CRITICAL REVIEW

Actions of the Nitrites on the Peripheral Circulation and Myocardial Oxygen Consumption: Significance in the Relief of Angina Pectoris*

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Myocardial ischemia is best viewed as a discrepancy between myocardial oxygen demands and availability of oxygen to the heart. Although the fundamental action of each nitrite is generalized direct vasodilation, in patients with coronary arterial disease the dynamic factor mediating favorable effects of these agents on angina pectoris appears largely to be reduction of myocardial oxygen requirements. Thus, the salutary effect of sublingual nitroglycerin is most related to venodilation which results in peripheral pooling of blood and reduction of heart size, thereby diminishing systolic wall tension and oxygen consumption of the ischemic left ventricle. With rapid introduction of nitrite into the circulation following inhaled amyl nitrite, marked direct peripheral arteriolar dilation results in decline of systolic tension and oxygen utilization of the heart and relief of myocardial ischemic pain. Thus, a peripheral circulatory mechanism of action of the nitrites is described which is immediately available for improvement of angina pectoris and is operative even in absence of coronary dilation.

The precise mechanisms of action of the nitrites in the relief of myocardial ischemic pain have been the subject of considerable debate despite their efficacy for over a full century following their introduction into clinical medicine by Brunton. The nitrites as a group are generally considered to include the inorganic nitrite ion and the organic nitrites and nitrates, each of which possesses the same fundamental effect of directly relaxing smooth muscle of arterioles and veins. The most important agent of this group clinically is the organic nitrite, glyceryl trinitrate (nitroglycerin). Although nitroglycerin produces coronary vasodilation in normal man, it does not appear to regularly increase coronary flow in patients with coronary artery disease. Although many aspects of the nitrites continue to excite controversy, advances in the past few years have provided important information and new concepts concerning their pharmacodynamic effects. This review focuses attention on certain of the recent studies that have delineated the actions of nitrites on the peripheral circulation and thereby have permitted improved understanding of the mechanisms of action of these agents in the treatment of angina pectoris.
**Myocardial Oxygen Consumption**

It has been the traditional view that the relief of angina pectoris is accomplished by enhancement of blood flow to the ischemic myocardium.\(^2\)\(^-\)\(^5\) Although certain studies in patients have suggested improved flow in apparently ischemic areas,\(^6\) the diseased arteries in patients with coronary atherosclerosis often are not capable of responding to vasodilator drugs. Further drug-induced dilation may not be possible in ischemic muscle since hypoxia itself is the most potent stimulant for coronary vasodilation;\(^7\) yet, the ischemic pain is often relieved by these antianginal agents without an increase in coronary blood flow.\(^8\)\(^-\)\(^11\) The pathophysiologic basis of myocardial ischemia is perhaps best viewed as a discrepancy between myocardial oxygen demands and the availability of oxygen to the heart.\(^12\)\(^-\)\(^13\) Thus, angina can be diminished by reducing myocardial oxygen consumption as well as it could be by improving coronary blood flow.

Further, the extent of myocardial ischemia which develops following experimental coronary occlusion has been demonstrated to be directly related to the level of oxygen requirements of the heart existing at the time of interruption of blood flow.\(^14\)

It is now acknowledged that the oxygen consumption of the heart is critically related to the interplay among three major hemodynamic related factors.\(^15\)\(^-\)\(^19\) Thus, most important is (1) the intramyocardial tension which is the product of transmural ventricular systolic pressure and the radius of the ventricle divided by its wall thickness. The other two principal variables directly related to myocardial oxygen demands are (2) the heart rate and (3) the contractile state of the heart. The central concept constructed in this report is that the salutary clinical benefits derived from the nitrites in the treatment of angina pectoris result largely and perhaps predominantly from the actions of these substances on reducing myocardial oxygen consumption rather than on increasing coronary blood flow.
FIGURE 2. Plethysmographic tracing in a normal subject in which forearm venous tone was determined by an equilibration method in which venous pressure was held constant while venous volume was allowed to vary. Forearm circumference (venous volume) was measured continuously before and after the administration of nitroglycerin. Note that following nitroglycerin the forearm circumference increased, while forearm venous pressure was held constant at 30 mm Hg signifying that dilation of the capacitance vessels had occurred. ART PRESS = phasic systemic arterial pressure. (Reproduced by permission; Mason DT, Braunwald E, Circulation 32:755, 1965.)

