

## PULMONARY CIRCULATION AT EXERCISE

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### Abstract

The pulmonary circulation is a high flow and low pressure circuit, with an average resistance of 1 mmHg.min.L<sup>-1</sup> in young adults, increasing to 2.5 mmHg.min.L<sup>-1</sup> over 4–6 decades of life. Pulmonary vascular mechanics at exercise are best described by distensible models. Exercise does not appear to affect the time constant of the pulmonary circulation or the longitudinal distribution of resistances. Very high flows are associated with high capillary pressures, up to a 20–25 mmHg threshold associated with interstitial lung edema and altered ventilation/perfusion relationships. Pulmonary artery pressures of 40–50 mmHg, which can be achieved at maximal exercise, may correspond to the extreme of tolerable right ventricular afterload. Distension of capillaries that decrease resistance may be of adaptive value during exercise, but this is limited by hypoxemia from altered diffusion/perfusion relationships. Exercise in hypoxia is associated with higher pulmonary vascular pressures and lower maximal cardiac output, with increased likelihood of right ventricular function limitation and altered gas exchange by interstitial lung edema. Pharmacological interventions aimed at the reduction of pulmonary vascular tone have little effect on pulmonary vascular pressure-flow relationships in normoxia, but may decrease resistance in hypoxia, unloading the right ventricle and thereby improving exercise capacity. Exercise in patients with pulmonary hypertension is associated with sharp increases in pulmonary artery pressure and a right ventricular limitation of aerobic capacity. Exercise stress testing to determine multipoint pulmonary vascular pressures-flow relationships may uncover early stage pulmonary vascular disease.

### 1. Introduction

The pulmonary circulation is a low pressure, high flow circuit. Low pressure prevents fluid moving out of fluid from the pulmonary vessels into the interstitial space, and allows the right ventricle to operate at minimal energy cost. Exercise increases oxygen uptake (VO<sub>2</sub>) and carbon dioxide output (VCO<sub>2</sub>) up to some twenty fold above resting values, and this increase in gas exchange is matched by an increase in cardiac output up to some 6-fold. The 6-fold increase in cardiac output is needed for the increased convective transport demands of these gases to and from exercising muscles. Exercise may thus be a considerable stress on the pulmonary circulation, taking the entire cardiac output while keeping the lungs dry and the right ventricle compensated.

An additional stress is imposed upon the pulmonary circulation by decreased inspired PO<sub>2</sub> at altitude. Hypoxia causes pulmonary arterioles and venules (to a lesser extent) to constrict, which may increase pulmonary capillary pressures (Pcp) to the point of excessive transudation, and pulmonary artery pressures (Ppa) to the point of excessive right ventricular afterload. Even though the maximum VO<sub>2</sub> (VO<sub>2</sub>max) decreases in hypoxia, thereby

decreasing the maximum pulmonary flow required for gas exchange, both  $P_{cp}$  and  $P_{pa}$  may reach the limits of compensation, resulting in lung edema or right heart failure, or both.

Since the essential stress of exercise imposed on the pulmonary circulation is an increase in cardiac output, with the additional burden of an increase in pulmonary vascular pressures in hypoxia, in this chapter we will first review concepts of pulmonary vascular pressure-flow relationships and right ventriculo-arterial coupling. We will then examine available data on invasive and non invasive measurements of pulmonary hemodynamics at exercise, in humans and in different animal species, in normoxia and in hypoxia. A final part of the chapter will be devoted to typical pathophysiological applications to patients with cardiopulmonary disease.

Only dynamic exercise will be considered here, as static exercise is associated with an increase in systemic vascular resistance, a limited increase in cardiac output or  $\dot{V}O_2$ , and eventual intrathoracic pressure changes (131), making it a more complex stress that is less relevant for the study of pulmonary vascular mechanics and right ventricular function. High levels of dynamic exercise may be generated with variable levels of resistive effort, but how this affects the pulmonary circulation is not exactly known. Therefore, in this chapter, exercise will be considered as a cause of increased cardiac output affecting pulmonary vascular pressures, and pulmonary hemodynamics at exercise will be explained using reference models of flow-related changes in pulmonary vascular mechanics.

## 2. Steady flow pulmonary hemodynamics

### 2.1. Pulmonary vascular resistance

How cardiac output affects the pulmonary circulation is usually understood in terms of “steady-flow” hemodynamics. This approach summarizes time-dependent pulmonary artery pressure and flow waves by their time-averaged or mean values, and defines pulmonary vascular pressure-flow relationships by a single point pressure difference-flow ratio calculated as a resistance. Accordingly, a single point resistance calculation serves to describe the flow-resistive properties of the pulmonary circulation, which is one aspect of pulmonary vascular function.

Thus pulmonary vascular resistance (PVR) is the difference between mean  $P_{pa}$  ( $P_{pa_m}$ ) and mean left atrial pressure ( $P_{la}$ ) divided by cardiac output  $Q$ :

$$PVR = (P_{pa_m} - P_{la}) / Q$$

This is most often implemented in clinical practice by measurements of  $P_{pa_m}$ ,  $P_{la}$  and  $Q$  via fluid-filled thermodilution catheters. These catheters are balloon-tipped, allowing for an estimate of  $P_{la}$  by a wedged or a balloon occluded  $P_{pa}$  ( $P_{pw}$  or  $P_{pao}$ ).

Sometimes a measurement of  $P_{la}$  or  $P_{pao}$  cannot be obtained, and a *total* PVR (TPVR) is calculated as

$$TPVR = P_{pa_m} / Q$$

Since  $P_{la}$  is not negligible with respect to  $P_{pa}$ , TPVR is larger than PVR and this difference may be flow-dependent. Thus TPVR is not a correct characterization of the flow-resistive properties of the pulmonary circulation. On the other hand, TPVR may be a more realistic

estimate of right ventricular afterload, as the right ventricle is exposed to Ppa and not to the difference between Ppa and Pla.

A resistance calculation derives from Ohm's law first described for electric circuits. The resistance is determined by vessel and fluid properties. The physical law that governs laminar flows of Newtonian fluids through non-distensible, straight circular tubes was originally proposed by the French physician Poiseuille and later put in mathematical equation by the German physicist Hagen. Poiseuille showed experimentally that flow was inversely related to the fourth power of the internal radius, and confirmed previous demonstrations that arterial pressure remains high in arteries down to 2 mm in diameter while venous pressure is low in animals. The Hagen-Poiseuille law states that resistance R to flow of a single tube is equal to the product of the length l of the tube and viscosity  $\eta$  and a constant 8 divided by the product of  $\pi$  and the fourth power of the internal radius r. More generally R can be calculated as a pressure drop  $\Delta P$  to flow (Q) ratio:

$$R = l \cdot \eta 8 / \pi \cdot r^4 = \Delta P / Q$$

The fact that r in the equation is to the fourth power explains why R is exquisitely sensitive to small changes in tube caliber (a 10% change in radius results in almost 50% change in resistance). Accordingly, PVR is a good indicator of the state of constriction or dilatation of pulmonary resistive vessels and is useful for detecting changes in arteriolar vessel caliber due to changes in tone and/or structure.

The limits of normal resting pulmonary vascular pressures and flows as derived from invasive measurements reported by ourselves in resting supine young adult healthy volunteers are shown in Table 1 (134,146,161). In that study population, Q was lower in women, who are smaller than men, and thus PVR in women was higher. However, there were no gender differences in pulmonary hemodynamics after correction for body dimensions. More recently, Kovacs et al exhaustively reviewed the literature on invasive hemodynamic measurements in normal subjects (111). They retrieved 47 studies on a total of 1187 individuals, of whom 225 were identified as women and 717 as men. Resting supine pulmonary vascular pressures were in agreement with our own. In particular, no mean Ppa higher than 20 mmHg was found, and there were no gender differences in indexed PVR. However, cardiac output was somewhat higher in Kovacs' group, averaging 7.3 vs 6.4 Lmin<sup>-1</sup>. This may be explained by the smaller proportion of female subjects (22 % in the report by Kovacs et al. vs. 40 % in our own studies) and possible uncertainties about quality of cardiac output measurements using the Fick method (57). It is obvious that the accuracy of the measurement of cardiac output is essential to resting or exercise PVR calculations.

Aging is associated with an increase in PVR. This is related to a slight increase in mean Ppa and a more important decrease in cardiac output leading to a doubling of PVR over a five decades life (11,68,69,88). According to the Hagen-Poiseuille law, assuming no changes in pulmonary vascular length or blood viscosity, a doubling of PVR should be associated with a 16% decrease in internal radius of small vessels. This type of change could be caused by remodeling or an increase in smooth muscle cell tone, both of which have been described to occur with age in arterioles of the systemic circulation (64,125).

Body position affects PVR through associated changes in systemic venous return. In the upright position, Pla, right atrial pressure (Pra) and cardiac output are lower than in the supine position. Because of pulmonary vascular de-recruitment, mean Ppa remains essentially the same. Accordingly, PVR is increased. This difference in upright vs. supine

PVR is important to keep in mind when examining changes in PVR during exercise performed upright as compared to supine (11,57,68,69,111,178).

## 2.2. Pressure-flow relationships

A difficulty with interpreting PVR changes with exercise is the flow-dependency of this variable.

The inherent assumption in a PVR calculation is that the mean  $P_{pa}$ -Q relationship is constant and crosses the pressure axis at a value equal to  $P_{la}$  (such that when flow is zero, theoretically,  $P_{pa_m} = P_{la}$ ). Then, PVR is constant, independent of the absolute pressure or flow (Fig 1, curve A) (155).

The relationship between  $(P_{pa_m} - P_{la})$  and Q has been shown to be reasonably well described by a linear approximation over a limited “physiological” range of flows, with a zero extrapolated pressure intercept in well oxygenated lungs in supine resting intact animals including man (155,178,183). This suggests complete recruitment and minimal distension of the normal well oxygenated pulmonary circulation. However, hypoxia and a number of cardiac and respiratory diseases increase both the slope and the extrapolated intercepts of multipoint  $(P_{pa_m} - P_{la})$  vs. Q plots (155).

While an increase in the slope of  $P_{pa_m}$ -Q is easily understood as being caused by a decreased cross-sectional area of pulmonary resistive vessels, the positive extrapolated pressure intercept has inspired various explanatory models.

## 2.3. The Starling resistor model of the pulmonary circulation

To explain the non-zero and positive extrapolated pressure intercept, Permutt et al. conceived a vascular “waterfall” or “Starling resistor” model made of parallel collapsible vessels with a distribution of non-zero and positive closing pressures (174). The waterfall analogy refers to the fact that the flow rate (Q) over a waterfall is independent of its height (the pressure difference between upstream and downstream). Instead, an “external” factor (in the case of a waterfall, fluid momentum) controls the flow rate. The Starling resistor itself was actually a device: a collapsible tube inside of a closed chamber that could be pressurized, thus providing an “external” control over the flow rate. Starling used this device in the circuit of his heart-lung preparation to control blood pressure (171). Permutt et al. postulated that in the pulmonary circulation, as flow decreased, arteries would be progressively de-recruited, accounting for a low flow  $P_{pa_m}$ -Q curve that is concave to the flow axis, and intercepts the pressure axis at the lowest closing pressure needed to be overcome to generate a flow. At higher flows, complete vessel recruitment and negligible distension account for a linear  $P_{pa_m}$ -Q curve with an extrapolated pressure intercept representing a weighted mean of closing pressures. In this model, the mean closing pressure is the effective outflow pressure of the pulmonary circulation. At higher flows,  $P_{la}$  is equal to the mean closing pressure. However, at lower flows,  $P_{la}$  is less than the mean closing pressure and becomes irrelevant to flow, analogous to the height of water below a waterfall. Instead, other factors analogous to the external pressure acting on collapsible tube in the Starling resistor determine the effective outflow pressure of the circuit. In that situation, a PVR calculation becomes misleading because of flow-dependency. That is, changes in flow then change PVR without changing the functional state of the pulmonary circulation (Fig 1, curve B). However, according to Permutt, when  $P_{la}$  in the PVR equation is replaced by the mean effective closing pressure, PVR reflects the functional state of the pulmonary circulation in all circumstances (174).

A characteristic typical of a vascular system made up of collapsible vessels is the functional dissociation between inflow, outflow pressures and flow rate when the closing pressure is

higher than the (apparent) outflow pressure (151). For the pulmonary circulation, a useful experiment is to progressively increase  $P_{la}$  from near zero while keeping  $Q$  constant. As long as  $P_{la}$  is lower than the closing pressure, the increase in  $P_{la}$  does not affect  $P_{pa_m}$ . When  $P_{la}$  is higher than the closing pressure, any increase in  $P_{la}$  is transmitted to  $P_{pa}$  in a one-to-one ratio. Thus, the pressure at the inflection point of the  $P_{pa_m}$  vs.  $P_{la}$  relationship is the closing pressure and should be equal to the zero flow pressure intercept of the linear  $(P_{pa_m} - P_{la})$  vs.  $Q$  relationship. This is indeed a feature of de-recruited upright lung zones described by West (232), and has been observed in pulmonary hypertension after acute oleic acid lung injury (121) (Fig 2). A pulmonary closing pressure may become higher than  $P_{la}$  because of either an increased alveolar pressure with or without increased tone, or because of a decreased  $P_{la}$  with respect to alveolar pressure in the presence of a low cardiac output.

However, experimental data have been accumulated that cannot be explained by the Starling resistor model of the pulmonary circulation. In embolic pulmonary hypertension, multipoint  $(P_{pa_m} - P_{la})$ - $Q$  relationships were linear at physiological flow rates, but an inflection point in  $P_{pa_m}$  vs.  $P_{la}$  relationships could not always be identified (84). Furthermore, the slope of  $P_{pa_m}$ - $Q$  was independent of embolism size, while one would expect larger size emboli to have a greater effect on incremental resistance (the slope of  $P_{pa_m}$  vs.  $Q$ ) than on the extrapolated pressure intercepts of  $P_{pa_m}$  vs.  $Q$  (33). Moreover, in these experiments, inflection points of  $P_{pa_m}$  vs.  $P_{la}$  plots were not correlated to extrapolated pressure intercepts of  $P_{pa_m}$  vs.  $Q$  (144). It was also noted that in embolic pulmonary hypertension, the slope and pressure intercept of  $P_{pa_m}$  vs.  $Q$  was flow dependent, with lower incremental resistance and higher pressure intercepts in studies in which flow was increased by opening systemic arterio-venous fistulae rather than decreased by inflating an inferior vena cava balloon to decrease venous return (33,84,144).

Other concerns about the Starling resistor model of the pulmonary circulation are its inability to explain shifts of  $P_{pa}$ - $Q$  relationships with increased extrapolated pressure intercepts in conditions of increased hematocrit (105). The Hagen-Poiseuille equation and the Starling resistor model would indeed predict increased viscosity of the blood to increase the slope of  $(P_{pa_m} - P_{la})$ - $Q$ .

Finally, an implicit assumption in the use of Starling resistor model to date is that perfused pulmonary resistive vessels, or arterioles, can only be fully distended. This is in contradiction with experimental evidence (113).

Thus the Starling resistor model of the pulmonary circulation appears adequate to explain pressure-flow relationships in de-recruited lung regions in healthy states and possibly in certain pathological states such as lung edema, in situations of limited changes in distension caused pressure and/or cardiac output. However, it does not explain the effects of emboli or increased hematocrit on steady-flow pulmonary vascular pressure-flow relationships.

## 2.4. Distensible models of the pulmonary circulation

Zhuang et al. modeled the feline pulmonary circulation taking into account not only morphometry but also mechanics (i.e., distensibility) of the pulmonary vascular tree and rheological properties of each of its branched segments (242). The authors used the sheet flow theory of Fung et al for the capillary blood flow (61) and an analogous “fifth power law” for arteries and veins, and predicted  $P_{pa_m}$  vs.  $Q$  curves with a slight curvilinearity concave to the flow axis over physiological ranges of flow that was progressively enhanced at decreasing flow. This curvilinearity was generated via arterial, capillary and venous distensibility based on experimental data (195,196,238,239), with no need to invoke a closing pressure (242).

This distensible or compliant model has been shown to predict parallel shifts of Ppa-Q plots to higher pressures, induced by various interventions such as embolism, changes in lung volume, and hypoxia (21,141,144) and even a functional dissociation between Ppa and Pla at constant Q (21,144).

Marshall and Marshall (140) modified the model to account for hypoxic pulmonary vasoconstriction and were able to reasonably fit experimental data from dogs (141). Subsequently, Bshouty and Younes (21) added vasomotor tone and the effects of gravity, and confirmed that the nonlinearity in the Ppa<sub>m</sub>-Q curve is primarily a function of the distensibility of the vascular bed. Similarly, Melot et al. (144) demonstrated that Ppa<sub>m</sub>-Q curves altered by pulmonary embolism could be mimicked via a pressure-induced loss of distensibility coupled with arterial and capillary obstruction.

Experimentally, Nelin et al. showed in normoxic and hypoxic pigs that a sufficient number of Ppa<sub>m</sub>-Q coordinates, between 5 and 10, enables visualization of a slight curvilinearity (166). The same observation was reported in isolated perfused mice lungs by Tuscherer et al. (219). As illustrated in Figure 3, constructed from their data, pulmonary embolization was associated with a shift of slightly curvilinear Ppa<sub>m</sub>-Q plots to higher pressures. The best polynomial fit of these Ppa<sub>m</sub>-Q<sub>m</sub> relationships may still be linear, but distensibility permits a proportionally less increased Ppa<sub>m</sub> at the highest Q. One can also observe from the figure that pressure intercepts derived from the higher flow regions of the Ppa<sub>m</sub> - Q curves are higher than those derived from the lower regions of the curves. Using the Starling resistor model, this would have been improperly interpreted as increased closing pressure with increased flow.

Linehan reasoned that previously reported compliant models were too complex, requiring a large number of parameters not identifiable from pressure and flow measurements alone (128). Accordingly, he developed a simpler distensibility model based on only two parameters, and showed its adequacy to describe Ppa<sub>m</sub>-Q relationships at variable hematocrits in perfused dog lung lobes with the following equation:

$$Ppa_m = \frac{[(1 + \alpha Pla)^5 + 5\alpha R_0 Q]^{\frac{1}{5}} - 1}{\alpha}.$$

where the hematocrit is captured in the total pulmonary vascular resistance at rest, R<sub>0</sub> and the vessel distensibility  $\alpha$  is assumed constant throughout the pulmonary vasculature. This model allows for prediction of Ppa<sub>m</sub> at given levels of Pla, Q, hematocrit and distensibility. Nelin et al used it to obtain a very good fit of multipoint Ppa<sub>m</sub>-Q curves from isolated pig lungs in normoxia and in hypoxia (166)

The Linehan equation can also be used to estimate vessel distensibility  $\alpha$  from given values of resistance, Ppa<sub>m</sub>, Pla and Q. Reeves et al used pulmonary hemodynamic data obtained by right heart catheterization at rest and during exercise in normoxic healthy volunteers, and was able to recalculate a value of  $\alpha$  averaging 2 %/mmHg (182). This value was remarkably identical to the 2 %/mmHg distensibility measured on isolated vessels from a variety of mammalian species (113). Reeves et al also showed that  $\alpha$  is the lower limit of the range of estimated values in exercising horses, and tends to decrease with aging and with chronic but not acute hypoxic exposure (182). Similar values of  $\alpha$  were calculated by Argiento et al from echocardiographic measurements of pulmonary vascular pressures and flows in normal volunteers (4).



## 2.5. Left atrial pressure, pulmonary artery wedge and capillary pressures

Whatever the reference model, experimental data clearly demonstrate that  $P_{La}$  is transmitted upstream, in a close to 1:1 manner, in the fully recruited pulmonary circulation. It is then obvious that changes in  $P_{La}$  will affect  $P_{cp}$  as well. Pulmonary capillary pressure must be less than  $P_{pa}$  and greater than  $P_{La}$ , which is typically estimated by wedged or occluded  $P_{pa}$  ( $P_{pw}$  or  $P_{pao}$ ). Reasonably accurate estimates of pulmonary capillary pressure can be obtained from the analysis of  $P_{pa}$  decay curves after arterial occlusion (29). Normal resting human values have been reported by Maggiorini et al (134) (Table 1). Based on measured distribution of resistances in perfused normal lungs, with 60 % arterial resistance and 40 % capillary + venous resistance, Gaar et al showed (62) that  $P_{cp}$  can be approximated by the equation:

$$P_{cp} = P_{La} + 0.4 \times (P_{pa_m} - P_{La})$$

However, when normal lungs are perfused with very high flows, up to 7–10 times normal, like during high levels of exercise, the distribution of resistances is altered, such that upstream resistance decreases and the Gaar equation cannot be used (20). The arterial occlusion method to estimate  $P_{cp}$  at high flows has been validated using the isofiltration technique (20). To our knowledge, estimates of  $P_{cp}$  by single arterial occlusion have not been reported in normal exercising humans.

## 3. Pulsatile flow pulmonary hemodynamics

### 3.1. Pulmonary vascular impedance

The study of the pulmonary circulation as a steady flow system is a simplification, since pulmonary arterial pulse pressure, or the difference between systolic and diastolic  $P_{pa}$  is on the order of 40 to 50 % of mean pressure, and instantaneous flow varies from a maximum at mid-systole to around zero in diastole. Accordingly, an improved evaluation of pulmonary arterial function should theoretically be offered by the relationship between pulsatile pressure and pulsatile flow. This relationship can be quantified by the calculation of pulmonary vascular impedance (PVZ).

