Maximal coronary flow and the concept of coronary vascular reserve

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CORONARY FLOW can usually be increased above resting levels by reactive hyperemia after transient coronary arterial occlusion,1-13 exercise,7, 11, 14-21 pacing,22-26 or injection of agents like dipyridamole,7, 17, 18, 20, 21, 27-37 other vasodilating agents,4-7, 10, 11, 30, 38 or hyperosmolar iiodinated contrast media.4, 6, 39-43 If the stimulus produces maximal coronary vasodilatation, then the increment of coronary flow above the resting level will be maximal. This increment, often termed the ''coronary vascular reserve,'' is beginning to be measured in human beings to give information about the coronary vascular bed.9, 13, 15, 17, 19-29, 33-43 However, it is easy to misinterpret the information, so that it is important to understand the basic physiology that underlies the concept of coronary vascular reserve.

Basic physiology

In 1964 Mosher et al.44 studied coronary autoregulation and featured the coronary pressure-flow diagram that is the best way of describing coronary vascular reserve. If the left main coronary artery of the dog is cannulated, it is possible to change coronary pressure without changing aortic pressure. As a result, left ventricular work and oxygen consumption can be kept constant while the effects of changing coronary perfusion pressure on coronary flow can be studied, both when coronary vessels have tone and after maximal vasodilatation. Figure 1 shows the results of such a study in a normal heart. The pressure-flow relationship when the vessels have tone (line A) has a central linear portion that usually has a slight positive slope; that is, there is little steady-state change of flow with change of pressure. This phenomenon is known as autoregulation, and the linear portion extends over a range (the autoregulatory range) of about 70 to 130 mm Hg, although these limits can vary in different experiments. Below the lower limit of the autoregulatory range coronary flow decreases markedly when perfusing pressure is lowered, and above the upper limit coronary flow increases considerably as perfusing pressure is raised. The pressure-flow relationship during maximal vasodilatation (line D) is approximately straight, although in many recent careful studies it has been shown to curve at the lower end.45, 46 The maximal flow at any given pressure is mainly a function of the total cross-sectional area of the coronary resistance vessels; with fewer or smaller resistance vessels the maximal flow will be less than normal. The two vertical dashed lines in the figure (R1 and R2) indicate the coronary vascular reserve; for accuracy this increment in flow should be termed the coronary flow reserve because there is also a coronary resistance reserve that has been used by some investigators.27, 28, 33-37 It is important to note that no single value represents the coronary flow reserve because of the dependence of the flow reserve on perfusing pressure.

In figure 2 the same diagram has superimposed on it a second autoregulation line (A2) that represents an increased level of resting coronary flow that might be caused by anemia, left ventricular hypertrophy, or increased contractility. The maximal flow attainable at any pressure is not altered much, or may even be reduced, by these changes, so that the higher autoregulated flow causes the coronary flow reserve to decrease. However, if left ventricular hypertrophy is caused by hypertension, then the absolute coronary flow reserve might be normal or increased (R3) despite a raised resting coronary flow because of the elevated perfusing pressure.47

One issue pertaining to ventricular hypertrophy deserves emphasis. Hypertrophy has been shown to be associated with normal or slightly reduced resting coronary flow per gram of myocardium48 and therefore
with an increased total resting flow for the whole ventricle. However, the maximal total flow to the hypertrophied ventricle at any perfusing pressure is not increased if hypertrophy is acquired after a few years of age because the total cross-sectional area of the coronary resistance vessels does not increase.\textsuperscript{49-51} As a result, with acquired ventricular hypertrophy the coronary flow reserve at any given pressure is less than normal no matter how flows are measured: if total flows are measured then resting flow is high and maximal flow is normal, whereas if flows per gram are measured resting flow is normal but maximal flow is reduced.

Coronary flow reserve can also be reduced if the maximal flow at any given pressure is reduced so that the pressure-flow relationship during maximal vasodilatation is less steep than that for normal hearts (figure 3, line D\textsubscript{2}). A change of this type can occur because of polycythemia,\textsuperscript{52} diseases of the large or small coronary arteries,\textsuperscript{33} tachycardia,\textsuperscript{53} a large increase in left ventricular diastolic pressure,\textsuperscript{44} or a marked increase in contractility.\textsuperscript{54} With these changes the coronary flow reserve is reduced at any perfusing pressure, even if resting coronary flow is normal. Except for the group with coronary artery disease, the reduced maximal flow does not indicate a reduced total cross-sectional area of the coronary arterial bed.

