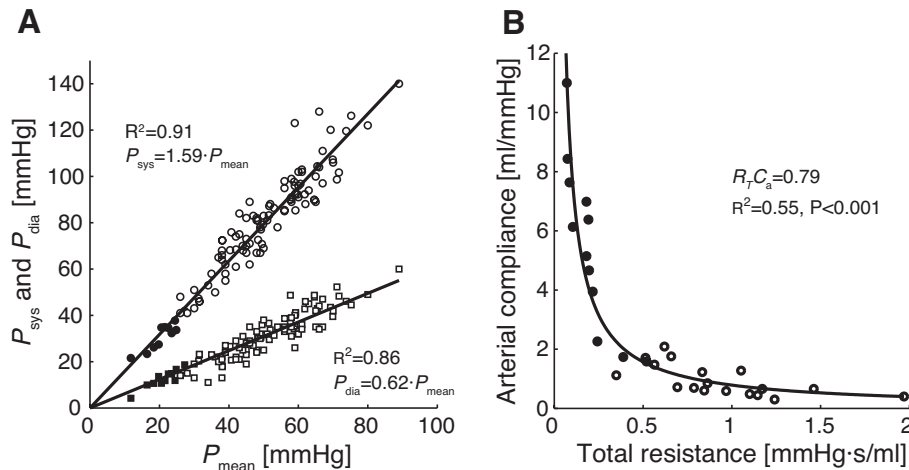


Figure 2 - (A) Interrelationship of pulmonary artery pressures for the control subjects and PAH patients (group 1 and group 2a + 2b in table 1); (B) inverse proportional relation between total vascular resistance ($R_T = Z_0 + R_p$) and arterial compliance (C_a) for the control subjects (group 1) and subset of PAH patients (group 2a). PAH patients are indicated with open symbols, control subjects are indicated with filled symbols. The goodness-of-fit of the relationships is expressed as the coefficient of determination (R^2).

Proportional pressure components and inverse RC-relation

Figure 2A shows the strong relations of diastolic and systolic pressure with mean pressure in the experimental data (control subjects, Group 1, and PAH patients, Groups 2a + 2b). In the experimental data ratios K_{sys} and K_{dia} were found 1.59 ± 0.15 and 0.61 ± 0.09 , respectively. These values were not statistically different from the ratios obtained using the arterial-ventricle model with model parameters set at values of Group 1: $K_{sys} = 1.55$ and $K_{dia} = 0.64$, respectively. Figure 2B shows the strong inverse proportional relation between R_T and C_a for all subjects in Group 1 and 2a ($R^2 = 0.89$, $P < 0.001$), with a RC-time of 0.79 second. Note that the RC-time does not differ significantly in the control subjects (0.82) and PAH patients (0.76; see Table 1).

Sensitivity analysis

Arterial parameters

Figure 3 shows the effect of isolated changes in arterial parameters on the arterial pressures (P_{sys} , P_{dia} and P_{mean} ; top row) and pressure ratios (K_{sys} and K_{dia} ; bottom-row), under the condition of a non-constant $R_T C_a$ -time (scenario 1) and a constant $R_T C_a$ -time (scenario 2). Parameters were varied from 50% to 250% of baseline values (Group 1; Table 1). The figure depicts that P_{sys} , P_{dia} , P_{mean} vary considerably with varying parameters, as well for K_{sys} and K_{dia} in case of a non-constant RC-time. In case of a constant RC-time K_{sys} and K_{dia} remain constant supporting the experimental results in Figure 2A. Note that, with non-constant $R_T C_a$ -time (scenario 1) the effects on K_{sys} and K_{dia} were reversed but of similar magnitude, while for the constant $R_T C_a$ -time (scenario 2) the K_{sys} and K_{dia} are almost constant.

