EDITORIALS

Nitroglycerin and Myocardial Ischemia

Can it be that less than a decade ago, every medical student was admonished never to administer nitroglycerin to a patient with acute myocardial infarction? The late Dr. Charles Friedberg, author of the tome that became the most widely read text in cardiology did so, and this concept went unchallenged through many years of "modern" medicine. The upsurge of interest in acute infarction as a research topic in the early 1970s, with concomitant development of hemodynamic monitoring, led to a major reversal of medical opinion; the accumulated experimental evidence indicates that therapy with nitroglycerin is capable of reducing the hemodynamic, electrocardiographic, and biochemical manifestations of acute ischemia in patients with acute infarction. One of the investigative groups heavily involved in these advances were Awan and associates, the authors of the article on nitroglycerin in this month's issue of Chest (see page 14). This article returns investigations full circle to an objective hemodynamic and electrocardiographic evaluation of the effects of therapy with nitroglycerin ointment upon the magnitude of myocardial ischemia in patients with chronic angina and explores the potential mechanisms for these observed responses.

The efficacy of therapy with nitroglycerin in relieving the symptoms of angina pectoris or in preventing its occurrence during atrial pacing and of increasing the level of exercise tolerance has ample, long-standing, and deserved recognition. Since these symptoms bear a definitive relationship to the development of myocardial ischemia, the subsequent demonstration that therapy with nitroglycerin substantially reduced the extension or severity of ischemia in experimental coronary arterial occlusion or during the course of acute myocardial infarction in man is entirely consistent.

As indicated by the current study, the beneficial effects of therapy with nitroglycerin in relieving ischemia are related to a number of actions, rather than to a single one. Preeminent is the effect that therapy with nitroglycerin exerts upon the peripheral circulation, both by dilatation of the arteriolar system and by augmentation of the venous capacitance. These actions produce a reduction in both preload and afterload, with significant reduction of the left ventricular volume and wall tension, and, therefore, a reduction in the myocardial demand for oxygen. In patients with coronary arterial disease and elevated left ventricular end-diastolic pressure, therapy with nitroglycerin seldom causes an appreciable increase in heart rate, despite a mild decline in systemic blood pressure. The absence or attenuation of this baroreceptor response may reflect a "defect" in the autonomic control of heart rate in patients with heart failure which apparently involves the sympathetic and parasympathetic system. In patients with normal left ventricular end-diastolic pressure, reflex tachycardia rarely exceeds 15 percent of the heart rate measured before treatment.

The reduction in myocardial consumption of oxygen that is caused by the decrease of venous return and peripheral vascular resistance is accompanied by changes in coronary blood flow, which are the result of both a direct action of the drug upon coronary arteriolar resistance and an indirect increase in the coronary diastolic pressure gradient secondary to reduction of the left ventricular diastolic pressure and diminished extrinsic compression of small vessels. Nitroglycerin has a greater dilator action on the large coronary arteries than on the smaller ones. Since larger vessels are less involved in the regional autoregulatory response to ischemia, it is at least theoretically possible to direct blood away from an ischemic zone, even as total flow increases, if small vessels in the ischemic zone have already been fully dilated.

Whether the effect on coronary circulation occurs earlier than the effect on the peripheral vasculature remains unclear; however, some investigators have contended that the direct coronary effects occur first and tend to prevent or blunt a secondary decrease in coronary blood flow because of systemic hypotension. In contrast, others contend that peripheral effects reducing the demand for oxygen play the most important role.

Even though further information is necessary,
The present clinical work indicates that by reducing myocardial needs for oxygen and by possibly improving coronary perfusion, therapy with nitroglycerin may become an adequate treatment for reduction of the size of the infarct, particularly in the presence of left ventricular failure.10 In these patients in whom left ventricular end-diastolic pressure is not elevated, combined therapy with nitroglycerin and an adrenergic agonist may further reverse ischemia by avoiding reduction of coronary blood flow.

The availability of nitroglycerin ointment permits the extension of these salutary effects clearly beyond the 15 to 20 minutes to which the sublingual form is confined. As described by Awan and colleagues in this issue, the beneficial activities of therapy with nitroglycerine are significantly prolonged to at least 150 minutes after its administration. The mechanisms by which this preparation prolongs exercise tolerance and reduces the extent of electrocardiographic manifestations of ischemia seem to be virtually identical to those encountered with the sublingual agent (namely, marked increases of the capacitance of the venous bed and a reduction of the arteriolar tone). Parallel beneficial action on the coronary circulation may also be assumed to play an additional important role.

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Supported in part by grant HL 17651 from the National Institutes of Health.
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REFERENCES

15 Williams DO, Amsterdam EA, Mason DT: Hemodynamic effects of nitroglycerin in acute myocardial infarction: Decrease in ventricular preload at the expense of cardiac output. Circulation 51:421-427, 1975

Acute Pulmonary Vascular Injury

The role of blood-borne substances in the inflammatory process in systemic tissues is well known. Much has been learned about the role of leukocytes, platelets, coagulation and kinin cascades, and the role of vasoactive molecules (such as peptides and prostaglandins).1

But what about the inflammatory response in the pulmonary circulation? At a recent workshop of the National Heart, Lung, and Blood Institute on the "Mechanisms of Acute Respiratory Failure," one session was devoted to vascular mechanisms of acute pulmonary injury.2 The presentations of ex-