Effect of Nitroprusside on Regional Myocardial blood Flow in Coronary Artery Disease

Results in 25 Patients and Comparison with Nitroglycerin

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SUMMARY The effect of nitroprusside on regional myocardial specific blood flow (RMBF) was evaluated in 25 patients with the xenon-133 washout technique. Six patients were normal (group 1), six patients had coronary artery disease without collateral vessels (group 2), and thirteen patients had coronary artery disease with collateral vessels (group 3). In group 1, RMBF was unchanged following nitroprusside. RMBF decreased significantly in both group 2 and group 3, including seven patients in group 3 with high-grade collateral vessels. The results were compared to the effect of nitroglycerin in 31 patients previously studied using the same technique.

VASODILATOR THERAPY with nitroprusside and nitroglycerin has been shown to improve left ventricular performance in some patients with congestive heart failure due to ischemic heart disease. Although the effects on preload and afterload are different, both drugs reduce elevated left ventricular filling pressures and both (but especially nitroprusside) may improve cardiac output. Both drugs also decrease myocardial oxygen demand but only nitroglycerin has been shown to consistently reduce ischemic injury in patients with acute myocardial infarction. Reports of a beneficial effect of nitroprusside on indices of ischemia are limited, and it has been suggested that nitroprusside may actually increase ischemic injury in some patients by redistributing blood away from the ischemic area of myocardium. Thus, the present study was designed to evaluate the effects of nitroprusside on regional myocardial blood flow. The results are compared to the effect of nitroglycerin in similar patients reported in a previous study.

Mean arterial pressure and pressure-rate product were comparably reduced by both drugs. In contrast to the findings with nitroprusside, after sublingual nitroglycerin RMBF decreased markedly in normals and increased in patients with coronary artery disease and high-grade collaterals. The data suggest that nitroprusside may primarily affect resistance vessels within the coronary circulation, as opposed to the effect of nitroglycerin on conductance vessels. Thus, nitroprusside could result in redistribution of blood flow away from ischemic areas and potentially increase ischemic injury in some patients with coronary artery disease.

Materials and Methods

The study was performed in 25 patients undergoing cardiac catheterization for evaluation of chronic chest pain. Nineteen patients had coronary artery disease and six were normal. No attempt was made to alter the patients' chronic medical therapy and most were receiving propranolol at the time of the study. Informed consent was obtained in each case.

Standard left heart catheterization was performed in the fasting state after premedication with diazepam (10 mg p.o.). Pressures were measured through fluid-filled catheters connected to an external strain gauge transducer. Coronary angiography was performed using the femoral approach.

Coronary angiograms were evaluated independently by two observers. Collateral vessels were graded according to their angiographic appearance. Thus, faint opacification of an artery distal to a stenotic lesion from several small collateral vessels was classified grade 1; moderate distal opacification from several small vessels, grade 2; dense opacification of the distal vessel from one large or several small collateral vessels, grade 3; dense opacification of the distal vessel from two large collateral vessels, grade 4. The vessels from which collaterals arose were also evaluated.
Collaterals arising from vessels without significant lesions were classified as noncompromised, while those arising distal to a 75% or greater lesion were judged to be compromised.

The study was performed at the end of the catheterization procedure, at least 15 minutes following the last coronary artery injection and 30 minutes following administration of nitroglycerin prior to the coronary angiography. Measurements of regional myocardial specific blood flow were made using the xenon-133 washout technique as previously described in detail. Briefly, a Judkins coronary catheter was positioned in the left main coronary artery with the patient in the 30° left anterior oblique position, and control hemodynamic measurements were recorded. Immediately thereafter, 20–25 mCi of xenon-133 was injected into the left coronary artery and flushed with 3 cc of saline so as to enter the coronary as a bolus. Washout curves were obtained over the first 90 seconds following injection using an Anger scintillation camera as an external detector. Data were acquired and processed in a general purpose digital computer (PDP-11/20). Blood flow in ml/100 g/min was calculated from the initial 40 second washout of xenon-133 (using the Key formula) in the distal quadrants overlying the left anterior descending and left circumflex arteries. Regional myocardial specific blood flow in each patient was represented by the mean of the two values in order to provide a single measurement for comparison with other patients, both in the present study and in the nitroglycerin study.

