Clinical communications

The effects of sublingual nitroglycerin on myocardial blood flow in patients with coronary artery disease or myocardial hypertrophy

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Since the introduction of the organic nitrate compounds, glyceryl trinitrate and amyl nitrate, in the 1860's for the treatment of angina pectoris, they have maintained a dominant position among the group of pharmacologic agents used for the relief of this distressing and serious syndrome. Their proven efficacy has made them the standard by which all other antianginal drugs are judged. Yet, despite a century of clinical experience, the mechanism by which they produce their therapeutic response is still unclear. The original rationale for the use of nitrates was derived from the belief that anginal pain was brought about by peripheral vasoconstriction based on clinical observations of changes in peripheral pulses during an attack.[1] Subsequent studies have led to the conclusion, now commonly accepted, that angina pectoris results from myocardial ischemia elicited by a disturbance in the balance between coronary oxygen supply and myocardial oxygen demand. Gorlin[2] and his colleagues have recently documented the occurrence of cardiac ischemia by demonstrating myocardial lactate production during "spontaneous" angina pectoris. The demonstration of nitrate induced coronary vasodilatation in the revived human heart during Langendorff perfusion,[3] in patients studied by coronary arteriography,[4,5] as well as in many animal experiments, gives credence to the theory that the nitrates relieve the pain of angina through coronary vasodilatation and consequent improvement in coronary blood flow and myocardial oxygen supply. However, the clinical ineffectiveness of several drugs which have been shown experimentally to produce coronary vasodilatation, and the failure to detect increases in myocardial blood flow following sublingual administration of ni-

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Received for publication July 22, 1968.
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troglycerin in patients with coronary disease[6-9] does not substantiate this theory and, in fact, this evidence can be used to support the assumption made over 100 years ago that the therapeutic effect of the nitrates stems from their peripheral action.

Bernstein and associates[9] utilizing the xenon-133 method to measure myocardial blood flow in patients with arteriographically demonstrable coronary artery disease were able to show increases in myocardial flow in these patients following intracoronary injection of nitroglycerin, but not after sublingual administration. Based on their results they proposed the theory that nitroglycerin exerts a biphasic action consisting of an initial increase in myocardial blood flow subsequent to coronary vasodilatation and reduction in coronary vascular resistance, followed by a decrease in myocardial flow as the systemic effects of the drug predominate and arterial pressure falls.

Using the same radioactive inert gas method we have been able to observe increases in myocardial blood flow after sublingual administration of nitroglycerin in some patients with coronary disease by obtaining such measurements at a time concomitant with the clinical onset of action and before the systemic effects of the drug have become firmly established.

Methods

Nine patients undergoing selective coronary arteriography during cardiac catheterization were studied. All subjects were fasting and premedicated with 75 to 100 mg. of meperidine HCl and 50 to 100 mg. of pentobarbital or secobarbital. Coronary artery catheterization was performed via a right brachial arteriotomy utilizing a Sones catheter. Proper position of the catheter was confirmed by injection of 1 to 2 ml. of diatrizoate. Myocardial blood flow was measured by the selective injection of xenon-133 in saline into the right coronary artery in all cases and calculated in milliliters per minute per 100 Gm. from the rate of precordial disappearance of radioactivity detected by an external scintillation counter as originally described by Ross and associates.[10] A five-minute interval was allowed between diatrizoate injection and the initial myocardial blood flow measurement.

Following two control measurements of myocardial blood flow, subjects were given 0.3 mg. of nitroglycerin sublingually and xenon-133 injected 90 to 120 seconds later. In six of the nine subjects, myocardial blood flow was also measured 5 to 6 minutes after nitroglycerin administration. The coronary catheter was left in place throughout the study to allow rapid repeated measurements of myocardial blood flow and to avoid the necessity for additional injections of contrast medium. No significant obstruction to coronary flow by the catheter could be detected during the procedure. No subject experienced angina or electrocardiographic changes and in three patients no differences between control measurements were observed whether the catheter remained in place or was immediately withdrawn following injection of the xenon-133 solution.

Mercury strain gauge digital plethysmography was utilized to determine the onset of peripheral vasodilatation following nitroglycerin administration. This was considered the point at which a sustained increase in pulse amplitude was first observed.

Subjects were separated by clinical and arteriographic criteria into three categories: normal, those with coronary artery disease, and those with myocardial hypertrophy. Only one subject (H. M.) was completely normal from a cardiovascular standpoint. His pain syndrome was not typical of angina pectoris, and physical examination, resting and exercise electrocardiograms, and arteriography were all normal.

Five patients were considered to have coronary artery disease on the basis of abnormal arteriograms and the presence of at least one of the following: (1) typical history for angina pectoris, (2) positive exercise electrocardiogram, and (3) documented history of myocardial infarction.

