CHAPTER 8

THE ARTERIAL LOAD IN PULMONARY HYPERTENSION

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INTRODUCTION:

The pulmonary and the systemic circulation have in common that they transport an equal amount of blood. A major difference is, however, that the pulmonary circulation works at much lower pressures than the systemic circulation. Pulmonary pressure is lower since resistance is lower and the pulmonary vasculature is more compliant. In pulmonary hypertension, the right ventricular load increases due to an increase in pulmonary vascular resistance and decrease in pulmonary vascular compliance, ultimately leading to right ventricular failure. In recent years it has become clear that in pulmonary hypertension not only the contribution of resistance is of importance but that the decrease in arterial compliance plays an equally important role. Also in pulmonary hypertension the changes in resistance and compliance are fundamentally and quantitatively different from those in the systemic hypertension. Thus, changes in the pulmonary arterial tree and in pressure are considerably larger than in the systemic arterial tree.

This review describes the most important components of the arterial load on the RV in terms of resistance and arterial compliance, and the consequences of load changes for right ventricular work and function. We will end by a short comparison of the pulmonary and systemic circulation in health and hypertension. While the hydraulic load describes the load that the ventricular pump experiences, the muscles generate and feel wall stress, which is considered the muscular afterload. In general higher impedance relates to higher wall stress.

1: COMPONENTS OF ARTERIAL LOAD AND HOW THEY ARE MEASURED

The ventricle ejects blood against the arterial hydraulic load. This load can be described completely by the so-called pulmonary arterial input impedance that accounts for the relations between pulsatile pressure and flow. However, this description is not only difficult to derive but also complex to interpret.

Therefore several simplified descriptions of the arterial circulation have been proposed. One such a description is the Windkessel model that has an impedance close to the measured one, and consists of physiologically easily interpretable parameters. This model describes the hemodynamics of the systemic and pulmonary arterial circulation in terms of resistance and compliance (Fig.1). The resistance of the model is the Pulmonary Vascular Resistance, PVR, as commonly calculated as the ratio of mean Pulmonary Artery Pressure, mPAP, minus mean Pulmonary Capillary Wedge Pressure, PCWP, and Cardiac Output, CO. Resistance is mainly located in the small arteries and arterioles, since resistance strongly depends on vessel diameter, D; Poiseuille's law states that resistance is inversely proportional...
The Compliance, C, of the model is the storage capacity of all arteries and arterioles taken together. If we assume for a moment that the periphery is closed, the increase in pressure, $\Delta P$, resulting from a single Stroke Volume, $SV$, relates to Compliance as $C = SV / \Delta P$. Calculation of Compliance is, in practice, more difficult because there is blood leaving the arterial system through the periphery while cardiac ejection takes place. However, methods exist to derive compliance \textit{in vivo} $^{10-12}$. An overview of the methods has been given by Westerhof et al. $^{13}$. Here we have chosen to use the Pulse Pressure Method, since this method was shown to obtain reliable data $^{14,15}$. The model consisting of resistance and compliance is called the 2-element Windkessel and was introduced by Frank $^9$.

With the derivation of the input impedance, it became apparent that Frank's Windkessel is not complete. During early ejection the blood has to be accelerated, implying that blood mass plays a role, and the blood is ejected in a compliant pulmonary artery. The ratio of mass and compliance is characteristic impedance, $Z_c$, of the proximal pulmonary artery (or proximal aorta) $^{16}$. The $Z_c$ can be calculated from the slopes of Pulmonary Artery Pressure and Pulmonary Artery Flow in early ejection $^{2,13}$. It can also be calculated from the input impedance at high frequencies $^{2,13}$. Characteristic impedance is related to the wave speed (c) as $Z_c = c \cdot D / A$ with $D$ blood density and $A$ cross-sectional area of the pulmonary artery $^{17}$. By adding $Z_c$ to the Windkessel model the 3-element Windkessel results. This model thus consists of resistance, compliance and characteristic impedance, it, accurately describes the input impedance and all three parameters have a physiologic meaning and can be determined \textit{in vivo}.

Compliance is related to arterial wall elasticity and vessel size (i.e. radius and wall thickness), elastic arteries have a large compliance, stiff arteries a small compliance. The compliance of the arterial tree allows the arteries to expand passively during systole and to recoil during diastole. This has two important effects:

![Figure 1. Comparison of the circulation with a fire engine. The Windkessel is an air reservoir. Adapted from Westerhof et al. $^{13}$]
1) The compliant arteries are able to store the ejected blood volume in systole and release this volume during diastole resulting in constant peripheral blood flow during the whole cardiac cycle;

2) The compliant arteries damp/cushion the pressure so that pressure variations in the pulmonary artery are smaller than in the ventricle. In other words, in diastole the pressure in the pulmonary artery decreases much less than in the right ventricle.

