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Pulmonary vascular resistance
A meaningless variable?

Introduction

Almost 20 years ago, Adriaan Versprille published an editorial in this journal to explain why, in his opinion, the calculation of pulmonary vascular resistance (PVR) is meaningless [1]. The uncertainties of PVR were underscored a year later by McGregor and Sniderman in the American Journal of Cardiology [2]. Obviously, both papers failed to convince. A Medline search from 1985 to the end of 2002 reveals no less than 7,158 papers with PVR calculations. What is it that could be wrong in all this literature?

What is a resistance calculation?

A resistance calculation derives from a physical law first developed by the French physiologist Poiseuille in the early nineteenth century. Poiseuille invented the U-tube mercury manometer. He used the device to show that blood pressure does not decrease from large to small arteries to the then existing limit of cannula size of about 2 mm, and rightly concluded that the site of systemic vascular resistance could only be at smaller-sized vessels [3]. Since he could not penetrate to these minute vessels, he used small size glass tubes to investigate the determinants of resistance. Numerous painstaking measurements of pressures at variable continuous streamlined flows of Newtonian and non-Newtonian fluids of different viscosities, through variable dimension capillary glass tubes, led to what is presently known as Poiseuille’s law. It states that the resistance $R$ to flow, defined as a pressure drop ($\Delta P$) to flow ($Q$) ratio, is equal to the product of the length ($l$) of the tube by a viscosity constant ($\eta$) divided by the product of fourth power of the internal radius ($r$) by $\pi$:

$$R = \frac{\Delta P}{Q} = \frac{8 \cdot \eta}{\pi \cdot r^4}$$

A remarkable feature of Poiseuille’s resistance equation is its exquisite sensibility to changes in internal radius $r$, because it is at the fourth power.

Transposition to the pulmonary circulation

The transposition of Poiseuille’s law to the pulmonary circulation rests on the invalid assumptions that blood is a Newtonian fluid (that is with a velocity-independent viscosity), that the pulmonary resistive vessels are unbranched small rigid tubes of circular surface sections and that pulmonary blood flow is streamlined and non-pulsatile. But the approximations have less impact on calculated PVR values than the internal arteriolar radius, to which the Poiseuille’s resistance variable is so sensitive. Accordingly, it is reasonable to calculate PVR as the ratio of the pressure drop through the pulmonary circulation [mean pulmonary artery pressure (Ppa) minus left atrial pressure (Pla)] to pulmonary blood flow ($Q$) using the electrical principles described as Ohm’s law:

$$PVR = \frac{(Ppa - Pla)}{Q}$$

The resulting PVR value is a valid indicator of structural changes at the small resistive pulmonary arteriole level,
Pulmonary vascular pressure-flow relationships

However, PVR is flow-sensitive and this can be a source of confusion. The Ohm’s law resistance equation of pressure drop divided by flow implies that the (inflow minus outflow) pressure difference as a function of flow is linear and crosses the origin. If correct, resistance would be independent of either flow or pressure (Fig. 1). A PVR calculation assumes that if one were to increase Ppa and examine the resultant Ppa/Q relationship, it would display an extrapolated pressure axis intercept at a value equal to Pla. This assumption appears valid in well-oxygenated healthy lungs. Accordingly, normal healthy lungs appear to be fully recruited and maximally distended. Also, in intact animal models, progressive decreases in pulmonary vascular pressures with their associated decreasing flow do not induce a systemic baroreflex, thus changes in pulmonary sympathetic vasomotor tone is constant over a wide range of pulmonary arterial pressures and flow. However, hypoxia and many cardiac and respiratory diseases increase both the slope (PVR) and the extrapolated intercepts of multipoint (Ppa–Pla)/Q plots. Importantly, these pulmonary vascular pressure-flow relations still tend to remain linear over a physiological range of flows [2].

How is it possible that the extrapolated pressure intercepts of (Ppa–Pla)/Q plots are positive, meaning that the apparent back-flow pressure for pulmonary blood flow exceeds Pla? A possible answer is that pulmonary vessels are collapsible. Consider a circulatory system made of two rigid tubes connected by a collapsible tube surrounded by a pressure chamber (Fig. 1). This model is called the “Starling resistor”, because Starling used such a device in his heart-lung preparation to control arterial blood pressure. If the outflow pressure (Pla) is higher than the chamber pressure (Pc), then several aspects of the circulation exist. First, flow starts when the inflow pressure (Ppa) is higher than Pla and it increases linearly with the increase in the Ppa–Pla difference. Second, the (Ppa–Pla)/Q line crosses the origin. And third, PVR, the slope of the (Ppa–Pla)/Q relationship, is constant. If the Pc is higher than Pla, however, then flow starts when Ppa is higher than Pc, independent of the lower Pla value, and flow increases linearly with the increase in (Ppa–Pc). The Pc is also referred to as the closing pressure, because when intraluminal pressure decreases below Pc, the vessels collapse and flow ceases. Importantly, both the (Ppa–Pla)/Q line has a positive extrapolated intercept that is equal to Pla and PVR decreases with increasing flow. If either alveolar pressure or pulmonary vascular tone are increased enough to cause vascular collapse at values above Pla, then these conditions will also exist in vivo.