The remaining three subjects presented with histories of congestive heart failure, persistent cardiac enlargement and left ventricular hypertrophy. Coronary arteriograms were normal in two of these subjects who were felt to have idiopathic myocardial disease. One of these subjects (P. B.) had typical anginal episodes re-

lieved by nitroglycerin. The third subject in this group (W. H.) had long-standing rheumatic mitral disease and abnormal arteriograms. However, he had no history of angina or previous myocardial infarction. Exercise electrocardiograms were not performed in these three patients.

Results

The variability in control measurements for these studies was small, averaging ± 3 per cent of the mean control value for each subject. This is probably related to the fact that in most instances the catheter was left in place and not repositioned between measurements. The results are summarized in Table I and presented graphically in Fig. 1.

Group I, normal. The single normal subject showed an initial 14 per cent increase in myocardial flow. This measurement began 102 seconds after drug administration and 29 seconds before an increase in peripheral pulse amplitude was noted. A second measurement taken 370 seconds following drug revealed myocardial flow had fallen to 8 per cent below control values.

Group II, coronary artery disease. Initial measurements of flow in these five patients started an average of 109 seconds after drug and 21 seconds before onset of peripheral vasodilatation. One subject showed no change in myocardial flow, while four showed increases ranging from 3 to 13 per cent. The mean increase for this group was 5 per cent above control. A second measurement was obtained in three of these subjects 320 to 330 seconds following drug administration. Two subjects demonstrated decreases of 10 and 23 per cent below control; the remaining subject showed essentially no change.

Group III, myocardial hypertrophy. Flow measurements in these three subjects were taken an average of 97 seconds after drug and 25 seconds prior to the onset of peripheral pulse changes. Decreases in myocardial flow from 7 to 12 per cent were detected in all three. Repeat measurements were obtained in two of the three subjects 306 to 330 seconds following drug administration and revealed further decreases to 17 and 15 per cent below control levels.

Discussion

The measurement of myocardial blood flow by direct intracoronary injection of solutions of radioactive inert gas is based on the theory that the rate of exchange of an inert gas between tissue and blood is limited by blood flow.[11] Following the injection, coronary arterial blood concentration of the tracer becomes essentially zero and the gas which has been taken up by the myocardium begins to diffuse back

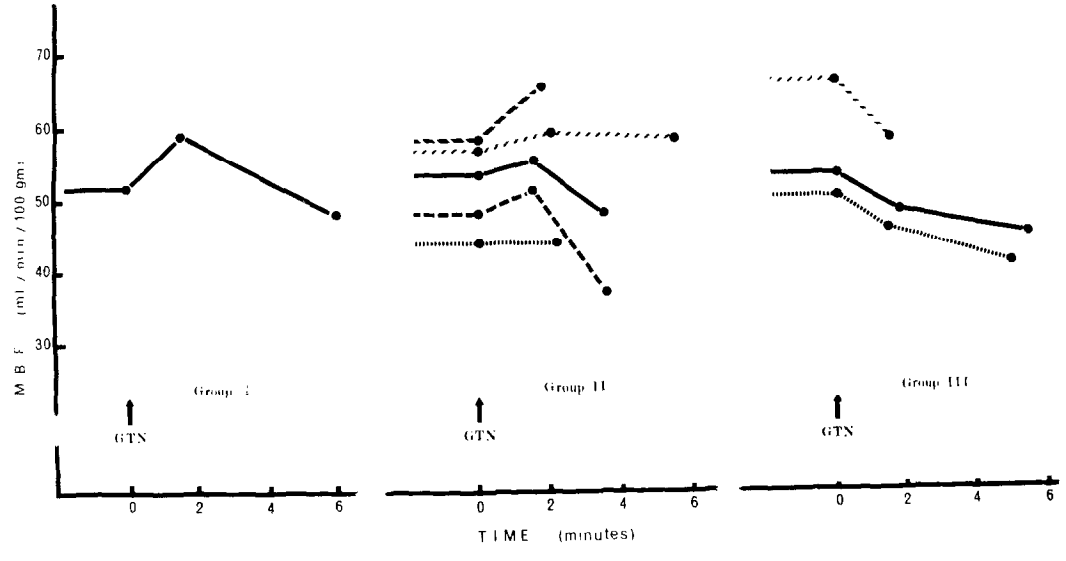

Fig. 1. Effects of sublingual glyceryl trinitrate, 0.3 mg., on myocardial blood flow in man. See text for details

Table I. Effect of glyceryl trinitrate on myocardial blood flow in man*

Subject	Sex	Age	Group†	MBF (ml./min./100 Gm.)			MBF (% change§		MBF time (sec.)		Onset peripheral vasodilatation (sec.)
				Control‡	Early	Late	Early	Late	Early	Late	
H. M.	M	31	I	52	59	48	+14	−8	102	370	131
R. H.	M	42	II	57	59	58	+4	+2	120	330	98
H. B.	M	36	II	58	65		+13		105		120
H. E.	M	49	II	44	44		0		130		118
G. R.	M	48	II	53	55	48	+3	−10	93	320	189
W. K.	M	46	II	48	51	37	+6	−23	96	330	127
J. B.	M	43	III	66	58		−12		90		119
P. B.	M	47	III	50	46	41	−7	−17	95	306	136
W. H.	M	46	III	53¶	48	45	−9	−15	105	330	112

*0.3 mg. administered sublingually.
†Group I, normal; group II, coronary artery disease; group III, myocardial hypertrophy.
‡Average of at least two measurements during control period.
§Difference between treatment and control measurements expressed as per cent of average control.
Interval from drug administration to start of xenon-133 washout.
¶Represents single measurement during control period.

into the blood. The exponential rate of washout of myocardial radioactivity is thus, theoretically, a function of capillary blood flow and is detected by an external counter positioned over the precordium.