The decrease of pressure in diastole depends on PVR and C. A large PVR means small run-off through the periphery and a small pressure decrease, and a large compliance implies a large storage volume which results also in a small pressure decrease in diastole. This combined effect can be formulated by the product of PVR and C, the units of this product is time ($\tau=R\cdot C$, seconds), and therefore called arterial time-constant, since PVR and C depend on the arterial tree and not on the heart. In reality this means that we can characterize the decay of pressure in diastole by a so-called exponential decrease with RC-time $\tau$ (Fig. 1 and 2).

**Figure 2. Schematic presentation of the effect of a decrease in Heart Rate (Left) and a shorter RC-time (Right) on Pulse Pressure.**

### 2: THE INVERSE RELATION BETWEEN RESISTANCE AND COMPLIANCE: THEIR PRODUCT IS CONSTANT

In PAH the elevated mean pulmonary artery pressure results from progressive vascular remodeling, vasoconstriction and thrombosis of small pulmonary arteries $^{18-20}$, and thus from the resistance increase. Clinicians usually define right ventricular (after)load in terms of PVR and this measure is often used as
a primary or secondary endpoint in clinical studies. However, this measure only reflects the non-pulsatile (steady) component of blood flow, and neglects the important contribution of compliance. Compliance namely takes into account the pulsatile components of the arterial load, and therefore compliance (or stiffness, the reciprocal of compliance) is an important factor contributing to systolic and diastolic pressure, and in turn systolic pressure determines systolic wall stress the true afterload on the cardiac muscle. The pulmonary arterial pulse pressure (PP, systolic minus diastolic pressure) is about equal to mean pressure (ratio of pulse pressure and mean pressure ~1) and is much larger than the ratio of systemic arterial pulse pressure and mean pressure (~0.40) (Fig. 3). This larger ratio emphasizes the contribution of arterial compliance to pulse pressure (and systolic pressure) in the pulmonary arterial system. Systolic pressure and pulse pressure are prognostic factors in systemic hypertension 25,26, but this is less clear in PAH. On the one hand pulmonary compliance was shown to be a prognostic factor for mortality 27, but on the other hand pulse pressure did not independently predict mortality 28.

To understand the hemodynamics of the pulmonary circulation in hypertension, studies have been carried out where PVR and C have been measured in healthy subjects and patients 29,30. It was found that resistance and compliance in the pulmonary circulation are inversely related by a hyperbola (Fig.4) 31-33. In other words their product, the RC-time, in the pulmonary circulation remains the same in healthy individuals, in patients with PAH, and CTEPH and even after treatment. The ranges of PVR and C have been given in Table 1. The study of Lankhaar et al. also showed that PVR and compliance in combination describe the RV afterload better than each separately 34.
In figure 4 it can be seen that in the early stage of PAH a small increase in PVR will be accompanied by a relative large drop in compliance. However, in the late stage when the vascular disease progresses, the increase in PVR will continue, but the drop in compliance will be limited since the vascular wall stiffness will reach a maximum.

We conclude that the early changes in the pulmonary vascular bed are characterized by the fact that a small change in PVR leads to a considerable change in compliance, and can therefore be detected better by a change in compliance than a change in PVR.

It has been shown that at a given flow arterial resistance and compliance are the main arterial parameters that determine Pulse Pressure, PP. The effect of RC-time and Heart Rate (HR) on PP are depicted in figure 2. A lower HR (thus longer heart period) increases PP and a shorter RC-time also increases PP. Since, in approximation \( C = \frac{SV}{PP} \) and \( R = \frac{P_{mean}}{CO} \) or \( \frac{P_{mean}}{SV \cdot HR} \), the T/RC is about equal to \( \frac{PP}{P_{mean}} \), and with HR not very much different and RC constant this explains why the ratio of PP over mean pressure is about 0.4 in health and hypertension.