SUBLINGUAL NITROGLYCERIN

The possibility was considered that one of the major therapeutic actions of nitroglycerin is to diminish the needs of the heart for oxygen, and that this effect might be dependent upon the drug’s action upon the peripheral circulation. Accordingly, the effects of this drug on the arterioles and veins of the human forearm were determined when the agent was administered sublingually in the manner employed in clinical practice.¹⁹ Forearm blood flow was measured with a strain gauge plethysmograph (Fig 1), and venous tone was determined both by an acute occlusion technique (Fig 1) and by several equilibration techniques (Fig 2) in which absolute changes in venous pressure were related to venous

FIGURE 3. Serial changes of arterial pressure, forearm blood flow, forearm vascular resistance, and venous tone before and after sublingual nitroglycerin in a normal subject.
ACTIONS OF NITRITES

AMYL NITRITE

TIME (Minutes)

Fig. 4. Serial changes of forearm vascular dynamics before and after inhalation of amyl nitrite in a normal subject.

volume. Nitroglycerin produced an increase in the distensibility of the venous system (decline in venous tone) (Fig 1 to 3) and thereby causes pooling of blood in the peripheral veins and diminishes the return of blood to the heart. Also, the drug produced a mild decrease in systemic arterial pressure with an elevation of forearm blood flow and thus a fall in calculated forearm vascular resistance (Fig 1 and 3).

The finding that sublingual nitroglycerin results in dilation of forearm veins and peripheral pooling of blood suggests the possibility that this drug might reduce ventricular size and intramyocardial tension, and thereby reduce myocardial oxygen requirements. In this manner, nitroglycerin influences the myocardial oxygen supply demand toward normal. Consonant with this view is that sublingual nitroglycerin decreases both end-diastolic and end-systolic dimensions of the intact human heart. In addition, the direct arteriolar dilator action of the drug lowers systemic arterial pressure. This effect further reduces myocardial oxygen consumption by decreasing systolic intraventricular pressure and by lowering the resistance to ventricular ejection and thus allowing greater emptying of the chamber. The direct action on the veins producing venous pooling and diminishing ventricular preload (reduced end-diastolic volume) appears to dominate over that on the arterioles of decreasing ventricular afterload (diminished systemic vascular resistance), since the cardiac output and stroke volume are reduced in normal subjects. The nitrites do not possess direct actions on ventricular contractility and thus do not influence myocardial oxygen consumption by this mechanism, although reflex cardiac stimulation induced by the depressor action of the drugs can indirectly increase contractility and raise oxygen needs.

It is concluded that the effectiveness of sublingual nitroglycerin in relieving ischemic pain is importantly related to the peripheral vasodilator action of the drug which results in reductions of ventricular loading and oxygen needs, despite the absence of accompanying decrease in coronary vascular resistance and improvement in diminished coronary blood flow. In other patients with angina pectoris, it is possible that the beneficial action is related to a combination of peripheral and coronary vasodilator effects in whom the coronary vessels and available collateral channels are capable of at least some dilation.

These considerations concerning the actions of nitroglycerin and angina pectoris are applicable to myocardial ischemia whether it is due to coronary artery disease or, in contrast, to ventricular hypertrophy which has exceeded the supply capacity of a normal coronary vascular bed such as in aortic stenosis and in idiopathic hypertrophic cardiomyopathies. Thus, a peripheral circulatory mechanism is described which is immediately available for the relief of angina pectoris in response to nitroglycerin and is operative even in the absence of action of the agent on the coronary blood vessels.

