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Right Ventricular Afterload and the Role of Nitric Oxide Metabolism in Left-sided Heart Failure

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Abstract

Awareness has grown in recent years that right ventricular (RV) function is equally important as left ventricular (LV) function in the setting of left-sided heart disease. Right ventricular dysfunction can be the consequence of an increased afterload imposed by the failing LV. The concept of “afterload” is physically most correctly described by vascular input impedance. However, for clinical purposes, afterload is most often modeled, and consists out of three components; pulmonary vascular resistance (PVR), pulmonary arterial compliance (PAC), and characteristic impedance. Whereas PVR is historically most described, PAC (which represents the distensibility of the vasculature) has rapidly gained recognition for its prognostic ability in both pulmonary arterial hypertension and left-sided heart disease. Due to the specific anatomy of the pulmonary circulation, PVR and PAC have an inverse hyperbolic relationship, which position can be shifted by varying wedge pressures. Knowledge of the afterload components helps to understand how elevated left-sided filling pressures increase pulsatile load on the RV. An increase in resistive load (known as “reactive” or “out-of-proportion” pulmonary hypertension) will ultimately complement the increase in pulsatile load. Perturbations in nitric oxide metabolism are believed to be crucial in this evolution, and have therefore been sought after as a major therapeutic target.

Keywords

Nitric Oxide; Pulmonary Arterial Compliance; Pulmonary Vascular Resistance; Right Ventricular Afterload

Introduction: The Importance of Right Ventricular Function

Right ventricular (RV) dysfunction has historically been under-appreciated outside a few specific clinical scenarios such as pulmonary embolism, right ventricular infarction or pulmonary arterial hypertension. In “classic” description of cardiomyopathies, impaired performance of the left ventricle (LV) was considered the primary problem. In contrast, the

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presence of RV dysfunction is traditionally thought to be secondary to LV failure. A few observations have changed this paradigm. First, there was the finding that, within the heart failure population, RV function is an independent prognosticator [1-4]. Second, exercise intolerance seems to correlate better with RV dysfunction than with LV dysfunction [5, 6]. Finally, elevated right sided filling pressures, as the expression of a failing RV, have been associated with organ dysfunction, and in particular, renal dysfunction [7, 8]. There are many mechanisms that may contribute to RV dysfunction in association with LV failure. First of all, the RV might suffer the same cardiomyopathic process as the LV, which explains why it may be more commonly observed in some non-ischemic cardiomyopathies. Moreover, overall decrease in coronary perfusion, sharing with LV dilatation in a limited pericardial space (ventricular interdependence), and septal dysfunction can all alter RV systolic and diastolic properties. However, even in the absence of the aforementioned mechanisms, the RV might still fail as a consequence of the increased afterload imposed by the failing LV [9, 10]. This review explains how the pulmonary vasculature changes in association with LV failure and how it determines RV afterload. Several disease states change intravascular pulmonary pressures, pulmonary vascular tone and vascular wall composition through diminished nitric oxide availability in these vessels. The term “afterload”, and its different components, will be clarified. Moreover, ways to diagnose increased RV afterload and treatment approaches will be highlighted.

Meaning of the Term Afterload

Although the concept of afterload is used on a daily basis by clinicians (e.g. “afterload reduction during treatment of heart failure”), it is unclear what the term really means and how to accurately measure it. Many papers and textbooks define the term differently, adding to the confusion [11]. In general terms however, afterload can be defined as the *external factors that oppose muscle fiber shortening*. Afterload is a crucially important determinant of myocardial (ventricular) performance [12]. In an isolated isotonic papillary muscle experiment, the afterload simply equals the weight the papillary muscle is required to lift. However, in the intact ventricle, the “external” factors are more complex and comprise opposition to contraction imposed by the valve, the vasculature, downstream pressure and the viscosity of the fluid (i.e. blood). Apart from the valve, the other external factors can be summarized as the “hydraulic” load; that is, the load imposed by the vascular tree and the viscous blood within it [13].

Also, afterload is frequently interpreted as the wall stress of the ventricle, as described by Laplace's law:

$$T = p \times r / 2 \cdot w,$$

where T is wall tension, p is the pressure inside the ventricle, r is the ventricle radius and w is the ventricle thickness.

