THE PHYSIOLOGIC EFFECT of nitroglycerin in patients with ischemic heart disease has been a focus of intense clinical investigation. However, some disagreement about the mechanisms by which nitroglycerin relieves myocardial ischemia still exists, for several reasons. The action of nitroglycerin may vary, depending on the dose or route of administration. Also, parenteral nitroglycerin can be given by bolus or slow infusion into the systemic or coronary circulation. To further complicate the issue, the patient population is not homogeneous. Myocardial ischemia may result from a fixed coronary stenosis that prevents an increase in coronary flow when myocardial oxygen requirements are increased, from coronary artery spasm, or from a combination of spasm and fixed coronary stenosis.

The preceding article by Brown and colleagues focuses on the effect of nitroglycerin on coronary stenosis diameter. These investigators used both sublingual and intracoronary nitroglycerin and made quantitative coronary angiographic measurements of coronary stenoses. In 46 patients, they showed that sublingual nitroglycerin dilates both the coronary stenosis and the adjacent artery. They then administered low-dose intracoronary nitroglycerin by infusion (25 μg/min) to other patients and found similar coronary dilatation and improvement in left ventricular performance in selected patients. None of these latter patients were reported to have coronary artery spasm, yet almost all patients showed dilatation of the coronary stenosis. These observations were interpreted to show that vasodilatation of epicardial coronary stenoses is usually a major component of the beneficial response to nitroglycerin in patients with coronary artery disease.

The observation that nitroglycerin may dilate coronary stenoses agrees with previous results using sublingual nitroglycerin. However, data in these reports conflict with those of Brown et al., i.e., although many coronary artery stenoses dilate after nitroglycerin, stenoses with the smallest luminal diameter often did not dilate. For example, when coronary stenoses were measured, only 14% (two of 14) of those 1.2 mm or smaller dilated at least 0.1 mm after nitroglycerin. In contrast, 59% (16 of 27) of stenoses greater than 1.2 mm dilated an average of 11% after nitroglycerin. The stenoses in which the diameter was 1.2 mm or smaller presumably would also be those most likely to limit coronary flow and have the largest pressure gradients across them. What caused these differences is not known. Quantitative angiographic techniques used by Brown et al. differ from those used in the other studies, but reported accuracy (approximately 0.1 mm), resolution and reproducibility of both seem similar. Perhaps studies in more patients using similar quantitative angiographic techniques will provide more insight about these conflicting observations (i.e., which coronary stenoses enlarge after nitroglycerin).

The data from the intracoronary infusion of nitroglycerin is particularly interesting. Parenteral nitroglycerin is being prepared more frequently by hospital pharmacies and used in hospitalized patients with ischemic heart disease. Probably, preparations for parenteral administration soon will be available commercially, and therefore, data on the effects of parenteral nitroglycerin on the coronary circulation are of immediate clinical relevance.

Brown et al. studied the effect on coronary artery diameter and ventricular performance of a low-dose intracoronary infusion of nitroglycerin in 17 patients with elevated pulmonary capillary wedge pressures. Eleven of these patients were selected because aortic systolic pressure did not change after intracoronary nitroglycerin or, at most, fell by 9 mm Hg. In these patients, nine coronary stenoses averaging 68 ± 9% diameter reduction before nitroglycerin infusion were analyzed. Although stenosis area increased 0.87–1.20 mm² after the nitroglycerin infusion, the percent reduction of the stenosis did not change because of dilatation in the adjacent vessel. In the 11 patients, left ventricular performance appeared to improve (maintained cardiac output at a reduced filling pressure). Brown et al. hypothesized that their method of intracoronary nitroglycerin administration, i.e., infusion of 50 μg over 2–3 minutes, was particularly important in achieving these good results. The proposed mechanism of action requires that these patients with coronary stenoses had ischemic myocardium in the absence of angina and/or ECG changes prior to intracoronary infusion of nitroglycerin. This may be so, but one can question whether stenoses of this severity uniformly produce myocardial ischemia at rest. Furthermore, although left ventricular performance appeared to improve after intracoronary nitroglycerin, right ventricular performance did not change (unchanged filling pressure and stroke volume). A more detailed look at the reported physiologic responses seems important. For example, the reported elevated right atrial pressures (> 10 mm Hg) suggest an important degree of right ventricular dysfunction. This elevation of right ventricular filling pressure is not usually seen.
in most patients with ischemic heart disease. Additionally, left ventricular and right ventricular performance are closely coupled. If left ventricular performance improved such that filling pressure decreased from 20 to 11 mm Hg, a concomitant fall in pulmonary artery pressure would occur. In this situation one can assume that right ventricular afterload falls, and as a result, a passive fall in the filling pressure of the right ventricle should occur. This was not observed.

