Determinants of microvascular flow

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This editorial refers to ‘A novel, hydrodynamic approach to the treatment of coronary artery disease† by J.J. Pacella et al., on page 2362

The Hagen–Poiseuille’s equation states that flow (Q) in a tube can be calculated as follows: (\Delta P/\pi r^4)/(8 \bar{\eta}), where l and r are the length and radius of the tube, respectively, \(\bar{\eta}\) the viscosity of the fluid flowing through the tube, and \(\Delta P\) the pressure gradient across the tube. By analogy with Ohms law, the total resistance \(R\) to flow is given by \(\Delta P/Q = R\) or \(Q = \Delta P/R\). By combining the two equations, we get \((8\bar{\eta}/(\pi r^4))\bar{\eta}\). In large vessels viscosity plays a minor role. For most clinical cardiologists, whose view of coronary artery flow is limited to that in the epicardial coronary arteries, the term \(r^4\) is all important. Once in a while they also argue about the term \(l\), especially if they see segments with long stenosis or several stenoses in series on coronary angiography. This equation is valid only for laminar flow in straight tubes. At stenoses and bifurcations, resistance is higher than that predicted by this equation due to energy loss through turbulence.

In the absence of stenoses, epicardial coronary arteries offer negligible resistance to flow and most of the resistance is at the microvascular level. The filled bars in Figure 1 show the distribution of resistances across the normal coronary circulation at baseline.1 The mean aortic pressure of 90 mmHg is reduced to a pre-capillary pressure of 45 mmHg because of resistance offered by coronary arterioles (150–300 \(\mu\)m in diameter). There is a further 30 mm drop of pressure across the capillary bed (the post-capillary pressure is 15 mmHg). The capillaries are very small in size and offer high resistance, but since they are arranged in parallel, the total capillary resistance decreases with increasing number of capillaries. There are 8 million capillaries in the heart. The drop across the venous bed is only 10 mmHg (mean right atrial pressure being 5 mmHg) since these are high capacitance vessels, which nevertheless have some smooth muscles. Thus, at rest, \(~60\%\) of total myocardial vascular resistance (MVR) is offered by the arterioles, 25\% by the capillaries, and 15\% by the venules.1

When hyperaemia is induced in the normal coronary circulation, smooth muscle relaxation results in dilatation of the arterioles and venules with no change in the capillaries. The total MVR decreases by \(~68\%\), and compared to rest, the arterial and venular resistances decrease by 86 and 98\% respectively (Figure 1).1 Because of a similar decrease in arterial and venular resistances, the capillary hydrostatic pressure remains unchanged. The arteriolar and capillary resistances now comprise 25 and 75\% of the total MVR, respectively. Thus, capillaries offer the most resistance to coronary blood flow (CBF) during hyperaemia and provide a ceiling to hyperaemic CBF. This importance fact is most often ignored or not fully appreciated. Because they are laid in parallel, the more the capillaries the higher the hyperaemic CBF and the less the capillaries the less the hyperaemic CBF. Conditions that are associated with lesser capillaries (either anatomically or functionally), such as myocardial infarction, hypertension, and diabetes, are associated with reduced CBFR despite the absence of coronary stenosis.

Viscosity can be defined as resistance to deformation. For Newtonian fluids like water, viscosity remains constant independent of the deformation rate. For non-Newtonian fluids, such as blood- and drag-reducing polymers (DRPs), viscosity changes with the deformation rate. That is, the greater the deformation rate, the easier it becomes to deform them. Most measurements of viscosity are derived by altering the shear rate in a tube. In this manner, Newtonian fluids exhibit zero velocity at the wall of the tube and maximal velocity at the centre with a characteristic hyperbolic flow profile.

As vessels decrease in size (<30 \(\mu\)m), there is a non-linear relation between vessel size and viscosity with relative effective viscosity increasing six to seven-fold at vessels of the size of capillaries (Figure 2).2 This occurs primarily because erythrocytes are larger than capillaries and have to deform and elongate as they travel through the capillaries. Therefore, the mobility of an erythrocyte is affected by its deformability. Elongation of erythrocytes over a particular vessel length over a given time can be measured as elongational viscosity. This parameter is even more important for DRPs that are coiled at baseline and then elongate and straighten out in a flowing tube. Factors that change viscosity at the microvascular level can change microvascular flow appreciably.

Electrostatic charge (both on the erythrocytes and the vessel wall) can affect erythrocyte mobility. The negative

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charge on the erythrocytes, from the presence of sialic acid in the sugar moiety of the membrane-bound glycoprotein, contributes to the repulsive forces among them. Reducing negative electric charge results in axial migration of erythrocytes without causing aggregation. Removal of sialic acid from the erythrocytes increases microvascular resistance to flow by approximately one-third. We have recently shown that in ischaemia microvascular flow can be increased by nitroglycerin by decreasing erythrocyte charge (presumably by increasing the erythrocyte nitrosothiol content) that in turn increases erythrocyte deformability and decreases viscosity.

