We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter

Pulmonary Vascular Reserve and Aerobic Exercise Capacity

Vitalie Faoro and Kevin Forton

Abstract

Pulmonary circulation has long been known to have specific proprieties of recruitment and distention to keep the hemodynamic pressure low even when facing very high blood flow. Aerobic exercise especially at high intensity has the particularity to increase considerably the cardiac output. The ability of the pulmonary circulation to face high blood flow with maintaining low pressures is considered as the pulmonary vascular reserve. Furthermore, high pulmonary vascular reserve has been shown to be characterized by low pulmonary vascular resistance, high pulmonary vascular distensibility, high pulmonary capillary volume, and high lung diffusing capacity allowing for lower ventilation at a same metabolic cost. The pulmonary vascular reserve thus reflects the capacity of the pulmonary circulation, including the capillary network, to adapt to high exercise levels. Interestingly, a high pulmonary vascular reserve is an advantage as it is associated with a superior aerobic exercise capacity (VO_2max). This observation strongly suggests that exercise capacity is modulated by the functional state of the pulmonary circulation. However, why or when pulmonary vascular reserve may be related to a higher aerobic exercise capacity remains incompletely understood. The present chapter will discuss the role of each component of the pulmonary vascular reserve during exercise and develop the factors able to influence the pulmonary vascular reserve in heathy individuals.

Keywords: pulmonary circulation, VO_2max, ventilation, diffusion capacity

1. Introduction

During aerobic exercise, muscular contractions increase oxygen peripheral demand proportionally to exercise intensity until a maximal level or maximal oxygen consumption (VO_2max). VO_2max is widely used as a cardiorespiratory fitness indicator as the capacity of oxygen consumption increases with exercise training with values approaching 80–90 ml/min/kg in endurance athletes vs 20–30 ml/min/kg in healthy sedentary subjects. The oxygen consumption is dependent on the interdependence of the different components of the convectional and diffusional oxygen transport systems from ambient air to the mitochondria. Every transport step is a potential VO_2max determinant: ventilation, pulmonary diffusion, blood oxygen transport (depending on cardiac output and arterial oxygen content), muscular diffusion, and mitochondrial activity. The importance of each contribution step varies under different health or environmental conditions. Nevertheless, one can reasonably assume that cardiac output (Q) is most important at sea level, while at higher altitudes, lung or/and muscle diffusion may become more critical [1, 2].

For many years, exercise physiologists have focused on the left side of the heart and the systemic circulation to explain aerobic exercise performance and limitation. However, more recently, robust and growing studies suggest that the right ventricle (RV) might also be an important determinant of maximal cardiac output and VO_2max [3, 4]. More broadly, the RV-pulmonary circulation unit, including the capillary network, has been identified as a potential factor modulating the aerobic exercise capacity in normoxia [5–8] and in hypoxia [7–10]. Indeed, pulmonary vascular reserve, or the ability of the pulmonary circulation to extend, recruit, and vasodilate to smooth an intravascular pressure increase, is critical in minimizing RV afterload and maximizing peak cardiac output at exercise [5, 6]. To discuss the potential importance of this phenomenon, the role of each physiological component of the RV-pulmonary circulation unit and interactions with gas exchange will be reviewed.

2. Right ventricle

Cardiac output increases with exercise intensity in order to ensure oxygen supply to the working muscles. Since the right and left heart are disposed in a series in the cardiovascular system, it is impossible for one ventricle to generate a blood flow exceeding that of the other. The maximal cardiac output is therefore depending on the "weakest" ventricle's performance. Increases in RV afterload may, thereby, possibly serve to limit overall cardiac output [3]. Additionally, the heart being constrained within a stiff pericardium, congestion in the RV may shift the interventricular septum to the left resulting in left ventricular diastolic volume restriction, further limiting maximal Q. This is observable in specific circumstances such as congestive heart failure or highly trained endurance athletes [3].

The normal right ventricle is a thin-walled flow generator perfectly adapted to face the low-pressure, high-compliant pulmonary circulation [3, 11]. However, RV anatomical and physiological properties are maybe not designed to face dramatical afterload increase at high levels of exercise. As compared to the left ventricle (LV), load increases are greater for the RV during exercise [12], and its contractile reserve may become insufficient for adequate blood supply to peripheral demand [12, 13]. Relative to the LV, the greater load that the RV faces during exercise is dominantly attributed to a larger exercise-induced increase in pulmonary artery pressure (PAP) relative to systemic vascular pressure [3].

Increased PAP during exercise is known to limit exercise capacity in pulmonary hypertension patients through a decreased maximum cardiac output by an overloaded right ventricle [11]. Recently it has also been suggested that the same phenomenon could appear in healthy individuals exercising at high workloads at sea level [5–8] but even more at altitude [7–10].

Invasive or noninvasive studies in healthy subjects described a ceiling level of the mean PAP approximating 40–50 mmHg when exercising at maximal workloads corresponding to the extreme afterload level which the RV can face while maintaining a high cardiac output [6, 14–17]. The RV is thus placed under great stress during intense exercise. This leads to the idea that RV outflow might become a limiting factor when the ventricular work demand is overwhelmed, particularly in cases of extreme cardiac outputs (high intensity exercise, endurance athletes) or increased PAP (pathological or hypoxic conditions). Recently, D'Alto et al. demonstrated that echocardiographic RV systolic function indices (tricuspid annular plane systolic excursion (TAPSE), S′, and TAPSE/PAP) correlate with maximal workload in healthy subjects. This finding illustrates that a higher RV contractility reserve, defined as the difference between peak exercise and rest, is an advantage to reach high exercise levels and suggests a potential role of the RV in exercise capacity limitation [13].

3. Pulmonary circulation

3.1 Pulmonary vascular resistance

Pulmonary circulation opposes resistances to the ejecting RV that can be quantified by the PAP at a given cardiac output [18]. According to Poiseuille's law, applicable for a Newtonian fluid flowing laminarly in a straight cylinder, flow and driving pressure are proportional. This would imply that with unchanged resistance every increase in flow would increase PAP. However, the pulmonary circulation has this specific property to reduce resistances by two possible mechanisms: (1) recruitment, enlistment of previously closed pulmonary capillary [19, 20], and (2) distension, expansion of already filled pulmonary capillaries when pressure increases [21]. It is generally accepted that the initial vascular recruitment at the onset of exercise followed by distension allows for the pulmonary circulation to face a high blood flow with limited increase in pressure and maintaining RV systolic function at minimal energy cost [22]. Indeed, low pressure in the pulmonary circulation is essential to prevent two potential exercise capacity limitation mechanisms: fluid leaking from the capillaries to the interstitial space with subsequent gas exchange alterations and RV outflow and oxygen transport limitation [18, 22].