Pulmonary vascular impedance is derived from a spectral analysis of the pulmonary arterial pressure and flow waves (235). This analysis is possible because the pulmonary circulation behaves nearly linearly, i.e., a purely sinusoidal flow oscillation produces a purely sinusoidal pressure oscillation of the same frequency. The sinusoidal pressure and flow waves can be related by the ratio of their amplitudes (modulus) and the difference in their phases (phase angle). To do so, both pressure and flow waves are decomposed into a series of sine waves with frequencies 1, 2, 3, etc times the heart rate, each with its amplitude and phase angle. Pulmonary vascular impedance modulus is then the ratio of amplitudes of the pressure and flow sine waves and PVZ angle is the phase difference between pressure and flow sine waves. The PVZ modulus and phase angle as a function of frequency are often represented graphically. Typical PVZ spectra at rest and at exercise in a dog are illustrated in figure 4 (48).

Pulmonary arterial impedance at zero Hz,  $Z_0$ , (the ratio of mean pressure to mean flow,  $P_{pa}/Q$ ) corresponds to TPVR. This parameter is mainly determined by the small resistance vessels as well as  $P_{La}$ . As frequency increases, the impedance is affected by more proximal elements of the arterial tree (235). The modulus of the impedance decreases from  $Z_0$  rapidly to a first minimum at 2–3 times the heart rate and then oscillates about a constant value. The impedance phase increases from a negative value at low frequencies, indicating that flow leads pressure, to zero at higher frequencies. The precipitous fall in modulus and the

negative phase of the impedance are a measure of the total arterial compliance. At high frequencies the rather constant modulus and nearly zero phase angle are a measure of the proximal arterial compliance.

The impedance modulus at high frequencies, when impedance phase is nearly zero and therefore wave reflections can be ignored, is the characteristic impedance  $Z_C$ . It is typically measured as the average modulus at higher frequencies (usually 10–20 times the heart rate). It can also be measured as the slope of the early systolic pulmonary artery pressure-flow relationship in the time domain (41).

The oscillations of the impedance modulus about its mean value result from distinct wave reflections. Increased magnitude of these oscillations implies increased reflections. A shift of the first minimum of modulus to higher frequencies indicates an increased wave velocity or a decreased distance to the dominant reflection site.

Characteristic impedance is dependent on the ratio of inertia to compliance of the pulmonary circulation, and can be approximated by the equation:

$$Z_C = [(\rho/\pi r^4)/(\Delta\pi r^2/\Delta P)]$$

Where  $\rho$  is the density of blood,  $r$  the mean internal radius,  $\rho/\pi r^4$  the inertance and  $\Delta\pi r^2/\Delta P$  the compliance of the pulmonary arterial tree.

The human PVZ spectrum has the same pattern as reported in canine studies, but with lower  $Z_0$  and  $Z_C$  (48,154). Resting  $Z_0$  and  $Z_C$  were 482 and 147 dyne.s.cm<sup>-5</sup>, respectively in dogs, and 73 and 22 dyne.s.cm<sup>-5</sup> in humans (48,154). These differences can be explained by differences in body size, and thus also in cardiac output and oxygen uptake, while vascular pressures are essentially the same (235).

Exercise in normal dogs has been shown by Elkins and Milnor to decrease PVR but to shift the PVZ spectrum to higher pressure and flow moduli at all frequencies with an increase in  $Z_C$  a shift of the first minimum of the ratio of pressure and flow moduli to higher frequencies and more negative phase angle (Fig 4). The authors explained the increase in  $Z_C$  by a decreased area compliance of the proximal pulmonary arterial tree because of increased distending pressure related to increased flow, with possibly a contribution of exercise-associated sympathetic nervous system activation. Sympathetic nervous system activation may indeed increase  $Z_C$  without significantly changing PVR (170). However, Elkins and Milnor also mentioned the possibility that an increase in proximal arterial dimensions with exercise was prevented by the electromagnetic flow probe placed around the main pulmonary artery, which caused a spurious increase in  $Z_C$  (48).

In the dog experiments reported by Elkins and Milnor, the ratio of oscillatory to total hydraulic power decreased from 0.4 at rest to 0.33 at exercise. This is counterintuitive in the presence of stiffer proximal pulmonary arteries, but was explained by an improved matching of impedances because of increased cross-sectional area of peripheral resistive vessels and subsequently decreased wave reflection.

Slife et al. investigated the effects of exercise on pulmonary arterial compliance (Ca),  $Z_C$  and PVR in 8 normal patients referred to the catheterization laboratory for the evaluation of a chest pain syndrome, but in whom no cardiovascular abnormality could be found (193). The hemodynamic measurements were performed using multisensor micromanometer technology, and Ca,  $Z_C$  and PVR either calculated or modeled with a three-element Windkessel model. Direct calculation versus modeling of PVR,  $Z_C$  and Ca yielded some



differences, but the changes associated with exercise were the same. Exercise was associated with a 50 % decrease in PVR and a 30 % increase in Ca ( $P = 0.06$ ) while  $Z_C$  did not change (Fig 5). The apparent discrepancy between changes in  $Z_C$  and Ca is explained by the sensitivity of  $Z_C$  to proximal stiffness and dimensions, while Ca integrates the distensibility of the entire pulmonary circulation. Thus unchanged  $Z_C$  would be explained by the balanced effects of proximal stiffening and increased cross-sectional area.

### 3.2. The time constant of the pulmonary circulation

Impedance calculations have not gained clinical acceptance because of perceived mathematical complexity and difficulty interpreting data in the frequency domain.

Accordingly, Lankhaar et al modeled PVZ as being determined by a dynamic interaction between PVR, Ca and  $Z_C$  (118,119). These authors showed PVR and Ca are related in a hyperbolic fashion and that their product, or the time constant ( $\tau=RC$ ) of the pulmonary circulation, is remarkably constant at approximately 0.7 seconds from normal to variable severities and etiologies of pulmonary hypertension. Saouti et al. subsequently showed that the constancy of  $\tau$  holds for individual lungs (189). These authors also reported on hemodynamic and magnetic resonance imaging measurements indicating that proximal arterial compliance given by the sum of main right and left pulmonary arterial compliance is only 19 % of total arterial compliance Ca (189). The time constant RC recalculated from the data of Slife et al (193) averaged 0.86 s at rest and 0.8 s at exercise ( $P$  NS), which suggests that the product of resistance and compliance also remains constant at exercise.

The hyperbolic relationship between compliance and resistance of the pulmonary circulation demonstrates that mild increases in PVR may markedly increase right ventricular (RV) afterload because of associated decreases in Ca. This analysis was used by Bonderman et al to explain persistent dyspnea at exercise in patients after successful pulmonary endarterectomy and no or mild residual increase in PVR (12). In that study, exercise increased PVR with little or no decrease in Ca in the patients, as opposed to healthy controls in which exercise caused a mild decrease in PVR and a marked increase in Ca. Furthermore, in these patients, Ca rather than PVR showed up as an independent predictor of exercise capacity.

The stability of the time constant of the pulmonary circulation explains the reported tight correlation between systolic, diastolic and mean Ppa in normal subjects and animals during a variety of activities, and in patients with pulmonary hypertension of all possible etiologies (27,212). Accordingly,  $Ppa_m$  can be calculated from systolic Ppa ( $Ppa_s$ ) using a simple formula: (27)

$$Ppa_m = 0.6 \times Ppa_s + 2$$

This notion is of practical relevance as non-invasive evaluations of the pulmonary circulation in clinical practice often rely on the measurement of a maximum velocity of tricuspid regurgitation (TRV) to calculate a  $Ppa_s$  using the simplified form of the Bernoulli equation and a measurement or estimate of Pra (240):

$$Ppa_s = (TRV^2 \times 4) + Pra$$

## 4. Right ventricular function

Because pulmonary artery pressures and flow are linearly related in the physiological range, and very high  $Q$  and thus also  $P_{pa}$  can be reached by trained endurance athletes (178), the question has been raised as to whether intense endurance exercise might exhaust RV adaptation to increased afterload (116), and be a cause of arrhythmogenic remodeling (117). It is therefore necessary to take a closer look at the coupling of RV to afterload, and what is known about it at exercise.

### 4.1. Right ventricular hydraulic load

Increased  $P_{pa}$  at exercise requires increased RV hydraulic power to sustain adequate forward flow. Hydraulic power is made of two components: the energy per unit time (power) to produce steady flow, which is the product of  $P_{pa_m}$  and  $Q$ , and the power to produce the pulsatile component of  $P_{pa}$  and  $Q$ . The latter can be calculated from the difference between the product of the integrations of instantaneous  $P_{pa}$  and  $Q$  waves and the product of  $P_{pa_m}$  and  $Q$ . Since mean flow determines oxygen transport, mean power may be considered useful whereas oscillatory power is “wasted”. As a consequence, the ratio of oscillatory to mean power, or oscillatory to total (mean plus oscillatory) power, should preferably be small (150).

Because of the proportional relationship between systolic, diastolic and mean  $P_{pa}$ , one would expect the ratio of oscillatory to total RV power to remain constant. This was indeed recently reported by Saouti et al. (190). These authors measured pulmonary artery pressures with right heart catheterization and pulmonary arterial flows by magnetic resonance imaging in 35 patients with idiopathic pulmonary arterial hypertension and in 14 patients without pulmonary hypertension. The range of  $P_{pa}$  was wide, from normal to markedly increased. Total power increased with severity of pulmonary hypertension, but the ratio of oscillatory to total power remained reasonably constant, at 23 %. Accordingly, the authors proposed that the total power of the RV should be equal to 1.3 times mean power in all circumstances. They acknowledged previous experimental and clinical studies showing a decreased oscillatory power fraction in pulmonary hypertension, part of which could be of methodological origin. Since the proportionality of pulmonary artery pressures appears to be maintained at exercise (212) the calculation of total RV power as 1.3 times mean power is probably transposable to exercise, but this will require confirmation by further studies.

### 4.2. Right ventriculo-arterial coupling

The calculation of RV power includes a measurement of cardiac output, and thus depends not only on the impedance of the pulmonary circulation, but also on ventricular function.

It has been suggested that power transfer and ventricular efficiency are near maximal in normal subjects. A simplified approach to test this has been given by Sunagawa et al. (209). These authors proposed a graphical analysis based on the right ventricular pressure-volume diagram (187,206).

The pressure-volume diagram allows for the determination of maximal ventricular elastance ( $E_{max}$ ), which is the best possible load-independent measurement of contractility, and of arterial elastance  $E_a \approx P_{VR}/T$  (with  $T$  the R-R interval), as a measurement of afterload as it is “seen” by the ventricle. The ratio of  $E_{max}$  to  $E_a$  is a measure of the coupling of the ventricle and the arterial load. The optimal matching of heart and load, i.e. where power transfer and cardiac efficiency are close to maximal, is found when  $E_{max}/E_a$  is about 1.5 in humans. An isolated increase in  $E_a$  (increased vascular resistance), or decrease in  $E_{max}$  (decreased cardiac contractility), decreases  $E_{max}/E_a$  indicating uncoupling of the ventricle from its arterial system, i.e. lower ventricular-vascular coupling efficiency. Assuming no

change in the vasculature, a decrease in  $E_{\max}/E_a$  is necessarily accompanied by a decrease in stroke volume. On the other hand, an isolated increase in preload associated with an increase in stroke volume leads to unaltered ventriculo-arterial coupling.

Calculating the  $E_{\max}$  to  $E_a$  ratio requires measurement of at least two end-systolic pressures and volumes, since the end-systolic pressure-volume relation does not go through the origin. A common approach is to reduce RV diastolic filling and measure a series of pressure-volume loops (187,206), but bedside manipulations of venous return are too invasive to be ethically acceptable. In addition, when applied to intact beings, changes in venous return are associated with reflex sympathetic nervous system activation, which affects the ventricular as well as vascular function. These problems can be overcome by a single beat approach, which was developed by Sunagawa for the left ventricle (210), and later shown to be applicable to the RV (17). The single beat method is based on the calculation of a maximal RV pressure  $P_{\max}$  from a non linear extrapolation of the early and late systolic portions of a RV pressure curve, and a synchronized relative change in RV volume from integrated pulmonary arterial flow. The extrapolated  $P_{\max}$  has been validated against direct measurements of pressures generated by a non ejecting RV beat in an experimental intact animal preparation (17).

The single beat method applied to intact animal preparations has shown that  $E_{\max}/E_a$  for the RV is decreased by propranolol, increased by dobutamine, and maintained in the presence of increased  $E_a$  due to acute hypoxic pulmonary vasoconstriction. In fact,  $E_{\max}$  increases in proportion to increased  $E_a$  in hypoxia, even in the presence of adrenergic blockade, which is compatible with the concept of homeometric adaptation of RV contractility (17).

The notion that RV functional adaptation to afterload is essentially systolic, through an increase in contractility, with secondary diastolic changes and increased RV dimensions (187) has been confirmed by a study which applied the single beat method to derive  $E_{\max}$  and  $E_a$  from magnetic imaging and invasive hemodynamic measurements in patients with severe pulmonary hypertension (114).

An alternative and maybe simpler approach was developed by Elzinga and Westerhof in 1978 (49). The authors described RV pump function curves by plotting mean RV pressure as a function of stroke volume (SV). The RV pump function curve is built from measurements of mean RV pressure and stroke volume, a calculated maximum RV pressure at zero stroke volume, and a parabolic extrapolation to a zero pressure stroke volume. In this representation, an increase in preload shifts the curve to greater stroke volumes with no shape change, while an increased contractility leads to a higher  $P_{\max}$  with no change in  $SV_{\max}$ .

This analysis has been used to explain more severe RV failure in the face of lower  $P_{pa_m}$  in pulmonary hypertension associated with systemic sclerosis, probably due to myocardial involvement by the disease process (169).

As present, there have been no reports on RV pump function curves or RV-arterial coupling analysis at exercise. This area is thus still open to investigation. It is hoped that developments in echocardiographic and magnetic resonance imaging techniques will be implemented for a better understanding of RV function at exercise, and be able to address the unsolved issue of validation against above mentioned gold standard invasive measurements.

## 5. Pulmonary hemodynamics at exercise in healthy humans

### 5.1. Pulmonary artery pressures: invasive measurements

The first catheterizations of the right heart in normal humans at exercise were reported in the late 1940's. The results showed a small increase, no change and sometimes a decrease in  $P_{pa_m}$  as cardiac output was increased with moderate exercise (87,185). In 1950, Cournand et al. observed a sharp increase in  $P_{pa_m}$  when cardiac output was increased to three and a half times the resting value (30). A similar sharp rise in  $P_{pa_m}$  at flows above 350 % of normal was reported a few years later in isolated perfused lungs (120). However, subsequent studies repeatedly reported a linear increase in  $P_{pa_m}$  as a function of flow in isolated perfused lungs (59,236) as well as in intact human beings studied using the unilateral balloon occlusion technique (to double the flow in the contralateral lung) and/or exercise (18,44). There has been a recent report of a "take-off" pattern of  $P_{pa_m}$ -Q relationships in normal subjects at exercise (216) reminiscent of the pioneering work of Cournand. The reasons why a small minority of studies report such an inflection point in  $P_{pa_m}$ -Q relationships are not entirely clear. In an editorial about pulmonary hemodynamics at exercise published in 1969, Fowler concluded that  $P_{pa_m}$ -Q relationships are generally best described by a linear approximation until the highest physiologically possible flows, and that previously reported take-off patterns were probably explained by a deterioration of the experimental preparation in isolated perfused lung studies, and either methodological problems or diastolic dysfunction with an increase in  $P_{la}$  in intact human studies (58).

It has to be emphasized that these considerations are relevant to studies at progressively increased cardiac output during incremental exercise stress tests. When the degree of exercise is constant,  $P_{pa_m}$  tends to return to baseline after approximately 5–10 min and during the following hour, in both the recumbent (188,194) and the sitting upright (43) positions, while cardiac output is maintained. This is explained by the initial sympathetic nervous system activation related to some degree of anxiety or excitement as a cause of blood displacement from the legs, with associated changes in  $P_{la}$ .

The rate of recovery of  $P_{pa_m}$  after an exercise test, is rapid, with values back to resting baseline or even below within the first minutes of post-exercise rest (194).

In 1989, Reeves, Dempsey and Grover reviewed the published data on invasive pulmonary hemodynamic measurements at progressively increased levels of bicycle exercise normal subjects (178). They compiled 196 measurements in the supine posture in 91 subjects (37,69,77,88,221) and 104 measurements in the upright posture in 24 subjects (11,73,181, and unpublished data provided by Wagner and Moon). Only healthy subjects with normal  $P_{pa_m}$  were included in the analysis, and the quality of reported measurements was checked. The authors referred the measurements to limits of normal of  $P_{pa_m}$  previously established by Reeves and Groves in a total of 106 subjects 6–83 years old, which showed an average  $P_{pa_m}$  of 14 mmHg with a SD of 3 mmHg, defining a normal range of 9–20 mmHg (179). These limits of normal have been repeatedly confirmed (111,134,146,161).

This analysis established that supine exercise is associated with only a slight decrease in PVR, in keeping with the notion that the normal pulmonary circulation is maximally dilated and relaxed at rest. In the upright position, the initial PVR was found to be higher, which can be explained by a de-recruitment caused by a lower cardiac output (via decreased venous return). The initially higher PVR accounts for more marked decrease in PVR at exercise reported in upright subjects. However, the upright and supine PVR-workload relationships converge at moderate levels of exercise, in keeping with the notion that  $P_{pa_m}$ -Q relationships are identical in fully recruited supine or erect lungs (Fig 6).

Reeves et al were able to find measurements at rest and at least two levels of exercise in 63 subjects (including 21 women), so that they could calculate linear regressions relating  $P_{pa_m}$  to  $Q$  in each of them. On average, each liter per minute of increase in cardiac output was accompanied by 1 mmHg increase in  $P_{pa_m}$  in young adult men and women exercising in the supine position (Table 2). The same average increase in  $P_{pa_m}$  per liter per minute of flow was found in 21 subjects exercising in the upright position. Aging to 60–80 years was found to be associated with a more than doubling of the slope of  $P_{pa_m}$ - $Q$  relationships (Table 2) such that:

$$\begin{aligned} P_{pa_m}/Q &\approx 1 \text{ mmHg} \cdot \text{min} \cdot \text{L}^{-1} && \text{in young adults} \\ P_{pa_m}/Q &\approx 2.5 \text{ mmHg} \cdot \text{min} \cdot \text{L}^{-1} && \text{in old adults} \end{aligned}$$

However, there was a large individual variation, as shown by SDs of 0.94 in the supine exercise group, and 0.43 in the upright exercise group. This wide variability in individual responses of  $P_{pa_m}$  to exercise was noted in earlier studies as well (58).

## 5.2. Pulmonary artery pressures: non invasive measurements

Repeating invasive hemodynamic studies in normal subjects is met with increasing ethical reticence, so that not many additional data are likely to be reported to address remaining unsolved issues regarding pulmonary vascular function at exercise. On the other hand, non invasive methods have improved along with technological advances allowing for increasingly valid estimations of  $P_{pa_m}$ ,  $Q$ ,  $Pla$  and indices of RV function. The most commonly used approaches for the evaluation of the pulmonary circulation rely on the estimation of systolic  $P_{pa}$  from the maximum velocity of tricuspid regurgitation (241) and recalculation of a  $P_{pa_m}$  based on the constant relationship between systolic and mean pulmonary artery pressures (27,212). Cardiac output can be estimated from the Doppler aortic flow (28) and  $Pla$  estimated from the ratio of transmitral Doppler and mitral annulus tissue Doppler ratio of early diastolic  $E$  and  $E'$  waves (163).

Grunig et al used systolic  $P_{pa}$  estimated from the maximum velocity of tricuspid regurgitation to show excessive responses to exercise in healthy relatives of patients with idiopathic pulmonary arterial hypertension as compared to controls (75). In 32 % of healthy relatives of pulmonary hypertensive patients, the maximum velocity of tricuspid regurgitation exceeded 3.1 m/s (or systolic  $P_{pa} > 40$  mmHg) as compared to 10 % of the healthy controls. The cut-off value of 3.1 m/s (or 40 mmHg) corresponded to values in excess of 90 % quartile of controls. Bossone et al. observed markedly increased maximum velocities of tricuspid regurgitation in exercising athletes (13), who often reach calculated systolic  $P_{pa}$  well in excess of 40 mmHg at exercise, as would be expected from previously reported increases in cardiac output at high levels of exercise in invasive studies (162,178). However, these studies did not report on estimations of cardiac output and  $Pla$ , so that pulmonary vascular pressure-flow relationships to evaluate pulmonary vascular function could not be determined.

Acknowledging the methodological limitations of echocardiographic pulmonary vascular pressures and flow measurements at rest and even more so at exercise, Argiento et al investigated the shape of multipoint  $P_{pa_m}$ - $Q$  relationships at exercise in 25 healthy volunteers (4). Mean  $P_{pa}$  increased from  $14 \pm 3$  to  $30 \pm 7$  mmHg (mean  $\pm$  SD) at the highest achieved levels of exercise, at which workload was  $170 \pm 51$  W, cardiac output was  $18 \pm 4$  L.min<sup>-1</sup>, close to predicted maximal values.

As illustrated in Fig 7,  $P_{pa_m}$  decreased to  $19 \pm 4$  mmHg after 5 min recovery, and had returned to baseline values after 20 min. The recovery of  $Q$  was fast as well, though

somewhat slower, with a persistent 15–20 % elevation above baseline after 20 min. Rapid recovery, but at different rates, of  $P_{pa_m}$  and  $Q$  after exercise testing limits the validity of post-exercise stress measurements to evaluate the functional state of the pulmonary circulation (31,156).

