Assessment of coronary artery stenosis severity depends on either determination of the anatomic dimensions of the stenosis by angiographic techniques or assessment of the functional significance of the stenosis by measurement of its effect on blood flow. Measurement of myocardial blood flow during maximal pharmacological vasodilation (vasodilator reserve) has been used to examine the functional consequences of a stenosis on perfusion of the dependent region of myocardium. In experimental animals, flow reserve measured with an electromagnetic flowmeter during pharmacological coronary vasodilation corresponds closely to quantitative coronary angiographic measurements of stenosis geometry. Studies using PET imaging with $\text{[13N]}$ammonia to measure coronary flow reserve in patients with coronary artery disease also demonstrated an inverse correlation between stenosis severity and flow reserve, but the relationship exhibited a greater degree of scatter than that obtained in animal models. It is not surprising that the correlation between stenosis severity and flow reserve would be less precise in patients with coronary disease, because atherosclerosis introduces potential variability in the behavior of both the epicardial stenotic segment and the coronary resistance vessels. Thus, a coronary stenosis in a patient with atherosclerosis may not produce a fixed degree of anatomic narrowing of the epicardial artery, and the resistance vessels may not predictably undergo maximal vasodilation in response to pharmacological vasodilators. Consequently, interpretation of coronary vasodilator reserve requires consideration of the dynamic characteristics of both the epicardial artery segment and the coronary resistance vessels.

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Epicardial Arteries

Lundmer et al demonstrated that intracoronary acetylcholine caused vasodilation in patients with atypical chest pain and angiographically normal coronary vessels but produced vasoconstriction in patients with atherosclerosis and angina pectoris. Furthermore, blockade of nitric oxide (NO) synthesis with intracoronary N\textsuperscript{G}-monomethyl-L-arginine (L-NMMA) caused a decrease in basal epicardial artery lumen diameter in patients with normal coronary arteriograms, demonstrating that NO normally contributes to maintenance of basal coronary vasodilator tone. Vita et al subsequently reported that acetylcholine can cause coronary vasoconstriction in patients with risk factors for atherosclerosis even with angiographically smooth coronary vessels. Data from both experimental animals and patients undergoing coronary angiography have demonstrated that normal epicardial arteries undergo vasodilation in response to increases of blood flow. This response is dependent on an intact endothelium, because removal of the endothelium abolished the flow-mediated vasodilation. Flow-mediated epicardial coronary artery dilation has been demonstrated in angiographically normal human coronary arteries by infusion of adenosine or papaverine distal to the site of measurement of coronary diameter, thereby avoiding exposure of the proximal artery to the direct effects of the pharmacological vasodilator. In patients with angiographically normal coronary arteries, metabolic vasodilation of the coronary resistance vessels during exercise or cardiac pacing also results in flow-mediated vasodilation of the epicardial arteries. In contrast, in patients with atherosclerotic disease, exercise caused no change or coronary artery constriction. After blockade of NO synthesis with L-NMMA, coronary dilation during pacing was similar in patients with and without risk factors, supporting the concept that vasodilation in response to pacing in patients without risk factors was the result of increased NO production.

Coronary Artery Stenosis

Autopsy studies of stenotic coronary artery segments have demonstrated that $\approx 75\%$ of atheromas are eccentric in location, leaving part of the arterial wall uninvolved. The existence of a relatively uninvolved segment of vessel probably explains the finding that coronary artery stenoses often do not behave as fixed narrowings but have some degree of compliance and some ability to undergo active vasomotion. Thus, sympathetic nervous system activation, serotonin, and ergonovine can produce constriction at the site of an eccentric atherosclerotic lesion, whereas nitroglycerin can cause dilation of coronary stenoses. The latter observation demonstrates that stenotic coronary segments are responsive to the vasodilating effects of NO. The intra-arterial pressure within a stenotic segment opposes the arterial wall elasticity and vasomotor tone, which act to collapse the vessel. For this reason, a compliant stenosis can undergo passive changes in lumen area secondary to changes in aortic pressure. Furthermore, interactions between the stenotic segment and the distal vasculature can also result in passive changes in severity of stenosis. Vasodilation of the resistance vessels will cause an
increase in blood flow and therefore an increase in blood velocity (kinetic energy) within the stenotic segment; the increased velocity causes a proportionate decrease in pressure (potential energy) acting to distend the stenosis. As the intraluminal distending pressure decreases with increasing flow, both active vasomotor tone and the arterial wall elasticity will tend to collapse the stenosis and worsen the degree of narrowing. With severe stenoses, these effects can be sufficient to cause a paradoxical decrease in blood flow in response to administration of vasodilators such as adenosine or dipyridamole, which act principally at the level of the resistance vessels.