During exercise, PAP increases along with Q but not always with a one to one ratio [15, 23]. In exercising subjects, the PAP can be measured at different exercise intensities or Q allowing for the calculation of the PAP vs. Q slope, as illustrated in **Figure 1**. The PAP vs. Q slope is a more accurate estimation of pulmonary vascular resistance (PVR) as compared to a single measure at rest [14, 22, 24]. Invasive catheterization and noninvasive stress echocardiography studies showed that pulmonary vascular response to exercise varies considerably from one individual to another, with slopes of mean PAP/Q ranging from 0.5 or 1 mmHg/l/min in young adults to 2.5 mmHg/l/min in elderly [14, 23]. This means that with a 10 l/min exercise-induced Q increase, for example, normal PAP increase would range from 5 to 25 mmHg. This great interindividual variability of pulmonary vascular response

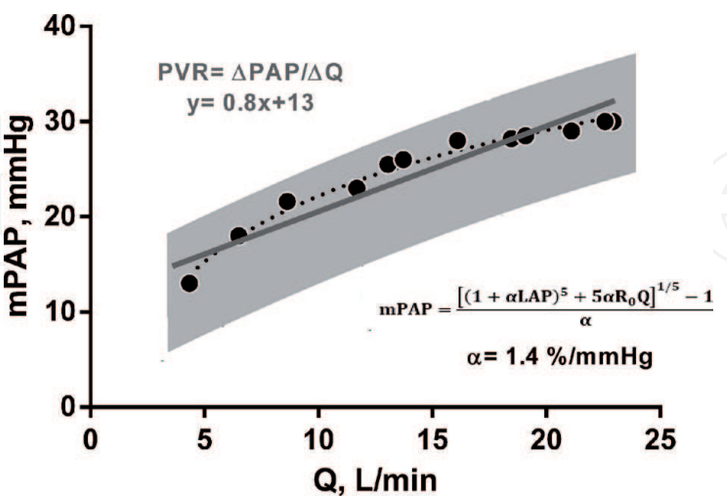

Figure 1.
Stress echocardiography multiple measurements of mean pulmonary arterial pressure (mPAP) at increasing flow (Q) from rest until maximal exercise in one healthy subject. Pulmonary vascular resistance (PVR) is evaluated from the angular coefficient of the mPAP vs. Q linear regression line (ΔmPAP/ΔQ). The PVR of 0.8 mmHg/l/min found in this example is in good agreement with limits of normal (gray background) [23]. From the curvilinearity of this PAP vs. Q relationship (dotted line), a mathematical distensible model relating mPAP, Q, left atrial pressure (LAP), and total PVR at rest (R0) allows for a calculation of a distensible factor: α (cfr formula). The present subject shows a distensibility (α) corresponding of 1.4% increase of the pulmonary vascular diameter per mmHg of pressure elevation during the entire exercise test and is in good agreement with previous reports [8, 14, 23, 26].

during exercise also suggests a great interindividual variability of RV energy cost. Interestingly, lower PAP/Q slopes have been found in fittest subjects [6–8, 10]. This observation suggests that lower RV output resistance helps to reach higher exercise intensities. Conversely, in patients with pulmonary hypertension, exercise is associated with a sharp increase in PAP (high PAP/Q slopes), and a right ventricular limitation affects exercise capacity [11, 25].

3.2 Pulmonary vascular distensibility

When multiple PAP are measured at increasing exercise or Q levels, it is possible to show that the PAP/Q relationship is not strictly linear but becomes curvilinear with a smoothened pressure increase at higher exercise intensities [14, 16, 26, 27]. The curvilinearity of the PAP/Q relationship reflects the distension of the pulmonary resistive vessels in order to limit the flow-induced pressure increase during exercise. This pulmonary vascular distension participates in decreasing PVR and RV afterload during exercise. The pulmonary vascular distensibility can be quantified with a mathematical model applied to the PA-Q relationship allowing the calculation of a coefficient of distensibility; α (**Figure 1**). Alpha depends on the mechanical properties of the lung vascular walls and represents the percentage change in arteriolar diameter per mmHg of arteriolar pressure increase with exercise [16, 24, 26]. Direct in vitro or indirect in vivo measurements showed an average of 2% increase in diameter per mmHg of distending pressure in healthy pulmonary vessels [14, 26]. Higher alphas, representing a more distensible pulmonary circulation, have been shown to be associated to lower blood flow resistances (PAP/Q slopes) [6]. However, it is interesting to note that the distensibility of the pulmonary vasculature does not stay constant with the onset of exercise but tends to decrease with exercise intensity, indicating that pulmonary vascular compliance decreases along with increases in flow and intravascular distending pressures [6, 16, 23]. Argiento et al. described a mean distensibility α at rest of 2.2%/mmHg decreasing to 1.3%/mmHg at maximal exercise in 88 young heathy adults [23].

Fit subjects, with a high aerobic capacity, have been shown to have enhanced exercise-associated decrease in PVR and increase in pulmonary arterial compliance. This has been demonstrated recently with higher VO_2max correlated to greater pulmonary arteriolar distensibility α [6, 8] associated with lower PVR at maximum exercise or lower PAP/Q slopes [6–8]. This observation was true at sea level but was even more pronounced at moderate or high altitude [7, 8, 10]. One could consider that a more distensible and low resistive pulmonary circulation is an advantage for aerobic exercise performance.

4. Pulmonary capillaries, gas exchange, and ventilation

It has previously been estimated that resistances in the pulmonary circulation are located for 60% at the precapillary level and for 40% at the capillary-venous level [28]. Pulmonary capillaries hemodynamic thus significantly contribute to changes in PVR during exercise and can therefore not be neglected.