Argiento et al measured 6 to 12  $P_{pa_m}$ - $Q$  coordinates at increasing levels of exercise. These pressure-flow relationships could be fitted using the distensibility model equations reported by Linehan et al. (128). This allowed for the calculation of a distensibility coefficient  $\alpha$  of  $1.7 \pm 1.8 \text{ \%}/\text{mmHg}$ , which is remarkably similar to those previously calculated based on invasive measurements in humans (182). On the other hand, checking for the best fit of these multipoint  $P_{pa_m}$ - $Q$  plots, by testing for increasing order polynomials, it could be shown that the data were best described by a linear approximation. In addition, there was a marked inter-individual variability in the slopes of  $P_{pa_m}$ - $Q$  plots, with maximal achievable  $P_{pa_m}$  around 40 mmHg. Such a variability is actually a feature of pulmonary hemodynamic responses to exercise. However, when the authors applied a normalization procedure to correct for intra-individual variability (176), they found a slope of  $P_{pa_m}$  vs.  $Q$  of  $1.37 \pm 0.65 \text{ mmHg} \cdot \text{min} \cdot \text{L}^{-1}$ , indicating a normal range from 0.03 to  $2.67 \text{ mmHg} \cdot \text{min} \cdot \text{L}^{-1}$ .

Further studies are obviously needed for a better definition of the limits of normal pulmonary hemodynamics at exercise.

### 5.3. Right and left atrial pressure

It has long been acknowledged that  $P_{pw}$  increases with exercise. Bevegaard et al found  $P_{pw}$  up to 25 mmHg in exercising athletes (11), while Granath et al frequently observed  $P_{pw}$  over 30 mmHg in elderly normal subjects (68,69). This increase in  $P_{pw}$  has been found to be strongly correlated to  $P_{ra}$ , even though  $P_{ra}$  rises less than  $P_{pw}$ . This is illustrated in Fig 9, which presents data from young healthy volunteers who participated in hypobaric chamber experiments on the effects of simulated altitudes up the summit of Mount Everest (180,181).

In their analysis of the pulmonary vascular pressure-flow relationships from at least 3 points during exercise, Reeves et al found a linear increase in  $P_{pw}$  with cardiac output. In 53 young adult men and women, the slope of  $P_{pw}$  vs.  $Q$  relationships was  $0.30 \pm 0.35 \text{ mmHg} \cdot \text{min} \cdot \text{L}^{-1}$ , increasing to  $1.93 \pm 0.94 \text{ mmHg} \cdot \text{min} \cdot \text{L}^{-1}$  in older subjects (Table 2) (178).

In a further analysis pooling all available  $P_{pa_m}$  and  $P_{pw}$ , Reeves and Taylor found a high correlation between these measurements during either supine or upright exercise, with slopes very close to one (183), suggesting a one-for-one mmHg upstream transmission of  $P_{la}$  (Fig 10).

$$P_{pa_m}/P_{pw} \approx 1 \text{ mmHg}/\text{mmHg}$$

Eighty % of the variability of  $P_{pa_m}$  at exercise in these studies was explained by  $P_{pw}$  (183).

A close to one for one upstream transmission of  $P_{pw}$  to  $P_{pa}$  corresponds to the prediction of Starling resistor as well as distensibility models of the pulmonary circulation (144).

Reeves and Taylor discussed the possible causes of increased  $P_{pw}$  at exercise, and whether  $P_{pw}$  in exercising conditions might be an accurate and precise estimate of  $P_{la}$ . They discarded intrathoracic pressure changes and swings at exercise as a cause of increased  $P_{pw}$  or increased gradient between  $P_{pw}$  and  $P_{la}$ , arguing that mean intrathoracic pressure averaged over several respiratory cycles would be near to zero and unchanged from the



resting state. Spurious overestimation of Pla by Ppw was excluded on the basis of a previous report of right and left heart catheterization studies in 10 normal male subjects investigated for chest pain syndromes (217). In that study, a high correlation between Ppw and left ventricular end-diastolic pressure was found, confirming pioneer studies in the 1950's, even though the agreement did not seem optimal, with most left ventricular end-diastolic pressures on the left of the line of identity. In a more recent retrospective study on over 11000 patients undergoing simultaneous right and left heart catheterization, Halpern and Taichman found that Ppw was correlated to left ventricular end-diastolic pressure, but rather loosely, with Bland-Altman limits of agreement from -15 to + 10 mmHg (79). Most recently, Tonelli et al studied 37 patients undergoing a right heart catheterization for suspected pulmonary hypertension, and showed that Ppw can be falsely elevated by balloon inflation volume, with a mean difference of 4 mmHg for full and half inflation (217). Thus while there is little doubt that increased Ppw reflects increased Pla at exercise, there is uncertainty as to how closely the measurements are related.

As for the cause of increased Pla at exercise, this may be explained by the left ventricle using the Starling mechanism to matching its flow output to peripheral demand (183). Left ventricular (LV) diastolic compliance decreases with increasing diastolic volume, which reaches a maximum at mild to moderate levels of exercise (208). This is due to intrinsic mechanical properties of the LV, with contribution of competition for space with the RV within the relatively non-distensible pericardium and possible sympathetic nervous system activation (180). Pericardial constraint may play an important role in decreasing diastolic LV compliance with increased venous return. This mechanism has been used to explain limited increases in stroke volume and end-diastolic volume but one-to-one transmission of increases in Pla to Pra with exercise (102). Elite endurance athletes have parallel increases of Pla and Pra at high levels of exercise, whereas less well trained or sedentary subjects have smaller increases in Pra than Ppw with exercise (201), which suggests that pericardial constraint is acting in the elite athletes at very high levels of exercise. Further confirmation of this theory is provided by studies with athletic animals in which removal of the the pericardium resulted in increased peak end-diastolic volume, stroke volume and maximal oxygen uptake (80,202).

Given the curvilinear relationship between diastolic ventricular pressure and volumes, it is curious that available data rather suggest a linear relationship between Ppw and cardiac output during exercise (183). A possible explanation for this apparent paradox is in the limited number of individual Ppw-Q points usually reported for each exercising subject. Stickland et al. addressed the issue in an invasive study in 8 healthy subjects of variable fitness, of whom 3 were considered to present with a low aerobic exercise capacity, as defined by a maximal oxygen uptake of less than 55 ml/kg/min, and 5 were considered to present with a high aerobic exercise capacity defined by a maximal oxygen uptake higher than 55 ml/kg/min (201). The authors hypothesized that while stroke volume normally reaches a plateau during submaximal exercise (5), this would not occur in endurance-trained athletes, due to improved left ventricular diastolic compliance (66,126). As illustrated in Fig 11, the fittest subjects indeed presented with a delayed increase in Ppw. It is interesting to note that neither Ppw nor Pra increased above normal before oxygen uptake values of approximately 30 ml/kg/min, corresponding to cardiac outputs in the range of 20 L.min<sup>-1</sup>. Above this level of exercise, both Ppw and Pra increased rapidly in the less fit subjects, but was very much delayed in the fittest subjects, in whom as expected stroke volume continued to increase. The observation of late increase in Ppw and Pra at exercise levels corresponding to cardiac outputs higher than 20–25 L.min<sup>-1</sup> was confirmed by Stickland et al in another study exploring the effects of lower body positive pressure on pulmonary gas exchange (200).

Argiento et al calculated Pla from the mitral E/E' ratio in normal exercising individuals and could not find a significant change over a range of cardiac outputs from 10 to 26 L/min, mean 18 L.min<sup>-1</sup> (4). Although the measurement has been validated at exercise (214), the authors wondered if this negative result might have been artifactual, or related to the fact that most subjects did not exercise at levels high enough to be associated with a significant increase in Pla.

Why the increase in Pla as a consequence of a pericardial constraint or altered left ventricular diastolic function would vary considerably from one subject to another remains unclear. A possible role of diastolic ventricular interaction may be invoked in relation to variable increases in Ppa<sub>m</sub> at given levels of flow and exercise capacity, leading to variable increases in RV diastolic volumes and competition for space with the LV within the non-distensible pericardium.

## 6. Mechanisms of decreased PVR at exercise

The question has been asked whether there is a humoral or neural contribution to decreased PVR at exercise. The pulmonary endothelium releases vasoconstrictors, such as endothelin-1, and vasodilators such as prostacyclin and nitric oxide (NO) that control pulmonary vascular structure and function (54). In systemic arteries, the ability of increased shear stress to stimulate endothelial NO synthase production to release NO and cause vasodilation is well recognized. In the pulmonary circulation, there is some evidence of this phenomenon in ferret lungs, in hypoxia, not in normoxia (25). In patients with pulmonary arterial hypertension, who often have excessive pulmonary artery smooth muscle cell tone, therapies based on the administration of endothelin receptor antagonists, prostacyclin analogues, or inhibitors of phosphodiesterase-5 to potentiate NO-cyclic guanosine monophosphate signaling have shown efficacy in controlling progression of vascular remodeling (143).

The administration of L-arginine analogues to inhibit NO synthase has been reported to increase PVR in resting sheep (110), horses (136), pigs (42,149) and healthy normal volunteers (197). The administration of the phosphodiesterase-5 inhibitor sildenafil in resting normal volunteers has been reported to be either without effect (76) or to decrease PVR (53). Sildenafil shifted Ppa<sub>m</sub>-Q relationships to lower pressures at exercise (53), but, the exercise-induced decrease in PVR was similar in subjects treated with or without L-arginine analogues or sildenafil (42,53,110,136,149).

The administration of the dual endothelin A and B receptor antagonist tezosentan did not affect PVR at rest but decreased PVR at exercise in swine, while the selective endothelin A receptor antagonist EMD122946 had no effect, which suggested that endothelin B receptor mediates increased pulmonary vascular tone in the porcine species (148). However, neither the dual endothelin A and B receptor blocker bosentan nor the selective endothelin A receptor blocker sitaxsentan affected PVR at rest or at exercise in normoxic volunteers, suggesting no participation of endothelin-1 to resting or exercise pulmonary vascular tone in healthy humans (51,158).

The interaction of endothelin and angiotensin II signaling pathways was considered in studies on pulmonary and systemic hemodynamics at exercise in male and female swine (32). The angiotensin II type I receptor blocker irbesartan decreased systemic vascular resistance at rest in both male and female swine, but paradoxically increased pulmonary vascular tone, in female swine only. The dual endothelin A/B blocker tezosentan decreased pulmonary vascular tone at exercise, and this effect was enhanced by irbesartan in female swine only. These results indicate that angiotensin II limits the vasoconstrictor influence of

endothelin 1 in female but not in male swine for reasons that are poorly understood but may be related to cross-talk between estrogen and endothelin signaling.

The possible role of prostacyclin in decreased PVR with exercise has also been investigated in experimental animals. Cyclooxygenase inhibition with meclofenamate in dogs (127) and in sheep (167) increased PVR at rest, but PVR fell by the same amount in treated and untreated animals at exercise. The cyclooxygenase inhibitor indomethacin did not affect resting or exercise PVR in swine (149).

Altogether, these experimental animal and human results indicate that low resting pulmonary vascular tone at rest and at exercise is maintained by a tonic release of prostacyclin and NO, with possibly a gender-related participation of angiotensin II to limit endothelin-related increase in pulmonary vascular tone in the porcine species. However, these mechanisms are not clearly involved in exercise-induced decreases in PVR. Endothelin signaling does not appear to participate in the control of pulmonary vascular tone at rest or at exercise in normoxic humans.

Since exercise activates the sympathetic nervous system, the question has also been raised whether this could play a role in observed changes in PVR. Increased sympathetic nervous system tone has consistently been reported to stiffen the large pulmonary arteries and thereby to increase  $Z_C$  (16,41,159,170). However, the associated changes in PVR are dependent on the level of activation and the balance of  $\alpha$  and  $\beta$  receptor stimulation principally in the distal arteries of the lung. A low level of sympathetic nervous system tone may decrease PVR because of a predominance of  $\beta$  receptor-mediated vasodilation, whereas a high level of sympathetic nervous system tone increases PVR because of a predominance of  $\alpha$  receptor-mediated vasoconstriction (16,170). In exercising sheep (107) and swine (203)  $\beta$ -adrenergic blockade with propranolol increased resting PVR and prevented the decrease in PVR associated with exercise. Alpha-adrenergic blockade with phentolamine tended to enhance the fall in PVR, but combined  $\alpha$ - and  $\beta$ -adrenergic blockade did not affect PVR. It is thus possible that  $\beta$ -adrenergic stimulation contributes to low PVR both at baseline and at exercise, but it is unclear if this mechanism contributes to the exercise-induced decrease in PVR.

Parasympathetic nervous system activation has been reported to decrease pulmonary vascular tone in cats (165) but this result was not confirmed in dogs (122). In swine, blocking the muscarinic receptors with atropine decreased PVR at rest but less so at exercise, in keeping with decreased parasympathetic nervous system activity at exercise (204).

In a review on the control of pulmonary vascular tone during exercise in healthy subjects and those with pulmonary hypertension, Merkus et al. considered the effects of endothelium-derived mediators, neuro-humoral activation, the renin-angiotensin system, natriuretic peptides, serotonin, adenosine, cyclic nucleotides, reactive oxygen species and potassium channel activation, and concluded that even if some of these interventions slightly decrease PVR at rest or at exercise, their role in exercise-induced decrease in pulmonary vascular tone remains uncertain (147).

The PVR of healthy lungs is already very low, leaving little room for further decrease, and multipoint pulmonary vascular pressure-flow relationships at exercise closely conform to model predictions which do not take into account possible smooth muscle cell-mediated changes in PVR. Reeves et al. calculated a mean difference between measured  $P_{pa_m}$  and predicted  $P_{pa_m}$  (by the Linehan distensibility model) of  $0.008 \pm 1.656$  mmHg on 267 measurements from healthy humans at rest and at exercise (180). As illustrated in Fig 12, a regression line through these data was calculated as  $y = 0.059x - 1.4$  ( $r^2$  0.078,  $P < 0.05$ ).

Therefore, the most likely explanation for decreased PVR or slopes of multipoint  $P_{pa_m}$ -Q plots less than the unit with exercise is vascular distension.

## 7. Animal data

It is possible to train large animals for hemodynamic measurements at exercise. The obvious advantages to studying experimental animals instead of human volunteers are easier access to invasive manipulations of the cardio-respiratory system and sampling of biological material. However, studies of the pulmonary circulation of different animal species for the purpose of comparative physiology is difficult because of different levels of metabolism and body size, which complicate the analysis of pulmonary vascular pressure-flow relationships, sequelae of general anesthesia and thoracotomy, and insertion of pulmonary flow probes that can alter proximal pulmonary arterial compliance and which requires pericardiectomy that delays the increase in  $P_{la}$  at exercise (183). There also may be differences in pulmonary vascular structure and function with a tendency for animal species without collateral ventilation to present with higher PVR and pulmonary vascular reactivity (229). Despite these limitations, some relevant studies are reviewed here.

Measurements in sheep suggest a delayed increase in  $P_{la}$  with exercise as compared to humans, but otherwise similar increases in  $P_{pa_m}$  as a function of changes in flow (107,168). This delayed increase in  $P_{la}$  has been ascribed to the removal of the pericardium for the insertion of pulmonary flow probes (183).

The porcine species has been reported to have higher resting PVR and  $Z_C$  compared to dogs and goats once adjusted for body dimensions (229). Pigs have no collateral ventilation, so that increased pulmonary vascular reactivity is needed to preserve ventilation/perfusion (VA/Q) relationships. Submaximal exercise in miniswine (average weight 26 kg) increasing oxygen uptake by a factor of 2.6 increased cardiac output by 10  $L \cdot min^{-1}$  and increased  $P_{pa_m}$  by an average of 18 mmHg, corresponding to an average increase in slope (i.e., TPVR) of 1.8  $mmHg \cdot min \cdot L^{-1}$  (95). In 2–3 months-old swine (average weight 22 kg), exercise to a 3–4 fold increase in oxygen uptake increased cardiac output by 4  $L \cdot min^{-1}$  and increased  $P_{pa_m}$  by 17 mmHg, corresponding to an average increase in slope of 4.3  $mmHg \cdot min \cdot L^{-1}$  (32). In these experiments, cardiac output was determined either by an aortic flow probe (32) or by the Fick method (95), avoiding mechanical constraints by measurement devices on the main pulmonary artery or confounding effects of pericardiectomy. With correction for body dimensions by a factor of 3, these slopes are in the range of those of exercising humans.

Exercise in horses (430 to 559 kg) up to approximately 60 % of their maximal oxygen uptake increased  $P_{pa_m}$  from 28 to 62 mmHg and cardiac output from 40 to 310  $L \cdot min^{-1}$  (90). This allows for the calculation of a slope of 0.3  $mmHg \cdot min \cdot L^{-1}$ , which is similar to humans if we assume a correction for body dimensions by a factor of 1/7. However, because of huge cardiac outputs achieved with exercise by horses,  $P_{pa_m}$  are also very high, around 60 mmHg at moderately severe exercise, up to 80–100 mmHg at maximal levels of exercise (183). Exercising horses also present with very high  $P_{pw}$ , up to 40–60 mmHg, which was shown to be associated with proportional increases in  $P_{cp}$  (137). Typical increases in  $P_{pa_m}$  and  $P_{pw}$  in exercising horses are illustrated in Fig 13. These pressure-flow relationships likely present extremes of right ventricular afterload and capillary pressure, and consequently extreme stresses on cardiac and lung function. It is remarkable that measured equine  $P_{pa_m}$ -Q relationships agree perfectly with the predictions of the Linehan distensibility model, with an  $\alpha$  value of approximately 1 %/mmHg (182).

## 8. Gas exchange at exercise

Exercise stresses the gas exchange function of the lungs because of the huge increase, up to factors of twenty, of oxygen uptake ( $\dot{V}O_2$ ) and carbon dioxide production ( $\dot{V}CO_2$ ) in the presence of markedly decreased oxygen content of mixed venous blood and shortened transit time of red blood cells. Two main adjustments take place: a three-fold increase in capillary blood volume, allowing to compensate for the decreased red blood cell transit time, and an increase in mean VA/Q relationship by a factor of three to increase alveolar  $PO_2$  ( $PAO_2$ ) and decrease alveolar  $PCO_2$  ( $PACO_2$ ) (34). These adaptations explain why pulmonary gas exchange is generally well preserved up to high levels of exercise, as assessed by maintained arterial  $PO_2$  ( $PaO_2$ ) and  $PaCO_2$ , and by chemoreflex decrease in  $PaCO_2$  above the ventilatory threshold.

In 1984, Dempsey et al. reported on exercise-induced hypoxemia in highly trained athletes, suggesting that extreme levels of exercise may reach the limits of lung function adaptation (35). In that study, the lowest  $PaO_2$  were observed in those athletes with lesser decrease in  $PaCO_2$ , which is an indication of lung mechanical constraints accounting for exercise-induced hypoxemia associated with abnormally well maintained capnia.

However, moderate exercise may already affect gas exchange as assessed by an increased gradient between alveolar and arterial  $PO_2$  (A-a $PO_2$ ) which widens until maximal exercise capacity. Studies in exercising healthy subjects using the multiple gas elimination technique (MIGET) have demonstrated that this is attributable in part to VA/Q inhomogeneity and, at the highest levels of exercise, to a diffusion limitation (63,67,81,162,226). Both VA/Q imbalance and diffusion limitation may be related to the state of the pulmonary circulation at exercise.

### 8.1. VA/Q relationships

Exercise-induced  $V_A/Q$  inhomogeneities have been demonstrated by the MIGET. This technique is based on the use of inert gases with different solubility to calculate the distributions of  $V_A$  and  $Q$  to 50 compartments of a mathematical lung model with  $V_A/Q$  increased from zero (shunt) to the infinite (dead space) passing through an ideal  $V_A/Q$  around one. The difficulty of this representation is that changes in distributions may be due either to changes in  $V_A$  or  $Q$  for any given compartment (145). For example, an apparent increase in flow distribution to a lung unit with a  $V_A/Q$  of 0.1 may as well be caused by a ten times less important decrease in ventilation. Thus changes in MIGET  $V_A/Q$  distributions can always be explained by changes in the distribution of perfusion and/or ventilation but one cannot discern the precise mechanism.

Gravity normally imposes a vertical gradient of pulmonary perfusion, which causes of physiologic inhomogeneity of  $V_A/Q$  (232). Increased  $Ppa_m$  at exercise counteracts the effects of gravity. Accordingly, radioactive tracer studies of  $V_A$  and  $Q$  distributions at exercise have shown more homogeneous  $V_A/Q$  because of a redistribution of  $Q$  to the upper parts of the lung (19,82).