Due to the rapid pulmonary excretion of the gas and because satisfactory time-concentration curves of precordial radioactivity are obtained within two minutes of introduction of the tracer into the circulation, this method permits rapid repeated measurements of regional blood flow. Certain considerations must be taken into account, however, when attempting to interpret the results of such flow determinations. Areas of myocardium with impaired circulation may receive only small amounts of the tracer compared to the major volume of tissue perfused and, hence, contribute relatively little to the washout curve. In addition, when one measures the rate of clearance of a radioactive gas, the result reflects both blood flow and volume of distribution of the tracer, clearance rate being related directly to the former but inversely to the latter. If flow and volume change proportionately there will be no difference in the rate of washout and thus no change in flow will be detected.[12]

In the studies reported here, the coronary catheter was not manipulated between isotope injections and since it seems unlikely that nitroglycerin would produce a decrease in the volume of tissue being perfused, the increase in clearance rate of myocardial radioactivity observed in some of the subjects after drug administration most likely reflects an actual increase in regional blood flow.

The early increase in myocardial blood flow after sublingual nitroglycerin administration was quite transient and presumably accounts for the inability of previous studies to detect this response using the nitrous oxide[6] or rubidium-84[8] methods since they require a 7 to 15 minute period of measurement. Bernstein and associates[9] utilizing the xenon-133 method could not demonstrate increases in myocardial blood flow after sublingual nitroglycerin, however, they did not start their measurements until three minutes after drug administration.

Due to certain limitations, the number of subjects we were able to study was small. Nevertheless, we feel that the results tend to substantiate the biphasic theory of action of nitroglycerin in some patients with arteriographically demonstrable coronary artery disease. Whether or not this biphasic action is responsible for the beneficial effects of the drug during

an anginal attack, however, remains to be demonstrated.

The actual hemodynamic events which can occur during an anginal attack and the subsequent administration of nitroglycerin are shown in Gorlin's[2] reported observations on myocardial blood flow made during a spontaneous episode of angina in a patient with severe coronary disease. At the time of pain, hypertension and a relative tachycardia were noted and myocardial flow was 51 ml. per minute per 100 Gm. A control measurement taken earlier during the study, when the patient was normotensive was 71 ml. per minute per 100 gm. Nitroglycerin was administered sublingually resulting in a rapid increase in myocardial blood flow to 88 ml. per minute per 100 Gm. and thereafter relief of pain and return of blood pressure, pulse, and electrocardiogram to base line.

The changes in myocardial blood flow after nitroglycerin in the subjects with myocardial disease is of some interest. The oxygen requirements of an enlarged, hypertrophied ventricle are increased due to an increase in number of contractile elements[13] and the increased wall tension required to maintain a systolic ventricular pressure.[11] At the same time, myocardial capillary concentration falls in proportion to the increase in fiber size and heart weight[15] resulting in a relative decrease in capillary blood supply. Presumably under these circumstances a "coronary reserve" no longer exists and with increased myocardial oxygen demand, angina pectoris and cardiac lactate production can occur in the absence of coronary disease[2] as exemplified by Subject P. B.

The decrease in myocardial blood flow following nitroglycerin administration in these patients is probably related to a decrease in ventricular size produced by the drug[16,17] with a consequent decrease in the ventricular tension-time index and a corresponding decrease in myocardial oxygen requirements.[18]

Summary

Using selective intracoronary injections of xenon-133 in saline, the effect of sublingual nitroglycerin on myocardial blood flow was studied in nine patients undergoing cardiac catheterization. One normal patient showed a 14 per cent increase in flow, 1½ minutes after drug administration, with a subsequent decline to 8 per cent below control at 6 minutes. Four of five patients with coronary artery disease showed increased flows of 3 to 13 per cent at 1½ to 2 minutes after taking the drug. In two of these subjects, flow decreased to 10 to 23 per cent below control at 5½ minutes. In the remaining three subjects with cardiomegaly and left ventricular hypertrophy, nitroglycerin produced a decrease of 7 to 12 per cent in myocardial blood flow at 1½ minutes and a further reduction to 15 to 17 per cent below control in two of the subjects at 5 minutes.

These results are felt to substantiate the theory that in some patients with coronary artery disease, nitroglycerin exerts a biphasic action with an initial increase in myocardial blood flow followed by a decrease in flow as the systemic effects of the drug become manifest. This biphasic action was not seen in patients with cardiac enlargement and hypertrophy.

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