Pediatr Cardiol (2011) 32:557–561
DOI 10.1007/s00246-011-9954-3

REVIEW ARTICLE

Pulmonary Vascular Resistance and Viscosity: The Forgotten Factor

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Received: 28 January 2011 / Accepted: 10 March 2011 / Published online: 25 March 2011

Abstract Calculating pulmonary vascular resistance is important in many fields of medicine. Although the influence of hematocrit on calculated resistance has been known for many years, it is rare to find the appropriate corrections in published articles. This review discusses the relationship between viscosity and resistance and shows how the effect of viscosity can be allowed for by calculating hindrance or relative viscosity.

Keywords Vascular resistance · Vascular hindrance · Blood viscosity

Introduction

Studies of pulmonary hypertension measure pulmonary arterial pressures and blood flows and then calculate pulmonary vascular resistance, an essential component of the underlying mechanisms. After reading many articles in this field, I remain astonished that so few of them consider the effect of changes in hematocrit on pulmonary vascular resistance.

The Resistance Concept

The concept of vascular resistance was taken from hydraulic and electrical engineering. The resistance is the ratio of the pressure (or voltage) decrease across a tube or vascular bed (or a wire) to the flow of fluid (current) through it. Thus (Eq. 1):

$$\text{Resistance} = \frac{P_1 - P_2}{F}, \tag{1}$$

where P_1 and P_2 are the upstream and downstream pressures, respectively, and F is flow.

As defined, resistance is a ratio of two measured quantities; to understand what controls resistance, we turn to the basic studies of Hagen and Poiseuille, who independently examined the steady laminar flow of Newtonian fluids through straight glass tubes. They described the relationship between pressure decrease and flow (resistance) as (Eq. 2):

$$\text{Resistance} = \left(\frac{8}{\Pi}\right)\left(\frac{l}{r^4}\right)\eta, \tag{2}$$

where l is tube length, r is tube radius, and η is viscosity.

Because a vascular bed has many tubes in parallel, we can modify this equation to be (Eq. 3):

$$\text{Resistance} = \left(\frac{8}{\Pi}\right)\left(\frac{l}{kr^4}\right)\eta, \tag{3}$$

where k is the number of parallel vessels. This is based on the electrical analogy of parallel circuits and has some confirmation in physiology [26]. The equation is presented in this way to show that resistance has three components: the first is a constant $8/\pi$; the second is a geometric component relating tube length, tube diameter, and numbers of tubes; and the third is viscosity. As the equation shows, increased pulmonary vascular resistance can be caused by (1) increased length of resistance vessels, which is seldom a factor, even with lung growth; (2) decreased radius of these vessels, which is the most common cause; (3) decreased number of resistance vessels, which may occur at times in

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Table 1 Comparison between glass tube and pulmonary vascular bed

Factor	Poiseuille tube	Lung
No. of tubes	One	Many
Wall	Rigid	Viscoelastic
Curvature of tube	None	Present
Cross-section	Circular	Often elliptical
Branching	None	Present
Ratio length to diameter	Large	Small
Tapering	None	Present
Internal surface	Smooth	Slightly rough
Fluid	Newtonian	Non-Newtonian
Flow	Steady	Pulsatile

various forms of congenital heart disease and some lung diseases; and increased viscosity, which occurs fairly frequently but is often disregarded. The conditions under which Hagen and Poiseuille made their measurements are not the same as those found in the body (Table 1).

Despite these many differences, pressure-flow relations in body segments are fairly well approximated by the Hagen–Poiseuille relationship. Endothelial roughness has little effect; the roughness is negligible in larger arteries, and in small vessels, where the roughness is substantial, the flow rate is too low for roughness to have much effect [32]. The elasticity of the vessel walls, the elliptical cross-section, the degree of tapering, and the amount of curvature are too slight to affect pressure-flow relations materially [3, 32]. Therefore, although blood is not a Newtonian fluid, this factor does not affect pressure-flow relations at normal flows and hematocrits beyond causing some slight curvature of the relationship [3, 5, 32]. These conclusions were substantiated in a detailed review of the subject by Roos [24].