However, MIGET studies have demonstrated a deterioration in  $V_A/Q$  distributions in proportion to level of exercise and increased  $Ppa_m$  in normal exercising humans (63,67,81,162,226), independent of level of exercise or inspired  $PO_2$  ( $PIO_2$ ) (63,162,226,228). The most likely explanation is that increased pulmonary vascular pressures are associated with an increased capillary filtration, causing interstitial edema. This alters the distribution of  $V_A$ , because of narrowing of airways and decrease in alveolar compliance, but may also alter the distribution of  $Q$  because of compression of blood vessels. Left atrial pressure and  $Ppw$  increase at exercise in proportion to  $Ppa_m$ , and it is



easy to calculate that at some point, corresponding to a  $P_{cp}$  of 20–25 mmHg (78), Starling forces governing pulmonary capillary filtration become disturbed such that excess fluid leaves the capillaries, overcoming the capacities of the lung lymphatic drainage. In a recent discussion about the mechanisms of altered gas exchange at exercise, Hopkins argued in favor of a role of interstitial edema based on a series of reports showing a typical  $V_A/Q$  deteriorations, persistent of  $V_A/Q$  mismatch after recovery, worsening of  $V_A/Q$  with exercise duration or severity of hypoxia, and improved hypoxic  $V_A/Q$  with oxygen breathing (89). The notion that exercise-induced deterioration in  $V_A/Q$  matching is caused by the development of interstitial edema is supported by experimental animal data. Lung lymphatic flow increases rapidly after the onset of exercise in sheep, in proportion to increased cardiac output and microvascular pressures (168). There is histologic evidence of interstitial lung edema in heavily exercised pigs (191). However,  $V_A/Q$  matching is better preserved during exercise in horses (9,99,227) than in pigs (92,95) while in both species a diffusion limitation does not seem to explain increased A-a $PO_2$  gradients, which remains poorly understood.

Refined measurements of the spatial distribution of pulmonary perfusion in healthy volunteers have more recently been made possible by the advent of functional MRI arterial spin labeling (93). This method has allowed the demonstration of a perfusion heterogeneity correlated to MIGET indices of  $V_A/Q$  mismatch in normal subjects exercising for 45 min at 70 % of their  $VO_{2max}$  (22). The only possible explanation for these findings is exercise-induced interstitial lung edema, even though the method could not detect a change in mean lung density.

## 8.2. Diffusion

Exercise increases lung diffusing capacity (Fig 14). Studies using the low  $O_2$  breathing method have demonstrated that exercise increases both the membrane and the capillary volume components of carbon monoxide diffusing capacity ( $DL_{CO}$ ), in proportion to increased cardiac output (104,184). Assuming a maximum expansion of capillary blood volume by a factor of 2.5 compensating for decreased red blood cell transit time, Dempsey calculated that for an athlete exercising at a high  $VO_2$  and cardiac output with a  $PAO_2$  of 100 mmHg and a mixed venous  $PO_2$  down to 20 mmHg, the mean red blood transit time would be shorter than the minimal transit time needed (0.6 s) to allow for complete end-capillary equilibrium (34). It is curious that  $DL_{CO}$  does not become asymptotic to some limiting value as cardiac output increases up to maximal exercise, as illustrated in Fig 14. It is possible that increased  $Pl_a$ ,  $P_{wp}$  and  $P_{cp}$  at high levels exercise serve to maximally increase capillary blood volume, to improve gas exchange, but that this is nevertheless counteracted by excessive red blood cell velocity, and eventual appearance of interstitial lung edema.

As pulmonary venous pressure and flow increase with exercise, capillaries may undergo a “stress failure” for  $P_{cp}$ 's > 40 mmHg (234). Stress-failure of the pulmonary capillaries occurs in race horses presenting which present with severe hypoxemia and hemorrhagic lung edema after high levels of exercise (233). However, alveolar edema as a cause of pulmonary shunting and increased A-a $PO_2$  has not been identified by MIGET studies in exercising humans (63,67,81,162,226).

Dempsey and Wagner analyzed relative contributions and mechanisms of inadequate ventilatory response,  $V_A/Q$  inequality and diffusion limitation to decreased arterial oxygenation and increased A-a $PO_2$  at exercise (36). They noted that exercise-induced hypoxemia depends on exercise intensity independent of age, gender and body position, and that the greatest inefficiencies in gas exchange occur in the animal species such as the dog or the horse, which have the highest body size-corrected  $VO_{2max}$ . While mechanical



constraints on ventilation emerged as the predominant cause of hypoxemia, increased A-aPO<sub>2</sub> at maximum exercise was exclusively explained by approximately equal contributions of V<sub>A</sub>/Q inequality and diffusion limitation, without identifiable pulmonary or cardiac shunting.

### 8.3. Pulmonary shunting of agitated contrast

In 2004, Eldridge, Stickland and colleagues reported on the occurrence of exercise-induced shunting demonstrated by agitated saline contrast echocardiography in subjects with otherwise no evidence of intrapulmonary or intracardiac shunt at rest (46,199). In these studies, exercise-induced pulmonary shunting of bubbles was correlated to cardiac output, Ppa<sub>m</sub> and A-aPO<sub>2</sub> at exercise, suggesting an impact on gas exchange (198). Agitated saline or gelatine contrast echocardiography is standard practice for the detection of cardiac shunts. The bubbles are of similar size, 10–35 mm, and do not normally traverse the pulmonary circulation. In the case of a cardiac right-to-left shunt, the appearance of contrast in the left heart chambers is immediate. In the case of pulmonary shunt, the appearance of contrast in the left heart chambers is delayed by 3–5 beats (Fig 15). However, there has been some controversy about the location and dimension of pulmonary vessels through which the bubbles travel, and the relationship of this phenomenon to gas exchange (94,129). Pulmonary shunting of agitated contrast could be explained by pressure-induced pulmonary capillary distension, causing a diffusion/perfusion imbalance with or without a true shunt measured by pure oxygen breathing or the MIGET, like seen in early stage hepato-pulmonary syndrome (157). In exercising athletes, intrapulmonary shunting measured by the retention of the less soluble gases in MIGET studies has always be found to be less than 1 % of cardiac output, averaging 0.2 % in normoxia and 0.1 % in hypoxia, which cannot explain more than 7 % of the total A-aPO<sub>2</sub> in normoxia and much less, < 1 % in hypoxia (94). It is not always possible to find a correlation between presence or graded severity of agitated saline contrast shunting and A-aPO<sub>2</sub> in either exercising athletes (116) or in patients with pulmonary vascular dilatations (145).

## 9. Right ventricular function at exercise

Traditional thinking about the determinants of exercise capacity focused on left ventricular function (186), even in conditions of hypoxic exposure and associated increase in pulmonary artery pressures that increase RV afterload (181,182,205). However, heavy exercise is associated with doubling or tripling of Ppa<sub>m</sub>, which imposes a marked increase in afterload added on to the stress of venous return-induced increase in preload on the normally thin-walled RV. This may explain why prolonged intense exercise results in altered indices of cardiac fatigue which disproportionately affect the RV (39,117,153,165). Right ventricular mass and dimensions have been shown by large scale MRI studies to increase in relation to the level of physical activity, independent of measures of left ventricular structure and function (1). It has been hypothesized that RV remodeling associated with a chronic high level of training in athletes might be a cause of cardiac rhythm disturbances (86,115)

### 9.1. Acute effects of exercise on right ventricular function

Inspection of individual pulmonary artery pressure-flow relationships at exercise suggests that subjects able to achieve higher maximum cardiac output and oxygen uptake also present shallower slopes, so that maximum levels of pulmonary artery pressures are in the range of 35–40 mmHg Ppa<sub>m</sub> (4,116). Echocardiographic measurements have been reported suggesting that pulmonary shunting of agitated contrast would be associated with enhanced pulmonary vascular reserve and RV function at exercise (116). As an example, when cardiac output increased from 5 to 15 L.min<sup>-1</sup> there was a 28 % reduction in PVR in the subjects with the greatest transpulmonary passage of agitated contrast, compared with a 4 % decrease

in PVR in subjects with minimal shunting of contrast. By tissue Doppler examination, subjects with the highest transit of agitated contrast had also higher RV maximal systolic myocardial velocity and isovolumic acceleration, while indices of LV function were not different. Furthermore, the exercise-induced increase in circulating B-type natriuretic peptide was lower in the subjects with the highest transit of agitated contrast, suggesting less RV distension. All of these measurements are in keeping with the idea of a better coupling of RV function to afterload in subjects with the highest transit of agitated saline. However, the concept of exercise-induced pulmonary vasodilatation allowing for improved maximal RV output but potentially worse pulmonary gas exchange remains debated (130). Decreased PVR allowing possibly for a higher RV flow output at exercise may also be explained by a higher left ventricular compliance (201).

Taking a step further, La Gerche et al investigated end-systolic wall stress of the right and left ventricles using MRI and echocardiography in endurance athletes and controls at exercise (115). Endurance athletes showed greater RV than LV remodeling, and peak exercise RV wall stress was greater in endurance athletes than in non athletic controls. These results were explained by greater RV enlargement and wall thickening corresponding to more loading in endurance athletes. In that study, end-systolic wall stress was calculated as the product of peak systolic pressure times internal radius, divided by wall thickness. Maximal wall stress is a good definition of afterload, as an alternative to arterial elastance (or end systolic pressure divided by stroke volume). However, this measure of maximal wall stress relies on peak systolic pressure, which is dependent on the mechanical properties of the arterial system to which the ventricle is connected.

The ratio of peak systolic pressure to end-systolic volume would appear to be a more acceptable surrogate of end-systolic elastance to measure contractility, as previously reported in normal subjects exercising in hypoxia (205), and a ratio of  $P_{pa_m}$  (instead of end-systolic) divided by stroke volume a reasonable surrogate to arterial elastance. Still the relationships between compliance and resistance are not identical in systemic and pulmonary circulations, so that approximations become inadequate for comparisons (188,235).

Thus, in spite of previous application to patients with pulmonary hypertension, MRI and echocardiographic estimates of RV wall stress based on systolic  $P_{pa}$  and end-systolic volumes and wall thickness that have shown good reproducibility (177), the measurement is composite and probably requires more validation against gold standards. However, the report by La Gerche and his colleagues is consistent with the emerging notion that athletes do not develop a balanced hypertrophy (193), but that RV changes are predominant (218).

## 9.2. Pharmacological interventions

There is little pulmonary vascular tone at exercise, so pharmacological attempts at decreasing PVR would not be expected to affect RV afterload or exercise capacity. The effects of drugs effective in the treatment of PAH have been investigated in normal volunteers exercising in normoxia, in acute normobaric hypoxia or in chronic hypobaric hypoxia. In normoxic conditions, sildenafil, bosentan or sitaxsentan did not affect maximum workload or  $VO_{2max}$  (51,53,65,96,158). It must be emphasized that the RV at high levels of exercise is stressed by combined increases in preload and afterload, and that pulmonary vasodilators also tend to increase systemic venous return, which could counteract any slight decrease in afterload obtained through a decrease in PVR.

## 10. Exercise in hypoxia

### 10.1. Hypoxic pulmonary vasoconstriction and remodeling

Hypoxic exposure induces pulmonary vasoconstriction followed by arteriolar remodeling. The hypoxic pressor response is characterized by marked inter-individual and inter-species variability, as it is intense in pig, horse and cow, moderate in rodents and humans and very low in dog, guinea pig, yak and llama (71). Chronic hypoxia induces pulmonary hypertension, in proportion to initial vasoconstriction. Initial hypoxic vasoconstriction is induced by inhibition of voltage-gated potassium channels localized in smooth muscle cells, which explains a quasi-immediate response, and there is secondary modulation by endothelium-derived mediators (230). Hypoxic vasoconstriction strengthens during the first 1–2 hours of hypoxic exposure in humans (74), but has been found to remain stable during one hour in anesthetized intact experimental animals (159).

The time-course of hypoxia-induced remodeling is less well known. In humans, chronic hypoxic exposure induces a rapid 5-minute increase in PVR followed by a slower further increase, leading to a stabilization after 2 hours (74) and a maximal response after approximately 24 hours (73,134). After six hours of hypoxic exposure, re-oxygenation immediately decreases PVR, without however a complete return to normal (38). The reversibility of increased PVR with re-oxygenation is largely lost after 24 to 48 hours exposure to hypoxia (73,134). These observations indicate that hypoxic exposure is associated with pulmonary vascular remodeling occurring within the first 24 hours.

The first description of human hypoxic pulmonary vasoconstriction was reported by Motley et al in 1947 in 5 conscious normal subjects who consented to a right heart catheterization. These subjects were acutely challenged with a fraction of inspired O<sub>2</sub> (FIO<sub>2</sub>) of 0.1, which increased Ppa<sub>m</sub> from 13 to 23 mmHg (152). The authors somehow selected strong « responders » to hypoxia. In later studies on a total of 39 normal subjects challenged with a FIO<sub>2</sub> of 0.125 (PaO<sub>2</sub>, 40 mmHg), hypoxia-induced increases in Ppa<sub>m</sub> ranged from 0 to 20 mmHg (146,161,162). Hypoxia did not increase PVR in 8 of these subjects, which is a 20 % proportion of “non responders” that is corroborated by other studies on the acute effects of normobaric hypoxia in normal volunteers (73).

A difficulty in studying the effects of hypoxia on the pulmonary circulation in conscious intact animals is the interference with the hypoxic ventilatory response. This decreases PACO<sub>2</sub>, increasing PAO<sub>2</sub> at any given PIO<sub>2</sub>. An acute normobaric hypoxic exposure with a fraction of FIO<sub>2</sub> progressively diminished to 0.12 does not much affect ventilation (40), so that PaCO<sub>2</sub> remains essentially unchanged or only slightly decreased (134,146,161). With prolonged hypoxic exposure, there is a progressive increase in ventilation allowing for adaptation with improved PAO<sub>2</sub> and PaO<sub>2</sub>. This takes a few days at a given level of hypoxia, and is an essential feature of the adaptation to altitude (123). It has been shown that markedly increased ventilation and hypocapnia are indispensable to the adaptation to extreme altitudes (231). However, the ventilatory response to hypoxia decreases over years, so that high altitude dwellers present with levels of ventilation at rest which are identical or only slightly increased compared to measurements in usual lowlanders at sea level (123). Further loss of ventilatory adaptation is a feature of chronic mountain sickness, or “Monge’s disease” characterized by severe hypoxemia and polycythemia (172,231). Since the main determinant of hypoxic vasoconstriction is PAO<sub>2</sub> (139), studies on the pulmonary circulation at high altitudes must always take the ventilatory adaptation into account. The same PaO<sub>2</sub> around 40 mmHg at rest is seen in high-altitude natives living at Morococha (Peru), at 4,540 m (172), and in lowlanders acclimatized in a few weeks at 7,000 m (73).

Another adjustment to take into account is in the stimulus-response curve for hypoxic pulmonary vasoconstriction. The relationship between  $\text{FIO}_2$  or  $\text{PAO}_2$  and hypoxic vasoconstriction expressed as a change in  $\text{Ppa}_m$  at a given flow or as an amount of flow diversion at a given  $\text{Ppa}_m$  has been generally found in experimental animal preparations to be either sigmoid-shape (7) or linear (70), with a continued constriction as long as  $\text{FIO}_2$  or  $\text{PAO}_2$  decreased. However, in isolated pig lungs at a constant flow, in which particular attention was paid to reach a steady state before each measurement, the  $\text{Ppa}/\text{PAO}_2$  curve was shown to be biphasic, with a maximum at a  $\text{PAO}_2$  between 30 and 60 mmHg, and a down-sloping portion called “hypoxic pulmonary vasodilation” at lower  $\text{PAO}_2$  (211). In dogs, a species with a pulmonary vasoreactivity to hypoxia comparable to that of man, the relationship between  $\text{Ppa}_m$ , or PVR, and  $\text{FIO}_2$  progressively decreased from 1 to 0.06, has been shown to be biphasic as well, with a downsloping at a  $\text{FIO}_2$  lower than of 0.1, corresponding to a  $\text{PaO}_2$  of 36–38 mmHg (15).

Evidence of hypoxic pulmonary vasodilation in man was obtained during Operation Everest II. In these studies, normal subjects decompressed in a hypobaric chamber for 40 days to an atmospheric pressure equivalent to the summit of Mount Everest, presented an average  $\text{Ppa}_m$  of 34 mmHg at rest and of 54 mmHg at exercise at a barometric pressure ( $\text{Pb}$ ) of 282 mmHg (7,620 m, resting  $\text{PaO}_2$  37 mmHg), that decreased to 33 and 48 mmHg respectively at a  $\text{Pb}$  of 240 Torr (8,840 m, resting  $\text{PaO}_2$  30 mmHg) (73). Because of a relative hypoventilation compared to acclimatized lowlanders, high altitude natives present a resting  $\text{PaO}_2$  of 40 mmHg at relatively lower altitudes, around 4,500 m.

In part related to the physiological inhomogeneity of  $\text{V}_A/\text{Q}$  distributions and associated variations in regional  $\text{PAO}_2$  and  $\text{PACO}_2$ , hypoxic vasoconstriction is inhomogeneous. This has been demonstrated using the fluorescent microsphere technique in swine (92) and functional MRI in humans (91). In the latter study, hypoxia-induced perfusion heterogeneity was more marked in subjects with a previous history of high altitude pulmonary edema (HAPE) (91).

Hypoxic pulmonary vasoconstriction is particularly intense in few percent of normal human subjects (75). Because hypoxia does not affect the longitudinal distribution of resistances (134), these subjects present with increased  $\text{Pcp}$  and, accordingly, are predisposed to HAPE (74,134). Lowlanders with a brisk hypoxic vasoconstriction traveling to high altitudes may also be exposed to the risk of right heart failure. This complication of high altitude exposure has been reported in high altitude cattle (85), infants of Chinese Han brought to high altitudes in Tibet (208), Indian soldiers transported to high altitude borders with China (3) and occasional Europeans travelling to the South American altiplano (98).

## 10.2. Hypoxic pulmonary hypertension

Because of hypoxic pulmonary vasoconstriction and subsequent remodeling,  $\text{Ppa}_m$  is increased at altitude, acutely as well as chronically. Maggiorini et al. catheterized subjects with or without a previous history of HAPE in normoxia, in acute normobaric hypoxia, and after 1–2 days at the altitude of 4559 m. In subjects without previous HAPE,  $\text{Ppa}_m$  increased from 14 mmHg in normoxia to 22 mmHg in normobaric hypoxia ( $\text{PaO}_2$  38 mmHg) and to 26 mmHg in hypobaric hypoxia ( $\text{PaO}_2$  45 mmHg). In subjects with previous HAPE,  $\text{Ppa}_m$  increased from 16 mmHg in normoxia to 27 mmHg in normobaric hypoxia, and to 38 mmHg in hypobaric hypoxia. Subjects with a previous HAPE had a higher PVR than controls in hypoxia and in normoxia, and PVR increased in hypoxia from acute to more chronic conditions (134). Similar observations have been reported using non invasive echocardiographic measurements (53).

Subjects with a previous HAPE have repeatedly been reported to present with an enhanced hypoxic pulmonary vasoconstriction, measured either invasively (47,101,108,134,222) or noninvasively (56,74,237). It is interesting that in these studies, normoxic PVR at rest as well as at exercise has been repeatedly shown to be increased in HAPE-susceptibles compared to controls (47,108,134,237), which points at a constitutional abnormality somehow linked to an increased pulmonary vasoreactivity.

Chronic hypoxic exposure in high altitude dwellers is characterized by a variable increase in  $P_{pa_m}$ . Penaloza and Arias-Stella plotted  $P_{pa_m}$  reported in high altitude studies as a function of arterial  $O_2$  saturation ( $SA_{O_2}$ ) and found a hyperbolic relationship (172) (Fig 16). However, when they plotted  $P_{pa_m}$  as a function of altitude of residence, they found that there were disproportionally high  $P_{pa_m}$  in Leadville, and low  $P_{pa_m}$  in Lhasa (Fig 16)

The reasons why relatively higher  $P_{pa_m}$  were recorded in Leadville (223) as compared to Lhasa (72) may be related to genetic predisposition. Centuries of living at high altitudes in the Himalayas has probably allowed for selection of fitter individuals with lower hypoxic pulmonary pressure response allowing for better survival and reproduction.. No such selection pressure has acted on human residents of Leadville, where the population is transient and similar to the rest of the US. Selection pressure may have acted on cattle in the North American high altitude pastures; in the first few years after introduction of cattle to these sites, Brisket's disease was more common than it is today.

Echocardiographic studies indicate that South American highlanders tend to present with a lower  $P_{pa_m}$  compared to acclimatized lowlanders at the same cardiac output (97,135,204). This is not apparent in invasive hemodynamic studies (6,173), but comparisons are difficult because of subject selection biases and maybe also technical limitations of echocardiographic estimates of pressures and flows.

The question has been asked whether pulmonary hypertension and right heart failure is characteristic of chronic mountain sickness, or "Monge's disease" defined by symptomatic polycythemia, severe hypoxemia and hemoglobin levels higher than 21 g/dl in men and 19 g/dl in women (124). Penaloza and Arias-Stella showed that patients with Monge's disease present with higher  $P_{pa_m}$  and lower arterial  $SA_{O_2}$  extrapolated on the same hyperbolic relationship as in healthy highlanders, suggesting identical pathogenesis of pulmonary hypertension (Fig 16).

There are very few studies looking into the effects of hypoxic exposure on pulsatile pulmonary hemodynamics, and all of these are on experimental animals. Acute hypoxia has been reported to increase  $Z_C$  in pigs and in goats, but not in dogs (55,132,229). Chronic hypoxia decreased  $Z_C$  in mice (220), in spite of demonstrated in vitro stiffening of the proximal pulmonary arteries (109). Associated changes in pulmonary arterial compliance are not exactly known, and even less is known about the effects of exercise.

Studies using the arterial occlusion technique in dogs (55,133) and minipigs (133) have shown that hypoxia-induced increase in PVR does not affect the longitudinal distribution of resistances. This has been confirmed in humans with or without a previous HAPE, in acute normobaric hypoxia as well as after 1–2 days of acclimatization to high altitude (134). Thus in resting human subjects in hypoxia,  $P_{cp}$  increases in proportion to  $P_{pa_m}$  in a manner is predicted by the Gaar equation. There are no reported  $P_{cp}$  estimates using the occlusion technique in human volunteers at exercise. As the arterial resistance decreases more than the capillary-venous resistance in lungs perfused at very high flows (20), it is possible that  $P_{cp}$  increases proportionally more than  $P_{pa_m}$  at exercise. However, this is hypothetical in the absence of reported measurements.