An increase in opposition to blood flow by any one of the aforementioned external factors will indeed lead to an increase in intraventricular pressure and thus wall stress, which drives oxygen consumption and is a stimulus for hypertrophy. However, intraventricular pressure can also be the result of the intrinsic contractility of the ventricle. In other words, the ventricle is partly responsible for its own wall stress, which makes wall stress not in accordance with the conceptual definition of afterload [12]. Exercise, for example, illustrates the potential discrepancy between afterload and wall stress. During exercise, vascular dilatation and recruitment occur (both in the systemic and pulmonary circulation), which would evoke most clinicians to state that hydraulic load or “afterload” decreases. Due to

increased contractility on the other hand, blood pressure and intraventricular pressure will rise, resulting in augmented wall stress. Intense and frequent exercise indeed leads to physiologic ventricular hypertrophy. This said, increases in wall stress and hydraulic load most often will parallel each other.

How to Measure Afterload?

Physically Correct Way: Arterial Input Impedance

Physicists agree that the correct way to measure and depict afterload of a pulsatile pump, is in the frequency domain [12]. Usually, a good starting point to approach afterload is calculating the ratio of pressure difference over flow (= resistance). This ratio is indeed the direct consequence of blood viscosity, vessel diameter, and elasticity of the wall - in other words, what we considered as afterload [14]. However, difficulties arise because in a pulsatile pump, such as the heart, pressure and flow vary over time in a non-sinusoidal pattern. The mathematical solution comes from Fourier-analysis, which allows discerning those waves in their sinusoidal components at different frequencies, that is a basic frequency (= heart rate) and the higher harmonics. The ratio of a pressure harmonic over a flow harmonic at each frequency is called the “input impedance” at that frequency. Each harmonic is thus characterized by a frequency, amplitude (modulus), and a phase angle. The latter describes its timing in relation to the basic frequency [15, 16]. A typical example is depicted in Figure 1.

This type of afterload description has several merits. First, it is exact and it permits complete reproduction of the pressure and flow waves when the impedance spectrum is known. Second, it allows pressure and flow to vary permanently without the assumption that afterload changes continuously. The changes in pressure and flow are the manifestations of the interaction between the ventricle and the fixed afterload. However, this method has obvious limitations as well. It requires simultaneous invasive measurements of pressure and flow in the proximal vessel. Moreover, the result is not a single number but a spectrum in the frequency domain, which is not easily interpretable for clinicians. As a result, this method is virtually never used outside research.

Ventricular Concept of Afterload: The 3-Element Windkessel Model

There have been simplified concepts to understand afterload. Frank proposed a model that consisted of 2 components; a resistance (R) and a compliance or capacitance (C) [17] Total peripheral vascular resistance R can be calculated as:

$$R = \Delta P / CO$$

whereby P is the mean pressure difference over the vasculature and CO is the cardiac output. Compliance can be seen as the storage capacity or distensibility of the vasculature and is determined by the elasticity of the arteries. It is most easily and most often calculated as:

$$C = \Delta V / \Delta P$$

whereby V is the change in volume in the vessels and P the change in pressure (*stroke volume over pulse pressure method*) [18, 19]. This model is known as the “2-element windkessel model,” as the compliance of the vasculature acts like the air reservoir

(“windkessel”) of fire engines, resulting in a fairly constant peripheral flow (Figure 2). The 2-element windkessel model is sufficient to describe the pressure decay during diastole in the proximal great vessel, given by the formula:

$$P_{\text{diast}}(t) = P_{\text{endsyst}} e^{-t/RC} + P_{\text{intercept}}$$

RC is the product of resistance and compliance and is also known as the arterial time constant that describes pressure decay during diastole.

Although the 2-element windkessel model perfectly describes the pressure decay in diastole, it falls short in the description of the relation between pressure and flow during systole [20]. This observation necessitated the introduction of a third element in the model. In the beginning of ejection, blood has to be accelerated. It seems logical that the mass of blood and the compliance of the proximal vessel are important determinants of this ejection. The ratio of blood mass over compliance is called the characteristic impedance Z of the proximal vessel [21]. It can be most easily calculated with the formula:

$$Z = c \times \rho / A$$

whereby c is the wave speed of the arterial pulse wave, ρ is blood density and A is the cross-sectional area of the proximal vessel. This represents the resistance to flow imposed by the proximal part of the vessel and actually equals the rather constant level of the aortic input impedance at higher frequencies (Figure 1). Figure 3 depicts a typical graphical representation of the 3-element windkessel model, analogue to an electrical circuit. Even though the 3-element windkessel model is scientifically less exact than input impedance, it is far more understandable in the clinical setting as it consists of parameters that can be easily calculated and have a physiological meaning.