4.1 Pulmonary transit of agitated contrast

The property of the pulmonary capillaries to distend during exercise can be studied by intravenous injection of an agitated contrast. Bubbles appearing in the right heart must transit through the pulmonary circulation to be observed in the left heart chambers with echocardiography. At rest, no bubble transit occurs from the

right to the left heart. However, during exercise in healthy individuals, pulmonary transit of agitated contrast (PTAC) occurs when contrast appears from the right to the left heart chamber after four to five heartbeats [29, 30]. Whether this exercise-induced bubble transit is explained by pulmonary capillary distension or by the opening of an arteriovenous shunt is still debated [31–33].

In a recent study, La Gerche et al. used PTAC to assess pulmonary vascular reserve in exercising healthy individuals. They observed that subjects with no or minimal bubble transit through the pulmonary circulation also showed higher PVR assessed by steeper PAP/Q slopes, and individuals with high PTAC had lower exercise-induced increases in PAP and greater PVR reduction [5]. This observation suggests that a greater pulmonary vascular reserve can occur through a possible enhanced capillary distensibility. Moreover, this physiological advantage was associated with improved RV function and higher maximal Q. The authors of this study concluded that higher PTAC is advantageous to lower RV afterload and creating less RV fatigue during prolonged and intense exercise [5]. In support of this previous finding, in a similar study, Lalande et al. found that the amount of bubbles transiting through the pulmonary circulation was proportional to the increase in pulmonary capillary pressure and volume during exercise [6]. In this study positive PTAC occurred during exercise when a twofold increase in vascular pressure allowed for a 20–30% increase in capillary blood volume [6]. Capillary recruitment and dilation seem thus crucial to unload the RV at high levels of exercise but is also crucial to maintain capillary pressure low during intense exercise. In numerous studies, West et al. highlighted that an abnormal increase in PAP and subsequent capillary pressure elevation above a 20–25 mmHg threshold at exercise could possibly lead to a capillary stress failure known to elicit interstitial lung edema and altered ventilation/perfusion relationships [34, 35]. Capillary damages have indeed previously been described in some endurance-trained athletes [36].

4.2 Lung diffusion capacity

Capillary blood volume can be estimated noninvasively from lung diffusing capacity measurements using double gas tracers: carbon monoxide (CO) and nitric oxide (NO) differing in their affinity for hemoglobin. The Roughton and Forster equation, $1/D\text{LCO} = 1/D\text{m} + 1/\theta V\text{c}$, states that lung diffusion from the alveola to the erythrocyte's hemoglobin is the result of two resistances in series: the alveolo-capillary membrane diffusion component and an intracapillary component. *D*LCO is the measured diffusing capacity of the lung for CO, *D*m the membrane component, θ the hemoglobin affinity for CO, and *V*c the capillary blood volume [37]. Transposing this equation for NO, which has particularly high hemoglobin affinity, two equations can be solved with two unknowns allowing for *V*c calculation [38].

Exercising at sea level is associated with an increase in DLCO, DLNO, Dm, and Vc linearly with the workload intensity without ceiling effect. This suggests that recruitment and distention of the pulmonary circulation does not reach a limit even at high exercise levels. Also, a predominant exercise-induced increase in *V*c relative to *D*m has been described suggesting a predominance of capillary distension rather than recruitment, whereas a recruitment would increase more Dm than Vc [39–41]. This is in keeping with the notion that exercise is associated with an increased diameter of pulmonary capillaries [6, 41–43]. Recent studies found indeed that the amount of blood in the pulmonary capillaries was a determinant of the aerobic exercise capacity [6, 8]. This observation is compatible with the hypothesis that exercise capacity is modulated by the functional state of the pulmonary circulation, including capillary vessels, and could be confirmed in more than 150 healthy adults tested in our laboratory (**Figure 2C**). Additionally, it also appeared that the

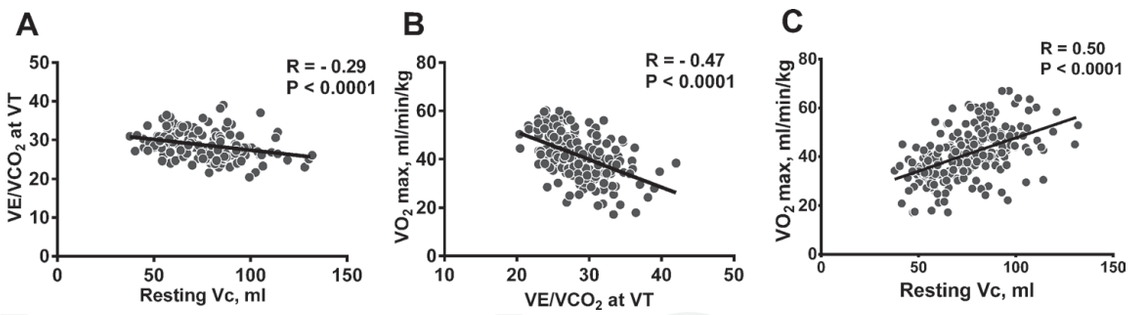

Figure 2.
Correlations between lung capillary volume measured at rest (Vc), ventilatory equivalent for CO_2 (VE/VCO_2) measured at the ventilatory threshold (VT), and aerobic exercise capacity (VO_2max). Larger blood capillary volume allows for better ventilation-perfusion adequacy decreasing ventilation at a given metabolic rate and higher aerobic capacity.

blood volume of the pulmonary capillaries (Vc) measured by the DLCO and DLNO method was correlated to the ventilation at a given metabolic cost (VE/VCO_2 ratio) measured during incremental cardiopulmonary exercise testing (**Figure 2A**). This founding, suggesting that better perfused lungs allows for lower ventilatory cost, is an advantage to reach higher exercise levels (**Figure 2B** and **C**).

The VE/VCO_2 ratio represents the ventilation level needed to evacuate 1 L of CO_2 for 1 minute and is therefore a good indicator of the ventilatory efficiency and represents the metabolic cost of ventilation. The VE/VCO_2 ratio can be measured at the ventilatory threshold, when metabolic acidosis is not yet pronounced and does not substantially influence ventilation. However, the slope of the VE versus VCO_2 relationship from rest until the respiratory compensation point might be more accurate to define the ventilatory chemosensibility [44].