### 10.3. The pulmonary circulation during hypoxic exercise

Exercise in acute normobaric or hypobaric hypoxia, or in chronic hypobaric hypoxia has been reported to shift  $P_{pa_m}$ -Q relationships to higher pressures (6,52,53,56,73). Invasive measurements performed on lowlanders progressively decompressed in a hypobaric chamber during the Operation Everest II show progressively increased slopes of  $P_{pa_m}$ -Q relationships with increasing altitudes (Fig 17) (73). In these experiments, there was a decrease in Ppw compared to sea level exercise, excluding upstream transmission of increased left ventricular filling pressure as a mechanism of increased slope.

Exercise in acute hypoxic conditions in lowlanders with a previous HAPE has been shown to be associated with markedly increased  $P_{pa_m}$  and PVR as compared to controls (47,108).

Exercise in subjects born and living permanently at high altitudes is associated with particularly steep  $P_{pa_m}$ -Q relationships. This is illustrated in Fig 18 constructed with right heart catheterization and non invasive echo-Doppler data from high altitude inhabitants investigated at high altitude versus lowlanders at sea level (4,6,11,13,73,173,204,223). Echo-Doppler studies were generally associated with lower cardiac outputs, at rest and at exercise, which is explained by differences in exercise protocols, the difficulty in obtaining good quality signals at high levels of exercise, and maybe a systematic underestimation. On the other hand, with the exception of Tibetans, highlanders have much steeper slopes of their  $P_{pa_m}$ -Q relationships, in spite of only moderate pulmonary hypertension at rest. The highest baseline  $P_{pa_m}$  values at rest and the steepest slopes of  $P_{pa_m}$ -Q were recorded by Penalzoza and Sime in patients with Monge's disease, with  $P_{pa_m}$  of 37 mmHg at rest climbing to 82 mmHg at mild exercise (173). Vogel et al reported resting  $P_{pa_m}$  of 25 mmHg increasing to 54 mmHg at moderate exercise with workloads ranging from 25 to 100 W in subjects living in Leadville, at the altitude of 3000 m (223). Banchero et al reported resting  $P_{pa_m}$  of 29 mmHg increasing to 60 mmHg at workloads around 80 W in subjects born and living in Morococha, at the altitude of 4540 m (6). In contrast, Groves et al measured a  $P_{pa_m}$  of 15 mmHg increasing to 35 mmHg at workloads ranging from 60 to 180 W in subjects living in Lhasa, at 3658 m (72), indicating slopes of  $P_{pa_m}$ -Q relationships at the upper limit of normoxic normal. In the only non invasive exercise study reported to date in highlanders, Stuber et al reported on echocardiographic measurements at rest and at a 50 W workload in subjects born and living in La Paz, at altitudes of 3600–4000 m (204). The results showed a  $P_{pa_m}$  of 20 mmHg at rest and 29 mmHg (slope of  $P_{pa_m}$ -Q: 3 mmHg.L<sup>-1</sup>.min<sup>-1</sup>) at mild exercise in highlanders without Monge's disease, and 23 mmHg increasing to 39 mmHg (slope of  $P_{pa_m}$ -Q 5: mmHg/L/min<sup>-1</sup>) at mild exercise in highlanders with Monge's disease.

Reeves et al. used the individual data of the Operation Everest II measurements to recalculate the effects of chronic hypoxic exposure in normal humans on TPVR and the pulmonary distensibility coefficient  $\alpha$  (28). The results showed an increase in TPVR from  $2.3 \pm 0.2$  to  $3.9 \pm 0.2$  Wood units and a decrease in  $\alpha$  from  $0.02 \pm 0.002$  to  $0.008 \pm 0.001$  mmHg<sup>-1</sup>. The same calculations on the individual data of acute hypobaric exposure experiments reported by Wagner et al in another group of healthy volunteers (226) did not show any difference in  $\alpha$ . However, in that study, PVR remained unchanged in hypoxia as well, so that the unchanged distensibility could be simply related to absent hypoxic pulmonary vasoconstriction. Further studies on larger groups of unselected subjects are needed to evaluate the effects of acute hypoxia on pulmonary vascular distensibility. There are no individual data reported that would enable distensibility to be calculated in highlanders with or without Monge's disease.



#### 10.4. Pulmonary gas exchange during hypoxic exercise

Exercise in hypoxia is associated with a marked deterioration in  $V_A/Q$  relationships. Wagner et al. reported on MIGET studies during Operation Everest II which showed a deterioration in  $V_A/Q$  matching that increased with severity of hypoxic exposure and exercise (226). The dispersion of blood flow as an index of  $V_A/Q$  inhomogeneity was correlated to  $P_{pa,m}$ , not to cardiac output,  $P_{pw}$  or ventilation. Alveolar-end-capillary diffusion limitation of  $O_2$  was observed at a  $VO_2 > 3 \text{ L}\cdot\text{min}^{-1}$  at sea level, of  $> 1\text{--}1.2 \text{ L}\cdot\text{min}^{-1}$  at a barometric pressure of 428 mmHg, and approximately of  $1 \text{ L}\cdot\text{min}^{-1}$  at the highest simulated altitudes. The recovered  $V_A/Q$  patterns and relationship to  $P_{pa,m}$  were compatible with alveolar interstitial edema as the primary cause of  $V_A/Q$  inequality.

Wagner et al. further investigated pulmonary gas exchange with the MIGET at the altitude of 5260 m in Bolivian highlanders usually living at the altitude of La Paz (altitude 3600–4000 m) versus acclimatized lowlanders who were relatively well matched for body weight and age (225). Maximum workload, cardiac output and  $VO_2$  were the same, but  $PaO_2$  was better preserved in highlanders in spite of decreased ventilatory response to exercise, and this was explained by a greater pulmonary diffusing capacity. There were no pulmonary hemodynamic measurements reported, so that the possible impact of  $P_{pa,m}$  on increased  $A-aPO_2$  was not assessed.

Because both hypoxia and exercise are associated with an increase in  $P_{pa,m}$ , a critical  $P_{cp}$  as a cause of excessive capillary filtration would be more easily reached in conditions of acute hypoxic exposure. On the other hand, exercise capacity is decreased in hypoxia, so that the flow-dependent increase in  $P_{pa,m}$  is limited as well. Still there is a significant risk of overperfused pulmonary capillaries, due to high  $P_{cp}$  and inhomogeneous hypoxic vasoconstriction, so that a patchy lung edema typical of HAPE may develop in a proportion of susceptible subjects (8). Heavy exercise may be a cause of increased red blood cells and protein in broncho-alveolar lavage fluid, and this is markedly increased when exercise is performed in hypoxia (45). Steeper  $P_{pa,m}$ - $Q$  relationships in subjects with a previous HAPE could be a cause of marked increase in  $P_{cp}$ , further increased in overperfused lung regions, leading to  $V_A/Q$  mismatch and eventual pulmonary capillary stress-failure (175).

#### 10.5. The right ventricle as a limiting factor of hypoxic exercise capacity

Decreased maximum exercise capacity at high altitude is explained by a decrease in arterial oxygen content and a limitation in maximal cardiac output (60). With acclimatization, the arterial oxygen content may be restored to sea level values because of an increased hemoglobin concentration, but maximal cardiac output remains depressed (23). The decrease in maximal cardiac output at altitude has been tentatively explained by the combined effects of decreased blood volume, hypocapnia, increased viscosity of the blood, autonomic nervous system changes, or depressed myocardial function, but has also been modeled by an altered coupling of convectional and diffusional oxygen transport systems (224).

An additional factor might be a limitation in RV flow output secondary to hypoxic pulmonary hypertension. An improvement in maximal workload and  $VO_{2max}$  together with a decrease in  $P_{pa,m}$  has indeed been reported after the intake of sildenafil, bosentan or sitaxsentan in hypoxic healthy volunteers (51,53,65,96,158). A decreased  $P_{pa,m}$  with an improved  $VO_{2max}$  has been observed in subjects susceptible to HAPE taking dexamethasone before altitude exposure (56). However, improved exercise capacity could not unequivocally be ascribed to associated inhibition of hypoxic pulmonary vasoconstriction when the pharmacological intervention was also associated with an improved arterial oxygenation, as occurs with sildenafil (53,65,96) or dexamethasone (56).

Improved arterial oxygenation is not observed with the selective or non selective endothelin receptor blockers sitaxsentan and bosentan, which decreased the hypoxic pressure response by approximately 50 % in either acute normobaric hypoxia or more chronic hypobaric hypoxia (51,158). Significant inverse correlations between systolic Ppa (echocardiography) and  $\text{VO}_2\text{max}$  have been observed (Fig 19), which is compatible with the notion that increased Ppa<sub>m</sub> at high altitudes limits exercise capacity by reducing maximal RV flow output (158). However, further studies are needed to confirm this hypothesis.

Considering the coupling of RV function to the pulmonary circulation, it is generally assumed that physiological levels of oxygen deprivation, up to an altitude equivalent to the summit of Mount Everest, do not negatively affect cardiac function. Echocardiography was used in 8 volunteers progressively decompressed in 40 days to the simulated altitude of Mount Everest (Operation Everest II), for measurements of LV volumes and evaluation of systolic function by peak systolic (brachial artery sphygmomanometry) versus end-systolic volume (echocardiography) relationships. This is a surrogate for completely invasive end-systolic elastance measurements as a gold standard of load-independent contractility. The results showed a decrease in the volumes of both the LV and the RV, compatible with hypovolemia, but a normal ejection fraction that increased adequately with exercise. The ratio of peak systolic pressure to end-systolic volume at rest and at exercise increased at all altitudes, indicating enhanced contractility, up to the simulated altitude of approximately 8400 m (205). Thus contractility appeared to be well preserved in healthy subjects at high altitudes, indicating excellent tolerance of the normal myocardium to extreme environmental oxygen deprivation.

However, the relative change in afterload conditions of the RV in hypoxia make that cardiac chamber potentially more vulnerable to increased PVR. Accordingly, additional resting echocardiographic measurements were reported in a similar series of experiments in 8 healthy volunteers at simulated altitudes of 5000 m to 8000 m (Operation Everest III) (14). The measurements confirmed previously reported mild pulmonary hypertension, preserved LV contractility, and decreased preload of both ventricles, but showed an abnormal LV filling pattern with decreased early filling and greater contribution of atrial contraction, without elevation of end-diastolic pressure. The authors thought that these LV diastolic changes could be explained by the combined effects of tachycardia and reduced preload, with possibly also effects of ventricular interdependence or hypoxia. Similar results were reported in 41 healthy volunteers who ascended in 24 hours to the altitude of 4559 m in the Italian Alps (2).

A complete evaluation right and left ventricular function by Doppler echocardiography with tissue Doppler imaging was reported in 25 healthy volunteers acutely breathing a fraction of inspired oxygen of 0.12 (99). These results suggested that short-term hypoxic exposure is associated with a preserved RV systolic function, either sympathetically-mediated or via homeometric adaptation to mild pulmonary hypertension. Also, there were early RV diastolic changes that probably reflected an increased afterload. Changes in diastolic filling patterns of both ventricles and increased LV contractility would be explained by acute hypoxia-induced activation of the sympathetic nervous system.

These measurements were most recently repeated in 15 healthy high altitude inhabitants of the Bolivian altiplano, at approximately 4000 m, as compared to age and body surface area - matched acclimatized lowlanders (97). Acute exposure to high altitude in lowlanders caused an increase in Ppa<sub>m</sub> to 20–25 mmHg, with mildly altered LV and RV diastolic function, and maintained RV systolic function. This profile was essentially unchanged after acclimatization and ascending to 4850 m, except for a higher Ppa<sub>m</sub>. The highlanders presented with relatively lower Ppa<sub>m</sub> and higher SaO<sub>2</sub>, but more pronounced alteration in

indices of diastolic function of both ventricles, a decreased LV ejection fraction, and decreased indices of RV systolic function. The estimated LV filling pressure was somewhat lower in the highlanders. Thus the cardiac adaptation of highlanders appeared qualitatively similar, with slight but significant deterioration of indices of both systolic and diastolic function, in spite of less marked pulmonary hypertension and better oxygenation. The authors explained these results by combined effects of a lesser degree of sympathetic nervous system activation, relative hypovolemia and may be some negative inotropic effects of a long lasting hypoxic exposure.

Echocardiographic measurements have also been reported in a study on high altitude Peruvian dwellers with a diagnosis of Monge's disease (135). The patients presented with trans-tricuspid gradients at an average of 34 mmHg, which is in the range reported in acclimatized lowlanders, and a RV dilatation with more alteration in indices of function than reported in either acclimatized lowlanders or healthy high altitude inhabitants. The reasons for more altered RV function in patients with Monge's disease are not entirely clear, but it is thought that repetitive bouts of pulmonary hypertension at exercise could play a role.

Recent progress in portable Doppler echocardiography has allowed improved evaluation of RV function in lowlanders with a reactive pulmonary circulation and exposed to high altitude. It is possible that a proportion of these subjects presents with a clinically silent high altitude acute right heart failure, characterized by a severe pulmonary hypertension, dilatation of right heart chambers with a septal shift, dilatation of the inferior vena cava with loss of inspiratory collapse, indicating increased right atrial pressure, and altered RV function with "post systolic shortening" (98). Post systolic shortening reflects ischemia and asynchronous contraction the RV, much like recently reported by MRI studies in severe pulmonary arterial hypertension (138).

There is thus indirect evidence that the RV during hypoxic exercise might be overloaded and functionally limited and thereby contribute to decreased exercise capacity. Chronic RV overload and/or hypoxia might be a cause of impaired RV function.

## 11. Exercise with cardiac or lung disease

Increased baseline PVR in patients with pulmonary hypertension implies that any increase in cardiac output associated with physical activity may be the cause of an excessive increase in  $P_{pa_m}$  and RV afterload. The dyspnea-fatigue symptomatology that is characteristic of pulmonary hypertension is essentially explained by the inability of the RV to adapt to increased afterload (26). The slope of  $P_{pa_m}$ -Q with exercise in pulmonary hypertension reflects the severity of pulmonary vascular remodeling and increased tone, but is also affected by associated changes in arterial and mixed venous blood gases, filling pressures of the left heart, sometimes alveolar pressure, and sympathetic nervous system activation (71). Accordingly, adding exercise to resting hemodynamic measurements in patients with pulmonary hypertension may help to understand changes in functional state and effects of pharmacological interventions. Exercise stress testing may be particularly useful for the detection of early or latent pulmonary vascular disease.

### 11.1 Exercise in patients with pulmonary hypertension

Pulmonary vascular pressure-flow relationships have been reported in patients with a variety of lung and cardiac diseases with flow increased by unilateral balloon occlusion and/or exercise, sometimes with inotropic drug interventions (50,83,103,106,160,241). A summary of this data is represented in Fig 20.

In these studies,  $P_{pa_m}$ -Q relationships were assumed to be best described by linear approximations, and extrapolated pressure intercepts higher than Ppw or Pla were explained by an increased pulmonary vascular closing pressure (142). Such an interpretation refers to the Starling resistor model of the pulmonary circulation, while, as already mentioned, distensible models might be more realistic. A common feature of  $P_{pa}$ -Q relationships in patients with pulmonary hypertension is that, like in normal subjects, PVR decreases with increased flow (142,155).

Janicki et al. investigated the pressure-flow responses of the pulmonary circulation in patients with left heart failure without and with pulmonary hypertension (defined by a  $P_{pa_m}$  higher than 19 mmHg), and in patients with various pulmonary vascular diseases (103). The authors were able to record 3 to 11  $P_{pa_m}$ -Q coordinates, while patients were exercising with workload increased every 2 minutes up to submaximal or maximal levels. In patients with no pulmonary hypertension, the slope of  $P_{pa_m}$ -Q was 3 mmHg.min.L<sup>-1</sup>. In patients with pulmonary hypertension secondary to heart failure the slope increased to 5.1 mmHg.min.L<sup>-1</sup>, reaching 7.2 mmHg.min.L<sup>-1</sup> in patients with pulmonary arterial hypertension (PAH). The changes in extrapolated pressure intercept of  $P_{pa_m}$ -Q with exercise were variable, with often values below the resting Ppw, and even negative in a few patients. This is physically impossible in any model of the pulmonary circulation, and has to be explained by exercise-induced pulmonary vasoconstriction and/or increased left atrial pressures at the highest levels of exercise.

Kafi et al. compared the effects of exercise to those of an infusion of a low dose of dobutamine assumed to be without effect on pulmonary vascular tone in patients with idiopathic PAH (106). Slopes and extrapolated pressure intercepts of  $P_{pa_m}$ -Q plots were respectively higher and lower with exercise (Fig 21) which was explained by exercise-induced vasoconstriction related to decreased pH and mixed venous blood PO<sub>2</sub> and may be also to sympathetic nervous system activation.

Castelain et al. investigated the effects of intravenous epoprostenol in patients with idiopathic PAH (24). Six weeks of treatment with epoprostenol increased exercise capacity as assessed by a 6-minute walk distance, but resting PVR was unchanged. Hemodynamic measurements at exercise showed a decreased slope of  $P_{pa_m}$ -Q relationships, explaining improved exercise capacity by a decreased RV afterload. The average slope of  $P_{pa_m}$ -Q decreased from 12 to 7 mmHg.L.min<sup>-1</sup>.m<sup>2</sup>, which was highly significant. It may be noted that, because of a dramatic decrease in PVR with exercise, the extrapolated intercepts increased from 18 to 23 mmHg, underscoring the difficulties of the functional interpretation of these extrapolations

One could argue that exercise measurements of  $P_{pa_m}$ -Q relationships do not allow for valid estimations of RV afterload, because the steady-flow approach neglects the effects of of systolic  $P_{pa}$  or peak RV pressure. However, PVR has been reported to be inversely correlated to pulmonary arterial compliance, with unchanged time constant of the pulmonary circulation, in various types of pulmonary hypertension and therapies (118,119) suggesting limited variability in responses of the functional state of the pulmonary circulation to disease processes. On the other hand, PVR divided by heart rate may be considered as a reasonable approximation of pulmonary arterial elastance (187). Therefore exercise-induced changes in PVR or slopes of multipoint  $P_{pa_m}$ -Q may provide clinically acceptable approximations of RV afterload.

Exercise in patients with pulmonary hypertension is associated with an increase in Ppw. In the study by Janicki et al, Ppw increased by 14–16 mmHg in patients with heart failure, and by 10 mmHg in patients with pulmonary vascular diseases (103). In heart failure,  $P_{pa_m}$

closely followed Ppw, while  $Ppa_m$  was less tightly correlated in pulmonary vascular disease. The authors noted that Ppw also increases at exercise in normal subjects, with reported increments up to 5 mmHg in young adults, but to 10–15 mmHg in elderly normal men, highlighting that the limits of normal of Ppw-Q relationships are not exactly known. Nevertheless, tight relationships between  $Ppa_m$  and Ppw are characteristic of left heart failure. After cardiac transplantation in patients with severe left heart failure, pulmonary hypertension, and very high Ppw, the postoperative decrease in Ppw was followed by a proportional decrease in  $Ppa_m$  (160)

In summary, exercise hemodynamic studies in patients with pulmonary hypertension allow for an improved understanding of functional state, exercise capacity and effects of therapeutic interventions. Exercise stress tests provide less information about pulmonary vascular function, as the slope and probably also shape of  $Ppa_m$ -Q relationships are affected by exercise-induced pulmonary vasoconstriction and changes in left atrial pressure. Studies of pulmonary vascular pressure-flow characteristics for different types of pulmonary hypertension would ideally rely on interventions which cause purely passive increases of flow. Whether this might be achieved by low-dose dobutamine, as suggested by previous experimental animal (17) and clinical (106) studies requires further confirmation.

## 11.2 Exercise stress tests for the detection of latent pulmonary vascular disease

While efficacious targeted therapies have been developed for PAH, disappointment remains about persistently high failure rates and mortality (143). Accordingly, the idea has emerged that earlier administration of these drugs might be more effective, and that exercise stress hemodynamics might detect latent or early pulmonary vascular disease. Invasive right heart catheterization studies at exercise have been reported in high risk patients (112,216), while non invasive stress echocardiographic approaches are being developed for the purpose of larger scale application in lower risk patients (13,31,75,156).

Diagnosis of early pulmonary vascular disease requires an unequivocal definition of limits of normal. At the latest expert consensus conference on pulmonary hypertension, held in Dana Point in 2008, pulmonary hypertension was defined by a  $Ppa_m$  above than 25 mmHg at rest (143). This is higher than the upper limit of normal (111,133,146,161,179). Thus more work is needed to define the range of normal values for  $Ppa_m$ , that have no impact on exercise capacity or survival.