Inhaled Amyl Nitrite

The effects of inhaling amyl nitrite differ strikingly from those observed after sublingual nitroglycerin. These differences are due to the rapid entrance of the nitrite into the circulation, thereby producing marked direct arteriolar dilation and large decrease in arterial pressure (Fig 4), intermixed with powerful reflex sympathetic activity induced by baroreceptor stimulation and hyperventilation. Thus, arterial pressure falls precipitously while forearm blood flow increases, indicating a marked fall in vascular resistance (Fig 4 and 5A). These changes are opposed by the activity of the sympathetic nervous system since, after adrenergic blockade, amyl nitrite results in even greater reductions in arterial pressure and calculated vascular resistance.
FIGURE 5. A. Two segments of the recording, obtained by the acute venous occlusion method discussed in the legend to Figure 1, in a normal subject before and 30 seconds and 45 seconds after the inhalation of amyl nitrite. The tracing on the left was obtained during the control period and that on the right shows two occlusion curves recorded successively 30 and 45 seconds after the drug. For abbreviations and explanation of values below the tracing see legend of Figure 1. Note that after amyl nitrite the rate of rise of pressure in the forearm vein has increased, while the rate of rise of the plethysmographic tracing has increased only slightly, indicating that profound venoconstriction had occurred. B. Two segments of recordings following adrenergic blockade with guanethidine obtained in the same subject whose tracings are shown in Figure 5A. Amyl nitrite increased the rate of rise of forearm circumference proportionately more than the rate of rise of venous pressure after guanethidine than before, indicating that the venoconstriction which had occurred was less than that noted before guanethidine had been given in Figure 5A. (Reproduced by permission; Mason DT, Braunwald E, Circulation 32:755, 1965.)

Accompanying the marked arterial depressor action of inhaled amyl nitrite is powerful reflex venous constriction which overrides the direct effect of venodilation of the nitrite (Fig 5A and 6A). Thus, the cardiac output is elevated as a consequence of marked decline of the resistance to ventricular emptying (diminished afterload) coupled with both the reflex constricting effect on the veins enhancing venous return and sympathetic stimulation of cardiac contractility. That this venoconstriction is reflex in origin is shown by the finding that the response was markedly attenuated by the antiadrenergic agents, guanethidine or reserpine (Fig 5B and 6B). The efficacy of inhaled amyl nitrite in patients with angina pectoris is related to its predominant
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VENOUS TONE - mm.Hg/ml.

FIGURE 6. Recordings of arterial and venous pressures and forearm circumference following amyl nitrite inhalation in a normal subject. Venous tone was determined by the same equilibration method explained in the legend to Figure 2. Tracing A was recorded during the control period and B after guanethidine. After adrenergic blockade (B) amyl nitrite decreased forearm volume considerably less than during the control period (A), indicating that venoconstriction was markedly diminished. (Reproduced by permission; Mason DT, Braunwald E, Circulation 32:755, 1965.)

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effect on the arteriolar bed of markedly reducing systemic vascular resistance.\textsuperscript{12,13} In this manner, resistance to ventricular emptying is diminished, thereby reducing both intramyocardial tension and myocardial oxygen consumption. Thus, the tendency for reflex augmentation of venous return to increase the preload and work of the ventricle is overridden by the more striking effect of inhaled amyl nitrite of reducing ventricular afterload with consequent overall reductions of intraventricular systolic pressure and volume and diminished myocardial tension and oxygen demand. Paradoxically, the possibility is suggested that, on occasion, the amyl nitrite-induced rapid and marked fall of blood pressure might actually worsen ischemia if the reduction of coronary perfusion pressure causes a decline in coronary blood flow which is relatively greater than decreased oxygen needs.

