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

MATTHIAS DUPONT, MD,[1] AND W.H. WILSON TANG, MD[2]

*Genk, Belgium; and Cleveland, Ohio*

**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. RV 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 to consist of 3 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. Owing 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 one 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) ultimately complements the increase in pulsatile load. Perturbations in nitric oxide metabolism are thought to be crucial in this evolution and have therefore been sought as a major therapeutic target. (*J Cardiac Fail 2013;19:712–721*)

**Key Words:** Nitric oxide, pulmonary arterial compliance, pulmonary vascular resistance, right ventricular afterload.

## The Importance of Right Ventricular Function

Right ventricular (RV) dysfunction has historically been underappreciated 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 to be the primary problem. In contrast, the 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 (HF) 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, particularly 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 nonischemic cardiomyopathies. Moreover, overall decrease in coronary perfusion, sharing with LV dilation in a limited pericardial space (ventricular interdependence), and septal dysfunction can all alter RV systolic and diastolic properties. However, even in the absence of these mechanisms, the RV might still fail as a consequence of the increased afterload imposed by the failing LV.[9,10] The present review explains how the pulmonary vasculature changes in association with LV failure and how it determines RV

*From the [1]Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium and [2]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio.*

Manuscript received April 5, 2013; revised manuscript received July 29, 2013; revised manuscript accepted August 8, 2013.

Reprint requests: W.H. Wilson Tang, MD, Department of Cardiovascular Medicine, Heart and Vascular Institute, 9500 Euclid Avenue, Desk J3-4, Cleveland, Ohio 44195. Tel: (216) 444-2121; Fax: (216) 445-6165. E-mail: tangw@ccf.org

Funding: Dr. Dupont was supported by the Belgian American Educational Foundation (BAEF) for his research. Dr. Tang was funded by National Institutes of Health grants R01HL103931, P20HL113452, and R01HL115008 and the Cleveland Clinic Clinical Research Unit of the Case Western Reserve University CTSA (UL1TR 000439).

See page 719 for disclosure information.

1071-9164/$ - see front matter

© *2013 Elsevier Inc. All rights reserved.*

http://dx.doi.org/10.1016/j.cardfail.2013.08.004

afterload. Several disease states change intravascular pulmonary pressures, pulmonary vascular tone, and vascular wall composition through diminished nitric oxide (NO) 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 (eg, ''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 (ie, 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. Owing 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 (ie, resistance). This ratio is indeed the direct consequence of blood viscosity, vessel diameter, and elasticity of the wall—in other words, what we consider to be afterload.[14] However, difficulties arise because in a pulsatile pump, such as the heart, pressure and flow vary over time in a nonsinusoidal pattern. The mathematical solution comes from Fourier analysis, which allows discerning those waves in their sinusoidal components at different frequencies, ie, 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 permits complete reproduction of the pressure and flow waves when the impedance spectrum is known. Second, it allows pressure and flow to vary

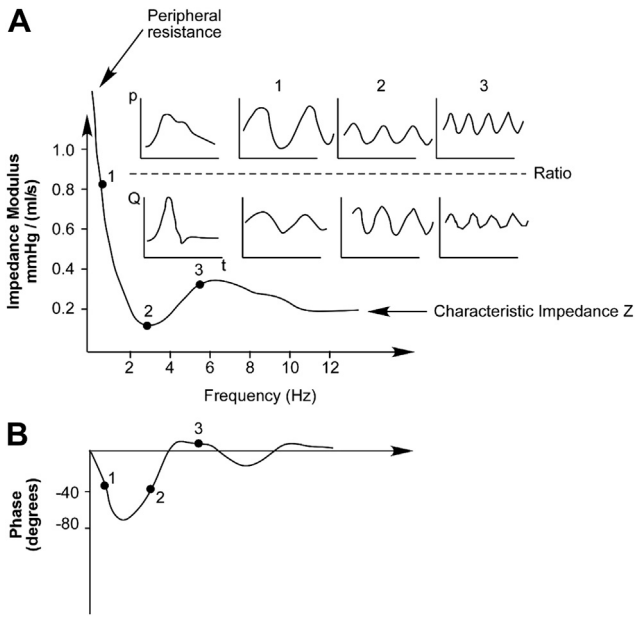



**Fig. 1.** Afterload depicted as arterial input impedance in the frequency domain. (A) Input impedance curves are constructed by discerning pressure (top) and flow (bottom) curves in their sinusoidal components at the fundamental frequency (heart rate) and at higher harmonics. The impedance modulus curve 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. (B) The phase angle curve is the result of subtracting the phase angles of the pressure and flow components.

