Summary and discussion

J.W. Lankhaar

Department of Pulmonary Diseases, Institute for Cardiovascular Research
VU University Medical Center, Amsterdam

11.1 Introduction

Knowledge on diagnosis and treatment of pulmonary hypertension (PH) has greatly improved during the last decade, but the disease still confronts clinicians with many challenges. The functional assessment of the pulmonary vascular bed in particular is difficult, because parameters that accurately describe its status are lacking. This hampers both diagnosis and treatment monitoring. The research described in this thesis aimed at assessing to what extent additional clinically relevant information is obtained when different hemodynamic measurements are combined using a mathematical model. Since our focus was on clinical application, we limited ourselves as much as possible to standard clinical measurements. In this concluding chapter, we review the most important results and seek to place them in context. Furthermore, we present some new hypotheses that may initiate further research.

11.2 Measurement accuracy

A model-based approach may demand a higher measurement accuracy for the signals than is presently the case. In this thesis, we mainly focused on measurements of pulmonary artery pressure and flow.

For accurate measurement of an arterial pressure waveform, high-fidelity catheter-tip manometers are preferred, but in clinical practice, pulmonary artery pressure is still most often measured with fluid-filled catheters. The drawbacks of fluid-filled catheters have long been recognized.\textsuperscript{1-3} This technique results in excessively smooth pressure signals in case of overdamping or resonance artefacts in case of underdamping. In literature, much attention has been paid to prevention of signal distortion due to the catheter transfer, but relatively little attention has been to removal of underdamping artefacts in retrospect. In Chapter 3, we presented a fully-automatic post-processing method for the correction of underdamping artefacts in blood pressure waveforms. Using simulations, we showed that the correction method, which is based on a Kalman filter, improves a distorted blood pressure signal to adequate levels
of accuracy over a wide range of damping characteristics, but especially in the clinically most common range. Using coronary artery pressures simultaneously measured with a fluid-filled and a catheter-tip manometer (as reference) during coronary angiography, we show that after correction, the root mean square error reduces from $2.4 \pm 0.9$ to $1.8 \pm 0.7$ mmHg ($p < 0.01$). In addition, we applied the method to 100 pulmonary artery pressures recorded digitally during right-heart catheterization, pulmonary angiography or vasodilator reactivity testing. In 85 cases (85%), fully-automatic correction was satisfactory; in the remaining cases, correction was satisfactory after manual adjustment of the parameters of the correction method. Comparison of the corrected and the uncorrected pressures showed that after correction, systolic pressure reduces (median 2.0%), diastolic pressure increases (median 6.5%) and pulse pressure also reduces (median 8.3%).

Flow can be measured with MR phase-contrast velocity quantification, which results in a cine of the main pulmonary artery cross-section of a single (average) heart beat. The grey value of the pixels in the phase images of the cine is proportional to the velocity perpendicular to the image plane. Volumetric flow can be calculated by multiplying the average velocity within the pulmonary artery cross-section with its area. Thus, volumetric flow can be measured without the assumption of a velocity profile (e.g. a parabolic profile). A drawback of the method is that it may suffer from phase offset errors that cause bias in the velocity. In Chapter 4, we validated an existing method for the correction of phase-offset errors for application to the main pulmonary artery flow. The method estimates the velocity bias from stationary tissue surrounding the vessel and uses a linear model to interpolate the estimate for the entire image. Its variation in time determines whether a pixel should be regarded stationary or non-stationary. Using the flow measured in the main pulmonary artery of 15 subjects and the measured velocity in a stationary phantom as a reference, the correction method reduced the phase offset error from 1.1 to 0.35 cm/s (RMS), equivalent with a reduction from 11% tot 3.3% of mean flow. Phase error correction strongly affected stroke volume (range –11 to 26%).

11.3 Circulatory modelling

A mathematical model should meet several requirements to be applicable to a clinical purpose. Among other things, a model should be as simple as possible, it should have identifiable parameters and its parameters and structure should be easily and unambiguously interpretable. In Chapter 5 and Chapter 6, we discussed a number of mathematical models that may fulfill these requirements.