Microvascular Impairment of Flow Reserve

Although vasodilator reserve was initially devised to quantify limitation of flow caused by an epicardial coronary stenosis, maximal flow rates can also be influenced by alterations at the microvascular level. Increased extravascular forces secondary to elevation of left ventricular diastolic pressure or tachycardia act to compress the intramyocardial microvasculature and limit peak flow rates. Structural abnormalities of the small vessels in hypertension, diabetes, and hypertrophic cardiomyopathy can limit vasodilation, thereby impairing maximal flow rates. In addition, hyperlipidemia has been found to impair endothelium-dependent resistance vessel dilation. Thus, in patients with hypercholesterolemia, the increases of coronary artery flow in response to intracoronary acetylcholine measured with a Doppler catheter were less than normal in patients with hypercholesterolemia, and the response was improved after 6 months of cholesterol-lowering therapy with pravastatin. These findings indicate that hyperlipidemia causes impairment of endothelium-dependent vasodilator responses not only in epicardial arteries but also in the coronary resistance vessels.

A more surprising finding has been the recent demonstration that hyperlipidemia can impair coronary resistance vessel dilation in response to non–endothelium-dependent dilators. Several investigators have reported that maximal myocardial blood flow rates measured with positron emission tomography using $^{15}$NH$_3$mAnmonia or $^{18}$O-labeled water during intravenous infusion of adenosine or dipyridamole are impaired in patients with hyperlipidemia and angiographically normal coronary arteries or normal exercise stress tests. Impaired resistance vessel dilation in response to endothelium-independent vasodilators in patients with lipid abnormalities can probably be explained by studies demonstrating size-related differences in vasodilator responses of the coronary small vessels. Studies in which coronary microvessels were directly visualized in beating hearts have shown that metabolic vasodilation occurs principally in arterioles $<$100 $\mu$m in diameter. Adenosine and dipyridamole also produce their vasodilator effects mainly in vessels of this size. However, up to 40% of total coronary resistance resides in small arteries 100 to 400 $\mu$m in diameter. Although these small arteries are not under metabolic control, they have the potential to influence maximal coronary flow rates importantly. In the normal heart, vasomotor tone in these small arteries is indirectly coupled to myocardial metabolic needs through endothelium-dependent flow-mediated NO production. Thus, when vasodilation of the arterioles causes an increase in blood flow, the resultant increase in endothelial shear will cause increased NO production and vasodilation of the small arteries.

In this way, arteriolar vasodilation also leads to dilation of the small resistance arteries. However, in the setting of hyperlipidemia, endothelium-dependent shear-mediated vasodilation of the small arteries may be impaired or lost. In this situation, adenosine or dipyridamole would be expected to produce a subnormal increase in blood flow, because these agents dilate only the arterioles but not the small arteries. Absence of flow-mediated vasodilation of the small arteries could impair minimum vascular resistance, because substantial resistance to blood flow resides at the level of these small arteries.

Response to Lipid-Lowering Therapy

Several investigators have reported that short-term lipid-lowering therapy can cause improvement of endothelium-dependent vasodilator responses in both epicardial coronary arteries and coronary resistance vessels. Egashira et al reported that in patients with hypercholesterolemia, pravastatin treatment over an 8-month interval had a beneficial effect on the response of the epicardial arteries (measured with quantitative angiography) as well as the resistance-vessel dilation produced by intracoronary acetylcholine. A regimen of lipid lowering in conjunction with cardiovascular conditioning of 6 weeks’ duration has been reported to improve flow reserve during intravenous infusion of dipyridamole in patients with elevated cholesterol, some of whom were known to have occlusive coronary artery disease. Intensive lipid-lowering therapy for 12 weeks in patients with documented coronary artery disease and hyperlipidemia caused a decrease in the size and severity of myocardial perfusion abnormalities measured with $^{15}$NH$_3$mAnmonia PET imaging during dipyridamole administration. It is reasonable to conclude that the improved flow reserve in these studies was principally the result of a functional improvement of endothelium-dependent vasodilator responses, because the interval of treatment was too brief to expect atheroma regression.