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[17] proposed a model that consisted of 2 components: a resistance (R) and a compliance or capacitance (C). Total peripheral vascular resistance R can be calculated as:

$$R = \Delta P / CO$$

where ΔP 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:

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

where ΔV is the change in volume in the vessels and ΔP the change in pressure (''stroke volume over pulse pressure method'').[18,19] This model is known as the ''2-element windkessel model,'' because the compliance of the vasculature acts like the air reservoir (''windkessel'') of fire engines, resulting in a fairly constant peripheral flow (Fig. 2). The 2-element windkessel model is sufficient to describe the pressure decay during diastole in the proximal great vessel, given by the formula:

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

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:

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

where 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 (Fig. 1). Figure 3 depicts a typical graphical representation of the 3-element windkessel model analogous 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 physiologic meaning.

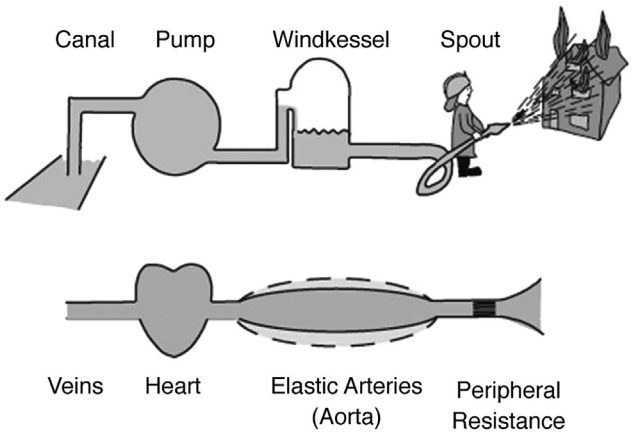



**Fig. 2.** The arterial windkessel concept. The compliance of the large arteries act as the air reservoir (windkessel) that is able to store blood. The combination of this compliance and the peripheral resistance result in a rather constant peripheral flow. Adapted from Westerhof et al[97] with permission.

### 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 et al[22] and is often used in studies of ventriculovascular interaction because ventricular function, ie, end-systolic elastance (Ees), and vascular load, ie, effective arterial elastance (Ea), are both expressed in mm Hg/mL and can be graphically represented in pressure-volume loops (Fig. 4). In fact, Sunagawa et al started from the 3-element windkessel model to derive the formula:

$$Ea = P_{es} / SV$$

where $P_{es}$ = 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 1 value that can be linked to ventricular end-systolic elastance, and the ratio quantifies ventriculo-arterial coupling.[25–27] The downside, however, is that it does not provide pathologic insight into the contributions of resistive and pulsatile load to the total afterload.

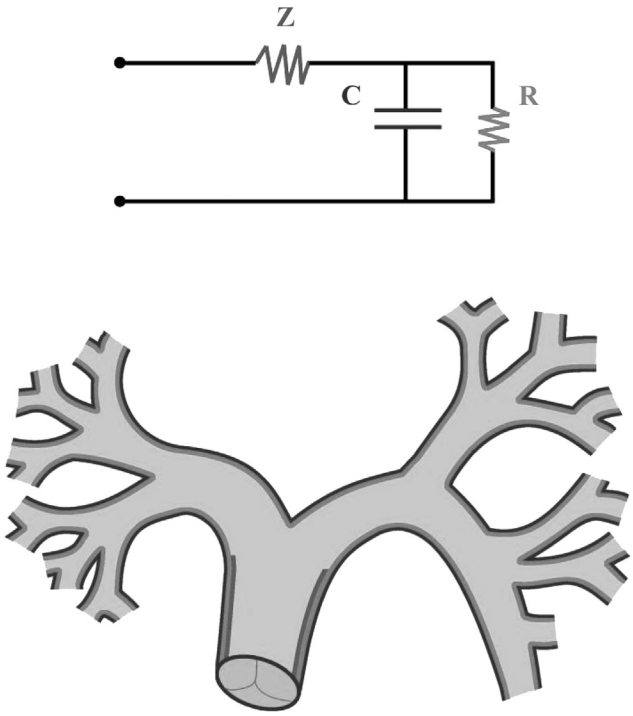



**Fig. 3.** The 3-element windkessel model. The upper part of the figure depicts the 3 elements of the Windkessel model: characteristic impedance Z, compliance C, and peripheral resistance R, analogous to an electrical circuit. The lower part demonstrates the anatomic correlates in the pulmonary circulation. Note that C and R are evenly distributed throughout the circulation.

## Differences in Afterload Between the Systemic and Pulmonary Circulation

The aforementioned afterload concepts and principles apply to both the systemic and the pulmonary circulation.

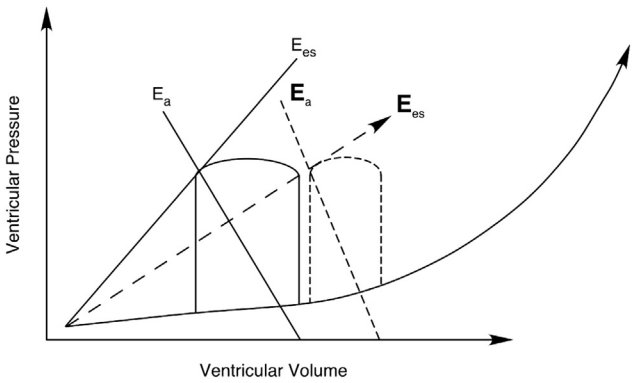



**Fig. 4.** Afterload shown as effective arterial elastance ($E_a$) in pressure-volume loop. Afterload is represented by the slope of $E_a$ curve, ie, the curve that connects the end-systolic pressure point with the end-diastolic volume point (on the *x*-axis). Likewise, ventricular contractility can 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.