Tolle et al. catheterized patients referred for unexplained dyspnea and suspicion of pulmonary hypertension. The results allowed the authors to correlate exercise-induced pulmonary hypertension, defined by a  $Ppa_m$  higher than 30 mmHg, to dyspnea-fatigue symptoms, supporting the notion of exercise-induced pulmonary hypertension as a disease entity (216). Kovacs et al. catheterized patients with systemic sclerosis, and showed that  $Ppa_m$  higher than 30 mmHg and PVR at the upper limits of normal are associated with decreased exercise capacity (112). Tolle and colleagues identified patterns of  $Ppa_m$ - $VO_2$  (or Q) relationships associated with exercise-induced pulmonary hypertension (216). They found a “take-off” pattern to be characteristic of normal subjects, while patients more often presented with “plateau” patterns. “Take-off” patterns of  $Ppa_m$ - $VO_2$  relationships might reflect increased Ppw at higher levels of exercise, or a progressive increase of the resistive component of exercise, affecting the intrathoracic pressure regimen, with increased pressures caused by active expirations or Valsalva phenomena. Reasons for “plateau” patterns of these relationships are not entirely clear, but might relate to expected slightly curvilinear shape of  $Ppa_m$ -Q curves together with a limitation in the increase of stroke volume. However, Kovacs et al found exercise-induced increase in  $Ppa_m$  to be linearly related to cardiac output (112).



The validation of stress echocardiography for the diagnosis of early pulmonary hypertension is on-going. It becomes clearer that pulmonary vascular pressures have to be related to pulmonary blood flow rather than to workload, and that internal controls are needed to avoid errors on single signal reading (156). It has already been possible to show that patients with systemic sclerosis and no abnormal increase in  $P_{pa_m}$  at rest may present with excessive increase in the slope of  $P_{pa_m}$ -Q, a decrease in maximal workload, but similar maximal  $P_{pa_m}$  compared to controls (100). These results underscore the need for adequate functional evaluation of the pulmonary circulation by pressure-flow relationships.

## 12. Conclusions and recommendations for further research

Dynamic exercise increases pulmonary blood flow and vascular pressures. The relationships between pulmonary blood flow, pulmonary arterial pressures and pulmonary artery wedge pressure have been characterized in experimental animal preparations and mathematically modeled. The most realistic description of pulmonary vascular pressure-flow relationships is provided by simple distensible models relating pressure, resistance, distensibility and flow. Proportional changes in pulmonary vascular resistance and compliance have been shown, allowing for prediction of a stable time constant of the pulmonary circulation in all circumstances. The understanding of proportional changes in pulmonary artery pressures and pulmonary capillary pressures has been achieved on the basis of measurements of longitudinal distributions of resistances. Valid approaches for the definition of right ventricular afterload have been developed.

However, several important aspects of the relationships between the pulmonary circulation and gas exchange or RV function remain incompletely understood. Areas still open to urgent investigation are listed below:

1. Improved validation against invasive gold standards of non invasive approaches for the study of pulmonary hemodynamics and right ventricular function.
2. Definition of the limits of age and gender-related normal of averaged slopes of multipoint  $P_{pa_m}$ -Q relationships at exercise in normoxic and in hypoxic conditions.
3. Definition of the limits of normal of derived distensibility in acute and in chronic hypoxia
4. Characterization of multipoint pulmonary vascular pressure-flow relationships in chronic mountain sickness and cardiac and pulmonary vascular diseases associated with pulmonary hypertension.
5. Definition of the time constant of the pulmonary circulation at exercise in relation to the time constant at rest.
6. Definition of expected increase in pulmonary capillary pressure with increased pulmonary artery pressures at high levels of exercise, and relation to gas exchange and exercise-induced lung edema
7. Measurements of right ventricular function at exercise, and relation to steady or pulsatile pulmonary hemodynamic measurements.
8. Effects of resistive versus dynamic exercise
9. Effects of environmental conditions such as immersion or extreme changes in temperature.



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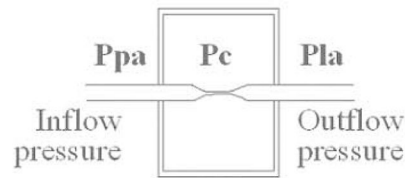
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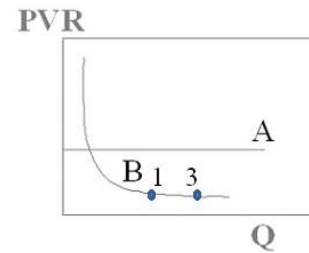
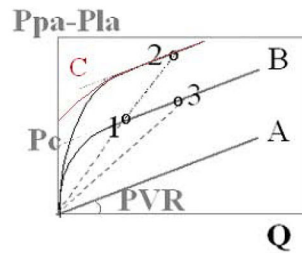
$$PVR = (P_{pa} - P_{la}) / Q$$

A:  $P_{la} > P_c$

B:  $P_c > P_{la}$

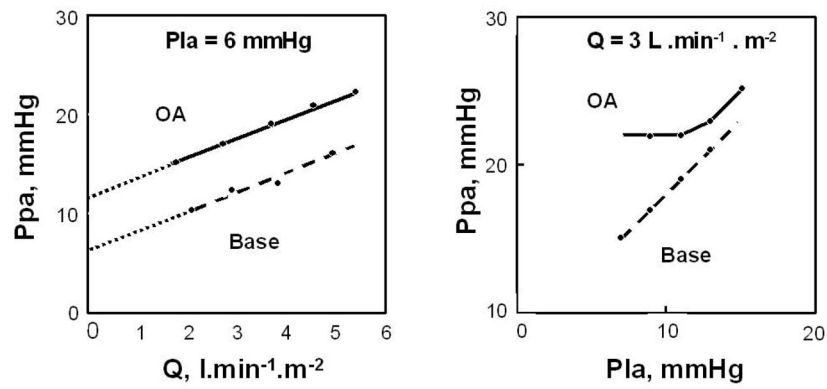
1  $\rightarrow$  2: vasoconstriction

1  $\rightarrow$  3 : no change in tone



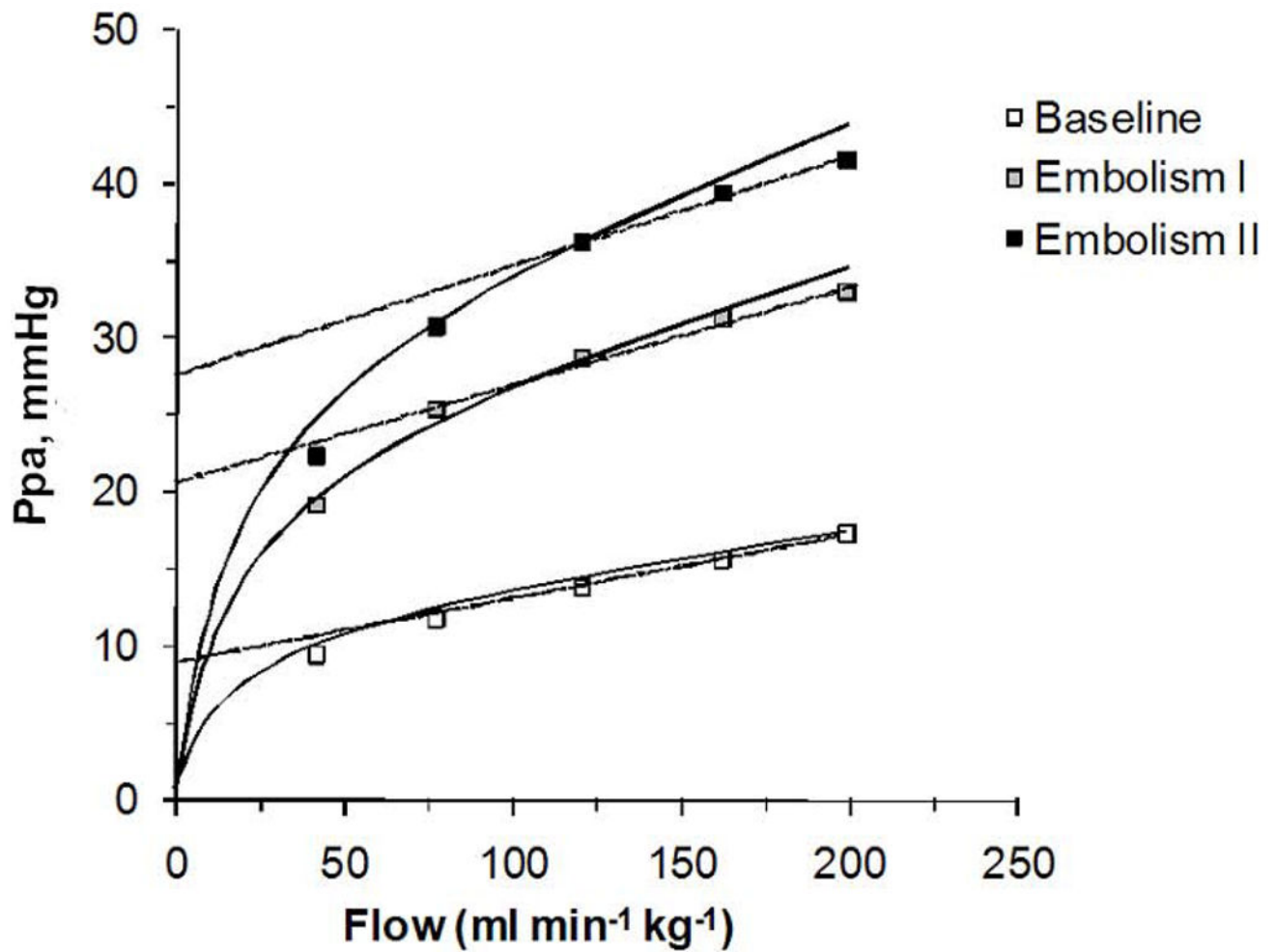
**Figure 1.**

Starling resistor model to explain the concept of closing pressure within a circulatory system. Flow ( $Q$ ) is determined by the gradient between an inflow pressure, or mean pulmonary artery pressure ( $P_{pa}$ ), and an outflow pressure which is either closing pressure ( $P_c$ ) or left atrial pressure ( $P_{la}$ ). When  $P_{la} > P_c$ , the  $(P_{pa} - P_{la})/Q$  relationship crosses the origin (A curve) and PVR is constant. When  $P_c > P_{la}$ , the  $(P_{pa} - P_{la})/Q$  relationship has a positive pressure intercept (B and C curves), and PVR decreases curvilinearly with increasing  $Q$ . The B and C curves are curvilinear at low flow representing recruitment. Also shown are possible misleading PVR calculations: PVR, the slope of  $(P_{pa} - P_{la})/Q$  may remain unchanged in the presence of a vasoconstriction (from 1 to 2) or decrease (from 1 to 3) with no change in the functional state of the pulmonary circulation (unchanged pressure/flow line). Adapted from reference 155. Permission pending.



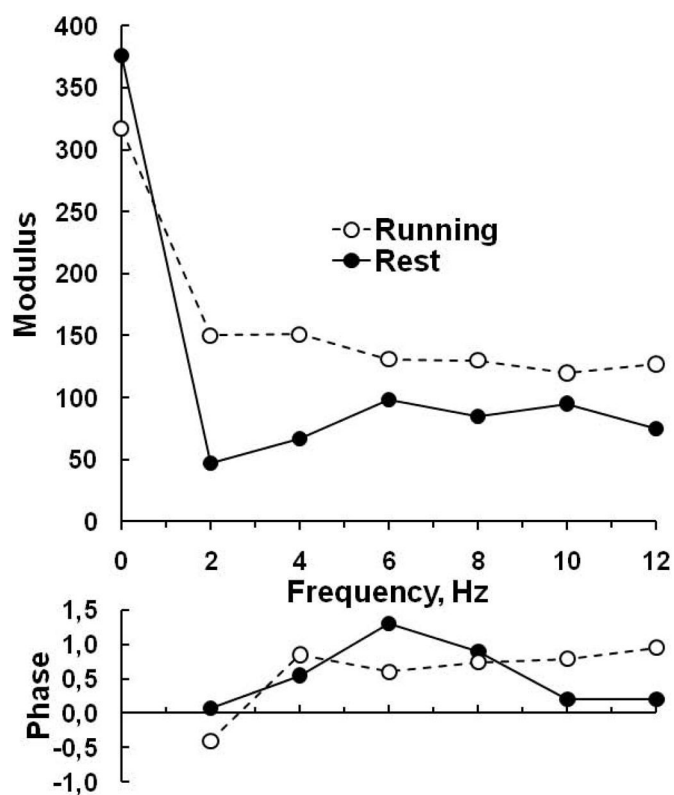
**Figure 2.**

Mean pulmonary artery pressure (Ppa) as a function of cardiac output (Q) at constant left atrial pressure (Pla), left panel, and Ppa as a function of Pla at constant Q in an anesthetized dog before (stippled line) and after (full line) injection of oleic acid (OA) to produce an acute lung injury. Lung injury was associated with a shift of linear Ppa-Q relationships to higher pressures, with increased extrapolated pressure intercept (small stipple line). Pla was transmitted to Ppa in a close to 1/1 relationship before oleic acid, but only at a pressure equal to the extrapolated pressure intercept of Ppa-Q after oleic acid, which is compatible with an increased closing pressure becoming the effective downstream pressure of the pulmonary circulation. From reference 121.



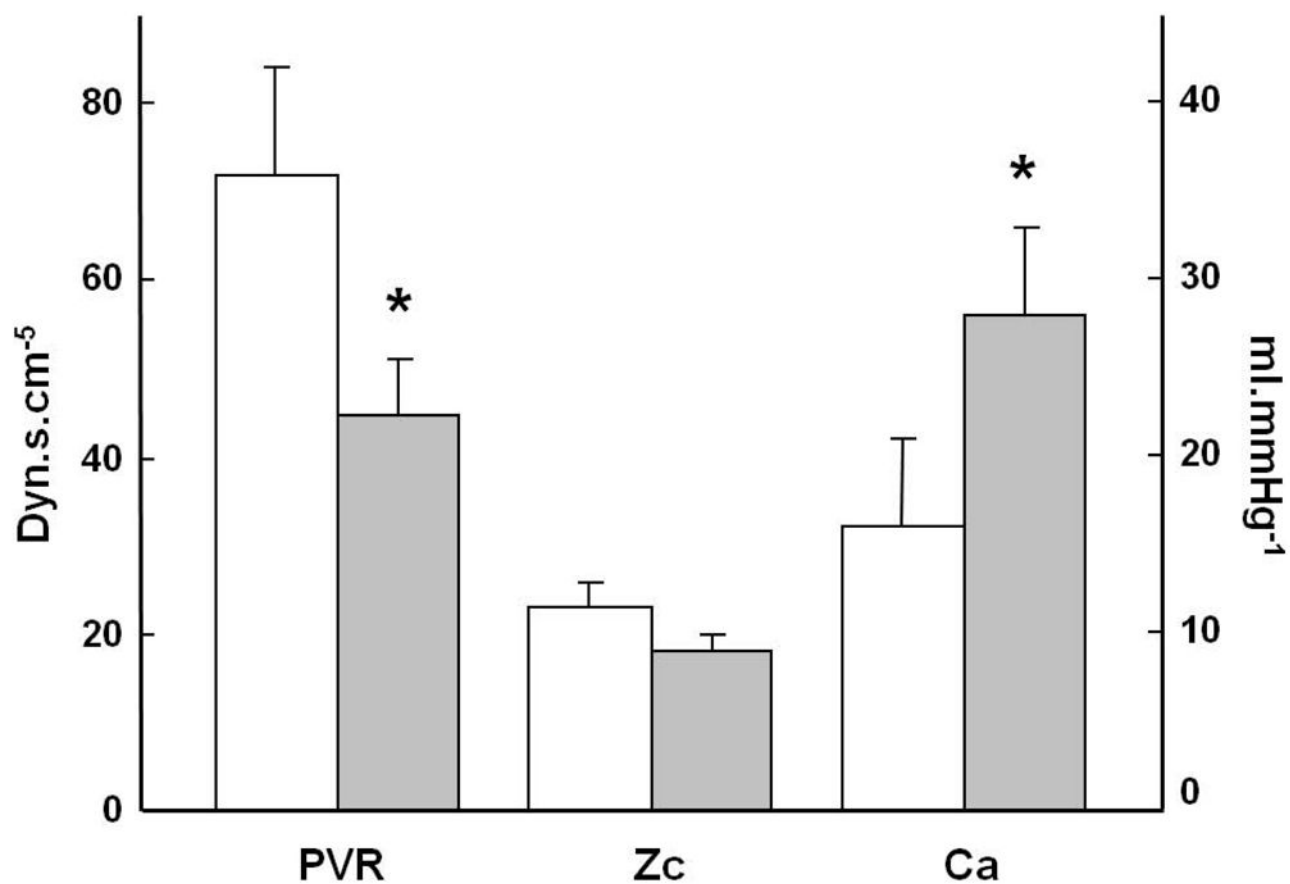
**Figure 3.**

Pressure-flow relationships of an isolated perfused mouse lung before (empty squares) and after (full squares) embolization. The shape of the multipoint pressure-flow relationship is increasingly curvilinear at decreasing flow. Extrapolated pressure intercept from best adjustments on “physiological” values for pressure and flow leads to spurious estimations of increased closing pressures. From reference 219



**Figure 4.**

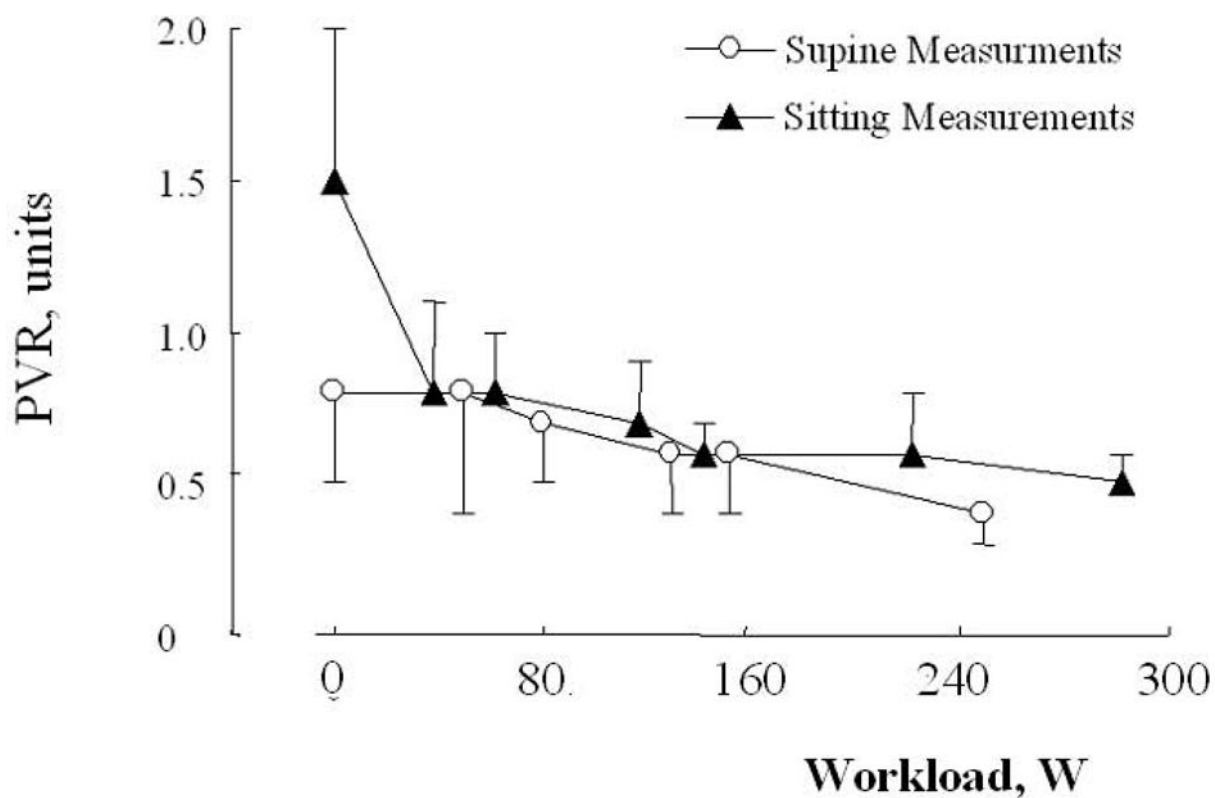
Pulmonary vascular impedance spectra in a dog, at rest and running. Running was associated with a decrease in 0 Hz impedance, but an increase in the ratio of pressure and flow moduli (in  $\text{dyne.s.cm}^{-5}$ ) at all frequencies, and a decrease in low frequency phase angle, suggestive of decreased proximal compliance of the pulmonary arterial tree. Drawn after reference 48



**Figure 5.**

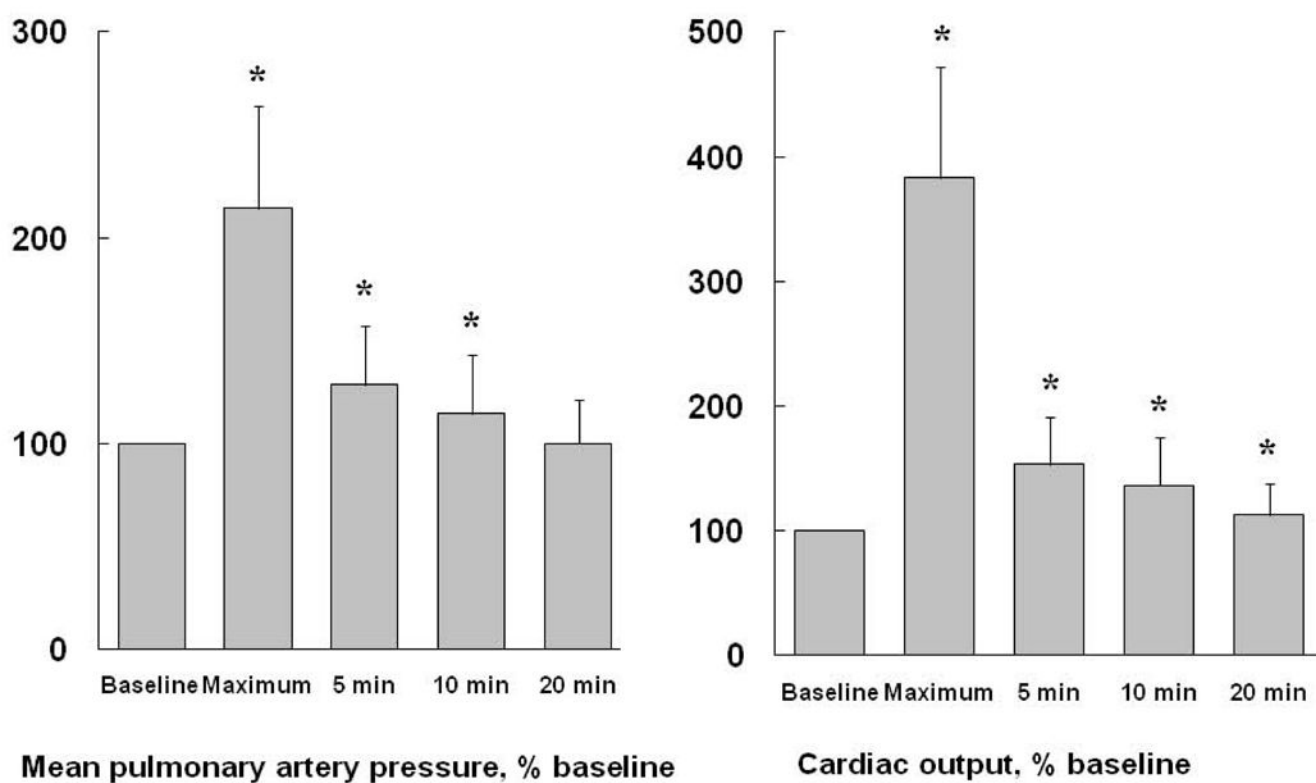
Effects of exercise (shaded columns) on pulmonary vascular resistance (PVR), characteristic impedance (Zc) and arterial compliance (Ca) in healthy human subjects. Exercise decreased PVR and increased Ca, while there was no significant change in Zc. Drawn from data in reference 193.