In addition to performing quadratic analyses, we obtained functional images in some of the patients by electronically dividing the camera crystal into a 32 by 32 matrix and calculating blood flow in each matrix area using the initial slope method described. These images represent flow rates and not concentration of the xenon-133. The highest flow rate was assigned the brightest intensity level (fig. 1). These images graphically depicted regional myocardial specific blood flow patterns before and after administration of nitroprusside and complemented the quantitative quadratic flow data.

Following collection of control hemodynamic and blood flow data, nitroprusside was infused in a dose sufficient to lower mean arterial pressure by 10 to 15%, which was the reduction observed in our previous study using the standard clinical dosage of sublingual nitroglycerin (0.4 mg). Infusion rates varied from 25 to 100 µg/min, with a mean of 40 µg/min. When blood pressure had been stabilized for 2–3 minutes at the desired level, repeat hemodynamic and blood flow measurements were made. No complications occurred as a result of the study.

The data were analyzed by evaluating the effect of nitroprusside in three groups of patients. As with our earlier study, group 1 consisted of patients who had normal coronary angiography. Group 2 consisted of patients with coronary artery disease, defined as lesions greater than 75% of the intraluminal diameter of either the left anterior descending or left circumflex artery, or one of their major branches (with or without concomitant right coronary artery disease) and no visible collateral vessels to the stenotic left coronary vessel from either the left or right coronary systems. Group 3 consisted of patients with coronary artery disease and varying grades of collateral vessels. Comparisons were made in each group between control and nitroprusside data using paired t-tests.

The effect of nitroprusside on hemodynamic data and regional myocardial specific blood flow was also compared to the effect of sublingual nitroglycerin on similar subgroups of patients. The nitroglycerin data had been previously obtained in 31 patients using identical techniques. Comparisons between nitroprusside and nitroglycerin data in the various subgroups were made using unpaired t-tests.

Results

Effect of Nitroprusside

The effect of nitroprusside on hemodynamics and regional myocardial specific blood flow in the three groups is shown in table 1. The hemodynamic effect was similar in all three groups. Mean and systolic aortic pressure were comparably reduced in each group. Heart rate was unchanged in the two groups with coronary artery disease, but increased slightly in the normal group (80 ± 5 (SEM) control, 84 ± 5 nitroprusside, P < 0.05). Pressure-rate product declined significantly in each group, the range being −10 ± 4% in group 1, −14 ± 5% in group 2, and −9 ± 3% in group 3.

Values for regional myocardial specific blood flow were progressively lower from group 1 to group 3, but the difference was not significant. Following nitroprusside,

![Figure 1. Patient 23 (group 3). Functional images before and after intravenous infusion of nitroprusside, and a subtraction image (baseline flow — nitroprusside flow). The increasing intensity of the gray to white scale reflects increasing flow rates (not concentration) of xenon-133, except in panel C in which increasing intensity reflects increasingly greater flow during the baseline study rather than after nitroprusside. Before nitroprusside infusion, the underperfused area was in the distal left circumflex region (arrow in panel A). During nitroprusside infusion (panel B), the tissue perfused by the left circumflex artery became even more underperfused relative to the left anterior descending artery distribution. The net decrease in perfusion is emphasized by subtracting the nitroprusside image from the baseline image. Increasing intensity reflects areas that are less well perfused as a result of the drug’s actions (arrow in panel C) and vice versa. On coronary arteriography, this patient demonstrated a normal left anterior descending artery which supplied a high-grade collateral vessel to a severely stenosed left circumflex artery. Thus, this pattern of altered regional myocardial blood flow suggests a coronary steal effect.](http://circ.ahajournals.org/content/73/4/733/F1.large.jpg)
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ABBREVIATIONS: CAD = coronary artery disease; MI = myocardial infarct; LVEDP = left ventricular end-diastolic pressure; C = control state; NP = during nitroprusside infusion; RMBF = regional myocardial specific blood flow; CVR = coronary vascular resistance; LAD = left anterior descending artery; LCF = left circumflex artery; RCA = right coronary artery.