Permutt et al. conceived a vascular waterfall model made of parallel collapsible vessels with a distribution of closing pressures [4]. At low flow, these vessels would be progressively derecruited, accounting for a low flow Ppa/Q curve that is concave to the flow axis and intercepts the pressure axis at the lowest closing pressure to be overcome to generate a flow. At higher flows, completed recruitment and negligible distension account for a linear Ppa/Q curve with an extrapolated pressure intercept representing a weighted mean of all the parallel circuit Pc values. In this model, the mean Pc is the effective outflow pressure of the pulmonary circulation. A Pla lower than the mean Pc is then only an apparent downstream pressure, irrelevant to flow as is the height of a waterfall. Resistance calculations remain applicable to evaluate the functional state of the pulmonary circulation even in these conditions, provided that the apparent downstream pressure (Pla) is replaced by the effective one (Pc).

But pulmonary vessels are also distensible. Accordingly, pulmonary circulation models have been developed that explain Ppa/Q relationships by a distribution of both resistances and compliances [5]. Positive extrapolated pressure intercepts of (Ppa–Pla)/Q plots can be predicted by concomitant increases in resistance and compliance of small resistive vessels [6]. Intuitively, one would rather imagine constricted vessels to be stiffer. However, it has been shown experimentally that con-
stricted arterioles become more distensible, probably because decreased surface section area places them on the steeper portion of the dimension-pressure curve.

In reality, provided a large enough number of Ppa/Q coordinates are generated and submitted to an adequate fitting procedure, Ppa/Q curves can always be shown to be curvilinear with concavity to the flow axis [7]. On the other hand, derecruitment can be directly observed at low pressures and flows. Both recruitment and distension probably explain most of the Ppa/Q curves. According to this integrated view, at low inflow pressures many pulmonary vessels are closed as their intrinsic tone and surrounding alveolar pressure exceed intraluminal pressure and those that are open are relatively narrow. As inflow pressure increases, previously closed vessels progressively open (recruitment) and previously narrow vessels progressively dilate (distension). Both mechanisms explain a progressive decrease in the slope of pulmonary vascular pressure/flow relationships (resistance) with increasing flow or pressure and account for apparent functional dissociation between Ppa and Q as reported, for example, in the acute respiratory distress syndrome [8].

A pressure/flow diagram to avoid errors based on isolated pulmonary vascular resistance calculations

As illustrated in Fig. 1, PVR calculations can give misleading information under conditions of changing cardiac output. Vasomotor tone in subjects with pulmonary hypertension may appear to be either increasing or decreasing while, in fact, the functional state of the pulmonary circulation remains unchanged. In his original physiological note on this topic 17 years ago Versprille apologized to the clinicians for not being able to offer an alternative solution while pointing at the limitations of PVR measures [1]. However, PVR measures are similar to other composite variables in having inherent limitations. Systemic vascular resistance carries similar limitations and for related reasons. Importantly, when assessing pulmonary vasomotor tone, measurements of primary variables always minimize the inherent inaccuracies of calculating derived measurements. For example, in pulmonary hemodynamic studies, directly measured pressures and pulmonary blood flow can be plotted on a pressure/flow diagram (Fig. 2).

On such a diagram, connecting the central starting point C to the origin defines PVR. However, a closing pressure Pc higher than the apparent outflow pressure Pla is possible, which causes the pressure/flow line drawn from point C to cross the pressure axis at increasing pressures up to a maximum corresponding to a horizontal line. It is indeed physically impossible that (Ppa–Pc) would decrease at increasing flow. On the other hand, a (Ppa–Pla)/Q line cannot cross the pressure axis at a negative pressure in the absence of a change in vasomotor tone. The (Ppa–Pla)/Q line and the line of maximum possible Pc at an actually measured initial point C determine a series of areas on the pressure/flow diagram. At increasing flow, any decrease in (Ppa–Pla) can only be vasodilation. At decreasing flow, any increase in (Ppa–Pla) can only be vasoconstriction. In addition, a decrease in (Ppa–Pla) at decreasing flow that is more than predicted by the initial PVR equation can only be vasodilatation. An increase in (Ppa–Pla) more than predicted by the initial PVR equation can only be vasoconstriction. As shown in Fig. 2, zones of uncertainties remain because the actual value of closing pressure is not known. An additional uncertainty is related to the assumption that the pressure/flow coordinates are best described by a linear approximation, but this is generally reasonable in the absence of extreme changes in flow.

Improved definition of pulmonary vascular resistance by a multipoint pulmonary vascular pressure/flow plot

Still, the resistive properties of the pulmonary circulation are best defined by the measurement of pulmonary vascular pressures at several levels of flow. The problem is to increase or to decrease flow with interventions that do not affect vascular tone. Exercise changes cardiac output but may lead to spuriously increased slopes with Ppa/Q plots [9]. This is probably due to exercise-induced pulmonary vasoconstriction, because of a decrease in mixed venous PO2, sympathetic nervous system activation and
exercise-associated increase in left atrial pressure. A better option may be to increase flow by an infusion of low dose dobutamine. There is experimental evidence that dobutamine has no effect on pulmonary vascular tone doses below 10 µg/kg per min [10].

**Conclusions**

The calculation of PVR is sensitive to pulmonary arteriolar tone and dimensions, but can be misleading when used to assess the functional state of the pulmonary circulation at increased or decreased cardiac output. In case of doubt, pulmonary hemodynamic determinations are better interpreted with the help of a pressure/flow diagram. The ideal is to define PVR using a multipoint pulmonary vascular pressure/flow plot.

**References**