Vascular Clinical Concept of Afterload: Effective Arterial Elastance

The effective arterial elastance is another way to describe vascular load. This method was first described by Sunagawa and co-workers and is often used in studies of ventriculo-vascular interaction because ventricular function, i.e. end-systolic elastance (E_{es}), and vascular load, i.e. effective arterial elastance (E_{a}), are both expressed in mmHg/ml and can be graphically represented in pressure-volume loops (Figure 4) [22]. In fact, Sunagawa et al. started from the 3-element windkessel model to derive the formula:

$$E_{\text{a}} = P_{\text{es}} / SV$$

whereby P_{es} = end-systolic pressure and SV = stroke volume. It was shown that this approximation of vascular load, derived from pressure volume loops, correlates excellently with values derived from simultaneous arterial pressure and flow measurements (input impedance) [23, 24]. The advantage of this afterload description is that it provides one value that can be linked to ventricular end-systolic elastance and the ratio quantitates ventriculo-arterial coupling [25-27]. The downside however, is that it does not provide pathologic insight in the contributions of resistive and pulsatile load to the total afterload.

Differences in Afterload between the Systemic and Pulmonary Circulation

The aforementioned afterload concepts and principles apply to both the systemic and the pulmonary circulation. Because the right and left heart are constructed in series, they necessarily transport the same amount of blood and thus have the same cardiac output in the absence of a shunt. However, there are important differences as well. The most obvious difference being that, in the pulmonary circulation, this equal cardiac output is realized at approximately one fifth of the pressures of the systemic circulation. This results from the lower resistance of the pulmonary circulation, due to the enormous amount of vessels in a parallel distribution (8-10 times as many as in the systemic circulation), and due to its higher compliance [28]. Not only the absolute values differ, the distribution of resistance and compliance throughout the vasculature differs as well. In the systemic circulation, compliance mainly resides in the proximal (central) vasculature (the aorta and great arteries), whereas resistance is located at the level of the arterioles (peripheral). The consequence is that resistance and compliance can evolve separate from each other. The best example is isolated systolic hypertension in the elderly, which is a typical example of a decreased compliance of the systemic vasculature. Resistance however is still normal or can even be decreased. This explains the variable systemic arterial time constant (which is often defined as the product of resistance and compliance).

The pulmonary circulation on the other hand is anatomically different, and characterized by a more equally distributed (over the whole arterial system) resistance and compliance. This makes that resistance and compliance usually evolve together but in opposite directions. The consequence is a pulmonary arterial time constant that remains rather stable throughout health and disease [29-32]. A second explanation of the relatively constant $R \times C$ product derives from arterial properties and thus also applies to the systemic circulation. Whenever resistance increases, assuming a constant cardiac output, intravascular pressure increases. This leads to arterial distention and thus decreased compliance. In the case of an elevated downstream pressure (for example, elevated pulmonary capillary wedge pressure as in the case of LV dysfunction), intrapulmonary pressures will also rise and cause vascular distention which results in a lower compliance. In this scenario however, resistance will not increase. The net result is a lower pulmonary arterial time constant ($R \times C$) when wedge pressure increases [33, 34]. It is also important to point out that another difference between the systemic and the pulmonary circulation is the relative contribution of pulsatile load to the total afterload. In the normal systemic circulation, the ratio of pulse pressure over mean pressure is approximately 0.4 whereas in the pulmonary circulation this ratio equals ≈ 1 [13].