Chronic heart failure and even more so pulmonary arterial hypertension increase the VE/VCO_2 slope by a combination of increased dead space related to low cardiac output, early lactic acidosis, and increased chemosensitivity in the context of an increased sympathetic nervous system tone in relation with the severity of the pathology [45]. The VE/VCO_2 slope has indeed been identified as a strong prognostic tool in patients with heart failure, and in some studies, its prognostic significance has outperformed the VO_2max [44]. In the other hand, endurance athletes are known to have shallow VE/VCO_2 slopes probably through a training-induced decrease in chemosensibility [46].

Interestingly, recent studies also showed a link between higher diffusion capacities (DLNO) and shallowest VE/VCO_2 slopes [6, 8] in keeping with previous notion that higher lung diffusing capacity allows for preserved gas exchange at a lower ventilatory cost [47]. In those studies, the higher diffusion capacities and lower VE/VCO_2 slopes were associated to higher aerobic capacity [6, 8].

5. Pulmonary vascular reserve

The pulmonary vascular reserve is the ability of the pulmonary circulation to accommodate high flows by moderating pressure increase with vascular recruitment, dilatation, and/or distension and allows low hemodynamic pressures in the pulmonary circulation. The more the pulmonary circulation is able to face high blood flow with maintaining low pressures during exercise the greater the pulmonary vascular reserve. This is critical in minimizing RV afterload and maximizing cardiac output during exercise. When pulmonary vascular reserve is compromised, RV ejection may also be compromised, increasing right atrial pressure and limiting maximal cardiac output [18]. Pulmonary vascular reserve avoids abnormal increase

in PAP and subsequently increases in pulmonary capillary pressure, protecting from an interstitial pulmonary edema [35, 48]. Finally, a better vascular reserve allows for a greater capillary distention increasing the lung capillary volume which has been shown to be associated with better ventilation-perfusion adequacy, better lung diffusion capacity, and lower ventilatory cost at a given metabolic rate [7, 8].

A pioneer study by La Gerche et al. demonstrated that favorable changes in pulmonary vascular reserve provide a physiological advantage for RV function during exercise [5]. Indeed, subjects with the higher PTAC had the lowest PVR and lowest exercise-induced B-type natriuretic peptide blood levels (usually elevated with ventricular volume and pressure overload) associated with higher maximal Q [5]. Subsequently, Lalande et al. observed that the individuals with the highest VO_2max had the greatest pulmonary vascular reserve, in this study defined as greater arteriolar distensibility α and capillary bed volume along with lowest PVR at maximum exercise [6]. Following these observations, Pavelescu et al. reviewed diffusion capacity measurements and echocardiographic measurements of the pulmonary circulation in a larger number of healthy subjects and confirmed that better aerobic exercise capacity is associated with lower PVR and higher lung diffusing capacity allowing for lower exercise ventilation [7].

Taken together, all those observations strongly suggest that exercise capacity is modulated by the functional state of the pulmonary circulation. A great pulmonary vascular reserve is therefore an advantage in endurance athletic performance especially when exercise is performed at extreme cardiac output levels. However, when or why pulmonary vascular reserve may allow for a higher aerobic exercise capacity is still incompletely described.

6. Influences of pulmonary vascular reserve

It is well-known that interindividual pulmonary vascular response to exercise varies considerably. Beyond that, different factors have been identified to influence the pulmonary vascular reserve such as body position, sex, race, age, and environmental factors.

6.1 Body position

Pulmonary vascular response to exercise testing is either performed in a supine position during catheterization or in a semi-recumbent position during stress echocardiography, while exercise testing is usually performed in a sitting or upright position. Invasive studies previously reported a lower resting PVR in the recumbent position compared with upright position explained by a vascular recruitment when venous return is increased with gravity [49]. However, the authors observed that differences faded and disappeared with exercise-induced cardiac output increase, because of vascular recruitment with pulmonary blood flow elevation. Accordingly, those observations have been confirmed recently by Forton et al. who compared maximal exercise testing in supine, semi-recumbent, and upright positions and showed no body position effect on PAP/Q relationships, alpha, and VO_2max [50].

Influence of posture [17] PAP rest supine (14.0 + −3.3 mmHg) versus upright (13.6 + −3.1 mmHg)

6.2 Race and sex

Racial differences have been suspected to influence pulmonary vascular reserve as black African Americans compared to white Americans of European descent are

known to have higher prevalence of hypertension and higher mortality rates for most cardiovascular diseases [51]. Recently, Simaga et al. tested this hypothesis and showed an intrinsically less distensible pulmonary circulation in healthy black sub-Saharan African men as compared to healthy white Caucasians, and this was associated with a lower aerobic exercise capacity [52]. Lower DLNO and DLCO are also reported in Africans as compared to sex-, age-, and body size-matched Caucasians and are explained by racial-related smaller lungs proportionally to body size [53]. However, those racial differences in pulmonary vascular function at exercise did not appear when women were compared [52]. This latest observation is in keeping with previous studies showing that premenopausal women have a more distensible pulmonary circulation with a coefficient of distensibility α up to 45% higher compared to age-matched men [23]. The underlying explanation is not clearly established but might be related to the hormonal context.

6.3 Aging

Exercise capacity decreases with aging, as does the pulmonary vascular reserve. Invasive measurements have previously showed that a reduction in pulmonary microvascular distensibility occurs with age [17, 24]. Consistently, La Gerche et al. noticed that individuals with low PTAC were older than those with positive PTAC [5]. More recently, Argiento et al. confirmed this aging effect observation with noninvasive echocardiographic measurements and showed that while maximal cardiac output was reduced in fifties or older individuals, PAP and PVR were higher with a lower alpha at maximal exercise [23].

Influence of age [17] PAP <30 (12.8 + −3.1 mmHg) versus 30–50 (12.9 + −3.0 mmHg) versus > 50 years (14.7 + −4.0).

6.4 Growth

Aerobic capacity increases gradually with age during childhood and adolescence. The kinetics of this evolution differs in girls and boys related to pubertal hormonal changes reaching a peak in VO_2max earlier in girls compared to boys. However, previous studies showed that VO_2max is not so much a matter of age when VO_2max is corrected by body weight [54, 55].