Unified Concept of Hemodynamic Action of Nitrites

The literature concerning the cardiocirculatory actions of the nitrite compounds has been contradictory and difficult to interpret. It now appears that much of this confusion has arisen from the assumption that the actions of the nitrites and organic nitrates are similar, whether they are administered orally, intravenously, or inhaled. Thus, it is improper to conclude that the direct and reflex indirect effects of nitroglycerin given sublingually, either qualitatively or quantitatively are the same as those determined from studies in which nitroglycerin is given intravenously or in which amyl nitrite is inhaled. It is concluded that each of the nitrite drugs directly relax vascular smooth muscle in all of the regional circulatory beds. When the nitrites enter the circulation slowly, such as following sublingual nitroglycerin or oral sodium nitrite, they dilate both the systemic arterial and venous beds.\textsuperscript{19,25,26} In this manner, arterial blood pressure falls slightly and central venous pressure is reduced, resulting in peripheral venous pooling and reduction in stroke volume and cardiac output.

In contrast, the rapid introduction of the nitrites into the circulation following inhalation of amyl nitrite or the intravenous administration of nitroglycerin,\textsuperscript{4,19} results in profound arteriolar dilation and thereby marked fall in systemic arterial blood pressure. This marked depressor effect leads to carotid baroreceptor stimulation and a marked reflex chronotropic effect and some attenuation of the intense direct arteriolar dilation. Although present evidence indicates that changes in blood pressure within the physiologic range in man do not produce reflex alterations in venous tone, it appears that the
NITRITES

Actions on the Peripheral Circulation

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Figure 7. Actions of nitrite compounds on cardiocirculatory dynamics. The effects of slowly absorbed sublingual nitroglycerin and oral sodium nitrite are contrasted to those of fast-acting inhaled amyl nitrite and intravenous nitroglycerin.

hyperventilation and anxiety which accompany the inhalation of amyl nitrite are largely responsible for the reflex venoconstriction. The cardiac output is elevated as a consequence of the marked decline of resistance to ventricular emptying coupled with predominant reflex venoconstriction and reflex enhancement of cardiac contractility. Conversely, the decrease in blood pressure following the oral administration of nitroglycerin is less marked and is not associated with an increase in respiratory rate. Thus, reflex venoconstriction is mild or does not occur and the direct predominant action of venodilation is observed. From these observations, it appears that the principal direct action of sublingual nitroglycerin in intact man is on the veins and that of inhaled amyl nitrite on the arterial bed.

LONG-ACTING ORGANIC NITRITES

From the observations presented, it is evident that the therapeutic efficacy of sublingual nitroglycerin in relieving angina pectoris is dependent to a major extent on its ability to dilate the peripheral arterioles and veins, thereby reducing ventricular preload and afterload which lead to reduction of myocardial oxygen requirements. The possibility was considered that long-acting nitrates might compromise the beneficial peripheral vascular effects of nitroglycerin, if the chronic administration of long-acting nitrate compounds produces nitrite tolerance. It was found that the administration of isosorbide dinitrate for six weeks did not alter the sublingual nitroglycerin-induced arteriolar dilation, but did significantly reduce the venodilator response to sublingual nitroglycerin. Thus, cross-tolerance between the long-acting nitrite and nitroglycerin was demonstrated in veins, an effect which is potentially deleterious. In addition, it appeared that tolerance may have developed to the long-acting nitrite itself since venous tone and arterial resistance were not diminished following its chronic administration, although the possibility remains that the agent did not produce vasodilation initially. It is logical to postulate that chronic reduction of the loading conditions and work of the heart might reduce the frequency and intensity of angina pectoris, and to speculate that the chronic administration of a long-acting vasodilator drug should affect such a decrease of ventricular loading and thereby diminish myocardial oxygen needs. In the case of the long-acting nitrite vasodilators, it appears that at least some of the potentially beneficial action of chronically reducing myocardial loading might be impaired by venodilator tolerance, an effect that also might attenuate the effectiveness of sublingual nitroglycerin.