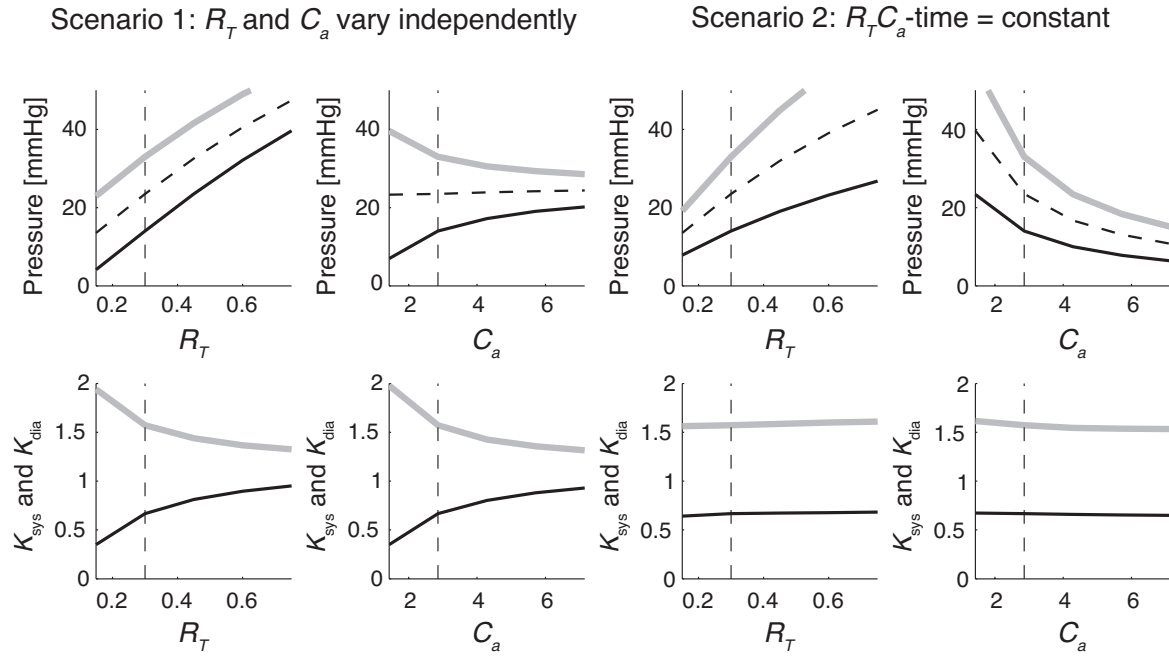


Figure 3 - Sensitivity analysis of isolated changes of arterial parameters to P_{sys} , P_{dia} and P_{mean} (upper panels), and to $K_{\text{sys}} = P_{\text{sys}} / P_{\text{mean}}$ and $K_{\text{dia}} = P_{\text{dia}} / P_{\text{mean}}$ (lower panels). The left four panels show results when total arterial resistance, R_T , or arterial compliance, C_a , is varied (scenario 1); the right four panels show the results when RC-time set constant in the model, i.e. an increase in R_T is accompanied by a proportional decrease in C_a (scenario 2). For all simulations, model parameters from Group 1 in table 1 were used, with baseline values represented by the vertical dashed lines. Systole is indicated by thick lines, diastole by thin lines, and mean pressure by dashed lines. The analysis shows that the ratios K_{sys} and K_{dia} are constant when RC-time is constant (bottom panels scenario 2).

Ventricular parameters

Figure 4 shows the effect of isolated changes in ventricular parameters to the arterial pressures and their ratios. The figure depicts that P_{sys} , P_{dia} , P_{mean} vary considerably with varying ventricular parameters, with the exception of intercept volume V_0 . The effects on K_{sys} and K_{dia} are small except for HR that has some effect on K_{sys} and K_{dia} . The simulations were performed assuming that left atrial pressure (P_{la}) is zero. However, a change of this pressure of 8 mmHg results in linear increases of 3.5% in K_{sys} and 6.2% in K_{dia} .

Contribution of heart rate to pressure proportionalities

Sensitivity analysis indicated that changes in heart rate affected both K_{sys} and K_{dia} , particularly at lower heart rates. This influence was further studied in experimental data of control subjects (group 1) and PAH patients (group 2a+2b). Results are shown in figure 5. The figure illustrates that although regression analysis did not reveal significant relations, an increase in heart rate shows a trend towards increasing K_{sys} and decreasing K_{dia} (thin lines). These trends seem to correspond to the trends found for simulation data