Comparison with Nitroglycerin

The hemodynamic effects of nitroprusside and nitroglycerin were similar in the present study. Mean arterial pressure was comparably reduced (−13 ± 2% with nitroprusside and −14 ± 2% with nitroglycerin), and heart rate showed little change following both drugs. Pressure-rate product also declined comparably and there was no significant difference in the percent decline of pressure-rate product following the two drugs in any group.

The different effect of the two drugs on regional myocardial specific blood flow in normal patients is shown in figure 3A. Nitroglycerin significantly reduced regional flow, while there was no significant change following nitroprusside (−31 ± 5% with nitroglycerin versus −4 ± 7% with nitroprusside, P < 0.01). This difference in flow resulted in the two drugs having opposite effects on coronary vascular resistance (fig. 3B). Coronary vascular resistance increased following nitroglycerin, but declined after nitroprusside.

*All nitroglycerin data were obtained from table 1.*
specific collaterals (X) compared and patients reduction in only (+40 ± 9% with nitroglycerin versus −14 ± 3% with nitroprusside, P < 0.01).

In coronary patients with well developed collaterals (grade 3–4, noncompromised), the two drugs also had a substantially different effect. As shown in figure 4, nitroglycerin resulted in a +10 ± 7% increase in regional myocardial specific blood flow in these patients, while nitroprusside resulted in a −16 + 4% decrease, P < 0.01. In patients with coronary artery disease without well developed collateral vessels, both drugs similarly reduced regional flow without a significant difference being apparent. In nine patients in whom a coronary steal phenomenon was possible because of the coronary anatomy (see above), analysis of distal quadrant flow data showed no such effect in any of the nine patients (table 2).

**Discussion**

The results of the present study suggest that despite similar effects on blood pressure and pressure-rate product,
nitroglycerin and nitroprusside have different effects on regional myocardial specific blood flow. In normal subjects (fig. 3), regional myocardial specific blood flow was unchanged following the administration of nitroprusside and coronary vascular resistance was reduced; on the other hand, nitroglycerin reduced regional flow and increased coronary vascular resistance in a similar group of normal subjects. In patients with coronary artery disease and well developed collateral vessels, regional myocardial specific blood flow significantly decreased following nitroprusside while it was substantially increased following nitroglycerin (fig. 4).

Normal Patients

Previous work has suggested that the coronary circulation can be divided functionally into two types of arteries: larger conductance and smaller resistance vessels. The latter are precapillary arterioles and are the major factor determining overall coronary vascular resistance. One explanation for the effect of nitroprusside on myocardial blood flow observed in normals in the present study is that its direct action on the coronary circulation includes vasodilatation of these precapillary resistance vessels. Thus, following the administration of nitroprusside, overall coronary vascular resistance decreases and regional myocardial specific blood flow tends to increase. This increase is negated by the reduced coronary perfusion pressure and/or reduced myocardial oxygen demand resulting from the peripheral action of the drug. (In our study, coronary sinus oxygen content was not directly measured, and we could only assume that myocardial oxygen demand was reduced because of the decline in the pressure-rate product.)

Previous studies of the effect of nitroglycerin on coronary flow using varying methods and routes of drug administration have yielded conflicting results, but studies in humans using sublingual nitroglycerin have usually demonstrated a fall in coronary flow. With the xenon-133 method, sublingual nitroglycerin also resulted in a decrease in regional myocardial specific blood flow. The fact that the effect of nitroglycerin on myocardial blood flow was opposite to that seen with nitroprusside suggests it has a different site of action in the above model of the coronary circulation. Indeed, previous studies have suggested that nitroglycerin primarily results in dilatation of larger conductance coronary vessels and has very little effect on the small arterioles. According to the above concept, total coronary flow should decrease following the administration of nitroglycerin due to the lower coronary perfusion pressure and reduced myocardial oxygen demands, but overall coronary vascular resistance should be unchanged. However, in our previous study, the decrease in regional myocardial flow after nitroglycerin was out of proportion to the fall in mean aortic pressure so that, as calculated, coronary vascular resistance actually increased, as has been found in an animal study. The mechanism is conjectural, but would involve reflex constriction of precapillary arterioles, perhaps by local autoregulation or by increased alpha adrenergic stimulation due to the nitroglycerin-induced fall in systemic pressure. Since the drug has no direct dilatory effect on these resistance vessels, coronary vascular resistance increases.

