General introduction

Taco Kind
Chapter 1

Introduction

PULMONARY HYPERTENSION (PH) is a disorder of the pulmonary vasculature, characterized by increased pulmonary pressure, leading to right ventricular (RV) overload. The course of the illness varies from patient to patient, with the worst prognosis seen in patients with the greatest degree of RV dysfunction. Thus, assessment of the current condition of a PH patient requires knowledge of arterial function as well as cardiac function. This chapter provides an overview of the current insights into anatomy and function of the pulmonary circulation and the application of invasive and non-invasive measurements to quantify the circulatory function in physiological and pathophysiological states.

Pulmonary circulation

The pulmonary circulation is complex in terms of anatomy and physiology and differs considerably from its systemic counterpart. In the systemic circulation, blood pressure is relatively high with an average arterial pressure of about 90 mmHg in the healthy adult. With this pressure and a normal blood flow of about 6-7 liter/min an optimal perfusion to all tissues can be maintained. The pulmonary circulation receives the same amount of blood as the systemic circulation, but due to the lower vascular resistance, the pulmonary artery pressure is much lower with an average value of about 14 mmHg in the healthy adult. The resistance is kept low due to the large number of pulmonary vessels and the large vascular volume that can be recruited. This large vascular volume and related large blood-gas exchange area facilitate efficient oxygenation and CO2 exchange. The low pressure prevents fluids moving from the pulmonary vessels into the interstitial space and allows the RV to operate efficiently.

In PH, microvascular narrowing and reduction of the recruitment capacity of blood vessels occur. These impairments result in an increase in vascular resistance, a decrease in vascular compliance, and as a consequence, an increase in pulmonary artery pressure (PAP). Clinically, the diagnosis PH is established when mean PAP is higher than 25 mmHg at rest. PH is classified in several clinical groups, such as pulmonary arterial hypertension (PAH) of which idiopathic PAH (i.e. with no apparent cause) is most common. Other clinical groups are pulmonary veno-occlusive disease, PH due to left heart disease, PH due to lung diseases, chronic thromboembolic pulmonary hypertension, and PH with unclear and/or multifactorial mechanisms.

Although increased PAP is the hallmark of PH, it has little value in predicting prognosis. It appears that the inability of the RV to cope with the progressive increase in pressure is the main cause of death. Due to the increased vascular resistance the RV
operates at much higher energy cost to maintain sufficient levels of oxygenation. This results in hypertrophy of the myocardial wall. Although this adaptation process continues over time, at a certain point the RV fails to hypertrophy sufficiently and starts dilating. Ultimately, the ventricle fails to maintain sufficient cardiac output, which is the main cause of death in these patients.

**Pulmonary vascular bed**

**Structural organization**

The pulmonary artery originates at the RV and bifurcates into the left and right pulmonary artery, extending into the corresponding lung. Subsequent branching of the arteries continues progressively over the arterial tree. The proximal arteries are the most compliant vessels, which contain elastic laminae in the tunica media (middle layer of the vessel) to facilitate compliance. More distal arteries are less compliant due to increased smooth muscle and decreased elastic laminae in the tunica media. These arteries regulate resistance and are therefore especially important in pressure regulation. The most distal pulmonary arteries are called the pre-capillary arteries (100-1000 µm). These vessels have hardly any smooth muscle cells and form a network containing more than 300 million vessels. Under physiological conditions, resistance of these vessels decreases passively due to distention and recruitment if pressure increases. In PAH, however, resistance in these vessel can hardly be reduced due to medial hypertrophy and because most vessels have already been recruited. As a consequence, total resting resistance is high and arterial compliance is low in PAH.

The pre-capillary arteries end in the pulmonary capillary network. This network is not treelike, but forms a very large sheetlike area that facilitates efficient blood oxygenation. From the pulmonary capillaries, oxygenated blood enters, via the venules, the pulmonary venous vessels, which continue to converge until the left and right pulmonary veins of both lungs are formed. These veins enter into the left atrium.