Estimating Right Ventricular Afterload in Clinical Practice

Clinicians need simple formulas or numbers to estimate afterload at the bedside. The most popular and easily obtained measure is pulmonary blood pressure. Despite its simplicity it is fair to say that, in general, it gives a good idea of afterload. Indeed, according to the previously mentioned formulas, intravascular pressure will rise when resistance increases, compliance decreases or downstream pressure increases. The most obvious pitfall relates to the fact that it does not correct for CO, resulting in potential misjudgment when CO is abnormal. For example, end-stage pulmonary arterial hypertension is accompanied by a low CO and a drop in pulmonary pressures compared to previous values, despite an ever increasing afterload.

When CO is measured, resistance and compliance can be calculated, with the former the most popular measure. Although these measures usually evolve together (but in opposite directions), it can be useful to calculate both to fully comprehend the pathophysiology of increased afterload (see below).

Changes in Right Ventricular Afterload in Disease States

Knowledge about afterload and its components helps in the understanding of pulmonary hypertension and RV failure, particularly in the setting of left heart disease. Left-sided heart disease is recognized as the most common cause of pulmonary hypertension [35]. It is defined as elevated mean pulmonary artery pressure (≥ 25 mmHg or ≥ 30 mmHg with exercise) in the presence of an elevated pulmonary capillary wedge pressure (≥ 15 mmHg) [36]. The most evident consequence of LV failure is indeed a rise in intracardiac filling pressures, which from the perspective of the RV, means an elevation in the downstream pressure. This will directly lead to higher intrapulmonary pressures and a decrease in compliance. In this so-called “passive” or “post-capillary” form of PH, pulmonary vascular resistance (PVR) is not increased. However, a considerable percentage of patients with left-sided heart failure may develop an increase in PVR (“reactive form of PH”), also accompanied by a decrease in compliance [37, 38]. Patients with this type of PH have a worse prognosis compared to those with “passive” PH alone [39]. In “reactive PH”, the increase in pulmonary pressures is more excessive than expected on the base of the left atrial pressure (LAP) increase alone. Therefore, often the term pulmonary hypertension “out-of-proportion” is used. When LAP is normalized by treatment, the rise in PVR might be fixed in the presence of vascular remodeling or reversible when functional vasoconstriction dominates. It is still conceivable that chronic backward transmission of increased LAP can be the driver of this whole process whereby ultimately capillary, arteriolar, and arterial changes in wall composition occur [40-42]. It is during the transition from normal to remodeled vasculature that induction of vascular serine elastase and matrix metalloproteinase and perturbations in metabolic pathways of angiotensin II, endothelin-1, prostacyclin, and nitric oxide (NO) play a crucial role [40, 43]. The observed vascular remodeling, although not as advanced as in PAH, is often not fully-reversible upon correction of LAP after cardiac transplantation or mechanical circulatory support [44]. That being said, it is unclear why some patients never develop a rise in PVR despite persistently-elevated LAP.

In other instances, pathology only reveals itself during exercise. Normal exercise physiology is characterized by a potential 6-fold increase in blood flow (Q) [45]. This provokes a linear increase in mean pulmonary pressure (mPAP), as a function of Q, during most of the course of exercise. Only in the beginning of exercise, this curve might be somewhat curvilinear (concave to the flow axis) due to dilatation and/or recruitment of the pulmonary vasculature (Figure 5) [36, 45-47]. However, the slope of the curve is steeper in certain pathologies such as PAH and heart failure with reduced (HFrEF) or preserved ejection fraction (HFpEF) [48, 49]. In heart failure, this primarily reflects a faster (compared to normal) ascend of wedge pressure during exercise due to diastolic and systemic vascular dysfunction [48, 50]. An alternative explanation for a steeper slope of the mPAP versus Q curve is a higher PVR, either due to high resting PVR or insufficient decrease in PVR during exercise [48]. Little is known about the evolution of pulmonary arterial capacitance (PAC) and its relation to PVR during exercise although it is hypothesized that their product remains constant [45]. Since functional impairment is the predominant manifestation of increased RV afterload, it is conceivable that exercise hemodynamics may play an increasingly important role for early diagnosis, subtyping, and treatment choices in several cardio-pulmonary pathologies [50].