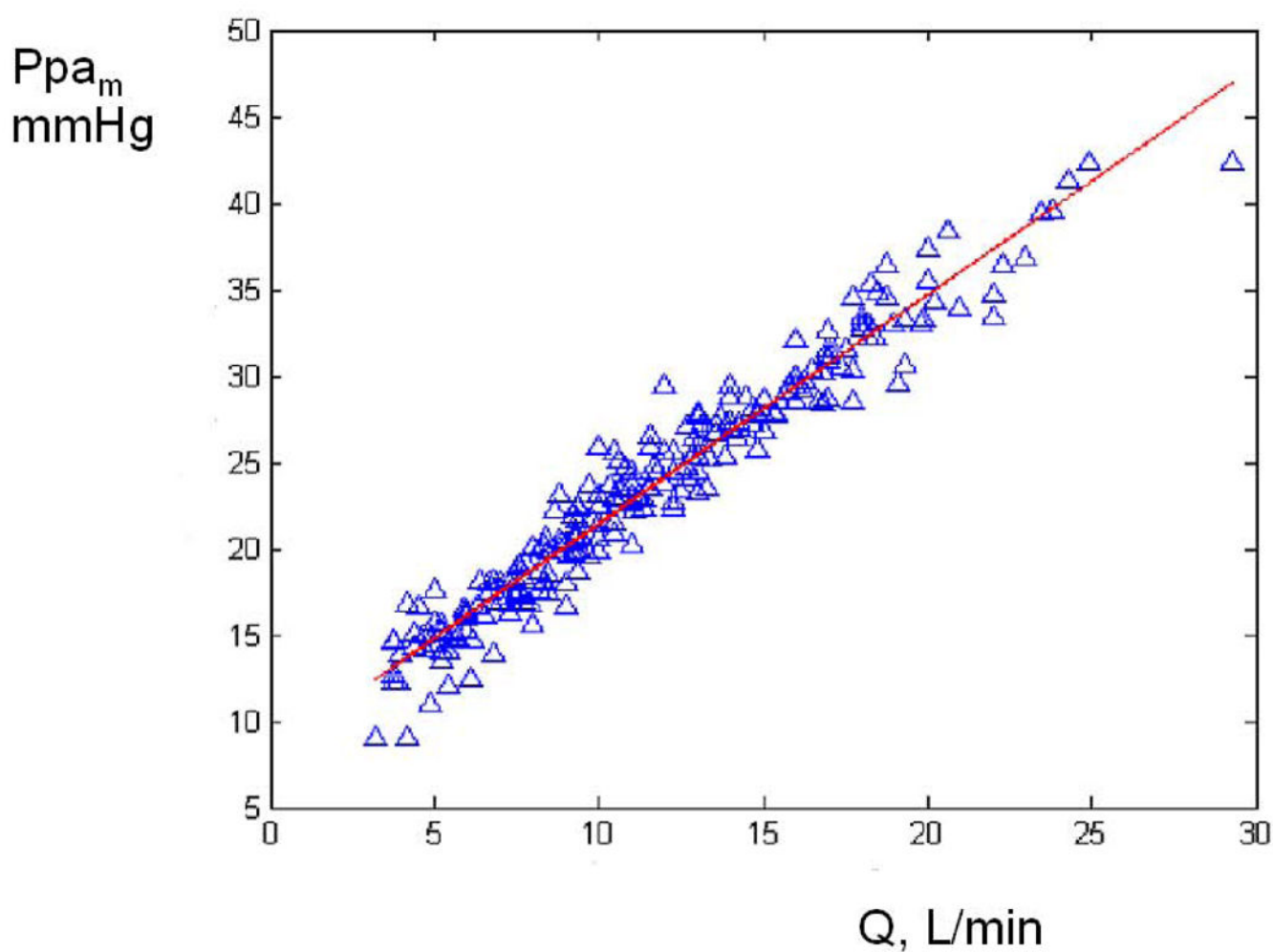
**Figure 6.**

Effects of increasing levels of exercise in the supine and in the sitting position on mean  $\pm$  SD (vertical bars) pulmonary vascular resistance (PVR, Wood units or  $\text{mmHg}\cdot\text{L}^{-1}$ ) in healthy volunteers. Initial PVR was higher in the sitting position, but otherwise PVR decreased slightly with increasing levels of workload, and this was similar in the supine and in the sitting positions. Redrawn after reference 179.

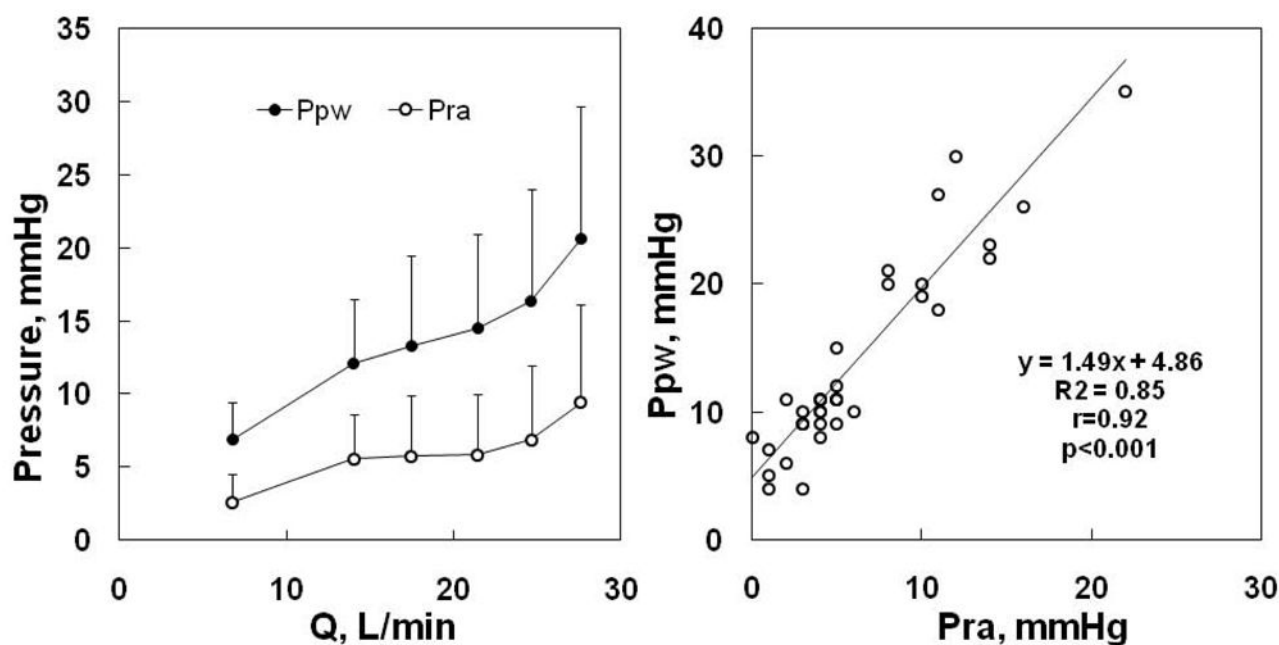


**Figure 7.**

Rapid recovery of mean pulmonary artery pressure (mPpa) and cardiac output (Q) after maximal exercise. Values are reported as mean  $\pm$  SD (vertical bars). \*:  $P < 0.05$  compared to resting baseline. After 20 min, Q is still higher than resting baseline. Drawn from reference 4, permission pending.

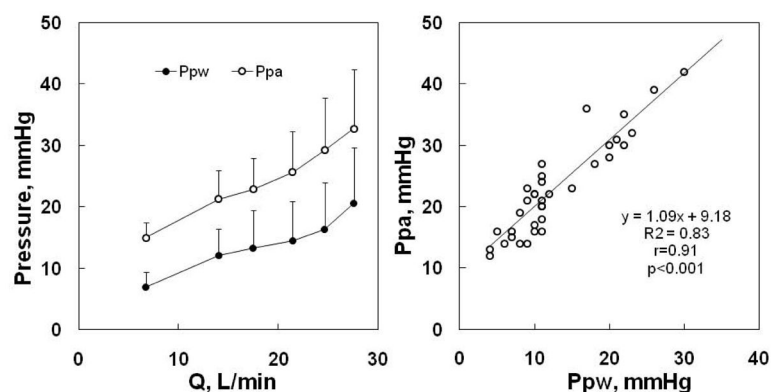


**Figure 8.** Linear relationship between mean pulmonary artery pressure ( $P_{pa_m}$ ) and cardiac output ( $Q$ ) in 25 healthy subjects during progressively severe exercise until maximum tolerated. The slope of  $P_{pa_m}$ - $Q$  was  $1.37 \text{ mmHg/L}\cdot\text{min}^{-1}$ . From reference 4. Permission pending.



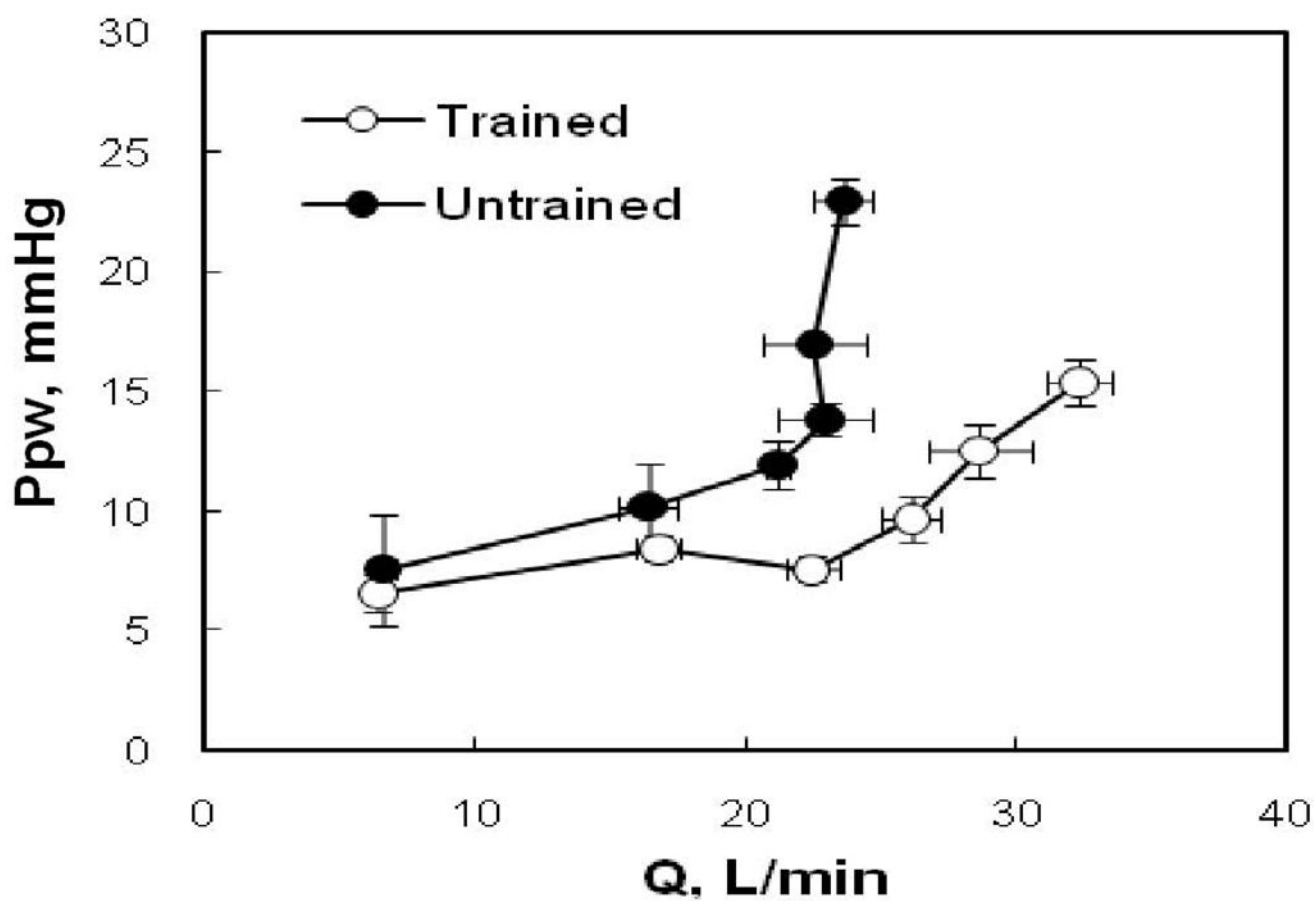
**Figure 9.**

Mean  $\pm$  SD (vertical bars) values of mean pulmonary artery wedge pressure (Ppw) and right atrial pressure (Pra) as a function of cardiac output (Q) during progressive exercise in normal volunteers, left panel, and Ppw vs Pra of the same subjects, right panel. Both Ppw and Pra increase with Q, but the gradient between the pressures tended to increase. The right panel shows that Ppw is correlated to Pra, but is higher than Pra by 5 mmHg at rest, and this increases with a slope of 1.45 mmHg increase in Ppw for every mmHg increase of Pra at exercise. From references 180 and 181.



**Figure 10.**

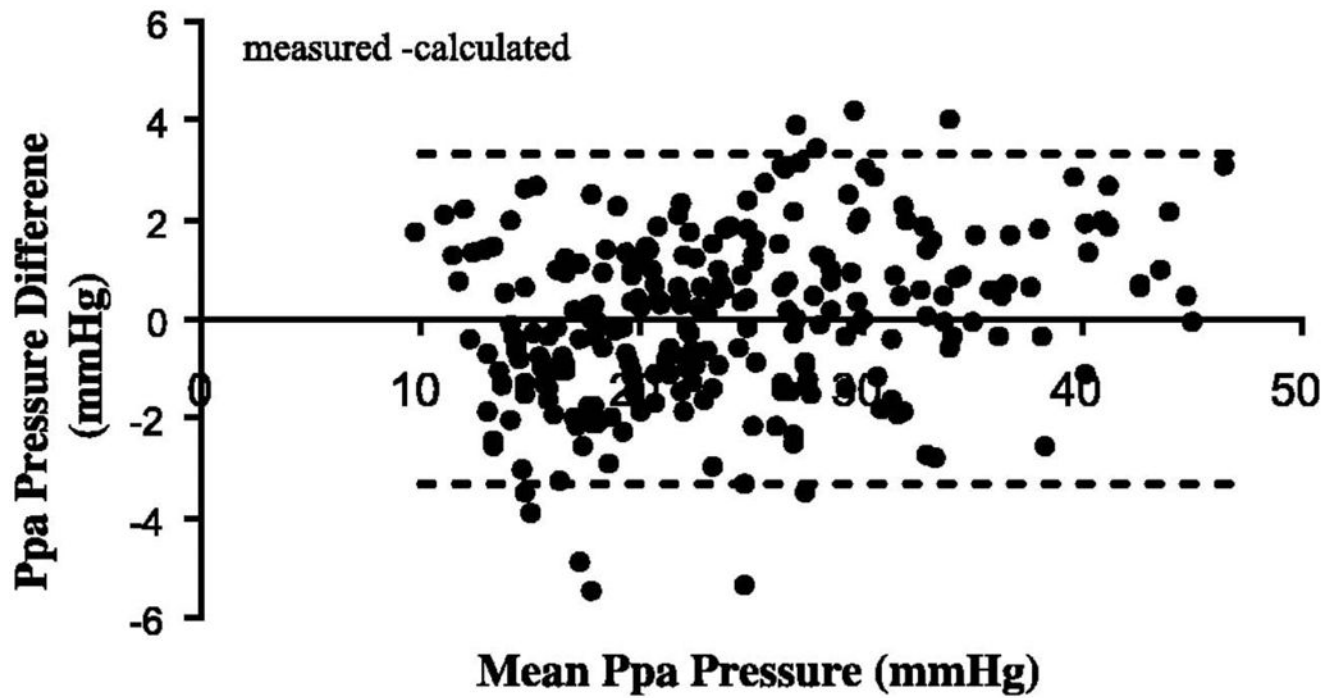
Mean  $\pm$  SD (vertical bars) values of mean pulmonary artery pressure (Ppa) and wedged Ppa (Ppw) as a function of cardiac output (Q) during progressive exercise in normal volunteers, left panel, and Ppa vs Ppw of the same subjects, right panel. Both Ppa and Ppw increase with Q, but the gradient between the pressures tends to remain unchanged. The left panel shows that Ppa is correlated to Ppw, but is higher than Ppw by 9 mmHg at rest, and this increases with a slope of 1.1 mmHg increase in Ppa for every mmHg increase of Ppw at exercise. From references 180 and 181



**Figure 11.**

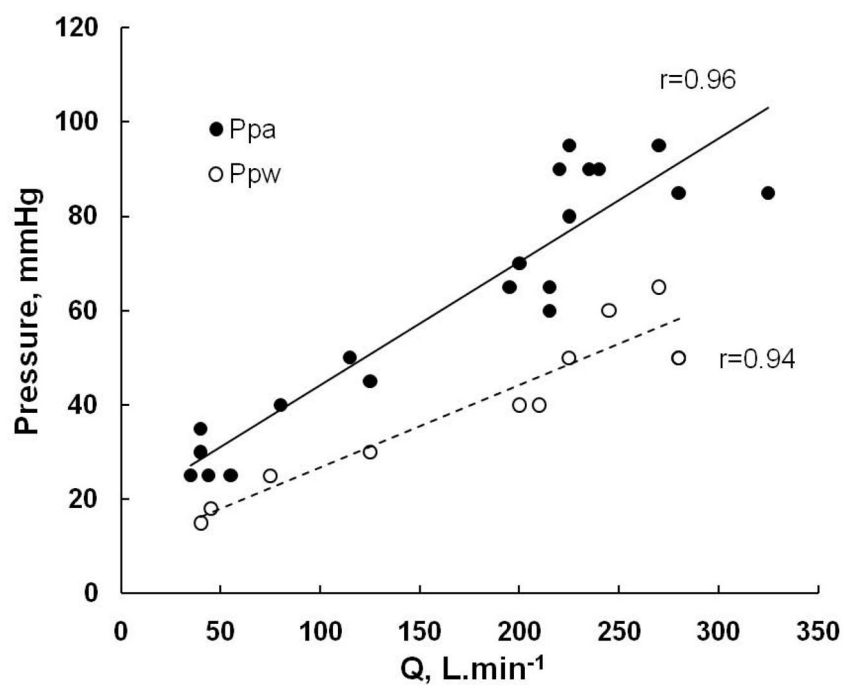
Individual mean  $\pm$  SE values of pulmonary artery wedge pressure (Ppw) as a function of cardiac output (Q) in subjects with a low (untrained) vs a high exercise capacity (trained). The increase in Ppw was delayed until higher Q in the fittest subjects, suggesting improved ventricular compliance. From reference 201.