### 3. WHY THE PRODUCT OF RESISTANCE AND COMPLIANCE IS CONSTANT.

Recently, the PVR and C were determined in single lungs and in lungs with emboli. It could be shown that the constant RC-time is an intrinsic property of a single lung, and remains constant when emboli are present. This implies that the inverse relation between PVR and C holds true for a single lung and for parts of lungs. From this it follows that if one lung is removed PVR will be doubled while compliance will be reduced to half, and the product remains the same.
There are two reasons explaining this constancy of the product of resistance and compliance. The first is based on basic arterial properties and thus occurs in both the pulmonary and systemic arterial circulation. An increase in vascular resistance will lead to an increased intravascular pressure, and due to the nonlinear elasticity of arteries \(^{37,38}\) elevated pressure will result in stiffer arteries and thus reduced compliance \(^{39-44}\). The second mechanism is based on the anatomy of the pulmonary arterial system. It was shown that the common pulmonary artery and proximal left and right arteries together contribute only 15-20% to total arterial compliance, suggesting that arterial compliance is distributed over the entire pulmonary arterial bed \(^{45}\). If we assume the following estimation it becomes clear how important peripheral arteries are in their contribution to compliance: a total number of arterioles with a length of 2 mm and diameter of 8 μm is about \(4 \times 10^9\) \(^{46,47}\). One such arteriole has a compliance of \(~0.5 \times 10^{-9}\) ml/mmHg. Total compliance in periphery is therefore: \(4 \times 10^9 \times 0.5 \times 10^{-9} = 2\) ml/mmHg. Since the whole pulmonary arterial system has a compliance of \(~4\) ml/mmHg (Table 1), a large part of arterial compliance is located in the periphery. This estimate is in line with earlier publications showing that a considerable proportion of the pulmonary arterial compliance is distal to the proximal large arteries \(^{48-55}\). Thus, with an embolus a (large) part of peripheral arteries is lost which means that their compliance is lost resulting in a decrease of the total compliance, and by the loss of vessels the resistance is increased.

In contrast to the distribution of compliance in the pulmonary circulation, in the systemic circulation the number of arterioles is about 10 times smaller, with resistance 10 times larger and compliance 10 times smaller. Thus in the systemic circulation the resistance is mainly located in the distal small arteries, and arterioles, while almost all compliance is located in the larger arteries, and mainly due to its large diameter and length, in the aorta \(^{54-58}\). In old age hypertension primarily the stiffness of the aorta is affected, and this means that total arterial compliance is decreased, but resistance is only little affected. This explains the change in the \(RC\)-time when systemic arterial load increases as in old age hypertension.

We conclude that in the pulmonary circulation arterial compliance is distributed over the entire arterial tree. This means that occlusion of a whole lung or lobe or segment not only resistance increases but also compliance decreases.
4: CONSEQUENCES OF THE CONSTANT PRODUCT OF RESISTANCE AND COMPLIANCE

a. Proportional relation of systolic and diastolic and mean pulmonary artery pressures

Above we have reasoned that with a constant RC-time and Heart Rate the ratio of pulse pressure and mean pressure remains the same. Since mean pressure also depends on both systolic and diastolic pressure, we can derive that there should exist a proportional relation between systolic and diastolic pulmonary artery pressure with mean pressure. These proportional relations indeed hold over a wide range of Pulmonary Artery pressures in healthy individuals and PAH \(^{59,60}\) (Fig. 5). Thus we propose that these proportional relations are the reflection of the hyperbolic relation between PVR and arterial compliance.

The linear relation between mean PAP and both systolic and diastolic pulmonary artery pressure implies that mean PAP is a measure for systolic PAP and can be calculated by the formula \(\text{meanPAP} = 0.61 \times \text{systolicPAP} + 2\text{mmHg}\) \(^{61}\). The advantage of measuring mean PA pressure is that this pressure is less affected by catheter artifacts than the systolic pressure. The proportionality also implies that an estimated systolic PAP by cardiac echo can give a good measure of mean PAP. However, to derive more data on pulmonary hemodynamics, like detailed pressure wave shapes, right heart catheterization remains essential for diagnosing PAH.

The proportional relation between systolic and diastolic pressure with mean pressure (Fig 5) implies proportionality of pulse pressure with mean pressure as well. Therefore, we hypothesize that mean, systolic, diastolic and pulse pressure all have similar prognostic value.

![Figure 5. Proportional relations between Systolic and Diastolic Pulmonary Artery Pressures with mean Pulmonary Artery Pressure. Adapted from Syyed et al.\(^{72}\)](image-url)
b. The ratio of oscillatory power and total power is constant

The energy used by the heart to propel blood to the arterial circulation is called the external hydraulic power and consists of two components. Mean hydraulic power is the energy used to produce net mean flow and is the product of mean pulmonary artery pressure and mean flow. The energy used in the production of the pulsatile components of flow and pressure is the oscillatory (or pulsatile) hydraulic power\textsuperscript{62,63}. Oscillatory power can be considered as not useful because it is not related to net transport of blood. Since oscillatory flow and pressure pulsations in the PA are considerable, and pulse pressure is about equal to mean pressure, the oscillatory power is considerable as well. It was found that oscillatory power is about 23% of total power (and thus \( \frac{23}{77} = 30\% \) of mean power), and that this fraction is remains the same in healthy subjects and in pulmonary arterial hypertension\textsuperscript{64}. This constant fraction is the result of the proportionality of pressures, (mean over systolic pressure) and thus also follows from the constancy of RC. Thus vasodilation by decreasing pressure and thus power output, does reduce the oscillatory component with the same proportion as the mean power.

We conclude that the constant RC-time of the arterial system results in proportionality between systolic, diastolic and mean pulmonary artery pressure, and also is the cause that oscillatory power remains a constant fraction of total power in health and disease.