It is not clear yet whether the absolute or the relative coronary flow reserve (maximal flow divided by resting flow) is more important. If maximal exercise demands a fourfold increase in coronary flow to permit the ventricle to function normally under stress, then it is the relative flow reserve that is the more important of the two measurements. Therefore with hypertensive ventricular hypertrophy a normal or moderately increased absolute coronary flow reserve can be associated with a reduced relative coronary flow reserve.

![Diagram](http://circ.ahajournals.org/) FIGURE 1. Diagram of pressure-flow relationships in normal left ventricle during autoregulation (A) and maximal vasodilatation (D). R\textsubscript{1} and R\textsubscript{2} are the coronary flow reserves at mean coronary perfusing pressures of 75 and 100 mm Hg when aortic pressure and heart rate are constant.

![Diagram](http://circ.ahajournals.org/) FIGURE 2. Diagram of pressure-flow relationships showing autoregulation lines in normal left ventricle (A\textsubscript{1}) and in either a normal left ventricle with anemia or increased contractility or a hypertrophied left ventricle (A\textsubscript{2}). Because pressure-flow relationships in maximally dilated vessels (D) are about the same for all these hearts, the coronary flow reserve of the normal ventricle (R\textsubscript{1}) is greater than that for the abnormal ventricle (R\textsubscript{2}). If, however, perfusion pressure is high, as in hypertension, then absolute coronary flow reserve (R\textsubscript{1}) may be normal or even increased.
flowmeters are capable of doing this. Marcus et al.\textsuperscript{9} have developed an ultrasonic velocity meter that can be placed on a coronary artery branch at surgery and can record changes in velocity with reactive hyperemia. This valuable but restricted technique does not measure absolute flow and assumes an unchanging vessel diameter so that flow will be proportional to velocity. A good relationship between flow and velocity has been demonstrated in preliminary studies by this group,\textsuperscript{9} but there are times when the method is likely to be unreliable. If, for example, the transducer is placed on a coronary artery beyond a stenosis, when flow is increased there will be a greater pressure drop across the stenosis and a decreased distal pressure that might narrow the vessel and alter the relationship of velocity to flow. Improvements in instrumentation are being made so that vessel diameter and thus flow can be measured.\textsuperscript{56} However, even when this capability exists, coronary flow reserve will still have to be judged by ratios of resting to maximal flows because the mass of myocardium perfused by that artery will not be known.

For use in patients not undergoing surgery there are catheter tip ultrasonic velocity meters\textsuperscript{57, 58} that can be placed in a major coronary artery. These are capable of measuring rapidly changing or stable flow velocities but have the drawbacks of not being able to measure absolute flow or to relate flows to a given mass of myocardium.

All other measurements must be made with steady-state flows; for example, during steady-state pacing or exercise, after giving a vasodilator with long-term action, or infusing the vasodilator continuously. Coronary sinus thermodilution or some of the diffusible indicator techniques are available for this purpose but have substantial limitations. Coronary sinus thermodilution does not define the mass of myocardium being drained,\textsuperscript{59} and diffusible indicators may take a long time to equilibrate or may require complex instrumentation for measurement. Perhaps the best of these diffusible indicator methods are the argon method,\textsuperscript{28, 29, 33-37} the \textsuperscript{133}Xe washout techniques,\textsuperscript{56, 61} or the \textsuperscript{81m}Kr method.\textsuperscript{62, 63} All of these diffusible indicator methods measure flow per unit volume or mass of myocardium but can yield absolute flows if ventricular mass is measured by echocardiography or angiography. Results may be less accurate with inhomogeneous than with homogeneous myocardial flows.\textsuperscript{64}