Pulmonary Arterial Capacitance

Of the different afterload components (resistance, compliance and characteristic impedance), resistance is by far the most studied, both in the systemic and pulmonary circulation. Only in recent years, the importance of compliance or capacitance was recognized, first in the systemic circulation. It was demonstrated that a higher pulse pressure, the denominator in

the compliance formula, is associated with worse survival and adverse events in the general population and in post-myocardial infarction patient population [51-53]. In the pulmonary circulation, resistance and compliance are related in such way that their product forms a constant in health and disease (Figure 6). Interestingly when compared to high PVR, diminished PAC was found to be a better prognosticator of all-cause mortality in patients with idiopathic PAH [54]. This finding is attributed to a higher sensitivity of PAC because it can be altered early in the disease process as small increases in PVR are often accompanied by large decreases in PAC [30, 40]. Our group has recently confirmed the higher prognostic ability of PAC in patients with left-sided heart failure and also observed the influence of wedge pressure on PAC. The increase in pulmonary pressure, which is the consequence of higher wedge pressure, causes vessel dilatation and lower PAC. Therefore, PAC unifies two hemodynamic effects, i.e. a hyperbolic inverse relation with PVR and a linear inverse relation with wedge pressure, in one variable which explains its higher prognostic ability [33, 34]. In addition we demonstrated that PAC could be increased, and thus pulsatile load could be lowered, after correction of the elevated left-sided filling pressures (Figure 6).

Nitric Oxide Metabolism as a Crucial Player in the Pulmonary Circulation

In both group one and group two PH, changes occur in pulmonary vessel wall composition and pulmonary vascular tone. These kind of pathophysiologic processes are governed by changes in certain metabolic pathways, from which the nitric oxide pathway is believed to be one of the major contributors to its homeostasis [55]. The gaseous transmitter NO is a highly diffusible molecule, a free radical, with a very short half-life of a few seconds in any biological medium [56]. It turned out to be the molecule that was once known as endothelium-derived relaxing factor [57, 58]. NO is produced out of L-arginine in a reaction catalyzed by nitric oxide synthase (NOS) from which three isoforms are known. NOS II, also called inducible NOS (iNOS) and NOS III (endothelial NOS; eNOS) are believed to be the most important isoforms in the lung. Despite its name, it is now assumed that iNOS is not only induced but also continuously expressed on epithelial cells in the lung [59]. NO causes (pulmonary) vascular relaxation [60]. Figure 7 depicts the metabolic pathways that lead to formation and degradation of NO and how it exerts its biological effects. The role of NO in pulmonary vasorelaxation and prevention of vascular remodeling can be demonstrated from both cross-sectional association studies and experiments, whereby NO production is either enhanced or blocked. For example, in healthy humans, infusion of acetylcholine, a NO synthase (NOS) agonist, provokes an increase in pulmonary blood flow whereas N-monomethyl-arginine (MMA), a NOS inhibitor, does the opposite [61, 62]. In patients with congestive HF and an elevated PVR, MMA infusion produces less vasoconstriction than in patients with HF and normal PVR. Hence, in HF patient with elevated PVR, NO bioavailability may already be substantially diminished. This may also explain why further inhibition of NOS had limited effect [63, 64]. Cross-sectional studies by our group and others demonstrate higher systemic levels of the NOS inhibitors MMA and asymmetric dimethylarginine (ADMA), and lower global arginine bioavailability (defined as the ratio of L-arginine/L-citrulline + L-ornithine) in patients with congestive HF [65-70]. Moreover, within this HF population, there appears to be a relationship between higher pulmonary pressures on the one hand and higher systemic ADMA-levels and lower arginine bioavailability. However, a counter-regulatory mechanism, compensating for the increased ADMA levels, also seems to exist under the form of increased expression of dimethylarginine dimethylaminohydrolase-1 (DDAH-1) in the failing myocardium. This enzyme is responsible for the degradation of ADMA and patients without PH had higher levels than those with PH [70].