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, rhe most obvious 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, owing to the enormous amount of vessels in a parallel distribution (8−10 times as many as in the systemic circulation) and 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 change separately 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, characterized by a more equally distributed (over the whole arterial system) resistance and compliance. This means that resistance and compliance usually change 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 × 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 elevated downstream pressure (eg, elevated pulmonary capillary wedge pressure as in the case of LV dysfunction), intrapulmonary pressures will also rise and cause vascular distention, which results in lower compliance. In this scenario, however, resistance will not increase. The net result is a lower pulmonary arterial time constant (R × 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 ∼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 rises 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 with previous values, despite an ever-increasing afterload.

When CO is measured, resistance and compliance can be calculated, with the former being the most popular measure. Although these measures usually change 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 (PH) and RV failure, particularly in the setting of left-sided heart disease. Left-sided heart disease is recognized as the most common cause of PH.[35] It is defined as elevated mean pulmonary artery pressure (≥25 mm Hg or ≥30 mm Hg with exercise) in the presence of elevated pulmonary capillary wedge pressure (≥15 mm Hg).[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 leads directly to higher intrapulmonary pressures and a decrease in compliance. In this so-called ''passive'' or ''postcapillary'' form of PH, pulmonary vascular resistance (PVR) is not increased. However, a considerable percentage of patients with left-sided HF 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 than those with passive PH alone.[39] In reactive PH, the increase in pulmonary pressures is more excessive than expected on the basis of the left atrial pressure (LAP) increase alone. Therefore, the term ''out of proportion'' PH is often 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 NO play a crucial role.[40,43] The observed vascular remodeling, although not as advanced as in pulmonary arterial hypertension (PAH), is often not fully reversible on 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 reveals itself only 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 arterial pressure (mPAP), as a function of Q, during most of the course of exercise. Only in the beginning of exercise might this curve be somewhat curvilinear (concave to the flow axis) owing to dilation and/or recruitment of the pulmonary vasculature (Fig. 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 (HFpEF) ejection fraction.[48,49] In HF, this primarily reflects a faster (compared with normal) rise of wedge pressure during exercise due to diastolic and systemic vascular dysfunction.[48,50] An alternative explanation for a steeper slope of the mPAP-vs-Q curve is a higher PVR due to either 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] Because 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 cardiopulmonary pathologies.[50]

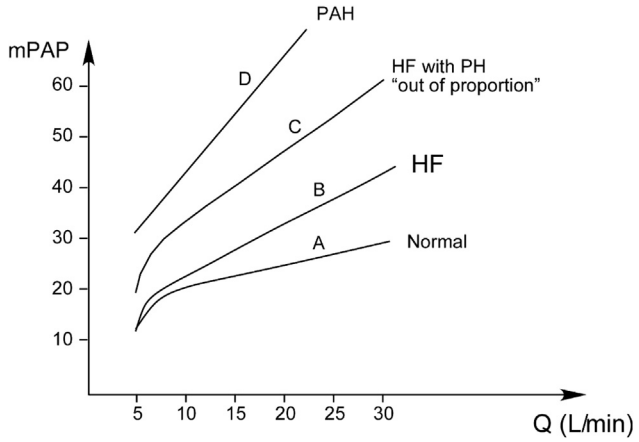



**Fig. 5.** The evolution of mean pulmonary arterial pressure (mPAP) during exercise. Most authors observe a more or less linear relationship between mPAP and cardiac output (CO), except during the initial phase of exercise, where the curve is somewhat curvilinear to the flow axis, representing initial recruitment and/or vasodilation. Because mPAP = pulmonary vascular resistance (PVR) × CO + pulmonary capillary wedge pressure (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) heart failure (HF) patient with reduced or preserved ejection fraction with normal PVR but steeper slope of the curve owing to rapid increase of PCWP; C) even steeper curve in HF patient with elevated PVR; D) pulmonary arterial hypertension (PAH) patient with very high PVR. PH, pulmonary hypertension; Q, blood flow.

### Pulmonary Arterial Capacitance

Of the different afterload components (resistance, compliance, and characteristic impedance), resistance is by far the most studied, in both the systemic and the pulmonary circulation. Only in recent years was the importance of compliance or capacitance 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 (Fig. 6). Interestingly compared with 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 because 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 HF as well as observed the influence of wedge pressure on PAC. The increase in pulmonary pressure, which is the consequence of higher wedge pressure, causes vessel dilation and lower PAC. Therefore, PAC unifies 2 hemodynamic effects, ie, a hyperbolic inverse relation with PVR and a linear inverse relation with wedge pressure, in 1 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 (Fig. 6).