Chapter 5 focused on the balance between accuracy and simplicity of models that describe the instantaneous pressure-volume ($PV$) relationship in the left ventricle (e.g. a time-varying elastance model). Such a model can be of great use in the study on the heart’s ability to generate flow and the interaction between contractility and loading conditions. The left ventricular PV-relations have been shown to be nonlinear, but it is unknown whether the generally used linear model is still accurate enough for simulations. Six models were fitted to the $PV$-data measured in five sheep and the estimated parameters were used to simulate $PV$-loops. Simulated and measured $PV$-loops were compared with the Akaike information criterion ($AIC$) and the Hamming distance, a measure for geometric shape similarity. Overall, a linear model indeed appeared to be the best model (lowest $AIC$). If only the shape of the $PV$-loops is important, all
models perform nearly identically (Hamming distance between 20 and 23%). Thus, for realistic simulation of the instantaneous PV-relation, a linear model suffices. It should, however, be noted that because the models are developed for the PV-relation of the left ventricle, they are not necessarily directly applicable to the right ventricle. The geometrical differences between the left and right ventricle may particularly translate into different instantaneous PV-relations. Future studies should elucidate this.

In Chapter 6, an overview was given of the arterial Windkessel model and its applications. Otto Frank described the arterial system in terms of resistance and compliance.\textsuperscript{9} This model explained aortic pressure decay in diastole, but fell short in systole. Therefore characteristic impedance was introduced as a third element of the Windkessel model.\textsuperscript{10} Characteristic impedance links the lumped Windkessel to transmission phenomena (e.g. wave travel). Windkessels are used as hydraulic load for isolated hearts and in studies of the entire circulation. They are used to estimate total arterial compliance from pressure and flow. Several of these methods were reviewed. Windkessels describe the general features of the input impedance, with physiologically interpretable parameters. Since it is a lumped model, a Windkessel is not suitable for the assessment of spatially distributed phenomena and aspects of wave travel, but it is a simple and fairly accurate approximation of ventricular afterload.

\subsection*{11.4 Hemodynamics of pulmonary hypertension}

Chapter 7 gave an overview of the possibilities of magnetic resonance imaging (MRI) and nuclear imaging of the right ventricle (RV) in pulmonary arterial hypertension. Many clinicians have recognized the unique possibilities of MRI for the study of RV anatomy. For the assessment of the RV in pulmonary hypertension, MRI has been proven to be of special clinical importance. It is, however, less well-known that if MRI measures of volume and flow are combined with pressure measurements, accurate description of RV function in relation to its afterload is possible. Furthermore, nuclear imaging techniques offer the opportunity to study the altered RV metabolism and to elucidate the possible contribution of ischaemia to RV failure in pulmonary hypertension. Since RV failure in pulmonary hypertension is the result of the complex interaction between geometry, structure, function, perfusion, and metabolism, MRI and nuclear imaging are promising techniques to study these phenomena and to evaluate the effects of therapy aimed at improving RV function in pulmonary hypertension.

In the study of Chapter 8, pulmonary artery pressure measured by right-heart catheterization and flow by MRI were combined with a three-element Windkessel model of the pulmonary vascular bed. Commonly, RV afterload is defined as pulmonary vascular resistance, but this does not reflect the afterload to pulsatile flow. The purpose of the study was to quantify RV afterload more completely in patients with and without PH using a three-element windkessel model. We estimated the windkessel parameters in patients with chronic thromboembolic PH (CTEPH; \( n = 10 \)) and idiopathic pulmonary arterial hypertension (IPAH; \( n = 9 \)). Patients suspected of PH but in whom PH was not found served as controls (NONPH; \( n = 10 \)). Peripheral resistance \( R \) and characteristic impedance \( Z \) were significantly lower and compliance \( C \) significantly higher in the NONPH group than in both the CTEPH and IPAH groups \(( p < 0.001)\). \( R \) and \( Z \) were significantly lower in the CTEPH group than in the IPAH group \(( p < 0.05)\). Remarkably, the parameters \( R \) (in mmHg·s/ml) and \( C \) (in ml/mmHg) of all patients obeyed the relationship \( C = \)
0.75/R ($R^2 = 0.77$), which is equivalent to a similar RC-time in all patients. Mean pulmonary artery pressure $P$ and $C$ fitted well to $C = 69.7/P$ (i.e., similar pressure dependence in all patients). Our results show that differences in RV afterload among groups with different forms of PH can be quantified with a windkessel model. Furthermore, the data suggest that the RC-time and the elastic properties of the large pulmonary arteries remain unchanged in PH.

