The Nitrates and Myocardial Ischemia

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IN THE CENTURY since Brunton reported relief of angina pectoris by nitrite of amyl, the efficacy of the nitrates for relief of ischemic cardiac pain has been unchallenged. Although these drugs remain a reference by which all newer antianginal medications are judged, we are not yet certain which of their actions causes their beneficial effects. In recent years, three general hypotheses have been considered.

Nitrates are coronary vasodilators. They increase coronary flow by lowering coronary resistance. This view is clearly untenable. If the term coronary vasodilator means a drug that increases coronary flow to normal, nonischemic myocardium, nitroglycerin in therapeutic doses is an extremely feeble and short-lived coronary vasodilator. At the same time, more potent coronary vasodilators, such as dipyridamole, are without comparable antianginal action. Therefore, in the early 1960s, this oversimplified explanation of the nitrates’ effect in angina pectoris was modified.

Nitrates in therapeutic doses have a specific vasodilator effect on the conductive, or conduit, coronary arteries. According to this hypothesis, nitrates in therapeutic concentrations dilate all the larger coronary arteries, but have only a slight and transient effect on the precapillary arterioles, which are predominantly controlled by the metabolic status of surrounding myocardium. Thus, nitrates can relieve spasm or simply diminish the normal tone of conductive vessels or of collateral vessels.

The therapeutic effect of nitrates does not depend on their coronary action at all. An alternative hypothesis proposes that relief of angina is secondary to the widespread systemic venodilation that nitrates produce. Thus, reduction of ventricular diastolic pressure and consequent relief of compression of deep left ventricular blood vessels promotes diastolic coronary flow to the inner layers of left ventricular muscle. Simultaneously, left ventricular oxygen consumption is lowered by reduction of left ventricular dimensions (Laplace relationship) and by reduction of systolic pressure.

There is no doubt that nitrates have both direct effects on the coronary arteries and indirect effects on the heart secondary to their general systemic actions. Contemporary belief appears to favor the predominant importance of the latter mechanism. One study in particular seems to support this conclusion.

In 1972, Ganz and Marcus induced angina in resting patients by rapid atrial pacing. Intracoronary injections of nitroglycerin frequently induced a brief increase in coronary sinus flow, but failed to relieve angina. In contrast, i.v. injection of nitroglycerin did not increase coronary sinus flow, but did lower blood pressure and relieve angina. They concluded that the antianginal effect must therefore be due to the action of the drug on the systemic circulation by decreasing myocardial oxygen demands. Although this conclusion may be valid in the setting of pacing-induced ischemia in resting subjects, extrapolation from this experiment to all other situations in which nitrates may diminish myocardial ischemia is not justified. Indeed, there is much evidence to support quite different mechanisms. However, consideration suggests that any conflict between the various theories of nitrate action is more apparent than real.

The Model

Our knowledge of the principles underlying coronary flow distribution is advanced enough to allow us to develop a conceptual model of the coronary circulation that is consistent with the mass of published observations. From this model, the mechanism of action of nitrates can be predicted in different experimental or clinical circumstances. This model has the following characteristics.

There are two functionally different types of coronary artery. There are conduit arteries, whose primary function is to carry blood. These terminate in small arteries, or arterioles, whose prime function is to regulate flow (fig. 1A). Normally, the resistance of the arterioles (R2) is considerably greater than that of the conduit arteries (R1). Both types of vessel have smooth muscle and both have intrinsic tone. But the tone of large and small vessels is modulated by different influences and may even react differently to the same stimuli. Thus, tone in large vessels is influenced by both α and β receptors, but only the effect of β-mimetic drugs has been demonstrated in arterioles.

Large-vessel tone is probably not immediately influenced by ischemia of downstream myocardium, though a small delayed dilator response has recently been reported. By contrast, in arterioles, tone is primarily determined by the metabolic status of the surrounding myocardium, possibly modulated through local concentration of adenosine.

Large-vessel tone is probably little influenced by drugs such as adenosine or dipyridamole but is markedly diminished by nitrates in low concentration. In contrast, arteriolar tone is lowered and can be abolished by adenosine and dipyridamole. Although little influenced by therapeutic concentrations of nitrates sufficient to produce sustained relaxation of large vessel tone, small vessels...
only dilate in response to much higher nitrate concentrations or to intracoronary injection.\textsuperscript{2} \textsuperscript{10} \textsuperscript{17} \textsuperscript{20} \textsuperscript{23} \textsuperscript{25}

Changes in large-vessel resistance may be largely masked by metabolically induced changes in arteriolar resistance. A change in the resistance of upstream conduit vessels (R1) may cause opposite changes in the resistance of downstream arterioles (R2) through autoregulation such that the sum of the resistances in series (R1 + R2) may be unchanged.