In this issue of Circulation, Huggins and associates reported the effect of 4 months of lipid-lowering therapy with simvastatin on the coronary vasodilator response to intravenous adenosine using PET $^{15}$NH$_3$mAnmonia in patients with ischemic heart disease. Although coronary angiography was not performed, the investigators reasoned that it should be possible to distinguish between myocardial regions perfused by a stenotic coronary artery and regions without a stenosis by the response of flow during vasodilation with adenosine before therapy is begun. According to this construct, myocardial segments were classified as normal (flow $>$2 mL min$^{-1}$ g$^{-1}$ during adenosine before simvastatin therapy) or abnormal (flow $<$2 mL min$^{-1}$ g$^{-1}$). The investigators note that even the “normal” segments had decreased peak flow rates in comparison with truly normal individuals. This was not unexpected, in light of previous data demonstrating that the response to endothelium-independent vasodilators is impaired in the setting of hyperlipidemia. Heart rate and arterial pressure,
variables that can affect flow reserve, were similar before and after treatment. Furthermore, other factors that impair flow reserve at the microvascular level, such as hypertension or myocardial hypertrophy, should influence flow reserve in regions perfused by normal or stenosed epicardial arteries equally. In normal segments, simvastatin treatment caused no change in myocardial blood flow during basal conditions and no change in the response to adenosine. In abnormal segments, in contrast, blood flow during high-dose adenosine was on average 47% greater after lipid-lowering therapy. Because lipid-lowering therapy did not improve the response to adenosine in normal segments, the investigators concluded that the effect of simvastatin in abnormal segments could not be the result of an effect on the microvasculature but rather resulted from augmented dilation of stenotic epicardial conduit vessels, most likely as the result of improved flow-mediated vasodilation. In a previous report, Czernin et al.27 found that in patients with hyperlipidemia, several of whom had known coronary artery disease, peak flow rates during dipyridamole infusion were modestly but significantly improved after a 6-week program of low-fat diet and cardiovascular conditioning. The peak flow rates before treatment reported by Czernin et al were intermediate between the normal and abnormal regions in the study by Huggins et al.,25 suggesting that the myocardial regions studied were not identical in these 2 reports. Huggins et al suggest that failure to find an improvement in regions designated as normal after lipid-lowering therapy may be related to longer duration and more extensive disease in their patients with manifest ischemic heart disease. An additional factor that might have affected the results of Huggins et al is that at the time the flow measurements were made, a number of patients were taking nitrates or calcium blockers, agents that are known to be active in the coronary vasculature. This may be especially important for nitrates, because these agents act by generating NO and consequently might obscure impaired endogenous endothelial production of NO in the measurements made before treatment.26 A functional interaction between endogenous NO and calcium blockers is less likely but cannot be entirely excluded.

The finding by Huggins and associates25 that simvastatin improved the vasodilator response in the segments with the lowest pretreatment flow reserve is of therapeutic importance, because these are the regions most vulnerable to developing ischemia during exercise or other stress. The conclusion by the authors that this effect resulted from recovery of flow-mediated vasodilation of stenotic coronary artery segments after lipid lowering is consonant with previous data demonstrating that normal coronary arteries exhibit flow-mediated vasodilation26 and that coronary stenoses can dilate in response to exogenous nitrates.26 Nevertheless, in the absence of coronary angiography, it is possible that other alterations of coronary anatomy could have contributed to the observed responses. For example, flow reserve is impaired in myocardial regions perfused by collateral channels and most likely would be indistinguishable from stenotic regions by PET imaging. Furthermore, endothelium-dependent small-vessel responses are impaired in small vessels perfused through collateral channels even in the absence of lipid abnormalities.27 Whether hyperlipidemia has an additional effect on small vessels in collateral-dependent regions is unknown but will be an important area for study, especially because of the current interest in promoting coronary angiogenesis, an intervention that will increase the myocardial dependency on collateral vessels.

References


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