Changes in blood viscosity are likely to have pronounced effects on CBF reserve. For instance, we have demonstrated that hyperaemic blood flow is attenuated by increasing serum triglyceride levels. In this experiment, MVR increased with increasing triglyceride levels, and the decrease in hyperaemia was associated with a decrease in microbubble velocity as measured with myocardial contrast echocardiography (MCE). A number of studies have shown an increase in blood viscosity with hyper-lipoproteinaemia. A strong positive correlation has been found between increased blood viscosity and coronary artery disease (CAD). Several studies have shown abnormal CBF reserve even in patients with CAD risk factors in the absence of CAD on angiography. Furthermore, it has been shown that the use of statins can normalize abnormal CBF reserve without affecting coronary artery morphology. Unfortunately, this important aspect of statin effect is ignored when considering their clinical effects because the microcirculation is often ignored by clinicians.

Using MCE, Pacella et al. have convincingly demonstrated the effects of DRPs on myocardium subtended by a stenosis during hyperaemia. Figure 3 illustrates the effect of non-critical stenosis and hyperaemia on the components of MVR. The resistance offered by a stenosis is offset by a decrease in arteriolar resistance due to autoregulation, with the result that total vascular resistance remains unchanged as does resting CBF. Now, when hyperaemia is induced, although the total MVR decreases when compared with the resting state without stenosis, it increases compared with the non-hyperaemic state with stenosis. During hyperaemia, arteriolar and venular resistances are already minimal, so the increase in resistance occurs mostly from an increase in capillary resistance due to capillary derecruitment in an effort to keep the capillary hydrostatic pressure from rising. Thus, the major reason for attenuation of CBF reserve caused by a stenosis is also capillaries rather than the stenosis itself. The derecruitment of capillaries results in a reduction in myocardial blood volume (MBV) and a perfusion defect. Pacella et al. have shown that DRPs reverse this effect with a concomitant decrease in MVR and a reversal in the attenuation of CBF reserve. DRPs are long macromolecules of length of up to 100 μm. They reduce resistance to flow at a constant pressure gradient mainly through decreasing turbulence (Toms effect) and without affecting viscosity. The effect of DRPs bring to light other possible determinants of microvascular flow. Turbulence is defined by Reynold’s number given by the formula $Re = \frac{\rho v L}{\mu}$, where $\rho$, $v$, and $\mu$ are the density, velocity, and viscosity of the fluid, respectively, and $L$ is the characteristic length, which for a circular tube is equal to its diameter. Thus, for a given fluid, the larger the $L$ and higher the $v$, the greater the turbulence. Turbulence typically occurs when Reynolds number exceeds 4000. It is generally believed that flow in blood vessels is laminar and, therefore,
turbulence is absent. But turbulence has been measured in straight tubes and not at bifurcations. It has also been measured in tubes with smooth surfaces, which may not be applicable to smaller blood vessels. Finally, turbulence has to occur distal to a stenosis, especially during hyperaemia.

Thus, the explanation provided by Pacella et al. for their findings (depicted in Figure 6 of their paper) appears reasonable. They argue that during hyperaemia, DRPs reduce turbulence induced energy dissipation distal to the stenosis and thus attenuate the resulting decrease in pre-capillary pressure, thereby preventing capillary derecruitment and the consequent increase in MVR with the occurrence of perfusion defects. In fact, the trend towards a decrease in distal left anterior descending artery pressure during DRP administration in their study supports their argument.

There are, however, other possible mechanisms by which DRPs may exert their beneficial effects that have also been alluded to in the paper by Pacella et al. Under normal circumstances, there is plasma skimming at arteriolar branch points, which leads to less number of erythrocytes entering capillaries (the Fahraeus effect).7 By forming microchannels within vessels, DRPs could reduce plasma skimming and thus deliver more erythrocytes to capillaries. Normally, at rest only half the capillaries have erythrocytes moving through them in a single file, whereas the other half contains only slowly moving plasma. The added number of erythrocytes would then start entering these latter set of capillaries, thus increasing MCE-derived MBV (microbubble rheology is similar to that of erythrocytes8,9 and they are not seen in capillaries where erythrocytes are absent). More functioning capillaries have been noted after DRP treatment in other models as discussed in their paper by Pacella et al. The decrease in MVR with DRPs noted by Pacella et al. implies that erythrocyte-free capillaries have a higher resistance than those with capillaries. Further experiments are needed to determine whether and why this is the case.

Defining the mechanism of capillary derecruitment has been limited by the inability to reliably measure pressure directly in the capillaries and small arterioles and veins. This very limitation also hinders our further understanding of the microvascular effects of novel agents such as DRPs that have been shown to have beneficial effects in other conditions such as haemorrhagic shock. Only a very small amount of DRPs is required for their biological effect and there are no side effects known at these doses. Thus, DRPs offer a novel form of treatment in low flow conditions and warrant further study in other models, such as peripheral vascular disease and diabetes. A means of directly measuring capillary pressure during intravital microscopy would greatly facilitate such studies.

Conflict of interest: none declared.

References