The serendipitous finding of a similar RC-time in all patients, led us to hypothesize that if the RC-time remains the same during therapy for PH, it might have important hemodynamic consequences. A constant RC-time implies that $R$ and $C$ are inversely related. As a consequence, if $R$ is small a small increase in $R$ will be accompanied by a large decrease of $C$. On the other hand, if $R$ is large, a considerable change of $R$ will be accompanied by only a small change in $C$. In Chapter 9, a study was presented to investigate this hypothesis. Data was analysed of two right heart catheterizations of 52 patients with pulmonary arterial hypertension and 10 with chronic-thromboembolic PH. The product of $R$ and $C$ (estimated by the ratio of stroke volume and pulse pressure) did not change during therapy ($p = 0.320$), implying an inverse relationship. Changes in cardiac index correlated significantly ($p < 0.001$) with changes in $R$ ($R^2 = 0.37$), better with changes in $C$ ($R^2 = 0.66$) and best with changes in both ($R^2 = 0.74$). We concluded that during therapy for PH, $R$ and $C$ remain inversely related. Therefore, changes in both $R$ and $C$ better explain changes in cardiac index than either of them alone.

### 11.5 Inverse relation between resistance and compliance

#### 11.5.1 Variation

A hyperbolic relationship between $R$ and $C$ implies that their product, the RC-time $\tau$, is constant. Indeed, on average we have found that the RC-time does not significantly differ between different, untreated patient groups (Chapter 8) and that RC-time does not significantly change during therapy (Chapter 9). We did, however, find considerable intra- and interindividual variation (on average 19% individual variation). Yet, this does not deny the existence of an (inverse) relationship between $R$ and $C$. Even in case of variation in $\tau$, it is clear that $R$ and $C$ are inversely related albeit perhaps not strictly hyperbolic. This can be seen from a plot of $C$ versus $R$ (Figure 8.4), in which $R$ and $C$ are always within a relatively narrow band around the hyperbola, and it also follows from the fact that the change in $C$ can very well be predicted from the change in $R$ (Figure 8.6). In addition, $R$ and $C$ vary almost always in reverse directions. Strictly speaking, it is therefore more accurate to refer to an inverse relation between $R$ and $C$ instead of a constant RC-time.

#### 11.5.2 Uniqueness

We have not investigated whether this inverse relation is a unique property of the pulmonary circulation or whether it also holds for the systemic circulation. There are several relevant differences between the pulmonary and the systemic circulation. The pulmonary circulation exhibits a uniquely tight linear relationship between systolic, mean and diastolic pressure. Such a relationship does not hold for the systemic circulation. In addition, the pulmonary circulation has shorter and more distensible vessels, its vessels show a relatively uniform branching pattern and a relatively uniform afterload because the only organs perfused are the lungs. The systemic circulation, in contrast, exhibits more heterogeneity both in architecture and in
function. It perfuses many different organs with large variations in demand and it has a number of regulatory mechanisms (e.g. cerebral autoregulation) that interact with each other.

We do not know whether the inverse relationship between pulmonary vascular resistance and compliance is directly related to the linear relationship between systolic, mean and diastolic pulmonary artery pressure, but this is likely. In Chapter 9 we have derived a simple estimator for the $RC$-time $\tau$

$$\tau = T \frac{\bar{p} - p_w}{PP}$$

(11.1)

with $T$ the heart period, $\bar{p}$ mean pulmonary artery pressure, $PP$ pulse pressure and $p_w$ the pulmonary capillary wedge pressure. This can be rewritten to

$$\frac{\tau}{T} = \frac{\bar{p} - p_w}{PP}$$

(11.2)

with $p_s$ and $p_d$ systolic and diastolic pulmonary artery pressure. Except $p_w$ all variables at the right hand side of this equation are in a fixed relationship to each other ($p_s$ and $p_d$ can both be written as a function of $\bar{p}$). It is therefore likely that the right hand side will not vary much and therefore also the left hand side will not vary much. Note that all relations found in Chapter 8 and Chapter 9 are measured in supine rest. Therefore variation of $T$ will be limited and thus the variation in $\tau$ also.