COMBINATION OF NITRITES WITH PROPRANOLOL

The beta-adrenergic receptor blocking drug, propranolol, inhibits sympathetic stimulation of the heart at rest and during exercise. Thus, myocardial oxygen requirements are diminished principally by the reduction in heart rate and diminished contractility. It is apparent that a combination of propranolol and nitroglycerin is potentially more beneficial than the use of either drug separately, since these two agents act through different mechanisms in diminishing the needs of the heart for oxygen. In addition, the favorable dilator effects of nitroglycerin on the peripheral vessels are opposed somewhat by reflex activation of the sympathetic nervous system. Further, the extent of reduction...
of myocardial oxygen demands afforded by direct systemic vasodilation is opposed by the reflex chronotropic and inotropic effects of cardiac adrenergic stimulation. It is postulated that the beneficial effects of sublingual nitroglycerin of reducing myocardial oxygen requirements might be overridden by intense baroreceptor responses, perhaps such as in younger patients with angina pectoris in whom reflex activity is relatively strong. It would appear that the salutary direct vasodilator effect of nitroglycerin can be extended by its combination with propranolol. Thus, the activation of the myocardium resulting as a reflex response to the depressor action of nitroglycerin is blocked by propranolol. Although recent studies have suggested a synergistic effect between isosorbide dinitrate and propranolol,\textsuperscript{30}\textsuperscript{--}\textsuperscript{31} other observations are not consistent with this view.\textsuperscript{31} Thus, the present remarks are confined to the use of nitroglycerin for abolishing acute ischemic pain in the presence of chronic treatment with propranolol.

**Conclusions**

It seems likely that the remarkable clinical effect of sublingual nitroglycerin of interrupting the pain of myocardial ischemia is largely dependent on the peripheral circulatory actions of the agent, particularly its powerful dilator effect on the systemic veins which produces systemic venous pooling and reduces venous return to the heart. Parenthetically, this venodilator action of nitroglycerin should be useful in the relief of acute pulmonary edema in patients with congestive heart failure.\textsuperscript{32} In regard to angina, the size of the heart and intramyocardial systolic tension are diminished, through reduction of ventricular preload by the drug thus leading to a decrease in the myocardial oxygen requirements and rapid relief of ischemic pain. Thus, this extra-coronary mechanism of vasodilation for relief of angina is operative even when the diseased coronary vasculature is not capable of dilating. Consistent with this drug-effect reduction of ventricular preload is the finding that sublingual nitroglycerin rapidly reduces the abnormally elevated end-diastolic pressure in the left ventricle while relieving angina.\textsuperscript{3} In addition, nitroglycerin-induced decline in systemic venous return provides an explanation for the syncopal episodes which are occasionally seen with nitroglycerin,\textsuperscript{33} the decrease caused by the agent of the prominent $a$ wave of the apex cardiogram in patients with angina,\textsuperscript{34} and the action of the drug of intensifying obstruction to left ventricular outflow in idiopathic hypertrophic sub-aortic stenosis.\textsuperscript{35}

It is of interest to point out that, in patients with coronary disease, the degree of development of collateral circulation in the heart has been demonstrated to be most dependent on the severity of regional atherosclerosis itself.\textsuperscript{36--37} Thus, it is postulated that, although these collateral channels appear to be of certain quantitative importance, they represent response to ischemia and impairment of native circulation. This view which directly relates the level of coronary blood flow to the severity of occlusive disease alone is consonant with the theme presented in this review that the antianginal action of nitrates is limited to the ability of the agents to lower myocardial oxygen demands rather than to improve the reduced coronary blood flow. Also consistent with these concepts implying that the therapeutically responsive variable in coronary disease is myocardial oxygen demand is the relief of ischemic pain by a variety of other means which also lower myocardial oxygen consumption such as propranolol,\textsuperscript{38} carotid sinus nerve stimulation,\textsuperscript{39} phlebotomy,\textsuperscript{40} weight reduction, and exercise training.\textsuperscript{41--42} The value of maintaining plasma lipids within normal limits at present appears directed at prevention and reduction of progression of plaques rather than resolution of existing atheromas.\textsuperscript{43} It appears that once a patient with coronary disease develops angina pectoris, the disease itself usually worsens faster than the formation of collaterals and perhaps any spontaneous decrease of pain might be due to necrosis of cardiac cells and thus diminished oxygen demands of the heart. From these observations, the various medical approaches in the treatment of angina are mediated by the common mechanism of lowering myocardial oxygen consumption rather than by favorably affecting the basic pathophysiologic abnormality of diminished coronary blood flow. It appears that the only method presently available for substantially elevating blood flow to the ischemic myocardium is coronary bypass with saphenous vein anastomosis in carefully selected patients,\textsuperscript{44--45} and recent data suggest that myocardial revascularization techniques to increase compromised blood flow through the development of collateral channels are largely ineffective.\textsuperscript{46--47}