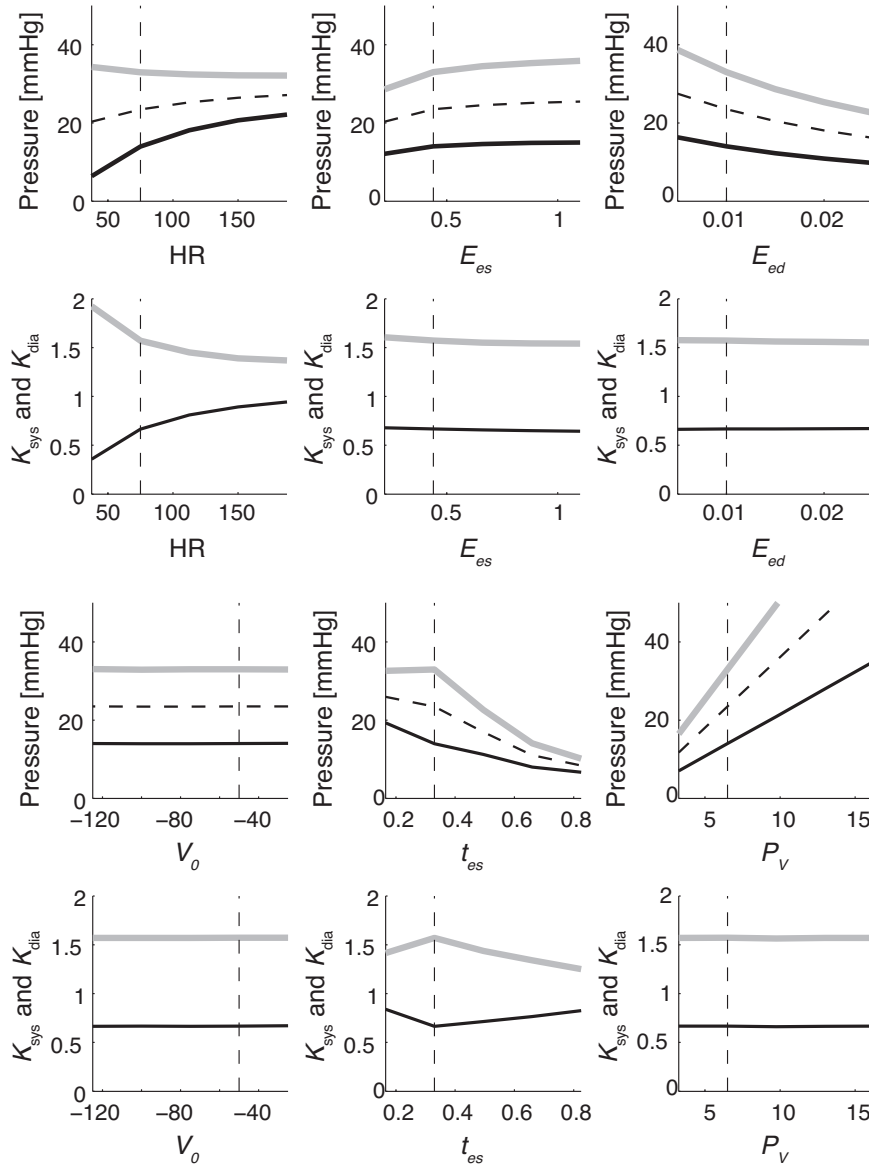


Figure 4 - Sensitivity analysis of isolated changes of ventricular parameters on P_{sys} , P_{dia} and P_{mean} (upper panels), and to $K_{\text{sys}} = P_{\text{sys}} / P_{\text{mean}}$ and $K_{\text{dia}} = P_{\text{dia}} / P_{\text{mean}}$ (lower panels). Results are shown for varying heart rate (HR), end-systolic and end-diastolic ventricular elastance (E_{es} and E_{ed}), intercept volume (V_0), time to reach end-systole (t_{es}) and venous filling pressure (P_v). For all simulations model parameters from group 1 in table 1 were used. Systole is indicated by thick lines, diastole by thin lines, and mean pressure by dashed lines.

(dotted lines; lines are equal to those in figure 4E but with a different range of heart rate). Note, however, that the simulation data is only based on baseline parameters, whereas the cardiac states in the experimental data are heterogeneous, possibly resulting in a more pronounced scatter around the trend.