### Nitric Oxide Metabolism as a Crucial Player in the Pulmonary Circulation

In both passive and reactive PH, changes occur in pulmonary vessel wall composition and pulmonary vascular tone. These kinds of pathophysiologic processes are governed by changes in certain metabolic pathways, from which the NO pathway is thought 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 biologic medium.[56] It turned out to be the molecule that was once known as endothelium-derived relaxing factor.[57,58] NO is produced from L-arginine in a reaction catalyzed by nitric oxide synthase (NOS), of which 3 isoforms are known. NOS II, also called inducible NOS, and NOS III (endothelial NOS) are thought 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 biologic 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, an NOS agonist, provokes an increase in pulmonary blood flow, whereas N-monomethyl-arginine (MMA), an NOS inhibitor, does the opposite.[61,62] In patients with congestive HF and elevated PVR, MMA infusion produces less vasoconstriction than in patients with HF and normal PVR. Therefore, in HF patients with elevated PVR, NO bioavailability may already be substantially diminished. This may also explain why further inhibition of NOS has 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

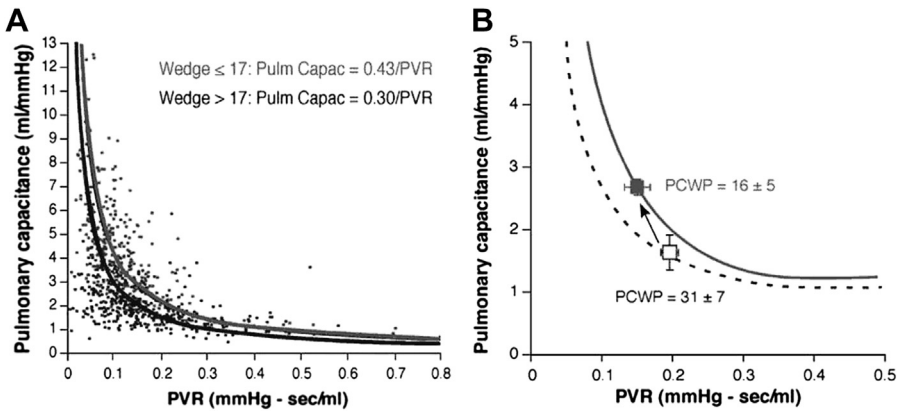



**Fig. 6.** The hyperbolic relationship between PAC and PVR. (A) Demonstration of the hyperbolic relationship between PVR and PAC in 724 patients with heart failure. Higher wedge pressures shift the hyperbola downward, representing a lower arterial time constant (PVR × PAC). (B) Treatment of elevated wedge pressure leads to a decrease in PVR and a relatively more pronounced increase in PAC, provoking an upward shift of the hyperbola. Reproduced from Dupont et al[34] with permission. Abbreviations as in Figure 5.

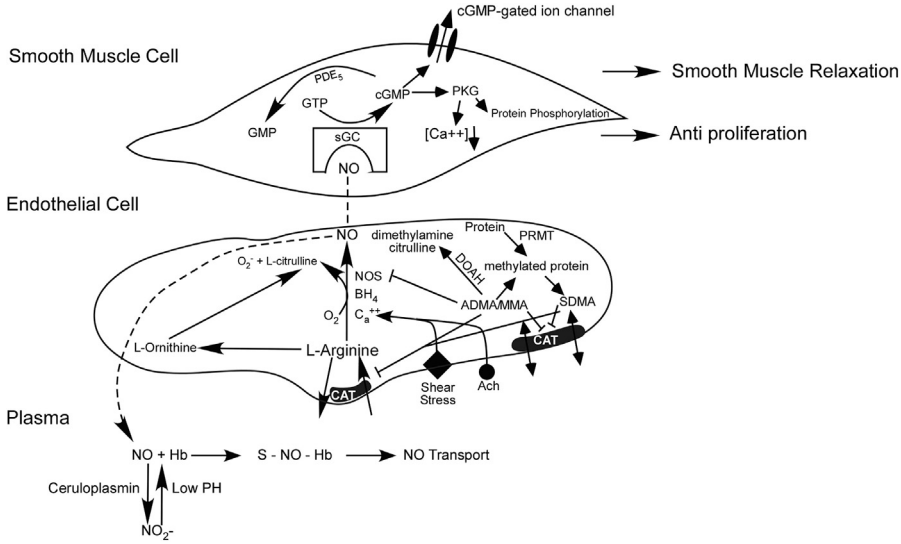



**Fig. 7.** Nitric oxide (NO) metabolism in pulmonary vasculature. NO is mainly synthesized in the endothelial cells from L-arginine by a set of enzymes, NO synthases, with calcium and $BH_4$ as cofactors. Inhibition of this reaction comes from a few methylated arginine-like metabolites: ADMA, MMA, and SDMA. The classic 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 antiproliferation and relaxation. Alternatively NO, when diffused into the plasma, quickly reacts with hemoglobin (Hb) and has possible effects at distance. Ach, acetylcholine; ADMA, asymmetric dimethylarginine; $BH_4$, tetrahydrobiopterin; $Ca^{++}$, calcium; CAT, cationic amino acid transport; cGMP, cyclic guanosine monophosphate; DDAH, dimethylarginine dimethylaminohydrolase; GTP, guanosine triphosphate; NO, nitric oxide; $NO_2^-$, nitrite; MMA, N-monomethylarginine; $PDE_5$, phosphodiesterase-5; PKG, protein kinase G; PRMT, protein arginine methyltransferase; SDMA, symmetric dimethylarginine; sGC, soluble guanylyl cyclase.