Strictly speaking, resistance is a steady-state concept: The loss of energy across the tube is due entirely to frictional resistance. If the flow is pulsatile, then we refer to impedance, in which energy losses are also incurred relative to inertance (acceleration of the fluid) and capacitance (distension of the tubes). We can break down pulsatile flow components into different harmonics of the fundamental frequency. In the pulmonary vascular bed, >95% of energy is contained in the first six harmonics [22, 23]. In vascular beds, the steady state component, i.e., the resistance, accounts for most of the energy loss, and it takes only approximately 30% more energy to perfuse the lungs with pulsatile rather than steady flow. Therefore, for simplicity we use the resistance concept.

Viscosity and Its Effects

It is almost universal to find corrections for body size by calculating flows per square meter of body surface area, but seldom is any correction made for viscosity. One of the reasons for this might be that viscosity is seldom measured in clinical practice, and it is difficult to make accurate viscosity measurements in the living body. There is, however, literature relating to the physiological effects of viscosity, and a few selected studies will be discussed.

"Viscosity" refers to the resistance offered by a material's attempts to deform it. If a stress is applied to a fluid to make it flow, the relationship of stress to flow defines the viscosity of the fluid. In vitro, this is measured in a viscometer, initially performed by measuring the flow of the fluid through tubes but later, and more accurately, by a variety of other instruments, e.g., cone and plate instruments [6, 25]. One of the complicating factors is that viscosity measurements depend on the shear rates used. The unit of viscosity is the Poise (P), named after Poiseuille, which has units $1\ \mathrm{P} = 1\ \mathrm{g\ cm^{-1}\ s^{-1}}$ (= 1 dyne sec $\mathrm{cm^{-2}}$). In the International System of Units, the analogous unit is the Pascal second, and $10\ \mathrm{P} = 1\ \mathrm{Pa\ s} = 1\ \mathrm{kg\ m^{-1}\ s^{-1}}$. Most physiological fluids have viscosity <1 P, and these are usually measured in centipoises (cP) which are 1/100th of a Poise. Water has a viscosity at 25°C of almost exactly 1 cP. Frequently viscosities are measured relative to the viscosity of water. Serum has a relative viscosity of 1.2 with little variability except for increasing at low temperatures. Plasma viscosity is similar to that of serum but may be greater and more variable with changes in fibrinogen and globulin concentrations as seen in the well-known hyperviscosity syndrome in macroglobulinemia [11, 19]. Fibrinogen is important not only for its direct effect on plasma viscosity but also for inducing increased aggregation of red blood cells [18, 20]. Under most circumstances, however, variations in plasma viscosity have only a minor effect on whole-blood viscosity.

In vitro measurements of blood viscosity, however, are not useful in physiology because of many factors unique to living systems. The viscosity of whole blood will change with shear rate, deformability of red blood cells (which are decreased greatly by iron deficiency), the Fåhraeus–Lindquist effect [8] (in which the viscosity decreases in tubes 10–300 μm in diameter because the red blood cells move to the axis of the vessels with a sleeve of plasma between them and the vessel wall), and even the white blood cell count. On the whole, however, hematocrit plays a major role in changing the viscosity of whole blood.

One of the early classical in vivo experiments was performed on the isolated dog hind-limb by Whittaker and Winton [33], who compared the effects of changes in hematocrit on a glass viscometer and a canine hind-limb. They pointed out the difficulties and inconsistencies of the glass tube viscometer due to variable effects of flow rates and tube diameters. The hind-limb preparation, however, showed more consistency. There were linear pressure-flow

curves, and the slope of the curves (reflecting viscosity) decreased as hematocrit increased. Compared with plasma or blood with hematocrit <5%, normal blood has a relative viscosity of 2.2 (SD 0.2), which approximately doubles when hematocrit increases from 45 to 70%. They found the relationship between blood viscosity and hematocrit to be (Eq. 4):

$$\frac{\eta}{\eta_0} = \frac{k}{1-\phi^{\frac{1}{3}}}, \tag{4}$$

where η is the viscosity of blood with hematocrit φ, η_0 is the viscosity of plasma, and k is a factor related to blood pressure, which was usually constant at 0.6 unless pressures were extremely low. This formula was based on one derived from colloid science, which in turn is related to Einstein's equation for spheres in suspension [6]. Other similar expressions have been derived [6]. Similar experiments performed by Benis et al. [3] and by Levy and Share [17] under more controlled conditions confirmed these results.