On the other hand, the maximal workload, endurance time, and maximum average running speed increase continuously with age attesting the complexity of the relations between VO_2 at exercise, weight or body dimensions, and the mechanical performance of muscular work [56].

The progression of endurance time and load at a given VO_2 with age is multifactorial and includes neuromuscular adaptations, movement technique, musculotendinous elastic energy storage, surface vs. weight ratio, body temperature, energy substrates use, and ventilatory response. Indeed, the VE/VCO_2 slope decreases with age reflecting a more efficient ventilatory response during exercise. This has been attributed to chemosensitivity maturation with age [54, 57]. Concomitantly, it is also known that diffusion capacity of DLCO and DLNO increases during adolescence. The link between these two observations remains to be clarified as the DLCO and DLNO increase has previously been mainly attributed to increase in height [58].

Experiments from our exercise laboratory on heathy adolescents show that pulmonary arterial distensibility and chemosensitivity decrease with growth, while maximal Q, RV function and diffusion capacity increase in relation to increased aerobic exercise capacity.

Taken together, the aforementioned findings suggest that the different components of the RV- pulmonary circulation unit are mature at different times. Creating

a probable optimal pulmonary vascular reserve and exercise capacity at adulthood but declining further with aging.

6.5 Pollution

Finally, some environmental factors have also been identified as potential pulmonary circulation stressors, namely, altitude and pollution. It has recently been shown that an acute exposure of 2 h to a dilute diesel exhaust increased the pulmonary vasomotor tone by decreasing the distensibility of pulmonary resistive vessels at high cardiac output or high exercise intensities [59]. Further studies are needed for a better understanding of this phenomenon and to evaluate the long-term consequences of diesel exposure on exercise capacity.

6.6 Hypoxia

Increasing visitors and athletes are traveling to altitude but not without consequences on their physical condition. It has long been known that aerobic exercise capacity decreases exponentially with altitude ascent with a significant decline starting above 1000 m. Numerous studies have been conducted in the field, but the underlying mechanisms are until now not fully understood. Although causes might be multifactorial, decreased oxygen transport to the exercising muscle, with a decrease in arterial oxygenation (SpO_2) and an altered maximum $\dot{Q}$, is fingered [1, 2, 60].

6.6.1 Right ventricle

At high altitude, in resting conditions, signs of altered diastolic but preserved or enhanced systolic RV function have been described in chronic [61] or acute hypoxic conditions [62, 63]. RV seems thus to tolerate hypoxic conditions. However, a recent study showed inhomogeneous RV contraction in hypoxia but not during exercise, suggesting that hypoxic stress is not trivial [63]. How much this could account for altered RV maximal outflow remains unknown as studies on right ventricular function during hypoxic exercise are sorely lacking [64].

6.6.2 Pulmonary circulation

Since the pioneer study of Von Euler and Liljestrand in 1946 that when airways are exposed to hypoxic air, a local vasoconstrictive reflex modifies the lung perfusion in favor of better oxygenated alveoli [65]. This hypoxic pulmonary vasoconstriction (HPV) is a protective mechanism allowing for substantial improvement in arterial oxygenation [66]. However, at altitude, when the entire lung is hypoxic, a global arteriolar vasoconstriction reduces the pulmonary vascular distensibility and increases the PVR. The subsequent hypoxic pulmonary hypertension is generally mild to moderate [64]. However, during exercise, this substantial increased afterload on the right ventricle might become substantial [64]. Hypoxia may therefore affect the pulmonary vascular reserve with increased likelihood of RV function limitation and/or altered gas exchange by interstitial pulmonary edema or ventilation/perfusion mismatch. How much this accounts for aerobic exercise capacity limitation at high altitude is still a matter of debate.

This last decade, a partial recovery of 10–25% of the hypoxia-induced decrease in maximal oxygen uptake has been reported with intake-specific pulmonary vasodilating interventions [67–72]. Indeed, specific pulmonary vasodilating interventions have been reported to improve the decreased aerobic exercise capacity in

hypoxia with little or no effect on normoxic exercise performance. Primary studies described an increase in maximal workload and VO_2max after intake of sildenafil, a phosphodiesterase-5 inhibitor used to treat erectile dysfunction in healthy hypoxic subjects [9, 67–69]. It has been suggested that the underlying mechanism was an increase maximal Q due to a reduced RV afterload after HPV inhibition or pulmonary vasodilation. Similar results were reported after administration of dexamethasone [70] or endothelin receptor blockers [71, 72]. In most of these studies, pulmonary vasodilation effect was also associated with improved arterial oxygenation probably allowing improved oxygen transport to the exercising muscles [69, 73]. De Bisschop et al. showed that pharmacological pulmonary vasodilation improved lung diffusion capacity and also correlated to enhanced exercise capacity at high altitude [74]. The principal suggested underlying mechanisms was related to a pulmonary vasodilation associated decrease in capillary filtration pressure protecting from an interstitial lung edema [74].

6.6.3 Lung diffusion capacity

Acute or chronic hypoxic exposure is associated with enhanced pulmonary diffusion capacity at rest [7, 75, 76]. Moreover, the hypoxia-induced increase in the capillary component being more pronounced than the membrane component suggests a capillary distension in addition to recruitment. This observation has been attributed to increased pulmonary perfusion pressure caused by HPV associated with a venous component of hypoxic vasoconstriction both possibly contributing to increase effective capillary pressure [77].

Interestingly, Taylor et al. showed that recruitment of pulmonary capillaries in response to exercise at high altitude is limited and may therefore be a significant source of exercise limitation [78]. This is keeping with previous correlation found between lung diffusing capacity for nitric oxide (DL_{NO}) and VO_2max at altitude [7, 8, 74].

6.6.4 Pulmonary vascular reserve

The reviewing of data collected during four different high-altitude expeditions (>4350 m) highlighted that individuals with a larger increase in PVR and larger decreased ventilation efficacity with ascent to high altitude were the ones with the greater VO_2max fall [7]. Higher aerobic capacity at high altitude was associated with more pronounced pulmonary vascular reserve as suggested by lower PVR, higher diffusion capacity, and lower VE/VCO_2 [7]. Similarly, pulmonary vascular reserve has been described as an aerobic performance limiting factor in Andean or Himalayan highlanders [10, 79]. This observation has also been confirmed at moderate altitude, even though the overwhelming determinant of decreased VO_2max and maximum workload is a decrease in arterial O_2 content CaO_2 [8].