Verifying maximal vasodilatation. It may be difficult in humans to be sure that maximal coronary flows have been achieved. If the ultrasonic velocity meter is used at surgery,\textsuperscript{9, 13} different durations of coronary occlusion...
can be used to demonstrate that a peak reactive hyperemic response has been achieved. According to Marcus et al., a 20 sec occlusion of a coronary artery in humans is sufficient to produce a maximal reactive hyperemic response. This is in keeping with the results of many studies in dogs; Dole et al. found that a 10 sec coronary occlusion produced maximal reactive hyperemia in anesthetized dogs, and Olsson and Gregg observed that 5 to 7 sec of occlusion achieved maximal reactive hyperemia in conscious dogs. On the other hand, other investigators who studied anesthetized dogs have found that at least 90 sec of occlusion is required to achieve peak reactive hyperemic flows. It is possible that the differences may be related to the degree of collateral flow that enters the artery beyond the occluder, in which case shorter durations of occlusion may not provide a maximal ischemic stimulus.

It is also appropriate to consider whether reactive hyperemic flows are the maximal achievable flows. Gould et al. found that peak flows after 10 sec of coronary occlusion were similar to those attained by infusing 0.15 mg/kg/min dipyridamole or giving it in a bolus of 0.4 to 0.68 mg/kg, but they did not show that these flows were maximal. Downey et al. obtained similar peak flows after 90 sec of coronary occlusion or after administration of papaverine. Most other investigators have found that peak reactive hyperemic flow, even after 90 sec of coronary occlusion, is below that achieved at similar heart rates and blood pressures with vasodilators like adenosine, ATP, chromonar, or papaverine. Hyperosmolar radiopaque contrast media have been used to increase coronary flow. Usually 3 to 8 ml of agents like meglumine diatrizoate (Renografin-76 or Hypaque-76) are given in a bolus. However, by comparison of the increases in coronary flow achieved by these bolus injections with those occurring after other agents or after maximal exercise (see below), it seems that these contrast media do not usually produce maximal coronary vasodilatation. This was also found in the study by Bookstein and Higgins, who compared many vasodilators; in their study the greatest increments in coronary flow were produced by infusion of ATP and papaverine, and this combination achieved flows more than twice as great as those achieved by giving Renografin-76 in a bolus of 5.6 ml or an infusion of 6 ml/min. It is also clear that pacing or isoproterenol does not give maximal coronary flows, and even maximal exercise may not do so. Thus, in practice, infusion of vasodilators like adenosine, ATP, or dipyridamole is most likely to produce maximal vasodilatation. If these drugs are given, then either a dose known to give maximal vasodilatation must be used or else increasing doses must be given until a maximal response is achieved. Dipyridamole in a dose of 0.5 to 0.75 mg/kg body weight usually gives maximal coronary vasodilatation, but there is a small risk that in a particular person that dose is not maximal. The alternative of giving multiple doses is time consuming, and if the increased dose decreases aortic pressure or changes heart rate, it may be difficult to determine whether a constant maximal flow has been attained.

**Interfering variables.** Increases in heart rate, contractility, or left ventricular diastolic pressure will reduce maximal flows at any pressure. Coronary flow reserve will be reduced but cannot then be interpreted as reflecting only a decreased cross-sectional area of the coronary arterial bed. Conversely, a fall in contractility may increase maximal flows and decrease resting flows, thereby increasing coronary flow reserve.

There will also be differences in absolute values of maximal coronary flow in hearts in people with different body sizes. In dogs this variation can be allowed for by relating maximal coronary flow to body weight; whether this correction applies to humans has not been studied.

**Range of pressure examined.** It is difficult in patients to examine coronary flow during autoregulation and maximal vasodilatation over a large range of perfusing pressures; in reported studies only one perfusion pressure has been selected. Therefore, because coronary flow reserve is a function of perfusing pressure, it is difficult to decide on its normality without reference to normal standards that do not yet exist. This difficulty applies both to absolute flow reserve or to the ratio of autoregulated and maximally dilated flows as can be seen from figure 1. The difficulty is intensified by the steepness of the maximally dilated pressure-flow line. For example, Brown et al. examined maximal flows after giving dipyridamole with and without sustained handgrip exercise. For the same coronary vascular resistance of 0.38 to 0.40 mm Hg/ml/min, blood pressure averaged 89 mm Hg before and 113 mm Hg during handgrip exercise; the coronary flows were 217 and 290 ml/min, respectively.