Adequate pressure regulation is compromised in PAH due to the increased vascular resistance and decreased arterial compliance. This leads to impaired capillary blood perfusion and thereby reduced oxygenation. As blood oxygenation is the main function of the lungs, information of the vascular characteristics and capillary blood perfusion can therefore be of great importance for evaluation of the extent of disease.

**Assessment of vascular function**

The muscular arteries and pre-capillary arteries mainly determine the total pulmonary vascular resistance (PVR). Resistance of a vessel can be calculated using Poiseuille’s equa-
tion, which is derived from the Navier-Stokes equations and describes laminar fluid flow in a long straight rigid tube with a circular cross section. In a clinical setting, Poiseuille’s equation is not very practical since it requires knowledge of individual radii and lengths of vessels and blood viscosity. Therefore, PVR is usually approximated (in analogy to Ohm’s law in electrical network theory) as the mean transpulmonary pressure gradient (i.e. mean pulmonary artery pressure minus pulmonary venous pressure or left atrial pressure) divided by cardiac output. The dimension is in mmHg·min/liter, called Wood’s unit, but can also be expressed in dynes·sec·cm⁻⁵ when multiplied by 80. With this approach, the pressure-flow relation is assumed linear with the slope equal to PVR. Although pressure-flow relations are always non-linear at small pressures (due to recruitment at small blood flows)¹³, pressure-flow relations are approximately linear over a large range of higher pressures¹⁴. This description of resistance has been proven useful in a clinical setting¹⁵. However, the clinical definition of resistance is an oversimplification since it assumes steady hemodynamics of the pulmonary vascular bed and completely neglects the pulsatile behavior of arteries (e.g. arterial compliance).

A more complete characterization of the vascular bed can be obtained from pulsatile pulmonary artery pressure and flow waves by calculating the arterial input impedance. Unlike PVR, input impedance cannot be expressed as a single number, but it consists of a magnitude and a phase as functions of frequency. Impedance can be derived from the

![Figure 1](image-url) - Example of an impedance spectrum obtained in a normal subject. The impedance is computed from pulmonary artery pressure and flow waveforms using Fourier analysis.
pulsatile pressure and flow waves and by application of Fourier analysis. An example of an impedance spectrum is shown in Figure 1.

Although the impedance spectrum is a complete characterization of the vascular bed, its application in a clinical or experimental setting is hampered by difficulties to recognize shape changes\textsuperscript{16}. To improve the understanding of vascular impedance several models of arterial input impedance have been proposed, such as lumped Windkessel models\textsuperscript{17,18}, tube models\textsuperscript{19,20} or anatomical distribution models\textsuperscript{19,21}.

Of these, lumped Windkessel models are most frequently used in literature. It was Otto Frank\textsuperscript{22} who introduced the two-element Windkessel model consisting of a resistance and compliance element. In later research, the Windkessel model was extended with a third element to account for the impedance of the proximal part of the arterial bed, which is related to wave transmission aspects of the arterial system\textsuperscript{18}, and a fourth element to account for the inertia of blood\textsuperscript{23,24}.

The three-element Windkessel model is most widely used as a vascular model both of the systemic and pulmonary vascular bed\textsuperscript{25-27}. The model forms a good description of the vascular impedance and can be deduced from the impedance spectrum (Figure 1). For example, the pulmonary resistance is found at zero frequency, while the steepness of the decrease in impedance modulus is closely related to total arterial compliance. Main
pulmonary artery characteristic impedance can be obtained as the average modulus at the higher frequency spectrum (>5Hz). This three-element Windkessel model was shown to be a good representation of the arterial system in PH and that the elements could be well estimated from clinical data\textsuperscript{25,26}.