systemic ADMA levels and lower arginine bioavailability. However, a counterregulatory mechanism, compensating for the increased ADMA levels, also seems to exist in the form of increased expression of dimethylarginine dimethylaminohydrolase 1 in the failing myocardium. This enzyme is responsible for the degradation of ADMA, and patients without PH had higher levels of it 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 (nose and sinuses) respiratory tract. In an attempt to measure eNO more uniformly and to 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 with healthy subjects.[72–74] According to Hare et al,[74] HF patients had higher resting eNO levels than normal, although that observation has not been confirmed in later studies with more standardized measurements.[75,76] However, patients with HF have more vasoconstricted pulmonary vascular beds, so it may seem that the NO pathway may serve as a counterregulatory process that compensates the vasoconstriction imposed by neurohormonal up-regulation (eg, 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, eg, decompensated HF.[77] Conforming 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, where 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, eg, NO administration and whether the product of PVR and PAC (time constant) remains a constant in these circumstances as well.

## Therapeutic Targets

Because preservation of RV function seems to be so important for good outcomes in HF, it seems reasonable to identify the pulmonary circulation as a therapeutic target to minimize RV afterload for effective filling of the LV. Because every elevation of left-sided filling pressures increases 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 remains to be proven. Nevertheless, once reactive PH has developed, this can become a treatment target 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 HF.[85–87] Inhaled NO is frequently used in the post-transplantation and postoperative settings 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 cyclic guanosine monophosphate, 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] nor were endothelin-antagonists and prostaglandins in this population.[94–96] One explanation might relate to the fact that these drugs were given to (eg, in the RELAX trial) the HFpEF population at large. We think 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.

## Disclosures

None.

## References


1. Polak JF, Holman BL, Wynne J, Colucci WS. Right ventricular ejection fraction: an indicator of increased mortality in patients with congestive heart failure associated with coronary artery disease. J Am Coll Cardiol 1983;2:217–24.
2. Ghio S, Gavazzi A, Campana C, Inserra C, Klersy C, Sebastiani R, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. J Am Coll Cardiol 2001;37:183–8.
3. Juilliere Y, Barbier G, Feldmann L, Grentzinger A, Danchin N, Cherrier F. Additional predictive value of both left and right ventricular ejection fractions on long-term survival in idiopathic dilated cardiomyopathy. Eur Heart J 1997;18:276–80.
4. de Groote P, Millaire A, Foucher-Hossein C, Nugue O, Marchandise X, Ducloux G, et al. Right ventricular ejection fraction is an independent predictor of survival in patients with moderate heart failure. J Am Coll Cardiol 1998;32:948–54.
5. di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. J Am Coll Cardiol 1995;25:1143–53.
6. Baker BJ, Wilen MM, Boyd CM, Dinh H, Franciosa JA. Relation of right ventricular ejection fraction to exercise capacity in chronic left ventricular failure. Am J Cardiol 1984;54:596–9.
7. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589–96.
8. Dupont M, Mullens W, Tang WH. Impact of systemic venous congestion in heart failure. Curr Heart Fail Rep 2011;8:233–41.
9. Abel FL, Waldhausen JA. Effects of alterations in pulmonary vascular resistance on right ventricular function. J Thorac Cardiovasc Surg 1967;54:886–94.
10. Kondo RP, Dederko DA, Teutsch C, Chrast J, Catalucci D, Chien KR, et al. Comparison of contraction and calcium handling between right and left ventricular myocytes from adult mouse heart: a role for repolarization waveform. J Physiol 2006;571:131–46.
11. Norton JM. Toward consistent definitions for preload and afterload. Adv Physiol Educ 2001;25:53–61.
12. Milnor WR. Arterial impedance as ventricular afterload. Circ Res 1975;36:565–70.
13. Saouti N, Westerhof N, Postmus PE, Vonk-Noordegraaf A. The arterial load in pulmonary hypertension. Eur Respir Rev 2010;19:197–203.
14. Milnor WR. Pulsatile blood flow. N Engl J Med 1972;287:27–34.
15. Chirinos JA, Segers P. Noninvasive evaluation of left ventricular afterload: part 1: pressure and flow measurements and basic principles of wave conduction and reflection. Hypertension 2010;56:555–62.
16. Chirinos JA, Segers P. Noninvasive evaluation of left ventricular afterload: part 2: arterial pressure-flow and pressure-volume relations in humans. Hypertension 2010;56:563–70.
17. O. F. Die grundform des arteriellen pulses. Zeitschr Biol 1899;37:483–526.
18. Stergiopulos N, Meister JJ, Westerhof N. Evaluation of methods for estimation of total arterial compliance. Am J Physiol 1995;268:H1540–8.