Nitric oxide is measurable in exhaled breath as well, likely reflecting the process of pulmonary NO metabolism. The measured NO in exhaled breath (eNO) is the result of NO

production by vascular endothelium (NOS III) and epithelial cells (NOS II) in the lower (lungs) and upper respiratory tract (nose and sinuses). In an attempt to measure eNO more uniformly and make study results more consistent, specific guidelines have been published on the required techniques to measure eNO both online (real-time display of NO concentration) and offline (delayed analysis after collection in a suitable receptacle) [71]. Studies have demonstrated conflicting results regarding eNO levels at rest in HF patients compared to healthy subjects [72-74]. According to Hare et al., HF patients had higher resting eNO levels than normal, although that observation has not been confirmed in other more contemporary studies with more standardized measurements [75, 76]. However, patients with HF have more vasoconstricted pulmonary vascular beds, thus it may seem that the NO pathway may serve as a counter-regulatory process that compensates the vasoconstriction imposed by neurohormonal upregulation (e.g. angiotensin II, endothelin) and sympathetic activity. NOS II expression is indeed induced by shear stress or cytokine storms induced by angiotensin II and increased sympathetic activity in e.g. decompensated heart failure [77]. Conform to this hypothesis is the demonstration that within HF patients, eNO is inversely correlated with PAP. However, this correlation is lost in the decompensated HF setting, whereby high pulmonary pressures were observed despite high eNO levels [74]. During exercise, HF patients demonstrate stable or even increased eNO levels according to multiple studies [73, 78, 79]. In contrast, failure to augment eNO in HF patients has been associated with increased mortality [80]. This is different from healthy subjects in whom a decrease in eNO during exercise is usually observed. Our group recently showed that increased eNO during exercise correlated with higher systolic PAP and diastolic dysfunction. This again argues for a compensatory mechanism where an increase in NO tries to keep vascular impedance low to maintain cardiac output [75]. So far, changes in NO metabolism are always described in terms of effects on, or associations with, disease severity, pulmonary pressures, or PVR. How changes in NO metabolism are related to changes in PAC is unknown. Based on the inverse relationship between PVR and PAC, one would expect that they are directly proportional (more NO bioavailability = higher compliance). It would be interesting to see how PAC is influenced by e.g. NO administration and whether the product of PVR and PAC (time constant) remains a constant in these circumstances as well.

Therapeutic Targets

As preservation of RV function seems so important for good outcomes in HF, it seems reasonable to identify the pulmonary circulation as a therapeutic target in order to minimize RV afterload for effective filling of the LV. Because every elevation of left-sided filling pressures will increase RV pulsatile load, the first aim should be to maintain low LAP with the aim to reduce congestion [8]. The different ways to achieve decongestion extend beyond the scope of this review, and it still needs to be demonstrated whether intracardiac hemodynamic monitoring consistently results in better outcomes [81-84]. Likewise, the hypothesis that good control of LAP will prevent the development of “reactive” PH is still yet to be proven. Nevertheless, once “reactive” PH has developed, this can become a treatment target on itself and medications that lower pulmonary vascular tone or antagonize vascular remodeling have been considered. Of these agents, NO-donating drugs and phosphodiesterase-5 (PDE5) inhibitors have demonstrated beneficial effects in hemodynamics and clinical outcomes in the setting of left-sided heart failure [85-87]. Inhaled NO is frequently used in the post-transplant and postoperative setting to avoid acute RV failure [88, 89]. However, its mode of administration and expense has prohibited a more general use. PDE5 inhibitors prevent the catabolism of cGMP, NO's second messenger, and can be administered orally. In patients with HFrEF and PH, sildenafil improves exercise capacity and quality of life [87, 90-92]. Similar hemodynamic benefits have recently been shown in patients with HFpEF and PH [92]. However, the effects of PDE5 inhibitor on

exercise capacity and quality of life in HFpEF were no different from placebo in the recent RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure) study [93], and neither had endothelin-antagonists and prostaglandins in this population [94-96]. One explanation might relate to the fact that these drugs were given to (for example in the RELAX trial) the HFpEF population at large. We believe that more efforts should be undertaken to point out the NO-deficient subpopulation in which treatment with NO donors might be more effective. Exercise-testing might serve this goal by identifying patients with an excessive rise in RV afterload during exercise. It is currently unknown whether the pulmonary vasodilators would be more effective earlier in the disease course and if they would be able to prevent the development of “reactive” PH in the first place.

Conclusion

The increased afterload on the RV, imposed by a failing LV, frequently causes RV dysfunction resulting in congestion and exercise intolerance. Afterload is more than pressure or resistance alone, and is best understood with the 3-elements (resistance, compliance and characteristic impedance) of the windkessel model in mind. More studies are needed to elucidate the pathophysiology of reactive, out-of-proportion PH and how this can be treated or prevented.