Patients with Coronary Artery Disease

The effect of nitroprusside on regional myocardial blood flow in patients with coronary artery disease has received only limited study. In the present series of patients, regional myocardial specific blood flow decreased substantially in nearly all patients with significant coronary lesions, including those with well developed collateral vessels. This finding is consistent with the hypothesis that the primary effect of nitroprusside in the coronary circulation includes vasodilatation of resistance vessels. Such an effect could result in redistribution of blood flow away from an ischemic area in patients with coronary artery disease, particularly when this area is supplied by well developed collateral vessels. We observed this effect in the two patients in the present study who had severe disease limited to one major vessel of the left coronary system, and in whom the stenotic vessel was supplied by a collateral from a normal vessel (fig. 1). This coronary steal could explain the increase in ischemic injury that has been demonstrated in some patients with acute myocardial infarction following the administration of nitroprusside. This effect was also observed in one patient without visible collaterals (table 2) and may be due to the presence of collateral vessels too small to be visualized with current cine techniques. (The effect was not observed in any patients following nitroglycerin administration.)

The effect of nitroglycerin on myocardial blood flow in the presence of coronary artery disease has been studied extensively. As in normal subjects, coronary blood flow usually decreases following its administration, and it has been concluded that the major antianginal effect of nitroglycerin is the result of the reduction in myocardial oxygen demand due to its peripheral action. However, some investigators have suggested that while nitroglycerin may reduce overall coronary blood flow, intramyocardial flow may be redistributed so that ischemic areas may actually have increased flow. This presumably would result from the previously described dilatation of conductance vessels, including collaterals. Thus, while overall coronary vascular
EFFECT OF NITROPRUSSIDE ON RMBF/Mann et al.

resistance would be unchanged or even increased, collateral resistance to the ischemic area would be relatively decreased and flow would thus increase. The increase in regional myocardial flow (even in the non-stressed state) in patients with coronary artery disease and high-grade collaterals supports this concept. Alternatively, it has been suggested that the nitroglycerin-induced reduction of end-diastolic wall tension would favor increased flow to an ischemic endocardium through reduced mechanical resistance, and Becker et al. have demonstrated an increase in the endocardial/epicardial flow ratio in the dog after nitroglycerin. This mechanism, however, would less adequately explain the observed difference between the effects of nitroglycerin and nitroprusside on collateral flow in the present study, since both drugs reduce left ventricular volume and pressure, and thus wall tension. However, change in end-diastolic pressure was not measured and it is possible that the more pronounced effect of nitroglycerin on this parameter could have influenced the flow results. Furthermore, it is also possible that a larger dosage of nitroprusside might have caused an additional reduction in end-diastolic volume and hence greater reduction in extravascular compression of coronary vessels with a beneficial effect on coronary flow. This mechanism has been postulated by Dirschinger et al. to explain apparent localized increases in perfusion following administration of intravenous nitroprusside in larger doses (average 100 \( \mu g / \text{min} \)) than used in our study. In the study by Dirschinger et al., which did not note presence or absence of collaterals, increases in perfusion were also seen following large doses of sublingual isosorbide dinitrate (15 mg) with the same mechanism of action postulated. Therefore, the dose of these vasoactive agents may influence their effects on myocardial perfusion.

In summary, the present study demonstrates that sublingual nitroglycerin in its usual clinical dosage (0.4 mg) and nitroprusside in dosage sufficient to lower blood pressure to comparable levels have different effects on regional myocardial blood flow both in normals and in patients with coronary artery disease. Although the limitations of the xenon washout technique — especially in differentiating between subendocardial and subepicardial flow — must be considered in evaluating this study, this is not a critical factor in comparing the effects of the two drugs, since the same techniques were used in both studies, yet strikingly different results were obtained. These data support previous animal studies which have also demonstrated a difference in the effect of the two drugs on coronary flow, suggesting that nitroglycerin and nitroprusside may have different sites of action within the coronary circulation and different effects on collateral blood flow. Therefore, although both drugs reduce myocardial oxygen demands through their peripheral actions, nitroprusside may redistribute flow away from an ischemic area, while nitroglycerin may increase collateral flow to the area. Thus, in the dosages employed in our study, nitroprusside may have potentially detrimental effects by increasing ischemic injury in some patients with coronary artery disease.