7. Conclusion

In conclusion, aerobic exercise capacity is depending on the integrity of the different components of the oxygen transfer from ambient air to the mitochondrial cytochromes. The RV function coupling to the pulmonary circulation and the pulmonary capillary network is one of multiple determinants of aerobic exercise capacity. It becomes increasingly clear that a high pulmonary vascular reserve is an advantage for high-intensity exercise performance in heathy subjects. The pulmonary vascular reserve is characterized by lower exercise PAP and PVR and higher

pulmonary vascular distensibility associated with greater capillary volume and gas exchange allowing for a lower ventilatory cost at a given metabolic rate. When and how the pulmonary vascular reserve modulates aerobic capacity still need to be clarified. However, age, race, sex, and environmental factors such as pollution and hypoxia have been identified as pulmonary vascular reserve influencers.

Author details

Vitalie Faoro* and Kevin Forton
Cardio-Pulmonary Exercise Laboratory, Université Libre de Bruxelles, Belgium

*Address all correspondence to: vfaoro@ulb.ac.be

References

[1] Wagner PD. New ideas on limitations to VO_2max. Exercise and Sport Sciences Reviews. 2000;**28**(1):10-14

[2] Calbet JA, Boushel R, Radegran G, Sondergaard H, Wagner PD, Saltin B. Determinants of maximal oxygen uptake in severe acute hypoxia. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2003;**284**:R291-R303

[3] La Gerche A, Rakhit DJ, Claessen G. Exercise and the right ventricle: A potential Achilles' heel. Cardiovascular Research. 2017;**113**(12):1499-1508

[4] Stembridge M, Ainslie PN, Shave R. Mechanisms underlying reductions in stroke volume at rest and during exercise at high altitude. European Journal of Sport Science. 2016;**16**(5):577-584

[5] La Gerche A, MacIsaac AI, Burns AT, et al. Pulmonary transit of agitated contrast is associated with enhanced pulmonary vascular reserve and right ventricular function during exercise. Journal of Applied Physiology. 2010;**109**(5):1307-1317

[6] Lalande S, Yerly P, Faoro V, Naeije R. Pulmonary vascular distensibility predicts aerobic capacity in healthy individuals. The Journal of Physiology. 2012;**590**(17):4279

[7] Pavelescu A, Faoro V, Guenard H, de Bisschop C, Martinot JB, Mélot C, et al. Pulmonary vascular reserve and exercise capacity at sea level and at high altitude. High Altitude Medicine and Biology. 2013;**14**(1):19-26

[8] Faoro V, Deboeck G, Vicenzi M, Gaston AF, Simaga B, Doucende G, et al. Pulmonary vascular function and aerobic exercise capacity at moderate altitude. Medicine and Science in Sports and Exercise. 2017;**49**(10):2131-2138

[9] Ghofrani HA, Reichenberger F, Kohstall MG, Mrosek EH, Seeger T, Olschewski H, et al. Sildenafil increased exercise capacity during hypoxia at low altitudes and at Mount Everest Base camp. Annals of Internal Medicine. 2004;**141**:169-177

[10] Faoro V, Huez S, Vanderpool R, Groepenhoff H, de Bisschop C, Martinot JB, et al. Pulmonary circulation and gas exchange at exercise in Sherpas at high altitude. The Journal of Applied Physiology. 2014;**116**(7):919-926

[11] Champion HC, Michelakis ED, Hassoun PM. Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit: State of the art and clinical and research implications. Circulation. 2009;**120**:992-1007

[12] La Gerche A, Heidbüchel H, Burns AT, Mooney DJ, Taylor AJ, Pfluger HB, et al. Disproportionate exercise load and remodeling of the athlete's right ventricle. Medicine and Science in Sports and Exercise. 2011;**43**:974-981

[13] D'Alto M, Pavelescu A, Argiento P, Romeo E, Correra A, Di Marco GM, et al. Echocardiographic assessment of right ventricular contractile reserve in healthy subjects. Echocardiography. 2017;**34**(1):61-68

[14] Reeves JT, Dempsey JA, Grover RF. Pulmonary circulation during exercise. In: Weir EK, Reeves JT, editors. Pulmonary Vascular Physiology and Physiopathology. New York, NY: Marcel Dekker; 1989. pp. 107-133

[15] Bossone E, Rubenfire M, Bach DS, Ricciardi M, Armstrong WF. Range of tricuspid regurgitation velocity at rest

and during exercise in normal adult men: Implications for the diagnosis of pulmonary hypertension. Journal of the American College of Cardiology. 1999;**33**:1662-1666

[16] Argiento P, Chesler N, Mule M, D'Alto M, Bossone E, Unger P, et al. Exercise stress echocardiography for the study of the pulmonary circulation. The European Respiratory Journal. 2010;**35**:1273-1278

[17] Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: A systematic review. The European Respiratory Journal. 2009;**34**(4):888-894

[18] Pinsky MR. The right ventricle: Interaction with the pulmonary circulation. Critical Care. 2016;**20**:266

[19] Hanson WL, Emhardt JD, Bartek JP, Latham LP, Checkley LL, Capen RL, et al. Site of recruitment in the pulmonary microcirculation. Journal of Applied Physiology. 1989;**66**:2079-2083

[20] Presson RG Jr, Baumgartner WA Jr, Peterson AJ, Glenny RW, Wagner WW Jr. Pulmonary capillaries are recruited during pulsatile flow. Journal of Applied Physiology. 2002;**92**:1183-1190

[21] Rosenzweig DY, Hughes JM, Glazier JB. Effects of transpulmonary and vascular pressures on pulmonary blood volume in isolated lung. Journal of Applied Physiology. 1970;**28**:553-560

[22] Naeije R, Chesler N. Pulmonary circulation at exercise. Comprehensive Physiology. 2012;**2**(1):711-741

[23] Argiento P, Vanderpool RR, Mule M, et al. Exercise stress echocardiography of the pulmonary circulation: Limits of normal and sex differences. Chest. 2012;**590**:4279-4288

[24] Reeves JT, Linehan JH, Stenmark KR. Distensibility of the normal human lung circulation during exercise. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2005;**288**:L419-L425