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Figure 1. Afterload depicted as arterial input impedance in the frequency domain

Input impedance curves are constructed by discerning pressure (A.top) and flow (A.bottom) curves in their sinusoidal components at the fundamental frequency (heart rate) and at higher harmonics. The impedance modulus curve (part A) is composed as the ratio of the pressure and flow amplitude at each harmonic. This ratio equals peripheral vascular resistance at 0 frequency and characteristic impedance at high frequency. The phase angle curve (part B) is the result of subtracting the phase angles of the pressure and flow components.

Figure 2. The arterial Windkessel concept

The compliance of the large arteries act as the air reservoir (=windkessel) that is able to store blood. The combination of this compliance and the peripheral resistance result in a rather constant peripheral flow. Adapted from Westerhof et al. with permission [97].

Figure 3. The 3-element Windkessel model

The upper part of the figure depicts the 3 elements of the Windkessel model; characteristic impedance Z , compliance C and peripheral resistance R , analogue to an electrical circuit. The lower part demonstrates the anatomical correlates in the pulmonary circulation. Note that C and R are evenly distributed throughout the circulation.

Figure 4. Afterload shown as effective arterial elastance (E_a) in pressure-volume loop
 Afterload is represented by the slope of E_a curve, i.e. the curve that connects the end-systolic pressure point with the end-diastolic volume point (on the x-axis). Likewise, ventricular contractility can be quantified by the slope of the end-systolic elastance (E_{es}) curve. The ratio of E_a over E_{es} defines arterial-ventricular coupling. In this example, the changes in E_a (increased) and E_{es} (decreased) in heart failure (dashed line) can be appreciated. This leads to an increased coupling ratio.

Figure 5. The evolution of mPAP during exercise

Most authors observe a more or less linear relationship between mPAP and CO, except during the initial phase of exercise where the curve is somewhat curvilinear to the flow axis representing initial recruitment and/or vasodilation. Because $mPAP = PVR \times CO + PCWP$, it is easily demonstrable that this linear relationship is only possible when PVR remains constant and PCWP is constant or has a linear increase itself. A) Normal situation. B) HFrEF or HFpEF patient with normal PVR but steeper slope of the curve due to rapid increase of PCWP. C) Even steeper curve in HF patient with elevated PVR. D) PAH patient with very high PVR. Abbreviations: mPAP, mean pulmonary artery pressure; CO, cardiac output; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; PAH, pulmonary arterial hypertension.

Figure 6. The hyperbolic relationship between PAC and PVR

A) Demonstration of the hyperbolic relationship between PVR and PAC in 724 patients with heart failure. Higher wedge pressures shift the hyperbola downwards representing a lower arterial time constant ($=PVR \times PAC$).

B) Treatment of elevated wedge pressure leads to a decrease in PVR and a relatively more pronounced increase in PAC provoking an upwards shift of the hyperbola. Dupont et al. with permission [34].

Figure 7. Nitric Oxide (NO) metabolism in Pulmonary Vasculature

NO is mainly synthesized in the endothelial cells out of L-arginine by a set of enzymes, NO synthases, and with calcium and BH₄ as cofactors. Inhibition of this reaction comes from a few methylated arginine-like metabolites; ADMA, MMA and SDMA. The classical effects of NO are achieved by the formation of cGMP through activation of sGC after diffusion into adjacent smooth muscle cells (paracrine effect). This results in anti-proliferation and relaxation. Alternatively NO, when diffused into the plasma, quickly reacts with Hb and has possible effects at distance.

Abbreviations: Ach, acetylcholine; ADMA, asymmetric dimethylarginine; BH₄, tetrahydrobiopterin; Ca⁺⁺, Calcium; CAT, cationic amino acid transport; cGMP, cyclic guanosine monophosphate; DDAH, dimethylarginine dimethylaminohydrolase; GTP, guanosine triphosphate; Hb, hemoglobin; NO, nitric oxide; NO₂⁻, nitrite; MMA, N-mono-methylarginine; PDE₅, phosphodiesterase 5; PKG, protein kinase G; PRMT, protein arginine methyltransferase; SDMA, symmetric dimethylarginine; sGC, soluble guanylyl cyclase;