**Effect of changing aortic pressures.** If technical advances in measuring coronary flows allowed flows to be examined at several perfusing pressures, two difficulties would be encountered. We do not know how much effect changing aortic pressure has on the maximally dilated pressure-flow line. Furthermore, a raised aortic pressure will increase myocardial oxygen consumption and blood flow, so that the coronary flow...
reserve will be changed relative to what would be found if coronary perfusing pressure and aortic pressure were dissociated (figure 4).

Coronary resistance ratio. Bretschneider\textsuperscript{27} introduced the concept of a coronary resistance ratio to assess coronary vascular reserve, and many investigators in Germany have followed his lead.\textsuperscript{28, 29, 33-37} He measured coronary flows before and after giving a vasodilator, calculated the resistance at each flow, and obtained the ratio of resistance during resting flow to resistance during maximal vasodilatation. The bigger the ratio the greater the fall in resistance with dilatation and hence the greater the coronary vascular reserve. Unfortunately this approach does not eliminate the variations in the magnitude of reserve at different perfusing pressures; although the minimal resistance is relatively constant at different pressures within the normal range, the autoregulated resistance will vary with pressure and with the heart’s requirements for flow. It is possible, however, that the resistance ratio is less sensitive than a flow ratio to changes in arterial pressure.

Results in humans. There have been several studies of the effects of various stimuli on coronary blood flow and vascular resistance in humans. In general, flows 2 to 2.5 times control flows and resistances about 45% to 50% of control values have been produced by pacing, injecting hyperosmolar contrast media, or infusing isoproterenol.\textsuperscript{22-26, 38-42} These are certainly not maximal. Greater changes are obtained with maximal exercise, with flows increasing 2 to 3.9 times control values and resistances falling as low as 36% of control values.\textsuperscript{15-17, 19} These changes may also not be maximal; Barnard et al.\textsuperscript{18} found that the large increase in coronary flow produced by near-maximal exercise in dogs could be increased another 35% by dipyridamole. The greatest changes have been produced by giving 0.5 to 0.75 mg/kg dipyridamole intravenously; flows from 3 to 5 times control values and resistances 20% to 37% of control have been described.\textsuperscript{17, 21, 28, 29, 33-37} These changes are consistent with the 5.5- to 6.3-fold increase in peak flow velocity described at surgery after occluding a coronary artery for 20 sec; it is possible that a decrease in contractility caused by anesthesia exaggerated the coronary flow (velocity) reserve in these patients.

Conclusions

If maximal coronary flow can be attained and measured, the value gives information about the total cross-sectional area of the coronary resistance vessels provided that interfering factors such as heart rate, contractility, end-diastolic pressure, and blood viscosity can be held constant or that allowance can be made for any changes that occur during the study. Furthermore, maximal flow depends to a large extent on perfusion pressure and so ideally should be measured at several different pressures.

The coronary flow reserve does give information about what might happen during maximal stress. Because its measurement depends on both the resting flow and the maximal flow, its interpretation is subject to all the interfering factors listed above for maximal flows and to what the autoregulated (resting) flow might be. The value of the flow reserve is also critically dependent on the perfusing pressure. Until we have good normal standards for these measurements and

\begin{figure}[h]
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\includegraphics{fig4}
\caption{Diagram of pressure-flow relationships when aortic and perfusion pressures rise together. D is the relationship during maximal flow and is assumed not to change as aortic pressure rises. A\textsubscript{1}, A\textsubscript{2}, and A\textsubscript{3} are the autoregulated pressure-flow relationships at three different left ventricular systolic pressures, which are associated with three different mean aortic (or coronary) pressures. The coronary flow reserve when mean aortic and coronary pressures are 100 mm Hg (R\textsubscript{1}) is not measured from the same autoregulated flow line as are the reserves measured at higher (R\textsubscript{2}) or lower (R\textsubscript{3}) perfusing pressures. The line joining the autoregulated flows at each pressure (●) therefore does not represent the autoregulated pressure-flow relationship, which cannot be obtained without dissociating coronary perfusing pressure from left ventricular systolic pressure.}
\end{figure}
until we can evaluate the meaning of a diminished coronary flow reserve in patients, we should be cautious in interpreting the values that we obtain.

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