[25] Claessen G, La Gerche A, Wielandts JY, Bogaert J, Van Cleemput J, Wuyts W, et al. Exercise pathophysiology and sildenafil effects in chronic thromboembolic pulmonary hypertension. Heart. 2015;**101**(8):637-644

[26] Linehan JH, Haworth ST, Nelin LD, Krenz GS, Dawson CA. A simple distensible vessel model for interpreting pulmonary vascular pressure-flow curves. Journal of Applied Physiology. 1992;**73**:987-994

[27] Krenz GS, Dawson CA. Flow and pressure distributions in vascular networks consisting of distensible vessels. American Journal of Physiology. Heart and Circulatory Physiology. 2003;**284**:H2192-H2203

[28] Cope DK, Grimbert F, Downey JM, Taylor AE. Pulmonary capillary pressure: A review. Critical Care Medicine. 1992;**20**:1043-1056

[29] Eldrige MW, Dempsey JA, Haverkamp HC, Lovering AT, Hokanson JS. Exercise-induced intrapulmonary arteriovenous shunting in healthy humans? Journal of Applied Physiology. 2004:797-805

[30] Stickland MK, Welsh RC, Haykowsky MJ, Petersen SR, Anderson WD, Taylor DA, et al. Intra-pulmonary shunt and pulmonary gas exchange during exercise in humans. The Journal of Physiology. 2004;**561**:321-329

[31] Hopkins SR, Olfert IM, Wagner PD. Point: Exercise-induced intrapulmonary shunting is imaginary. Journal of Applied Physiology. 2009;**107**:993-994

[32] Lovering AT, Eldridge MW, Stickland MK. Counterpoint: Exercise-induced intrapulmonary shunting is real. Journal of Applied Physiology. 2009;**107**:994-997

[33] Naeije R, Faoro V. Pathophysiological insight into shunted bubbles. Journal of Applied Physiology. 2009;**107**(3):999-1000

[34] West JB, Tsukimoto K, Mathieu-Costello O, Prediletto R. Stress failure in pulmonary capillaries. Journal of Applied Physiology (Bethesda Md):1985. 1991;**70**(4):1731-1742

[35] West JB, Mathieu-Costello O. Stress failure of pulmonary capillaries as a limiting factor for maximal exercise. European Journal of Applied Physiology. 1995;**70**(2):99-108

[36] Prefaut C, Durand F, Mucci P, Caillaud C. Exercise-induced arterial hypoxaemia in athletes: A review. Sports medicine (Auckland, N.Z.). 2000;**30**(1):47-61

[37] Roughton FJ, Forster RE. Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. Journal of Applied Physiology. 1957;**11**:290-302

[38] Guénard H, Varene N, Vaida P. Determination of lung capillary blood volume and membrane diffusing capacity in man by the measurements of NO and CO transfer. Respiratory Physiology. 1987;**70**:113-120

[39] Johnson RL Jr, Spicer WS, Bishop JM, Forster RE. Pulmonary capillary blood volume, flow and diffusing capacity during exercise. Journal of Applied Physiology. 1960;**15**:893-902

[40] Glenet SN, De Bisschop C, Vargas F, Guénard HJ. Deciphering the nitric oxide to carbon monoxide lung transfer ratio: Physiological implications. The Journal of Physiology. 2007;**582**:767-775

[41] Hsia CC, McBrayer DG, Ramanathan M. Reference values of pulmonary diffusing capacity during exercise by a rebreathing technique. American Journal of Respiratory and Critical Care Medicine. 1995;**152**:658-665

[42] Tamhane RM, Johnson RL Jr, Hsia CC. Pulmonary membrane diffusing capacity and capillary blood volume measured during exercise from nitric oxide uptake. Chest. 2001;**120**(6):1850-1856

[43] Zavorsky GS, Quiron KB, Massarelli PS, Lands LC. The relationship between single-breath diffusion capacity of the lung for nitric oxide and carbon monoxide during various exercise intensities. Chest. 2004;**125**(3):1019-1027

[44] Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO_2 and VE/VCO_2 slope in patients with heart failure: A prognostic comparison. American Heart Journal. 2004;**147**(2):354-360

[45] Deboeck G, Niset G, Lamotte M, Vachiéry JL, Naeije R. Exercise testing in pulmonary arterial hypertension and in chronic heart failure. The European Respiratory Journal. 2004;**23**(5):747-751

[46] Martin BJ, Sparks KE, Zwillich CW, Weil JV. Low exercise ventilation in endurance athletes. Medicine and Science in Sports. 1979;**11**(2):181-185

[47] Dempsey JA, Reddan WG, Birnbaum ML, Forster HV, Thoden JS, Grover R, et al. Effects of acute through life-long hypoxic exposure on exercise pulmonary gas exchange. Respiration Physiology. 1971;**13**:62-89

[48] West JB. Fragility of pulmonary capillaries. Journal of Applied Physiology. 2013;**115**:1-15

[49] Reeves JT, Taylor AE. Pulmonary hemodynamics and fluid exchange in the lungs at exercise. Handbook of Physiology. 1999; Section 12:585-613

[50] Forton K, Motoji Y, Deboeck G, Faoro V, Naeije R. Effects of body position on exercise capacity and pulmonary vascular pressure-flow relationships. Journal of Applied Physiology. 2016;**121**(5):1145-1150

[51] Jones DW, Hall JE. Racial and ethnic differences in blood pressure. Biology and Sociology. Circulation. 2006;**114**:2757-2759

[52] Simaga B, Vicenzi M, Faoro V, Caravita S, Di Marco G, Forton K, et al. Pulmonary vascular function and exercise capacity in black sub-Saharan Africans. Journal of Applied Physiology. 2015;**119**(5):502-507

[53] Simaga B, Forton K, Motoji Y, Naeije R, Faoro V. Lung diffusing capacity in sub-Saharan Africans versus European Caucasians. Respiratory Physiology and Neurobiology. 2017;**241**:23-27

[54] Ten Harkel AD, Takken T, Van Osch-Gevers M, Helbing W. Normal values for cardiopulmonary exercise testing in children. European Journal of Cardiovascular Prevention and Rehabilitation. 2011;**18**:48-54