**Right ventricle**

**Anatomy**

As discussed above, pulmonary hypertension is a disease of the small vessels, but RV function is the main determinant of prognosis. Adequate assessment of RV function can greatly improve the prediction of prognosis, allowing for optimization of treatment efforts. The RV receives mixed venous blood draining into the right atria from the systemic circulation via the superior and inferior vena cava. As a consequence of the low pulmonary pressure, the RV can be distinguished morphologically from the LV by a thin (free) wall and low-pressure structure. The shape of the RV is rather complex in contrast to the near conical form of the LV. In anterior view, the RV has a triangular shape, but in cross section, the RV appears like a crescent that is wrapped around the more elliptical LV (Figure 2). Both the septum and RV free wall play an important role in ejection of blood. The septum consists of oblique longitudinal fibers with spiral architecture leading to a twisting motion during contraction\textsuperscript{28}. In contrast, the predominantly transverse fiber orientation of the RV free wall leads to circumferential compression\textsuperscript{29}.

**Assessment of right ventricular pump function**

In PH, hypertrophy of the RV wall and enlargement of the RV cavity may occur (Figure 2). These alterations in geometry affect the primary function of the heart: ejecting a sufficient amount of blood into the circulation. Therefore, quantification of the RV geometry as well as changes of the geometry during contraction provides important information of the disease. During contraction, the following changes in geometry occur more or less simultaneously\textsuperscript{30}: 1) longitudinal movement of the tricuspid valve ring toward the apex; 2) compression of the RV by transverse movement of the free wall toward the septum (i.e. bellows action); 3) traction of the RV free wall by contraction of the LV. From these mechanisms, longitudinal movement of the tricuspid valve toward the apex is most prominent, and impairment during disease is easily observed. Therefore, different methods have been developed to quantify this movement as it is assumed to be a reflection of global RV function\textsuperscript{31}. In this context, global RV function is usually quantified as RV ejection fraction (RVEF), which is defined as the amount of blood ejected in one beat relative to the end-diastolic (start of contraction) RV volume.
Although RVEF provides important information on the global functional state of the RV, it is not an intrinsic ventricular characteristic. It depends on filling and loading conditions of the RV. For example, changes in loading conditions (e.g. by medical drugs, medical intervention, or exercise) affect RVEF but do not necessarily alter the structural behavior of the myocardial fibers. The main factors that determine cardiac performance are myocardial contractility (activation and inactivation), chronotropy (heart rate), loading conditions (ventricular preload, ventricular afterload, geometry), and heterogeneity in contraction (conduction velocity, dyssynchrony). Contractility is an important determinant of the overall pumping characteristics of the ventricle, but is difficult to measure. Contractility can be obtained from ventricular pressure ($P$) and volume ($V$) measurements from which $P$-$V$ loops can be constructed. In the 1970s, Suga and Sagawa introduced the time-varying elastance concept, $E(t)$, to describe LV pump function (Figure 3). $E(t)$ was defined as: $P(t)=E(t)\cdot(V(t)-V_0)$, with $V_0$ a constant intercept volume. $E(t)$ was shown to be practically independent of loading conditions in the physiological range and to be sensitive to inotropic interventions. In particular, it was shown that the slope of the end-systolic pressure-volume relation ($E_{es}$) was a sensitive and load-independent parameter.
of contractility (Figure 3). The time-varying elastance concept has been successfully applied in the LV in multiple disease conditions\textsuperscript{33,34}, and has also been applied in the RV\textsuperscript{35,36}.

For the estimation of the $E(t)$ (and thus also $E_e$) loading conditions should be varied to obtain multiple PV-loops over a range of different end-systolic pressure. This is usually performed by a temporal and gradual partial occlusion of the inferior vena cava. In hemodynamically compromised patients, such as in pulmonary hypertension, this procedure is ethically and practically not feasible. Therefore, several techniques have been proposed to approximate $E_e$ without the need of preload alterations. These methods are based on estimating maximum isovolumic ventricular pressure from a single ejecting pressure beat and are therefore called single-beat methods. These methods have potential for clinical application, but only few studies exist of their application on the RV\textsuperscript{37} and current assumptions of the isovolumic pressure waveform do not correspond to physiology and should be improved.