5: COMPARISON OF PULMONARY AND SYSTEMIC CIRCULATION

A major difference with the systemic arterial system, where almost all compliance is central, the pulmonary arterial system has a compliance which is more equally distributed over the whole arterial system. Thus, this anatomical difference in which compliance and resistance are inseparably connected over the pulmonary arterial tree, results in a constant RC product. Vice versa, the anatomical separation of compliance (central) and resistance (peripheral) in the systemic arterial tree results in a non-constant RC product (Table 1).

This has the following consequences:
1. Proportionality of pulmonary artery pressures (Fig. 5) and no proportional relation of systemic arterial pressures.
2. Pulse pressure in aorta is 40% of mean systemic pressure versus pulse pressure is 100% of mean PA pressure (Fig 3).
3. Ranges in pressures in systemic hypertension are relatively small compared to the enormous range in pressures in pulmonary hypertension (Fig. 6). Even though, the changes in compliance and resistance are much larger in pulmonary system than in systemic system. For instance, in (old age) systemic
hypertension resistance increases only by approximately 20% whereas compliance can decrease by a factor 3 (Table 1). In contrast, in pulmonary hypertension resistance can increase by a factor 18 and compliance can decrease by a factor 20 (Table 1).

4. Oscillatory power fraction (ratio of oscillatory to mean power) of the left ventricle is only about 10-13% and increases in systemic hypertension. Oscillations play a more important role in the pulmonary vascular bed, and therefore the RV oscillatory power fraction is much larger (23-33%) than in its systemic counterpart. In contrast to systemic hypertension, however, oscillatory power fraction remains constant in pulmonary hypertension.

Table 1. Windkessel parameters and time constant in pulmonary and systemic arterial system.

<table>
<thead>
<tr>
<th></th>
<th>Pulmonary Tree Normal</th>
<th>Pulmonary Tree Hypertension</th>
<th>Systemic Tree Normal</th>
<th>Systemic Tree Old age Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance, ml/mmHg</td>
<td>3.8</td>
<td>0.2</td>
<td>2.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Resistance, mmHg.s/ml</td>
<td>0.11</td>
<td>2.0</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>RC-time, $\tau$, seconds</td>
<td>0.4</td>
<td>0.4</td>
<td>2.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

![Diagram](image)

*Figure 6. In Systemic circulation when pressure increases (old age hypertension) Systolic, Diastolic and Mean pressure are not linearly related (Left). In contrast, pressure increases linearly in Pulmonary Hypertension (Right). Note also that the range in pressures and resistance are enormous in pulmonary circulation (Right) in comparison to systemic circulation (Left).*
6. EFFECT OF TREATMENT ON PVR CHANGE

Pulmonary arterial hypertension (PAH) results from excessive remodeling and vasoconstriction of predominantly small pulmonary arteries (i.e. resistance arteries) leading to an increase in PVR. PAH-specific therapy are aimed to lower PVR. From simple physiologic principles (i.e. Poiseuille’s law) it is to be expected that in PAH patients with more obstructed/narrowed vessels PVR lowering therapy will cause a larger PVR decrease than in PAH patients with less obstructed/narrowed vessels. This necessitates assessment of relative to baseline PVR changes rather than absolute PVR changes. Accordingly, we have shown from reported randomized clinical trials and own patients with PAH that the relative PVR change from baseline is more accurate and clinically valuable than absolute PVR changes (Figure 7; Saouti et al. Chest submitted). Therefore, relative PVR changes should be used for comparison of treatment response between patients and different drugs.

![Figure 7. Absolute changes in PVR after 3 months (A) and one year (B) of PAH-specific therapy, stratified according to a median baseline PVR of 1028 dynes. The effect of PAH-specific therapy on absolute PVR change in individual IPAH patients (n=80) after one year follow up, also stratified according to the same median baseline PVR (C). * p<0.05, ** p<0.01, # p=NS](image-url)
7. SUMMARY

The anatomical differences between pulmonary and systemic arterial system are the main cause of the difference in distribution of compliance. Compliance in pulmonary arterial system is distributed over entire arterial system, and stands at the basis of the constancy of the RC time. This distribution depends on the number of peripheral vessels, which is about 8-10 times more in the pulmonary system than the systemic tree. In the systemic arterial tree the compliance is mainly located in the aorta (80% of total compliance in thoracic-abdominal aorta). The constant RC-time in the pulmonary bed results in proportionality of systolic and diastolic with mean pressure and in turn, in the constant ratio of oscillatory and mean power. Furthermore, effectiveness of PAH-specific therapy should be evaluated by taking into account relative PVR changes rather than absolute PVR changes.

REFERENCE LIST


60. Syed R, Reeves JT, Welsh D, Raeside D, Johnson MK, Peacock AJ. The relationship between the components of pulmonary artery pressure remains constant under