[55] Tavares AC, Bocchi EA, Teixeira-Neto IS, Guimarães GV. A meta-analysis of cardiopulmonary exercise testing in pre-pubertal healthy children produces new information. Medical Express. 2016;**3**(1):1-9

[56] Cooper DM, Leu SY, Galassetti P, Radom-Aizik S. Dynamic interactions of gas exchange, body mass, and progressive exercise in children. Medicine and Science in Sports and Exercise. 2014;**46**:877-886

[57] Parazzi P, Marson F, Ribeiro M, Schivinski C, Ribeiro J. Ventilatory efficiency in children and adolescents: A systematic review. Disease Markers. 2015;**1**:1-10

[58] Thomas A, Hanel B, Marott JL, Buchvald F, Mortensen J, et al. The single-breath diffusing capacity of CO and NO in healthy children of European descent. PLoS One. 2014;**9**(12):e113177

[59] Wauters A, Vicenzi M, De Becker B, Riga JP, Esmaeilzadeh F, Faoro V, et al. At high cardiac output, diesel exhaust exposure increases pulmonary vascular resistance and decreases distensibility of pulmonary resistive vessels. American Journal of Physiology. Heart and Circulatory Physiology. 2015;**309**(12):H2137-H2144

[60] Fulco CS, Rock PB, Cymerman A. Maximal and submaximal exercise performance at altitude. Aviation, Space, and Environmental Medicine. 1998;**69**(8):793-801

[61] Huez S, Faoro V, Guénard H, Martinot JB, Naeije R. Echocardiographic and tissue Doppler imaging of cardiac adaptation to high altitude in native highlanders versus acclimatized lowlanders. The American Journal of Cardiology. 2009;**103**:1605-1609

[62] Netzer NC, Strohl KP, Högel J, Gatterer H, Schilz R. Right ventricle dimensions and function in response to acute hypoxia in healthy human subjects. Acta Physiologica. 2017;**219**(2):478-485

[63] Pezzuto B, Forton K, Badagliacca R, Motoji Y, Faoro V, Naeije R. Right ventricular dyssynchrony during hypoxic breathing but not during exercise in healthy subjects: A speckle tracking echocardiography

study. Experimental Physiology. 2018;**103**(10):1338-1346

[64] Naeije R, Dedobbeleer C. Pulmonary hypertension and the right ventricle in hypoxia. Experimental Physiology. 2013;**98**(8):1247-1256

[65] Von Euler US, Liljestrand G. Observations on the pulmonary arterial blood pressure in the cat. Acta Physiologica Scandinavica. 1946;**12**:301-320

[66] Brimioulle S, Julien V, Gust R, Kozlowski JK, Naeije R, Schuster DP. Importance of hypoxic vasoconstriction in maintaining oxygenation during acute lung injury. Critical Care Medicine. 2002;**30**(4):874-880

[67] Richalet JP, Gratadour P, Robach P, Pham I, Dechaux M, Joncquirt-Latarjet A, et al. Sildenafil inhibits altitude-induced hypoxemia and pulmonary hypertension. American Journal of Respiratory and Critical Care Medicine. 2005;**171**:275-281

[68] Hsu AR, Barnholt KE, Grundmann NK, Lin JH, McCullum SW, Friedlander AL. Sildenafil improves cardiac output and exercise performance during acute hypoxia, but not normoxia. Journal of Applied Physiology. 2006, 2006;**100**:2031-2040

[69] Faoro V, Lamotte M, Deboeck G, Pavelescu A, Huez S, Guenard H, et al. Effects of sildenafil on exercise capacity in hypoxic normal subjects. High Altitude Medicine and Biology. 2007;**8**:155-163

[70] Fischler M, Maggiorini M, Dorschner L, Debrunner J, Bernheim A, Kiencke S, et al. Dexamethasone but not tadalafil improves exercise capacity in adults prone to high altitude pulmonary edema. American Journal of Respiratory and Critical Care Medicine. 2009;**180**:346-352

[71] Faoro V, Boldingh S, Moreels M, Martinez S, Lamotte M, Unger P, et al. Bosentan decreases pulmonary vascular resistance and improves exercise capacity in acute hypoxia. Chest. 2009;**135**:1215-1222

[72] Naeije R, Huez S, Lamotte M, Retailleau K, Neupane S, Abramowicz D, et al. Pulmonary artery pressure limits exercise capacity at high altitudes. The European Respiratory Journal. 2010;**36**:1049-1055

[73] Olfert IM, Loeckinger A, Treml B, Faulhaber M, Flatz M, Burtscher M, et al. Sildenafil and bosentan improve arterial oxygenation during acute hypoxic exercise: A controlled laboratory trial. Wilderness and Environmental Medicine. 2011;**22**:211-221

[74] de Bisschop C, Martinot JB, Leurquin-Sterk FV, Guenard H, Naeije R. Improvement in lung diffusion by endothelin a receptor blockade at high altitude. Journal of Applied Physiology. 2011;**112**(1):20-25

[75] Snyder EM, Olson TP, Johnson BD, Frantz RP. Influence of sildenafil on lung diffusion during exposure to acute hypoxia at rest and during exercise in healthy humans. European Journal of Applied Physiology. 2008;**103**(4):421-430

[76] Agostoni P, Swenson ER, Bussotti M, Revera M, Meriggi P, Faini A, et al. High-altitude exposure of three weeks duration increases lung diffusing capacity in humans. Journal of Applied Physiology. 2011;**110**(6):1564-1571

[77] Maggiorini M, Mélot C, Pierre S, Pfeiffer F, Greve I, Sartori C, et al. High altitude pulmonary edema is initially caused by an increased capillary pressure. Circulation. 2001;**103**:2078-2083

[78] Taylor BJ, Coffman KE, Summerfield DT, Issa AN, Kasak AJ, Johnson BD. Pulmonary capillary reserve and exercise capacity at high altitude in healthy humans. European Journal of Applied Physiology. 2016;**116**(2):427-437

[79] Groepenhoff H, Overbeek MJ, Mulè M, van der Plas M, Argiento P, Villafuerte FC, et al. Exercise pathophysiology in patients with chronic mountain sickness exercise in chronic mountain sickness. Chest. 2012;**142**(4):877-884