**Aim and outline of this study**

It is clear that pulmonary hypertension is as much a disease of the pulmonary blood vessels as it is of the heart. Thus, insight into the current condition of a PH patient requires knowledge of both arterial and cardiac function, and the interaction between these two. This is a challenging task given the limited access to the cardiovascular system to perform hemodynamical measurements. Furthermore, conceptual difficulties may occur in the interpretation of measured variables in terms of cardiovascular parameters with clear physiological meanings.

This thesis aims to improve insights in hemodynamics of the cardiovascular system under physiological and pathophysiological conditions, focusing on clinical application of diagnostic tools in PH patients. To reach this goal, RV function was assessed by geometric shape changes during contraction. Furthermore, mathematical models of the cardiovascular system were used to study characteristics of the arterial function, RV function and their interaction.

*The first part: Cardiac function*

The clinical standard of RV pump function is RV ejection fraction (RVEF). This measure can be estimated non-invasively using several modalities (e.g. MRI). However, determining RVEF using image analysis is time consuming and depends on geometric assumptions, and this has limited the application in clinical practice. In Chapters 2 and 3 the focus is on simpler geometric measures to approximate RV function and the clinical value of these measures is investigated. In literature, many studies focused on longitudinal shortening of the RV during contraction\textsuperscript{31,38}. In contrast, RV transverse shortening has been studied less\textsuperscript{39-41} despite the importance of movement of the RV free wall towards the
septum in RV ejection\textsuperscript{30}. Therefore, in Chapter 2 longitudinal and transverse shortening of the RV are explored in healthy control subjects and in PH patients and the relation with RVEF are evaluated. The clinical value of these measures during follow-up is explored in Chapter 3.

In Chapter 4 the interaction is studied between changes in pulmonary vascular resistance and RVEF in PAH patients under PAH targeted therapies. Despite the fact that medical therapies reduce resistance, the prognosis of patients with PH is still poor. Possibly, a reduction in resistance does not necessarily improve RV function. The relations of these parameters and their prognostic value are described in this chapter.

In Chapter 5 the estimation of the time-varying elastance of the left ventricle from multiple PV-loops is discussed. This chapter provides practical solutions to improve the ease and robustness of the estimation of the elastance. The study is based on experimental data obtained in the left ventricle, but the developed approach can be transferred, in principle, to the analysis of RV data.

Measurements of multiple PV-loops require a reduction in cardiac preload, which is not applicable in patients with PH. If in addition to a PV-loop, the maximal isovolumic pressure ($P_{\text{max}}$) could be derived, then the end-systolic elastance can be estimated without the need of changes in preload. Therefore, in Chapter 6 several methods are evaluated to estimate $P_{\text{max}}$, and a new method is introduced to improve the accuracy in estimating $P_{\text{max}}$ with a potential for clinical application.

Second part: Vascular function

In Chapter 7 the time varying elastance model of Chapter 2 is combined with a three-element Windkessel model to simulate the pulmonary circulation. This model is used to provide an explanation of the proportional relations, between mean pulmonary artery pressure, systolic and diastolic pulmonary artery pressure, as reported previously\textsuperscript{42,43}.

In Chapter 8 we address the estimation of the parameters of the Windkessel model. This chapter is a mathematical approach how the model parameters can be estimated efficiently.

Subsequent techniques focus on estimation of pulmonary perfusion. Chapter 9 evaluates several mathematical techniques that can be used to estimate pulmonary perfusion parameters from MRI perfusion data (DCE-MRI). These methods are validated using realistic simulation data. The use of simulation data has the advantage that “true” perfusion values are known in advance so that the robustness of the estimation methods can be investigated. In Chapter 10 the same methods to estimate perfusion parameters are applied on pulmonary perfusion data measured during contrast MRI in healthy control subjects and in patients with PH.

The results and implications of this thesis are discussed in the concluding Chapter 11.
Chapter 1

References


General introduction

33. Burkhoff, D., Mirsky, I., and Suga, H. Assessment of systolic and diastolic ventricular proper-