How applicable is this information to the pulmonary circulation? Barer et al. [2] studied the effect of polycythemia induced in rats who breathed 10% oxygen for 3 weeks to simulate high altitude. Just as Whittaker and Winton saw in the canine hind limb, they observed linear pressure-flow relations in isolated perfused lungs. At a flow rate of 20 ml/min in isolated rat lungs, they found that pulmonary arterial pressure increased by 40% when hematocrit increased from 42 to 61% and, in another set of experiments, by 24% when hematocrit increased from 35 to 53%. They used a torque viscometer to measure viscosity in vitro of blood with hematocrits of 43.4% (SD 1.6%) and 62.2% (SD 2.2%). At a rate of 23 c/s, viscosity changed from 7.8 (SD 0.6) to 13.9 (SD 0.8) cP, and at a rate of 230 c/s it changed from 4.4 (SD 0.3) to 8.4 (SD 0.3) cP. They recognized that factors other than hematocrit affect pulmonary arterial pressures because these pressures were lower in controls compared with hypoxic rats, but in each group the effect of increased hematocrit in increasing pressure was similar. A further demonstration of the effect of hematocrit independent of the effects of hypoxic changes was that increased hematocrit in turn increased blood viscosity and mean pulmonary arterial pressure in normoxic rats whose red cell mass was increased by erythropoietin [34].

Hindrance

There are many times when knowing the hematocrit and making an allowance for apparent viscosity is important. One of the ways of doing this is to calculate the hindrance [9], which is defined as (Eq. 5):

$$\text{Hindrance} = \frac{\text{Resistance (mm Hg/l/min m}^2\text{)}}{\text{Absolute viscosity (Poise)}}. \tag{5}$$

As can be seen by referring to the original Poiseuille equation, removing the effect of viscosity leaves the pure geometric factor.

$$\frac{\left(\frac{8}{\pi}\right)\left(\frac{l}{r^4}\right)\eta}{\eta} = \left(\frac{8}{\pi}\right)\left(\frac{l}{r^4}\right). \tag{6}$$

For example, consider patients who are to undergo Fontan–Kreutzer single-ventricle repair. Because lung perfusion after surgery depends on gravity and the respiratory pump, it is essential to exclude increased pulmonary vascular resistance before surgery. Consider also the preoperative values of two patients who are to undergo Fontan–Kreutzer repair and who have the preoperative data listed in Table 2. Although a pulmonary vascular resistance of 3 Wood units/m^2 would be usually regarded as a safe value for surgery, note that in the anemic patient (column 3), the actual geometric component of the impediment to pulmonary blood flow (the hindrance) is twice as high as normal. This means that after surgery in the anemic patient, when hematocrit returns to normal, pulmonary vascular resistance would double (resistance = hindrance × viscosity), and the patient might not survive or might have to have the Fontan taken down and revised.

Now consider two patients with the preoperative data listed in Table 3. The first patient with a high pulmonary vascular resistance would in most centers be excluded from single-ventricle repair. However, in the patient with a high hematocrit at the time of cardiac catheterization (column 3), the effect of high viscosity conceals the fact that hindrance is normal. This would allow successful repair once the hematocrit returns to normal as it will after surgery.

Recently Ascuitto et al. [1] performed an elegant study of computational fluid dynamics analysis of nonpulsatile (passive) fluid flow through a conduit to investigate the effect of blood viscosity on flow through narrowed portions

Table 2 Viscosity and resistance: Patients 1 and 2

Hematocrit (%)	45	20
Pulmonary vascular resistance (mm Hg/l/min/m^2)	3	3
Absolute viscosity (Poise)	0.04	0.0205
Hindrance (mm Hg/l/min/m^2/Poise)	75	146

Table 3 Viscosity and resistance: Patients 3 and 4

Hematocrit (%)	45	75
Pulmonary vascular resistance (mm Hg/l/min/m^2)	6	6
Absolute viscosity (Poise)	0.04	0.0852
Hindrance (mm Hg/l/min/m^2/Poise)	150	70

of Fontan circulation (stenotic pulmonary arteries). They concluded that viscous energy losses across a stenosis increased in proportion to increased viscosity. Therefore, increased viscosity affects more than small resistance vessels, an added reason for taking viscosity into account, especially when planning Fontan-Kreutzer surgery.