19. Chemla D, Hebert JL, Coirault C, Zamani K, Suard I, Colin P, et al. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. Am J Physiol 1998;274:H500−5.
20. Wetterer E. Flow and pressure in the arterial system, their hemodynamic relationship, and the principles of their measurement. Minn Med 1954;37:77−86.
21. Westerhof N, Elzinga G, Sipkema P. An artificial arterial system for pumping hearts. J Appl Physiol 1971;31:776−81.
22. Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983;245:H773−80.
23. Kelly RP, Ting CT, Yang TM, Liu CP, Maughan WL, Chang MS, et al. Effective arterial elastance as index of arterial vascular load in humans. Circulation 1992;86:513−21.
24. Morimont P, Lambermont B, Ghuysen A, Gerard P, Kolh P, Lancellotti P, et al. Effective arterial elastance as an index of pulmonary vascular load. Am J Physiol Heart Circ Physiol 2008;294: H2736−42.
25. Kass DA, Kelly RP. Ventriculo-arterial coupling: concepts, assumptions, and applications. Ann Biomed Eng 1992;20:41−62.
26. Borlaug BA, Kass DA. Ventricular-vascular interaction in heart failure. Heart Fail Clin 2008;4:23−36.
27. Chantler PD, Lakatta EG, Najjar SS. Arterial-ventricular coupling: mechanistic insights into cardiovascular performance at rest and during exercise. J Appl Physiol 2008;105:1342−51.
28. Horsfield K. Morphometry of the small pulmonary arteries in man. Circ Res 1978;42:593−7.
29. Saouti N, Westerhof N, Helderman F, Marcus JT, Stergiopulos N, Westerhof BE, et al. RC time constant of single lung equals that of both lungs together: a study in chronic thromboembolic pulmonary hypertension. Am J Physiol Heart Circ Physiol 2009;297:H2154−60.
30. Lankhaar JW, Westerhof N, Faes TJ, Marques KM, Marcus JT, Postmus PE, et al. Quantification of right ventricular afterload in patients with and without pulmonary hypertension. Am J Physiol Heart Circ Physiol 2006;291:H1731−7.
31. Lankhaar JW, Westerhof N, Faes TJ, Gan CT, Marques KM, Boonstra A, et al. Pulmonary vascular resistance and compliance stay inversely related during treatment of pulmonary hypertension. Eur Heart J 2008;29:1688−95.
32. Bonderman D, Martischnig AM, Vonbank K, Nikfardjam M, Meyer B, Heinz G, et al. Right ventricular load at exercise is a cause of persistent exercise limitation in patients with normal resting pulmonary vascular resistance after pulmonary endarterectomy. Chest 2011;139:122−7.
33. Tedford RJ, Hassoun PM, Mathai SC, Girgis RE, Russell SD, Thiemann DR, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. Circulation 2012;125:289−97.
34. Dupont M, Mullens W, Skouri HN, Abrahams Z, Wu Y, Taylor DO, et al. Prognostic role of pulmonary arterial capacitance in advanced heart failure. Circ Heart Fail 2012;5:778−85.
35. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43−54.
36. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 2009;34:888−94.
37. Butler J, Chomsky DB, Wilson JR. Pulmonary hypertension and exercise intolerance in patients with heart failure. J Am Coll Cardiol 1999;34:1802−6.
38. Schwartzenberg S, Redfield MM, From AM, Sorajja P, Nishimura RA, Borlaug BA. Effects of vasodilation in heart failure with preserved or reduced ejection fraction implications of distinct pathophysiologies on response to therapy. J Am Coll Cardiol 2012;59:442−51.
39. Aronson D, Eitan A, Dragu R, Burger AJ. Relationship between reactive pulmonary hypertension and mortality in patients with acute decompensated heart failure. Circ Heart Fail 2011;4:644−50.
40. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. Circulation 2012;126:975−90.
41. West JB, Mathieu-Costello O. Vulnerability of pulmonary capillaries in heart disease. Circulation 1995;92:622−31.
42. Delgado JF, Conde E, Sanchez V, Lopez-Rios F, Gomez-Sanchez MA, Escribano P, et al. Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. Eur J Heart Fail 2005;7:1011−6.
43. Rabinovitch M. EVE and beyond, retro and prospective insights. Am J Physiol 1999;277:L5−12.
44. Stobierska-Dzierzek B, Awad H, Michler RE. The evolving management of acute right-sided heart failure in cardiac transplant recipients. J Am Coll Cardiol 2001;38:923−31.
45. Naeije R, Chesler N. Pulmonary circulation at exercise. Compr Physiol 2012;2:711−41.
46. Reeves JT, Linehan JH, Stenmark KR. Distensibility of the normal human lung circulation during exercise. Am J Physiol Lung Cell Mol Physiol 2005;288:L419−25.
47. Reeves JT, Moon RE, Grover RF, Groves BM. Increased wedge pressure facilitates decreased lung vascular resistance during upright exercise. Chest 1988;93:97S−9S.
48. Lewis GD, Murphy RM, Shah RV, Pappagianopoulos PP, Malhotra R, Bloch KD, et al. Pulmonary vascular response patterns during exercise in left ventricular systolic dysfunction predict exercise capacity and outcomes. Circ Heart Fail 2011;4:276−85.
49. Tolle JJ, Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM. Exercise-induced pulmonary arterial hypertension. Circulation 2008;118:2183−9.
50. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588−95.
51. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetieere P, et al. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male population. Hypertension 1997; 30:1410−5.
52. Mitchell GF, Moye LA, Braunwald E, Rouleau JL, Bernstein V, Geltman EM, et al, SAVE Investigators. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. Survival and Ventricular Enlargement. Circulation 1997;96:4254−60.
53. Domanski MJ, Mitchell GF, Norman JE, Exner DV, Pitt B, Pfeffer MA. Independent prognostic information provided by sphygmomanometrically determined pulse pressure and mean arterial pressure in patients with left ventricular dysfunction. J Am Coll Cardiol 1999;33:951−8.
54. Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. J Am Coll Cardiol 2006;47:799−803.
55. Moraes DL, Colucci WS, Givertz MM. Secondary pulmonary hypertension in chronic heart failure: the role of the endothelium in pathophysiology and management. Circulation 2000;102:1718−23.
56. Furchgott RF. The role of endothelium in the responses of vascular smooth muscle to drugs. Annu Rev Pharmacol Toxicol 1984;24: 175−97.
57. Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc Natl Acad Sci U S A 1987;84:9265−9.
58. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987;327:524−6.
59. Guo FH, de Raeve HR, Rice TW, Stuehr DJ, Thunnissen FB, Erzurum SC. Continuous nitric oxide synthesis by inducible nitric oxide synthase in normal human airway epithelium in vivo. Proc Natl Acad Sci U S A 1995;92:7809−13.
60. Greenberg B, Rhoden K, Barnes PJ. Endothelium-dependent relaxation of human pulmonary arteries. Am J Physiol 1987;252:H434−8.
61. Stamler JS, Loh E, Roddy MA, Currie KE, Creager MA. Nitric oxide regulates basal systemic and pulmonary vascular resistance in healthy humans. Circulation 1994;89:2035−40.