11.5.3 Mechanism

It is not a priori clear by which mechanism the pulmonary vascular bed maintains the inverse relation between its compliance and resistance. Chapter 10 focused on elucidating the mechanisms. We used a simulation model of the pulmonary arterial bed with a branching tree structure. The model parameters were based on published anatomical data and an assumed diameter-dependent viscosity and assumed values for the Young’s modulus and the ratio of radius and wall thickness. Both a constant and a pressure-dependent compliance were simulated. Using the pressure-dependent scaling, the model yielded realistic changes of compliance while simulations with the constant compliance resulted in too small compliance changes. Occlusion of the vascular bed up to 85% at the orders 5 through 17 (capillary level) resulted at maximum in moderate changes of the $RC$-time $\tau$ (range 0.45 to 0.65 s). Thus the distribution of resistance and compliance across the pulmonary arterial bed combined with a pressure-dependent model of compliance explains how the inverse relationship between resistance and compliance is maintained.

11.5.4 Clinical consequences

As we have pointed out in Chapter 9, a clinical consequence of an inverse relation between resistance and compliance is that in a patient who is developing PH, considerable loss of compliance precedes a considerable increase of resistance. Thus, both steady and pulsatile afterload will increase. A patient who has already developed severe PH will have double disadvantage because a large decrease in resistance would be required to gain some increase in compliance, while a patient with mild PH will gain both resistance and compliance and therefore have double advantage.
11.5.5 Possible clinical applications

The inverse relation between resistance and compliance provides additional knowledge about the circulation in a patient. This knowledge may be used in several clinical applications:

- **Noninvasive estimation of pulmonary artery pressure.** If compliance, or a related parameter, can be obtained noninvasively, the inverse relation between resistance and compliance can be used to obtain an estimate of resistance. Using pulmonary artery flow measured with MRI or echocardiography, the pressure could then be estimated noninvasively from flow.

- **Assessment of the vascular bed with an ‘acute’ λ.** In Chapter 9, we have introduced the parameter λ, which is the length of the arrow that connects to points in the ‘RC-plane’. We have shown that λ correlates strongly to cardiac index but that it is pure vascular parameter. If a vasodilatory test is performed during a right-heart catheterization, two points in the ‘RC-plane’ are available. By connecting these, an acute value for λ can be obtained. Because λ is a vascular parameter, it might be a valuable parameter for assessment of the state of the pulmonary vascular bed and it might even be a prognostic parameter.

- **Compliance as an early marker of disease.** At low resistances, small changes of resistance will be accompanied by large changes of compliance (see Section 11.4). Therefore compliance may be a more sensitive marker of vascular changes in the early phase of the disease. When changes in resistance are still hardly measurable, compliance will show large changes. Therefore, compliance may be a useful parameter for screening on PH. In addition, it is an attractive parameter for clinical practice because compliance or compliance-related parameters can be measured noninvasively. Indeed, recent studies have shown that compliance or a related parameter is a strong prognostic factor and that it can be obtained noninvasively.

- **Wedge pressure estimation.** Wedge pressure is an important parameter that is difficult to measure. If Equation (11.1) is rewritten,

\[
p_w = \bar{p} - PP \frac{\tau}{T}
\]

wedge pressure can be expressed in quantities that are easily measurable. Note that if a pulmonary artery pressure waveform of sufficient quality is available, τ can be estimated from the diastolic decay. If no pressure waveform is available, a value of τ = 0.6 s can be assumed.

11.6 Conclusion

The research in this thesis aimed at assessing to what extent additional clinically applicable information is obtained when different hemodynamic measurements are combined using a mathematical model. We could not show a direct diagnostic advantage of a model-based approach, but we did show that a model-based approach provides important insight in the pulmonary hemodynamics and thereby helps to explain findings in patients with PH.

References