In conclusion, the fundamental action of each of the nitrite compounds is a generalized direct vasodilation. With the rapid introduction of these agents into the circulation, there is a mixture of this direct relaxing effect on vascular smooth muscle and indirect reflex vasoconstrictor actions. The relief of angina pectoris with sublingual nitroglycerin appears to be most related to direct venodilation, while with inhalation of amyl nitrite this symptom is
abated by marked direct arteriolar dilation. Angina pectoris can be considered pathophysiologically to result from an unfavorable relation of myocardial oxygen requirements to coronary blood flow. In the treatment of ischemic pain, the variable factor mediating the beneficial effects of the nitrates is reduction of myocardial oxygen requirements. Moreover, the common mechanism by which nearly all types of antianginal measures relieve ischemic pain is the decrease of oxygen needs of the heart, rather than the improvement of coronary blood flow. Finally, since the extent of development of coronary collateral circulation is most critically related to the severity of coronary disease itself, it appears that the responsive variable which allows improvement by both spontaneous and therapeutic means is reduction of myocardial oxygen consumption rather than the traditional concept of augmentation of diminished coronary blood flow.

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NIH Pulmonary Academic Awards

The National Heart and Lung Institute, National Institutes of Health, is inaugurating a new program of Pulmonary Academic Awards for the purposes of 1) improving pulmonary training programs in U.S. schools of medicine or osteopathy and 2) fostering academic careers in the respiratory-disease field. The program is designed to meet the rapidly growing need for highly trained researchers, clinicians, and teachers concerned with pulmonary physiology and with the prevention, diagnosis, and relief of emphysema and related chronic respiratory disorders.

Emphysema, chronic bronchitis, and similar chronic lung disorders currently kill an estimated 36,000 Americans each year and partially or completely disable more than a million others. Despite the already serious and steadily increasing health problem posed by these diseases, medical schools have experienced difficulties in attracting sufficient numbers of well-qualified students into the respiratory-disease field. As a result, many hospitals are unable to fill vacancies for chiefs of pulmonary sections and many medical schools have been unable to fill academic posts in the respiratory-disease area.

To help overcome these problems, Pulmonary Academic Awards, made on a competitive basis to schools of medicine or osteopathy, will provide support for periods of five years, with the possibility of renewal for an additional three years, to enable recipient schools to design challenging respiratory-disease curricula that will attract high-quality students into this field and provide them with superior training in the most modern techniques. • attract promising young teacher-investigators into academic careers in the respiratory-disease field and strengthen the pulmonary training staffs of recipient institutions.

• facilitate the exchange of ideas, methods, and techniques of multidisciplinary pulmonary training among recipient institutions.

Awards will be limited to one per eligible school, with the number of awards to be made during 1971 and subsequent years contingent upon the availability of funds for this program.

The National Heart and Lung Institute hopes, through this program, to provide an impetus for schools that do not have an identifiable pulmonary curriculum to develop one; for schools that have a pulmonary curriculum that needs strengthening to improve it; and for schools that need someone to devote a major effort to the pulmonary curriculum, either to support a member of the staff or to recruit someone for the purpose. Medical schools and schools of osteopathy are being invited to submit applications for these awards to the National Institutes of Health by February 15, 1971. Instructions for making application and policies governing Pulmonary Academic Awards may be obtained from the Training Grants and Awards Branch, National Heart and Lung Institute, National Institutes of Health, Bethesda, Maryland 20014.