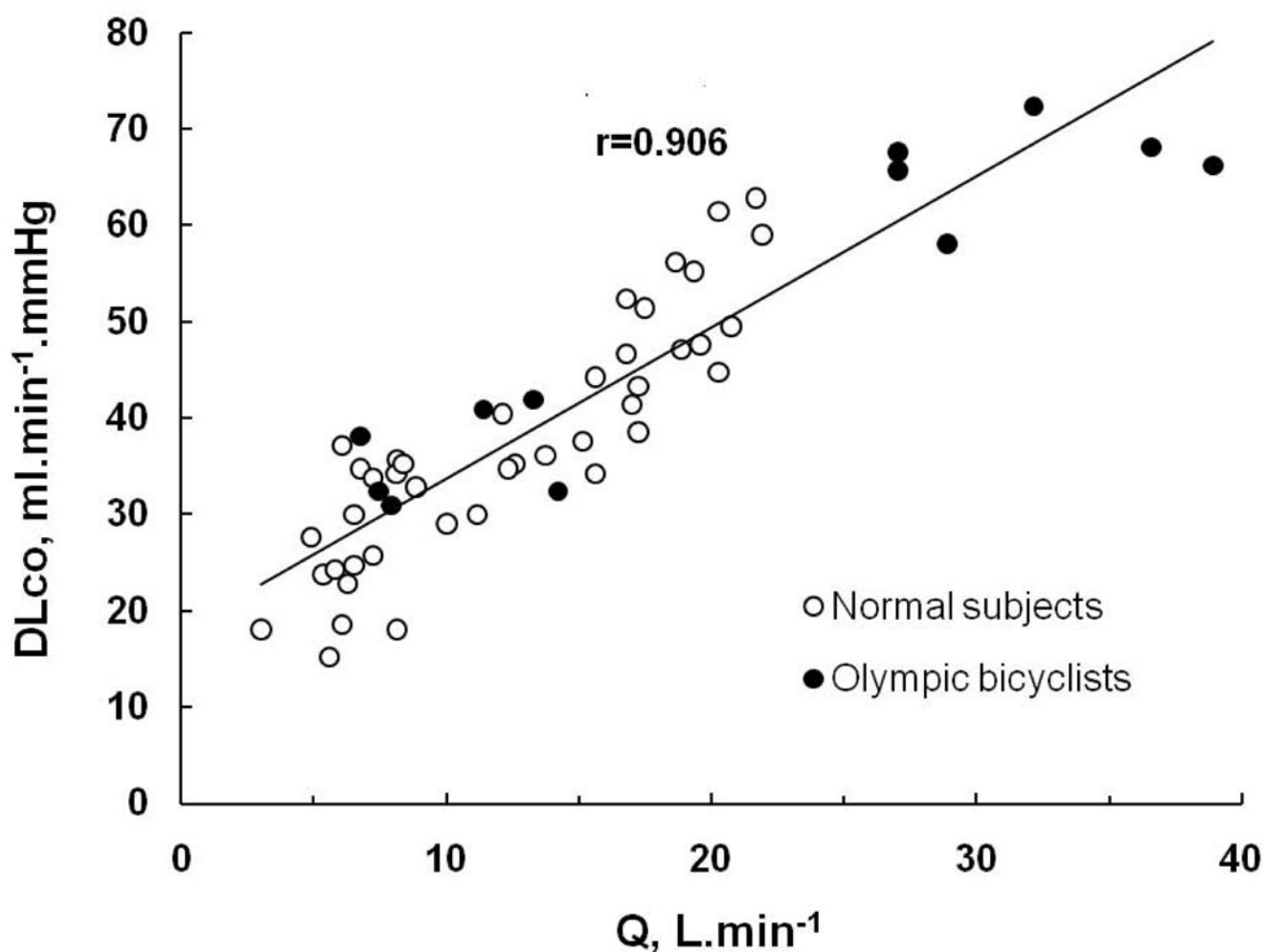


**Figure 12.**

Predicted minus measured mean pulmonary artery pressure (Ppa) as a function of mean Ppa in healthy exercising volunteers. The stippled line shows 2 SD, which is equal to 1.7 mmHg. This presentation is suggestive of a good agreement. The prediction of Ppa was obtained using the distensibility model of Linehan. From reference 182.



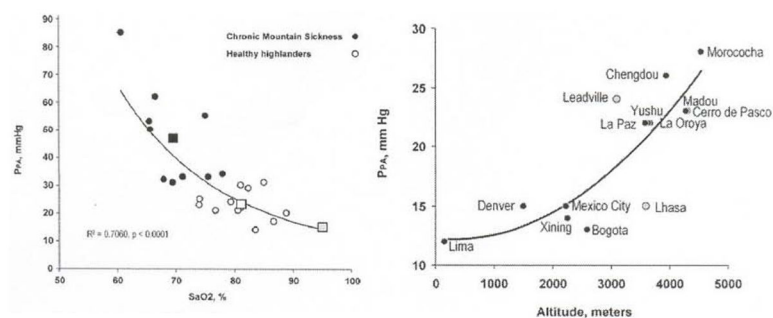
**Figure 13.** Mean values for pulmonary artery pressure (Ppa) and pulmonary artery wedge pressure (Ppw) as a function of cardiac output (Q) in exercising horses. Exercise in horses is associated with marked increases in pulmonary vascular pressures. From reference 183.



**Figure 14.** Relation of pulmonary carbon monoxide diffusion capacity ( $DL_{CO}$ ) to pulmonary blood flow ( $Q$ ) at increasing levels of exercise.  $DL_{CO}$  increases in proportion of  $Q$ , even in Olympic cyclists with very high  $Q$ . From references 104 and 183.

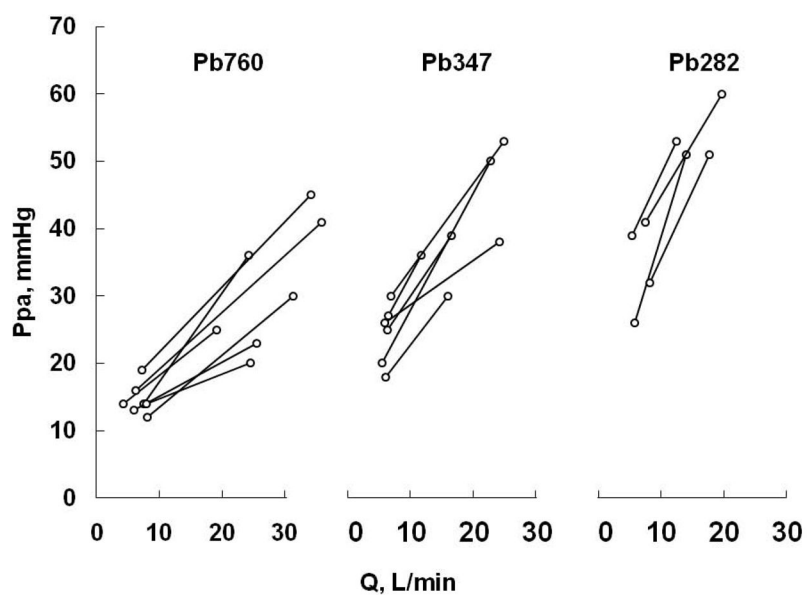


**Figure 15.** Echocardiographic apical 4 chamber views at rest (left panel) and at exercise (middle and right panels) after the injection of agitated contrast, showing appearance in the left heart chambers after 4–5 beats at moderate exercise, and more so at intense exercise. Courtesy of A La Gerche.



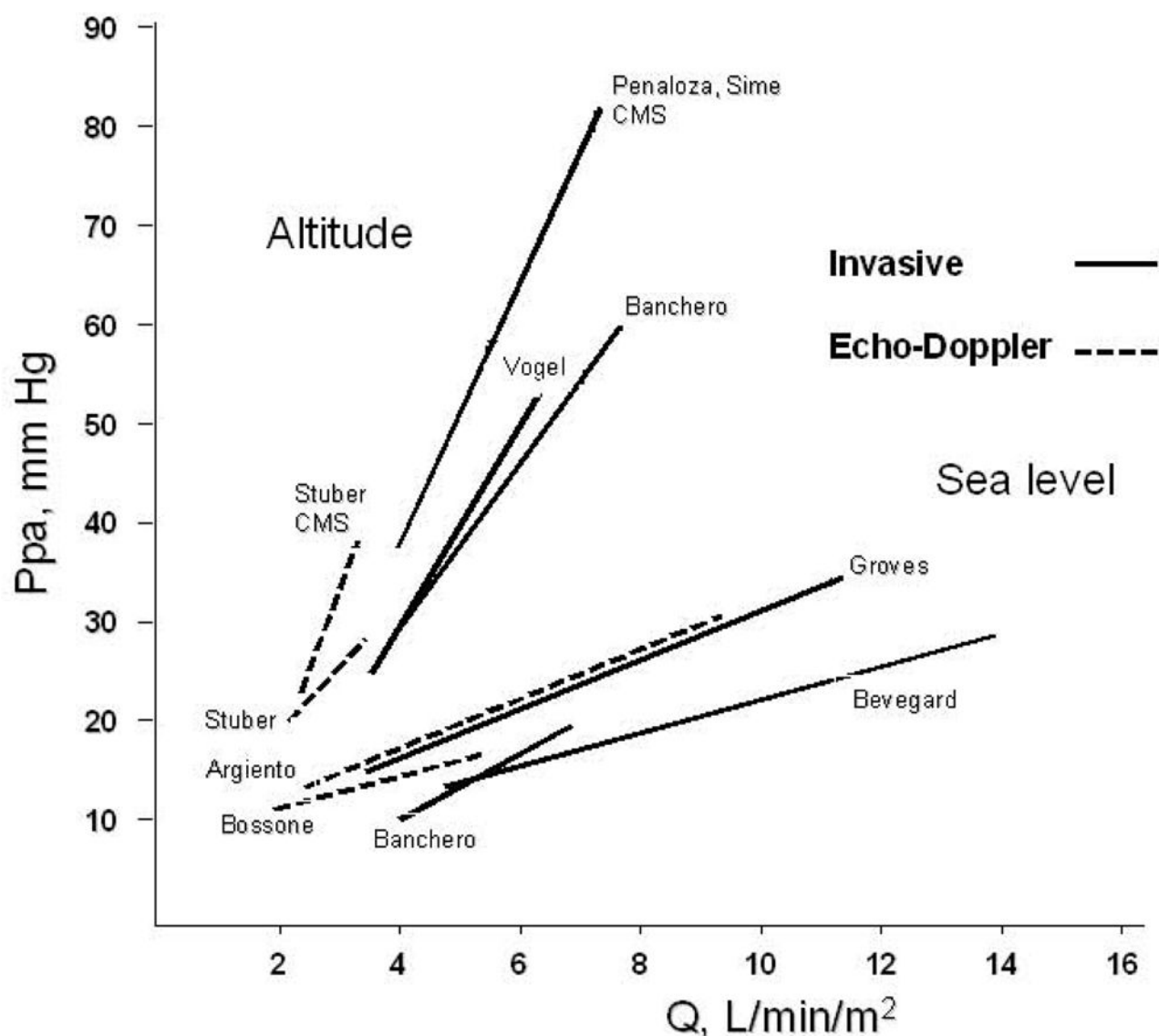
**Figure 16.**

Curvilinear relationships between mean pulmonary artery pressure ( $P_{PA}$ ) and arterial oxygen saturation ( $SaO_2$ ) in healthy highlanders (empty symbols) and highlanders with chronic mountain sickness (full symbols), left panel, and between mean pulmonary artery pressure ( $P_{PA}$ ) and altitude of locations (right panel). Extremes are observed in Lhasa and in Leadville. Hypoxia is a major determinant of  $P_{PA}$ , but there is ethnic variability. From reference 172. Permission pending.



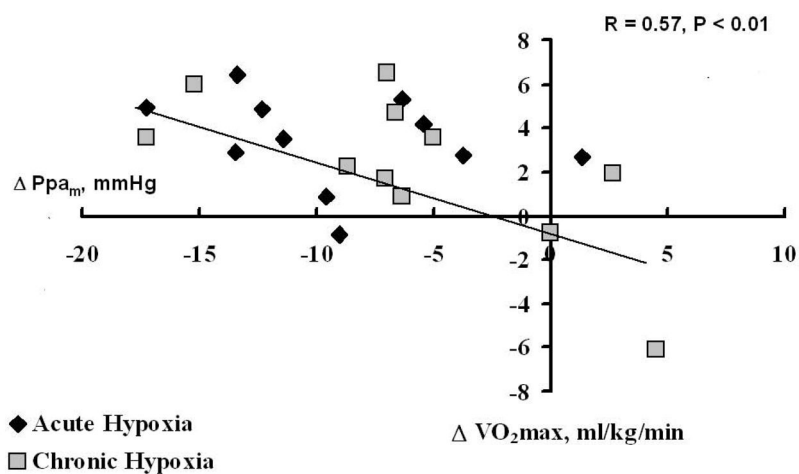
**Figure 17.** Mean pulmonary artery pressure (Ppa) as a function of cardiac output (Q) at exercise in healthy subjects at sea level, barometric pressure (Pb) 760 mmHg, and after acclimatization at two levels of simulated altitudes. Baseline Ppa and the slope of Ppa-Q increase with altitude. From reference 73.





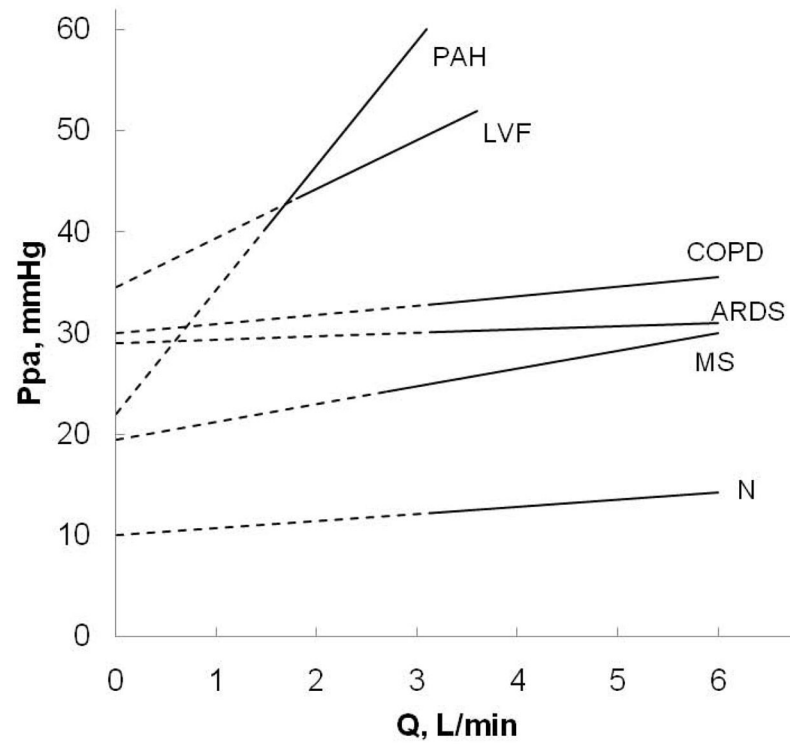
**Figure 18.**

Averaged mean pulmonary artery pressures (Ppa) versus indexed cardiac output (Q) plots measured invasively (cardiac cath, full lines) or noninvasively (echo-Doppler, stippled lines) in highlanders exercising at high altitude and in lowlanders exercising at sea level. From references 1,4,6,11,13,73,173,204,223, with indications of names of first authors in the figure. With the exception of Tibetans in lhasa, highlanders present with higher resting Ppa and increased slopes of Ppa-Q. Slopes of Ppa-Q are particularly steep on patients with chronic mountain sickness (CMS). Courtesy of Dante Penalzoza.



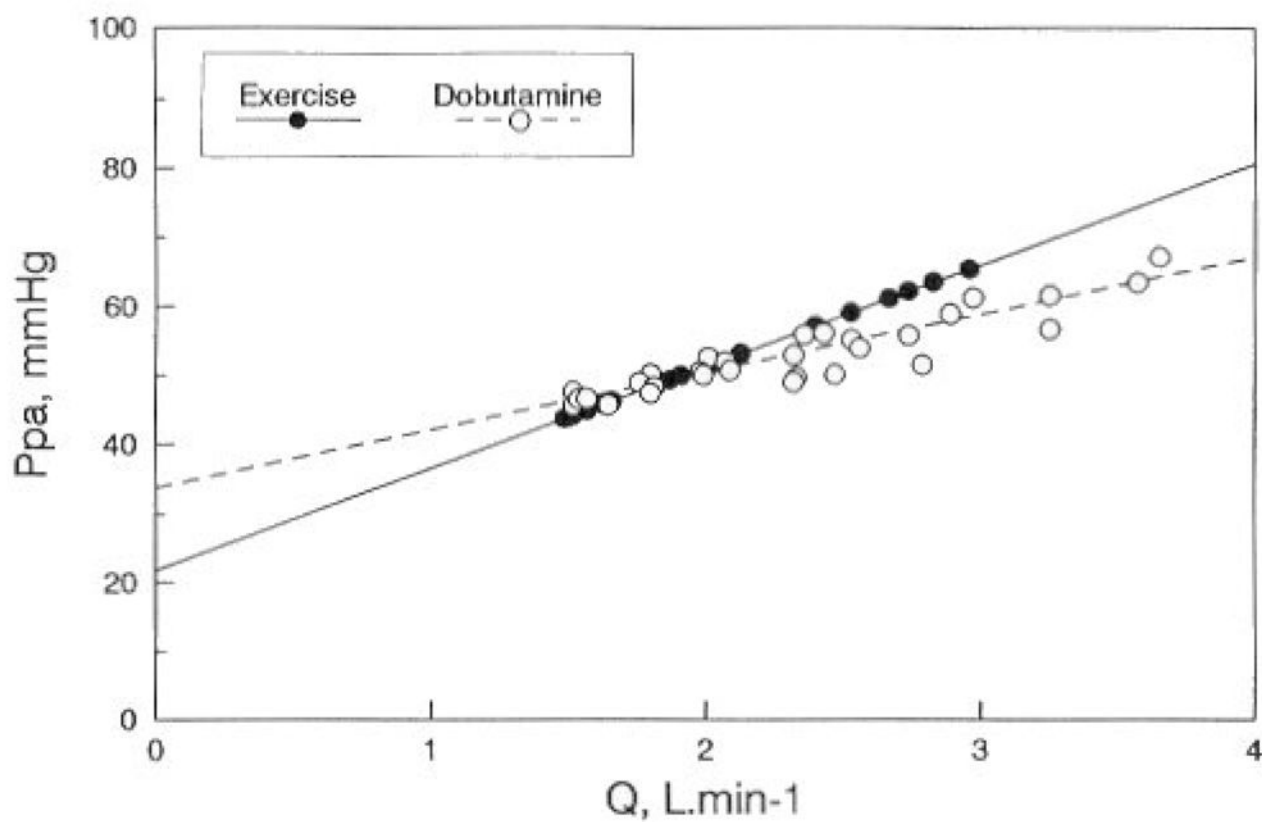
**Figure 19.**

Correlation between hypoxia-induced increase in mean pulmonary artery pressure ( $Ppa_m$ ) and decrease maximal oxygen uptake ( $VO_{2max}$ ) in healthy volunteers in either acute normobaric or more chronic hypobaric hypoxic conditions. From reference 158. Permission pending.



**Figure 20.**

Two point mean pulmonary artery pressure (Ppa) cardiac output (Q) plots in normal subjects (N), or patients with mitral stenosis (MS), acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), left ventricular failure (LVF) and pulmonary arterial hypertension (PAH). All Ppa-Q plots are shifted upward to higher pressure with an increased extrapolated pressure intercept (stippled lines). Left atrial pressure was equal to the extrapolated pressure intercept in LVF. Constructed with mean data reported in references 50,83,103,106,160,241.



**Figure 21.**

Plots of mean pulmonary artery pressure (Ppa) as a function cardiac output (Q) in patients with idiopathic pulmonary arterial pressure, with Q increased at exercise or by an infusion of low-dose dobutamine. The slope of Ppa-Q was higher with exercise. From reference 106. Permission pending.

**Table 1**

Limits of normal of pulmonary blood flow and vascular pressures

<b>Variables</b>	<b>Mean</b>	<b>Limits of normal</b>
Q L/min	6.4	4.4 – 8.4
Q, L/min.m <sup>2</sup>	3.8	2.5 – 4.5
Heart rate, bpm	67	4 – 100
Ppa systolic, mmHg	19	13 – 26
Ppa diastolic, mmHg	10	6 – 16
Ppa, mean, mmHg	13	7 – 19
Ppao, mmHg	9	5 – 13
Pcp, mmHg	10	8 – 12
Pra, mmHg	5	1 – 9
PVR, dyne.s.cm <sup>-5</sup>	55	11 – 99
Psa, mean, mmHg	91	71 – 110

Legend: Q: cardiac output; Ppa: pulmonary artery pressure; Ppao: occluded Ppa; Pcp: pulmonary capillary pressure (measured by single occlusion); Pra: right atrial pressure; PVR: pulmonary vascular resistance; Psa: systemic arterial pressure; limits of normal: from mean – 2 SD to mean + 2 SD

n = 55 healthy resting volunteers (n = 14 for the measurement of PCP) Source: references 146,133,161.

**Table 2**

Slopes of pulmonary vascular pressure-flow relationships in normal subjects

	Supine measurements		Upright measurements	
Normal young men and women				
Variables	n	Slope	n	Slope
Q, Ppa <sub>m</sub>	63	1.00	21	1.01
SD		0.91		0.43
Q, Ppw	53	0.30	16	0.84
SD		0.35		0.39
Normal old men				
Q, Ppa <sub>m</sub>	14	2.54		
SD		0.77		
Q, Ppw		1.93		
SD		0.94		

Legend: Q: cardiac output; Ppa<sub>m</sub>: mean pulmonary artery pressure; Ppw: wedged Ppa

Young adults were aged 20–30 yearsd, old men were aged 60–80 years

Souce: Reference 178