Thus, resting coronary flow may be normal despite considerable narrowing of a conduit artery. Similarly, measures that constrict conduit vessels, such as infusion of an alpha agonist, phenylephrine in the pig\textsuperscript{20} and the cold pressor test in normal man,\textsuperscript{27} do not reduce coronary flow; and therapeutic levels of nitrates that dilate conduit arteries\textsuperscript{14} \textsuperscript{28} and lower their resistance\textsuperscript{20} \textsuperscript{22} produce no substantial increase in coronary flow.\textsuperscript{2} \textsuperscript{10}

When arterioles are fully dilated, changes in large-vessel resistance will cause changes in coronary flow. When arterioles are widely dilated by ischemia or pharmacologic interventions such that their ability to autoregulate further is compromised, changes in upstream resistance of conduit vessels (R1) cause changes in total resistance and flow.

Thus, intracoronary phenylephrine infusion (which increases R\textsubscript{c}) reduces flow if arterioles (R\textsubscript{a}) have been previously fully dilated by adenosine infusion.\textsuperscript{26} In patients in whom arterioles are maximally dilated by critical upstream narrowing of a conduit artery, a cold pressor test, which increases R\textsubscript{c}, will reduce coronary flow.\textsuperscript{27} Nitrates in a dose sufficient to dilate only large vessels may increase flow to myocardium that is already ischemic.\textsuperscript{29}

Conduit arteries are the usual site of atherosclerotic narrowing. When narrowing is severe, even minor changes in the normal tone of smooth muscle at the site of narrowing (A in figure 1B) may precipitate or relieve ischemia. Such narrowing can be diminished by nitrate therapy.\textsuperscript{24} \textsuperscript{28} \textsuperscript{30} Thus, in the presence of severe atherosclerotic narrowing, relief of ischemia by nitrates may be due to relaxation of normal smooth muscle tone at the site of stenosis.

Both normal and atherosclerotic conduit arteries can be the site of spasm (abnormally increased tone). Spasm is the principal cause of angina at rest,\textsuperscript{31} and sometimes on effort,\textsuperscript{12} \textsuperscript{32} in the absence of critical organic stenosis. Relief of ischemia in this context by nitrates is principally due to relief of spasm.

Blood flow to muscle distal to a diseased artery may depend on collateral circulation. In the presence of coronary obstruction involving primarily a single conduit vessel, downstream flow may be maintained through collateral channels arising from neighboring relatively normal coronary arteries (R\textsubscript{c} in figure 1B). Dilation by nitrates of collaterals (R\textsubscript{c}) or the vessels from which they arise (N) increases collateral flow to ischemic muscle in the dog\textsuperscript{31} and in man,\textsuperscript{34} improves contraction of ischemic segments\textsuperscript{35} and reduces the size of experimental myocardial infarction.\textsuperscript{36}

Thus, in the presence of coronary obstruction localized to a single territory, with collateral development, nitrates will augment collateral flow through vasodilatation of collateral vessels or of the conduit vessels from which they arise. Whether this is the principle or only a contributory reason for their benefit depends on the other factors discussed here.

Distribution of coronary flow to all parts of the myocardium is dependent on the maintenance of normal arteriolar resistance. Mechanical forces, even in the normal heart, favor flow to superficial muscle layers over flow to deep layers, and the relatively even distribution of flow according to metabolic need is believed to be due to metabolically determined autoregulation. After coronary narrowing (A in figure 1A), the vasodilator reserve of arterioles in deep muscle layers becomes preferentially reduced. Flow to deep layers is then highly dependent on adequate tone of superficial arterioles in downstream, potentially ischemic muscle.

Thus, in the presence of underperfusion, interventions that further reduce arteriolar tone, such as ischemia, intracoronary nitroglycerin\textsuperscript{32} or dipyridamole\textsuperscript{38} \textsuperscript{39} and infusion of adenosine,\textsuperscript{39} increase flow to superficial muscle at the expense of flow to deep muscle layers. This form of "coronary steal" occurs within the territory in which flow is jeopardized.

\begin{figure}
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\includegraphics[width=\textwidth]{figure1}
\caption{Models of (A) normal coronary circulation and (B) a circulation in which one branch is the site of atherosclerotic narrowing. R1 = resistance of conduit arteries; R2 = resistance of arterioles; N = normal conduit artery offering resistance R1N; A = abnormal narrowed conduit artery offering resistance R1A; Rc = resistance of collateral pathways; R2N = arteriolar resistance in territory of normal coronary artery ("nonischemic"); R2A = arteriolar resistance in territory of abnormal coronary artery ("potentially ischemic"); Dipyrid = dipyridamole; Aden = adenosine.}
\end{figure}
Similarly, maintenance of flow to both deep and superficial layers of potentially ischemic muscle distal to an obstruction largely depends on maintenance of normal resistance in the arteriolar beds (R2N) of neighboring nonischemic muscle. Interventions that decrease the resistance of these vessels, such as infusion of isoproterenol, adenosine, chromonar, dipyridamole or intracoronary nitroglycerin, produce a greater decrease in arteriolar resistance in the nonischemic (R2N) than in the already largely dilated arterioles in ischemic myocardium (R2A). This will divert collateral flow from ischemic to nonischemic myocardium, and can be described as "coronary steal" between one vascular territory and another.