These same considerations apply to evaluating pulmonary vascular resistance in patients with pulmonary arterial hypertension, whether it is primary or secondary to congenital heart disease. Many such patients, especially those with Eisenmenger syndrome, are cyanotic and polycythemic, and may even have red cells made rigid by iron deficiency. It would be prudent to maintain a reasonably normal hematocrit when evaluating their pulmonary vascular resistance, or if phlebotomy is judged unwarranted, at least to see that it does not change substantially when evaluating the effects of a new therapeutic agent.

Other patients affected by hyperviscosity due to polycythemia are neonates secondary to placental overtransfusion or intrauterine hypoxia [13, 16]. The hyperviscosity may contribute to the pulmonary hypertension seen in some of these neonates.

Viscosity and Hematocrit

Calculating hindrance requires knowledge of absolute viscosities, and these may not be readily available. An acceptable alternative is to calculate relative viscosity from the relationship between viscosity and hematocrit, which is based on standard data in the literature (Fig. 1).

Hematocrit on the *X*-axis is plotted against viscosity relative to plasma on the left *Y*-axis or relative to a standard hematocrit of 45% on the right *Y*-axis. The thin parallel lines around the central thick curved line are rough indications of variability.

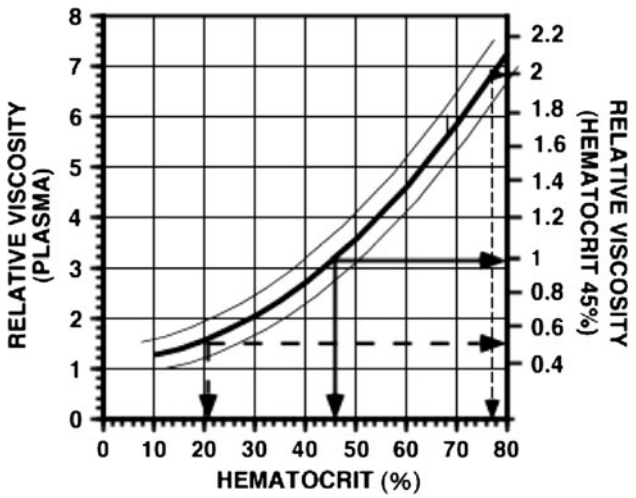

Fig. 1 Relation of viscosity to hematocrit

As hematocrit increases, viscosity increases as well, so that with hematocrits >60% there is a marked effect on the calculation of resistance. To use this figure, calculate a resistance standardized to a hematocrit of 45% by dividing the calculated resistance by the relative viscosity on the right axis. Thus, a resistance of 6 Wood units with a hematocrit of 75% becomes a standardized resistance of $6/2 = 3$ Wood units, and a resistance of 3 Wood units with a hematocrit of 20% becomes a standardized resistance of $3/0.5 = 6$ Wood units.

Increased Blood Viscosity and Normal Hematocrit

Although the most common cause of increased blood viscosity is increased hematocrit, in certain patients high viscosity can be associated with a normal hematocrit.

1. As described previously, rarely macroglobulinemia or hyperfibrogenemia increases viscosity.
2. In sickle cell disease, not only does viscosity increase during deoxygenation of sickle cells, leading to microthrombi and sickle cell crises, but even oxygenated sickle cells are more rigid because of internal polymerization, so that blood of a patient with sickle cell disease has substantially increased viscosity [7, 27].
3. Transient increases in blood viscosity may occur when intravascular contrast agents are used in angiography, with the degree depending more on osmolality than viscosity of the injected agent [14, 28, 29]. The tendency is for blood viscosity to increase, sometimes markedly, at high shear rates and to decrease at low shear rates such that the final effect on pulmonary vascular resistance is difficult to predict. These increases in blood viscosity may account for some of the harmful side effects of contrast media in patients with increased pulmonary vascular resistance, but the viscosity changes are usually transient.
4. Iron deficiency is know to make red blood cells more rigid [4, 30] and has been proposed as one of the causes of microthrombosis in patients with cyanotic heart disease. Its effect on blood viscosity is unclear. Some studies have found that microcytosis and iron deficiency increase blood viscosity modestly [10, 15, 21], whereas others have described no change or even a decrease in blood viscosity [12, 31]. The discrepancy may be due in part to whether measurements were made at high or low shear rates.

Conclusion

Viscosity plays a major role in evaluating pulmonary vascular resistance. Although flow through vascular beds is

complex and cannot easily be related to ideal physical laws, a reasonable approximation to apparent viscosity can be determined by referring to the hematocrit.

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