62. Cooper CJ, Landzberg MJ, Anderson TJ, Charbonneau F, Creager MA, Ganz P, et al. Role of nitric oxide in the local regulation of pulmonary vascular resistance in humans. Circulation 1996;93:266−71.
63. Cooper CJ, Jevnikar FW, Walsh T, Dickinson J, Mouhaffel A, Selwyn AP. The influence of basal nitric oxide activity on pulmonary vascular resistance in patients with congestive heart failure. Am J Cardiol 1998;82:609−14.
64. Habib F, Dutka D, Crossman D, Oakley CM, Cleland JG. Enhanced basal nitric oxide production in heart failure: another failed counter-regulatory vasodilator mechanism? Lancet 1994;344:371−3.
65. Usui M, Matsuoka H, Miyazaki H, Ueda S, Okuda S, Imaizumi T. Increased endogenous nitric oxide synthase inhibitor in patients with congestive heart failure. Life Sci 1998;62:2425−30.
66. Pullamsetti S, Kiss L, Ghofrani HA, Voswinckel R, Haredza P, Klepetko W, et al. Increased levels and reduced catabolism of asymmetric and symmetric dimethylarginines in pulmonary hypertension. FASEB J 2005;19:1175−7.
67. Tang WH, Wang Z, Cho L, Brennan DM, Hazen SL. Diminished global arginine bioavailability and increased arginine catabolism as metabolic profile of increased cardiovascular risk. J Am Coll Cardiol 2009;53:2061−7.
68. Wang Z, Tang WH, Cho L, Brennan DM, Hazen SL. Targeted metabolomic evaluation of arginine methylation and cardiovascular risks: potential mechanisms beyond nitric oxide synthase inhibition. Arterioscler Thromb Vasc Biol 2009;29:1383−91.
69. Saitoh M, Osanai T, Kamada T, Matsunaga T, Ishizaka H, Hanada H, et al. High plasma level of asymmetric dimethylarginine in patients with acutely exacerbated congestive heart failure: role in reduction of plasma nitric oxide level. Heart Vessels 2003;18:177−82.
70. Shao Z, Wang Z, Shrestha K, Thakur A, Borowski AG, Sweet W, et al. Pulmonary hypertension associated with advanced systolic heart failure: dysregulated arginine metabolism and importance of compensatory dimethylarginine dimethylaminohydrolase-1. J Am Coll Cardiol 2012;59:1150−8.
71. American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005;171:912−30.
72. Clini E, Volterrani M, Pagani M, Bianchi L, Porta R, Gile LS, et al. Endogenous nitric oxide in patients with chronic heart failure (CHF): relation to functional impairment and nitrate-containing therapies. Int J Cardiol 2000;73:123−30; discussion 31−4.
73. Agostoni P, Bussotti M. Exhaled nitric oxide and exercise performance in heart failure. Arch Physiol Biochem 2003;111:293−6.
74. Hare JM, Nguyen GC, Massaro AF, Drazen JM, Stevenson LW, Colucci WS, et al. Exhaled nitric oxide: a marker of pulmonary hemodynamics in heart failure. J Am Coll Cardiol 2002;40:1114−9.
75. Schuster A, Thakur A, Wang Z, Borowski AG, Thomas JD, Tang WH. Increased exhaled nitric oxide levels after exercise in patients with chronic systolic heart failure with pulmonary venous hypertension. J Card Fail 2012;18:799−803.
76. Seshadri N, Dweik RA, Laskowski D, Pothier C, Rodriguez L, Young JB, et al. Dysregulation of endogenous carbon monoxide and nitric oxide production in patients with advanced ischemic or nonischemic cardiomyopathy. Am J Cardiol 2003;92:820−3.
77. Tonelli AR, Haserodt S, Aytekin M, Dweik RA. Nitric oxide deficiency in pulmonary hypertension: Pathobiology and implications for therapy. Pulm Circ 2013;3:20−30.
78. Funakoshi T, Yamabe H, Yokoyama M. Increased exhaled nitric oxide and impaired oxygen uptake ($VO_2$) kinetics during exercise in patients with chronic heart failure. Jpn Circ J 1999;63:255−60.
79. Bussotti M, Andreini D, Agostoni P. Exercise-induced changes in exhaled nitric oxide in heart failure. Eur J Heart Fail 2004;6:551−4.
80. Katz SD, Hryniewicz K, Hriljac I, Balidemaj K, Dimayuga C, Hudaihed A, et al. Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. Circulation 2005;111:310−4.
81. van Veldhuisen DJ, Braunschweig F, Conraads V, Ford I, Cowie MR, Jondeau G, et al. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. Circulation 2011;124:1719−26.
82. Bourge RC, Abraham WT, Adamson PB, Aaron MF, Aranda JM Jr, Magalski A, et al. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. J Am Coll Cardiol 2008;51:1073−9.
83. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet 2011;377:658−66.
84. Ritzema J, Troughton R, Melton I, Crozier I, Doughty R, Krum H, et al. Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure. Circulation 2010;121:1086−95.
85. Guazzi M, Tumminello G, di Marco F, Guazzi MD. Influences of sildenafil on lung function and hemodynamics in patients with chronic heart failure. Clin Pharmacol Ther 2004;76:371−8.
86. Lepore JJ, Maroo A, Bigatello LM, Dec GW, Zapol WM, Bloch KD, et al. Hemodynamic effects of sildenafil in patients with congestive heart failure and pulmonary hypertension: combined administration with inhaled nitric oxide. Chest 2005;127:1647−53.
87. Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. Circulation 2007;116:1555−62.
88. Argenziano M, Choudhri AF, Moazami N, Rose EA, Smith CR, Levin HR, et al. Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. Ann Thorac Surg 1998;65:340−5.
89. Kieler-Jensen N, Lundin S, Ricksten SE. Vasodilator therapy after heart transplantation: effects of inhaled nitric oxide and intravenous prostacyclin, prostaglandin E1, and sodium nitroprusside. J Heart Lung Transplant 1995;14:436−43.
90. Behling A, Rohde LE, Colombo FC, Goldraich LA, Stein R, Clausell N. Effects of 5′-phosphodiesterase four-week long inhibition with sildenafil in patients with chronic heart failure: a double-blind, placebo-controlled clinical trial. J Card Fail 2008;14:189−97.
91. Guazzi M, Vicenzi M, Arena R, Guazzi MD. PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: results of a 1-year, prospective, randomized, placebo-controlled study. Circ Heart Fail 2011;4:8−17.
92. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation 2011;124:164−74.
93. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2013:1−10.
94. Anand I, McMurray J, Cohn JN, Konstam MA, Notter T, Quitzau K, et al. Long-term effects of darusentan on left-ventricular remodelling and clinical outcomes in the Endothelin-A Receptor Antagonist Trial in Heart Failure (EARTH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364:347−54.
95. McMurray JJ, Teerlink JR, Cotter G, Bourge RC, Cleland JG, Jondeau G, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. JAMA 2007;298:2009−19.
96. Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997;134:44−54.
97. Westerhof N, Lankhaar JW, Westerhof BE. The arterial windkessel. Med Biol Eng Comput 2009;47:131−41.