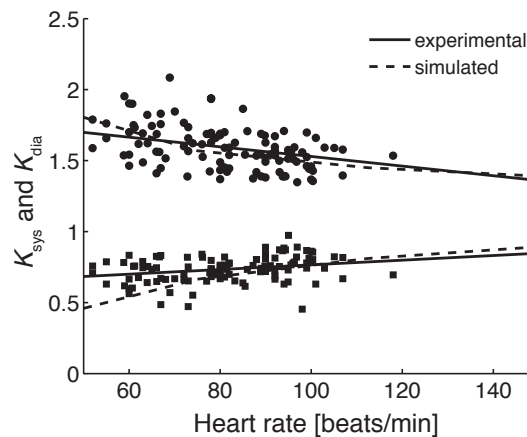


Figure 5 - Effect of heart rate (HR) on pressure ratios K_{sys} (dots) and K_{dia} (squares) in the control subjects (group 1) and PAH patients (group 2a +2b). Although regression analysis did not reveal significant relations, an increase in heart rate shows a trend towards increasing K_{sys} and decreasing K_{dia} (thin lines). The experimental data and the simulated data show similar trends (dotted lines as in figure 4).

Simulated and experimental pressure relations

Sensitivity analysis also revealed that isolated changes of model parameters yielded either constant pressure ratios, or had effects ‘mirrored about unity’ on K_{sys} and K_{dia} (Figure 3 and 4). This mirrored behavior implies a constant product of these ratios, which is close to unity in the simulations (e.g. for baseline values: $1.55 \cdot 0.64 = 0.99$) as well in experimental data ($1.59 \cdot 0.61 = 0.97$; Figure 2A). These results confirm the previous observation of Chemla et al.²⁰ that mean pulmonary pressure is the geometric mean of systolic and diastolic pressure. This can be understood, since the product of K_{sys} and K_{dia} is close to unity so that $P_{mean} = \sqrt{P_{sys} \cdot P_{dia}}$. This relation, however, is independent of a constant RC-time.

Discussion

We found that the proportional relations between systolic and diastolic pressure with mean pressure¹⁻³ are based on the constant RC-time of the pulmonary arterial system, a finding previously reported by Lankhaar^{4,5}. This association was observed using an interaction model of the pulmonary circulation^{6,7} of which the data are presented in Figures 3 and 4. Cardiac parameters had negligible effect on the proportionality of pressures, except for a small effect of heart rate (Figure 5).

Originally, the pressure relations were reported as linear relations with a slope and intercept. Since the intercept values appeared to be small we neglected these values for simplification of the analysis. Hence, the slopes can be interpreted as the pressure ratios $K_{sys} = P_{sys} / P_{mean}$ and $K_{dia} = P_{dia} / P_{mean}$. Using our model with baseline control parameters

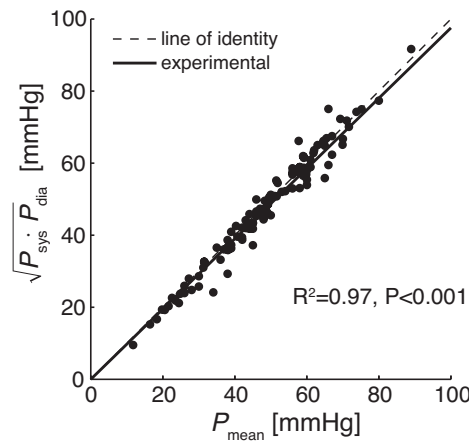


Figure 6 - Relation between P_{mean} and $\sqrt{P_{\text{sys}} \cdot P_{\text{dia}}}$. Clearly, all points are close to the line of identity (gray line), implicating that P_{mean} is the geometric mean of P_{sys} and P_{dia} .²⁰

(Group 1 in table 1) experimentally derived proportional pressure relations could be reproduced accurately: simulated K_{sys} and K_{dia} were very close to our experimental ratios (1.55 and 0.64 vs. 1.59 ± 0.15 and 0.61 ± 0.09 , Figure 2A). The relations are also quantitatively close the relations reported by Chemla et al.³ who were the first to show linear pressure relations, as: $P_{\text{mean}} = 0.61 \cdot P_{\text{sys}} + 2$, which can be rewritten to $P_{\text{sys}} = 1.64 \cdot P_{\text{mean}} - 3.3$. This relation was based on high-fidelity measurements in a group of normal subjects and in PAH patients. Similar relations were derived by Friedberg et al.² using echocardiography ($P_{\text{mean}} = 0.69 \cdot P_{\text{sys}} - 0.22$ or rewritten to $P_{\text{sys}} = 1.55 \cdot P_{\text{mean}} + 0.32$) and by Syeed et al.¹ using high-fidelity pressure sensors ($P_{\text{sys}} = 1.5 \cdot P_{\text{mean}} - 0.45$). Our results also agree with the reported relations between P_{dia} and P_{mean} by Syeed et al.¹, who derived $P_{\text{dia}} = 0.71 \cdot P_{\text{mean}} - 0.66$. Therefore we can conclude that the proportionality of pressures in the pulmonary artery is a universal finding. The proportionality also implies that pulse pressure is proportional to mean pressure with a factor of about 0.99 ± 0.23 ($= K_{\text{sys}} - K_{\text{dia}}$), i.e. pulse pressure is close to mean pressure in magnitude.