References


Thallium-201 Scintigraphy in Unstable Angina Pectoris

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SUMMARY Thallium-201 scintigraphy was performed during the pain free period in 98 patients with unstable angina. Scintiscans were positive in 39 patients, questionable in 27 patients and normal in 32 patients. Eighty-one patients responded favorably to treatment (group 1). Seventeen patients had complicated courses (group II) and despite maximal treatment with propranolol either developed infarction (six patients) or continued to have angina necessitating coronary surgery (11 patients). In group I during the pain free period 26 of 81 patients had positive thallium-201 scans, whereas 20 patients had an abnormal ECG at that time; during angina 18 patients had transient ECG changes. In group II during the pain free period 13 of 17 patients had positive scans, whereas two patients had abnormal ECG at that time; during angina 12 patients showed transient ECG changes. The sensitivity to recognize group II was 76% for thallium-201 scintigraphy, 11% for ECG during the pain free period; 70% for ECG during angina; 94% for the combination of either positive scans or abnormal ECG. Thus, 1) positive thallium-201 scans occur in patients with unstable angina, 2) positive scans can be obtained during the pain free period, 3) thallium-201 scans are more frequently positive in patients with complicated course.

SCINTIGRAPHY WITH THALLIUM-201 has proved to be a sensitive method for detecting acute myocardial infarction (AMI). However, scintigraphic myocardial defects with thallium-201 may represent either myocardial infarction or ischemia as previously demonstrated in patients with AMI by repeated myocardial imaging. Other investigators have demonstrated that scintigraphic defects, indistinguishable from those seen in AMI, can be obtained following exercise-induced ischemia or ischemia resulting from coronary spasm in variant angina.

It would seem relevant for the application of thallium-201 scintigraphy in the Coronary Care Unit (CCU) to evaluate the results of scintigraphy in patients who have repeated episodes of myocardial ischemia, i.e., patients with unstable angina, since this group constitutes an important portion of CCU admissions.

The purpose of this study was twofold: 1) a description of the pattern of thallium-201 scintigraphy in patients with unstable angina; 2) an evaluation of a potential predictive value of thallium-201 scintigraphy in identifying patients with unstable angina who may have a poorer prognosis or greater tendency to develop AMI subsequently.

Materials and Methods

Ninety-eight patients with unstable angina were studied with thallium-201 scintigraphy within 18 hours of the last anginal attack. Patients with a history or electrocardiographic evidence of previous infarction were excluded from the study because thallium-201 defects in these patients can be due either to the previous infarction or myocardial ischemia. Patients with left bundle branch block or electrocardiographic signs of left ventricular hypertrophy were not included, because these pre-existing ECG abnormalities might obscure ECG characteristics of ischemia.

Unstable angina was defined as a history of typical angina pectoris with increasing frequency and severity of complaints within a short time period (in most patients in this study within 7–10 days), frequently with progression to anginal attacks at rest and during the night. In 84 patients this clinical syndrome occurred without previous angina, while in 14 patients previously stable angina had been present. The observation period in the CCU did not exceed five days. The results in this study also include a subsequent follow-up in the medical ward of approximately 2½ weeks. Electrocardiograms were obtained at least twice daily, and especially during an attack of angina pectoris, during the first 2–4 days after admission. Cardiac enzymes (CPK, SGOT, SGPT, and LDH) were obtained at the time of admission and subsequently each six hours until 24 hours after admission, unless the patient continued to have new attacks of angina. The electrocardiographic and enzymatic diagnosis of infarction was made according to the criteria of the New York Heart Association.

All patients were treated with bedrest, sedation, nitrates and propranolol following admission to the CCU. The dose of propranolol was increased as needed for control and prevention of attacks of angina, unless the heart rate dropped below 50 beats/min. The maximal dose given was

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