The effect of intracoronary nitroglycerin on left ventricular performance in patients before and during transient myocardial ischemia has been reported.\textsuperscript{9, 10} Brown et al. pointed out that the method of administration of nitroglycerin may explain the difference between their study and most others. Other investigators usually used bolus injections of 50–150 µg of nitroglycerin.\textsuperscript{9–12} This exposed the coronary bed to higher nitroglycerin doses for a short period. Whether the effects on coronary flow and distal pressure and coronary diameter differ between bolus injection or infusion of nitroglycerin is unknown. In animal experiments, Schaper found that intracoronary injection of nitroglycerin causes a marked increase in coronary flow. However, even if intracoronary nitroglycerin is administered by constant infusion, this increase in coronary flow is transient.\textsuperscript{1} The coronary hemodynamic effect of constant infusion intracoronary nitroglycerin in patients is unknown. Brown et al. hypothesized that a low-dose intracoronary infusion causes persistent dilatation of epicardial coronary arteries and coronary stenoses without the transient coronary arterial dilatation seen after bolus injection of intracoronary nitroglycerin.

The effect of intracoronary nitroglycerin on pacing-induced transient ischemia was evaluated by Ganz and Marcus.\textsuperscript{8} In a series of elegant experiments, Ganz and Marcus administered 75 µg of intracoronary nitroglycerin into either the left coronary artery or right coronary artery during pacing-induced transient ischemia. In 22 patients, 75 µg of nitroglycerin was administered by bolus (over approximately 3 seconds) and in three by slow infusion over approximately 1 minute. In no patient was ischemia relieved with intracoronary nitroglycerin (bolus or infusion), but i.v. nitroglycerin was effective in relieving ischemia, presumably because of changes in myocardial oxygen demand.

Recent investigation has shown that exercise may provoke coronary spasm in some patients, accompanied by either ST depression or elevation.\textsuperscript{13–16} Similar studies were performed to further evaluate this observation.\textsuperscript{10} Coronary angiography during pacing- and exercise-induced angina revealed that nonstenotic coronary artery segments were usually unchanged or dilated only a small amount. In addition, coronary stenosis diameter increased slightly in some cases during both pacing- and exercise-induced angina. Coronary artery spasm was not seen. A bolus of intracoronary nitroglycerin (50–100 µg) during pacing- or exercise-induced angina caused further large-vessel coronary arterial dilatation and a transient increase in coronary flow but did not alter angina or ECG signs of transient ischemia. Intravenous nitroglycerin was then administered and angina and ECG changes improved as blood pressure decreased in each patient.

Several groups who administered nitroglycerin (50–150 µg) into the left coronary artery did not show important changes in left ventricular performance.\textsuperscript{11, 12} In these studies, left ventricular performance was evaluated by measurements of aortic and left ventricular pressures, global and regional wall motion determined angiographically, beat-to-beat measurements of stroke volume, aortic root blood velocity and acceleration, and left ventricular dP/dt.

Most investigators agree on some of the physiologic actions of nitroglycerin. It directly affects the coronary circulation through coronary artery dilatation. Both angiographically normal and stenotic arteries may dilate after nitroglycerin. Nitroglycerin also indirectly affects the coronary circulation through peripheral arterial and venous dilatation and reflexly mediated changes in heart rate. These systemic alterations generally decrease myocardial oxygen demand and compensatory coronary arterial constriction usually occurs. In usual doses, the magnitude of systemic venous dilatation is greater than systemic arterial dilatation; thus, right and left atrial pressures decrease more than arterial pressure. When nitroglycerin is administered directly into the coronary artery, large-vessel coronary artery dilatation occurs associated with a brief increase in coronary flow, which rapidly returns to pre-nitroglycerin levels. This occurs before changes in arterial or atrial pressures.

The dose and route of administration may be important variables in determining the magnitude of responses, but further investigation in this area is important. Individual patient responses may also be variable.

Investigation of the coronary and systemic effects of nitroglycerin might include coronary hemodynamics in selected patients by regional measurements of blood flow, oxygen saturation, and lactate metabolism. In appropriate patients, proximal and distal coronary pressures could be measured with catheters developed for intracoronary streptokinase infusion and coronary pressure gradients directly measured. Actual measurements of coronary flow and pressure gradients would allow calculation of true coronary stenosis resistance. Clinical evaluation of an intracoronary nitroglycerin infusion with lower doses using protocols similar to those of Ganz and Marcus\textsuperscript{8} or Pepine et al.\textsuperscript{10} might also be important.

To further evaluate left ventricular compliance and left ventricular function, the instantaneous relationship between ventricular pressure and volume before and after nitroglycerin could be measured. An alternative approach is to measure beat-to-beat high-fidelity aortic and left ventricular pressures and aortic root blood velocity before and during nitroglycerin's effect. These measurements allow calculation of peripheral resistance, aortic input impedance, left ventricular work and power. In addition, beat-to-beat
changes in left ventricular performance can be measured with this technique, in contrast to average changes over several seconds, when stroke volume is measured by indicator-dilution or Fick techniques. Changes in regional wall motion in the setting of unchanged systemic hemodynamics would also seem a reasonable approach and could be done using either contrast or radionuclide angiography or two-dimensional echocardiography.

The provocative data presented by Brown and co-workers warrant continued investigation to determine if the direct coronary effect of nitroglycerin is an important mechanism for relief of myocardial ischemia in patients with effort angina. The studies we have proposed might be helpful in clarifying the issue.

References
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