Nitrates can have beneficial, noncoronary effects on the ischemic myocardium. Ischemia is frequently associated with elevated ventricular diastolic pressure which, by compressing the coronary vessels in the deep left ventricular muscle in diastole, can impede coronary flow. Reduction of left ventricular end-diastolic pressure by venectomy or by nitrate administration causing venodilation and venous pooling reduces this compression, facilitates coronary flow in diastole, and may abolish ischemia. Reduction of ventricular filling pressure may be associated with reduction in ventricular volume, which through the Laplace relationship, reduces myocardial oxygen consumption.

Thus, the effect of nitrates in diminishing ventricular filling is a variable factor in diminishing myocardial ischemia. Its role is greatest when ventricular diastolic pressures are elevated.

Nitrates can also promote oxygen sparing by reducing systemic arterial pressure. Their effect on blood pressure varies with several factors, including posture. However, the greater the decrease in blood pressure, the greater the reflex tachycardia evoked, a consequence that produces opposite or oxygen-wasting effects. Thus, nitrates may sometimes cause benefit by lowering blood pressure, especially when there can be no reflex tachycardia, e.g., during pacing or \( \beta \) blockade.

Discussion

These comments are not an attempt to review comprehensively the extensive literature on this subject (more than 1300 publications in the last decade alone), nor do they broach the question of how nitrates influence smooth muscle at the cellular level. Rather, they are an attempt to reconcile, in a logical way, some of the apparently conflicting evidence and opinions. In doing so, only a few appropriate examples have been cited.

The principal conclusion to be drawn is that the mechanisms by which nitrates relieve ischemia vary according to the experimental or clinical circumstances. It is therefore inappropriate to generalize from any one situation to all other situations.

For example, in the studies of Marcus and Ganz, nitroglycerin was introduced directly into the coronary artery of subjects paced to ischemia. Passing through the arterioles in relatively high concentration they caused a transient increase in coronary flow. This increase could be expected to take place chiefly in areas in which ischemia had not already caused arteriolar dilatation. Indeed, if large-vessel dilatation was absent or limited, coronary steal from areas already ischemic might even have caused some increase in ischemia. A similar explanation could account for the absence of relief of angina observed by Pepine and his colleagues when they injected a bolus of nitroglycerin into the coronary arteries of patients subjected to pacing-induced ischemia.

In the study of Marcus and Ganz, the principal effect of intravenous nitrates was peripheral. The subjects were resting and there was a predictable marked decrease in blood pressure. Because they were paced, however, there could be no reflex tachycardia. Thus, the rate-pressure product decreased, resulting in oxygen sparing and relief of pain. Also, in the face of reduced oxygen demand, there was predictable metabolically initiated constriction of arterioles and a decrease in coronary sinus flow. The study was not designed to distinguish between flow reduction in ischemic and nonischemic areas; presumably, flow reduction was confined to the nonischemic areas, and it is possible that through reversed steal flow may actually have increased in the ischemic areas.

Wald et al. carried out a comparable study in patients with resting angina, but they were not paced and were presumably nonischemic at the time of study. In this case, intracoronary nitroglycerin in relatively high dosage would again be expected to vasodilate arterioles, an effect that would be less marked in the territory of narrowed vessels, where restricted flow upstream would already have caused downstream vasodilation due to autoregulation. Intracoronary nitroglycerin could then be expected to increase the proportion of flow to less ischemic territory, a result they observed after intracoronary nitroglycerin.

In conclusion, no single explanation of "how nitrates work" to relieve myocardial ischemia is applicable to all circumstances. Four principal actions exist; each may predominate at different times. (1) When conduit vessels are narrowed by atherosclerotic lesions or by spasm, relaxation of normal or increased smooth muscle tone of these vessels by nitrates must be of predominant importance. (2) When a vessel is occluded or narrowed and its territory is supplied, all or in part, by collaterals, nitrate-induced dilatation of the collaterals or the conduit vessels from which they arise probably contributes significantly to the beneficial results observed. (3) Nitrate-induced reduction of venous tone resulting in venous pooling probably has beneficial effects both on oxygen supply and demand, especially when ventricular diastolic pressures are elevated. (4) When nitrates are given in circumstances that result in reduction of systolic pressure, there will be significant oxygen sparing, especially if reflex tachycardia is prevented.

By suitable manipulation of the variables, each of these effects can be demonstrated, which suggests that
each is operative to a variable extent, depending on the circumstances.

References

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