Several studies in the systemic circulation have shown that brachial and especially aortic pulse pressure are better determinants of cardiovascular events than mean pressure²¹⁻²³. We here show that, in the pulmonary circulation, pulse pressure can be deduced from mean pulmonary pressure and is proportional to it, and, thus, does not provide more information than mean pressure.

Using our model we showed that for non-constant RC-time (scenario 1), the pressure ratios were strongly influenced by arterial parameters, while for constant RC-time (scenario 2) changes in arterial parameters had negligible effect on the pressure ratios. From this we conclude that the constant RC-time is a necessary condition to maintain the proportional relations reported in literature¹⁻³. The constant RC-time is also present in our experimental data (Figure 2B) and corresponds to previous observations that RC-time is

similar in health and disease⁴, and also before and after treatment⁵.

Sensitivity analysis indicated that ventricle parameters hardly affected pressure ratios with the exception of heart rate. However, the influence of heart rate proved to be small for the range of heart rate variation observed in supine resting conditions (Table 1 and Figure 5). Even so, with our model the small influence could be predicted (Figure 5), underpinning the validity of the model.

Clinical consequences of the constant RC-time are that cardiac output can be increased more when a resistance decrease is accompanied by a compliance increase (as in mild PH) than when resistance alone decreases with only very small increase in compliance (as in severe PH) (5). Another consequence of the constant RC-time is the recently observed proportionality in oscillatory power and total hydraulic power generated by the RV²⁴.

In the present paper we aimed to explain the relation between the empirically derived constant RC-time and the proportionality of pulmonary artery pressures, rather than why the RC-time of the pulmonary arterial tree is constant.

We hypothesize that the constant RC-time can be explained by two mechanisms. The first mechanism has been suggested by Sniderman et al.²⁵ who stated that an increase in resistance leads to an increase in pressure (Ohm's law), which in turn leads to a decrease in compliance as a result of the nonlinear pressure-diameter relation of pulmonary arteries. This would imply that the constant RC-time does not result from structural changes but from the elastic properties of the arteries. The second mechanism could be based on a rather uniform distribution of resistance and compliance over the vascular bed. This is in contrast to the systemic circulation where the large arteries (in particular the aorta) are the most compliant vessels²⁶, but serve virtually no role in the regulation of pressure. In contrast, the small arteries and arterioles play a key role in pressure regulation and mainly determine the vascular resistance.

The hypothesis of uniform distribution of resistance and compliance in the pulmonary tree is supported by the observation that compliance of the proximal arteries is rather small compared to the total compliance of the pulmonary system¹⁸. It has also been observed that RC-time is constant both in normal and obstructed vascular beds, implicating small variations in RC-time along artery branches.

Validation of these hypotheses requires a distributed model of the pulmonary vascular bed accounting for anatomical and mechanical vessel characteristics. Another advantage of such a model is that regional impedances and the effect of wave reflections on global RC-time can be studied.

Finally, we acknowledge some potential limitations of this study. Windkessel parameters were estimated by ignoring left atrial pressure. This results in an overestimation of peripheral resistance and thus RC-time. However, the relative variance in RC-time was

comparable to Lankhaar et al.⁵ which may indicate only a small variation in atrial pressure and is not of relevance as it is just a systemic error. Another limitation regards the estimation of RV elastance parameters. These parameters could probably be estimated more accurately using multiple pressure-volume loops instead of the ‘single beat method’ used here, although our model reproduced the empirical pressure relations well.

Conclusions

We conclude that the constant RC-time is a necessary condition to have proportional relations between systolic and diastolic pressures with mean pulmonary artery pressure. With the constant RC-time, pressure ratios were hardly affected by variations in arterial and ventricular parameters. Although pressure ratios were sensitive to variations in heart rate, the absolute variations in heart rate was so small to have significant effects. Future studies should elucidate the physiological mechanism behind this constant value of RC-time in the pulmonary circulation.

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