Effect of Sublingual Nitroglycerin on Regional Flow in Patients With and Without Coronary Disease

Jawahar Mehta, M.D. and Carl J. Pepine, M.D.

SUMMARY We evaluated the effects of sublingual nitroglycerin on indices of regional coronary flow and coronary resistance (CR) in 12 selected patients with coronary artery disease (CAD) and eight with normal coronary arteries (NCA), using continuous thermodilution. Resting total left ventricular flow, reflected by coronary sinus flow (CSF), and anterior regional flow, reflected by great cardiac vein flow (GCVF), in NCA and CAD patient groups were similar. However, in a subgroup of six patients, with CAD limited to the anterior descending artery, GCVF was lower and anterior regional CR (CR\textsubscript{ANT}) higher than the NCA subjects. Nitroglycerin reduced the systolic pressure-heart rate product similarly in both patient groups. CSF and GCVF in NCA subjects declined 15% and 17%, respectively, as total CR (CR\textsubscript{T}) and CR\textsubscript{ANT} increased. In the CAD subgroup, consisting of patients with CAD limited to the anterior descending, GCVF increased 48% as CR\textsubscript{ANT} declined 50%, and CSF was unchanged. In the other CAD subgroup of patients with CAD in the right and/or circumflex arteries, GCVF declined 32% and CR\textsubscript{ANT} increased 46% as CSF was minimally increased.

These data imply that sublingual nitroglycerin reduces both CSF and GCVF in NCA patients as oxygen demands decrease. In certain CAD patients, however, nitroglycerin alters regional coronary venous blood flow, suggesting a redistribution of flow from normally perfused to hypoperfused regions.

NITROGLYCERIN REDUCES or prevents clinical and hemodynamic manifestations of myocardial ischemia. Because of these beneficial responses, this agent’s potential to decrease ischemic injury and possibly limit infarct size is under close investigation.\textsuperscript{1-3} The primary mechanism by which nitroglycerin may be effective is thought to relate to potent venodilator properties that reduce left ventricular filling pressure and diastolic wall tension.\textsuperscript{4-5} Nitroglycerin also lowers systolic pressure through systemic arteriolar dilation.\textsuperscript{6} These effects lessen the myocardial oxygen requirement. The effect of nitroglycerin on coronary flow, however, is controversial. Some\textsuperscript{6-8} suggest that nitroglycerin may have a prominent action on collateral channels, thereby increasing blood flow to ischemic regions. When this response occurs across the myocardial wall, subendocardial flow may increase at the expense of epicardial flow, and total flow may remain unaltered. In contrast, others\textsuperscript{9} have suggested that flow to the ischemic zone may decline with nitroglycerin as oxygen requirements and perfusion pressure decline. These seemingly conflicting data may be related to different techniques and experimental designs. Furthermore, data obtained in animals with acute myocardial ischemia are difficult to extrapolate directly to man with chronic coronary disease.

We recently evaluated a thermodilution method to continuously assess regional left ventricular flow in man using a multithermistor catheter.\textsuperscript{10} The purpose of this investigation was to study the regional coronary venous blood flow responses to sublingual nitroglycerin in patients with and without coronary artery disease (CAD) using this technique. In patients with coronary disease, regional flow responses were analyzed relative to the angiographic location of significant coronary obstruction.

Methods

Patient Selection

Twenty male patients, age 38–61 years (mean 53 years) who underwent clinically indicated right and left cardiac catheterization were included in this study. Informed consent was obtained in each case. Twelve of these patients had significant coronary obstruction. The latter was defined as ≥70% diameter narrowing in at least one of the three major coronary arteries. Each of these patients was clinically stable and was thought to have evidence of transient myocardial ischemia based on a history of typical angina pectoris and the electrocardiographic ST segment response during stress testing. These patients were selected because the location of the coronary obstruction conformed to a pattern that allowed evaluation of the left ventricular region supplied by the anterior descending branch of the left coronary artery. Six had significant obstruction limited to the anterior descending branch, while the right or circumflex coronary arteries had no significant obstruction. The other six patients had significant obstruction only in the right and/or circumflex arteries, while the anterior descending had no significant obstruction. The remaining eight patients had angiographically normal coronary arteries (NCA) and were undergoing cardiac catheterization to help define a vague chest pain syndrome. No subjects had evidence for heart failure or other forms of heart disease.

Catheterization

No premedication was used, and nitroglycerin was omitted for at least 8 hours before study. Catheter-
ization was performed in a postabsorptive state. A #8 Sones catheter was positioned, via the right brachial artery, in the aorta to measure systemic arterial pressure using a Statham P23Db transducer. Mean pressure was obtained by electronic filtration. This catheter was also advanced to the left ventricle to record left ventricular end-diastolic pressure at high amplification. A multithermotilization catheter\textsuperscript{10–12} was advanced from an antecubital vein and positioned in the coronary sinus. The distal thermistor was advanced to the great cardiac vein. Catheter position was localized\textsuperscript{10} and frequently checked using magnification fluoroscopy and injection of 1–2 ml of Renografin 76 (meglumine diatrizoate). The position was confirmed at the beginning and end of each measurement period by comparison with a videotape recording. Electrocardiographic lead V\textsubscript{5} was recorded and monitored continuously.

**Recording and Measurements**

Arterial and left ventricular pressures were recorded during a hemodynamically stable control period. During this period coronary sinus flow (CSF) and great cardiac vein flow (GCVF) were measured as previously described.\textsuperscript{10–12} These blood flows were recorded simultaneously as the aortic pressure was recorded.

After control recording, sublingual nitroglycerin 0.3–0.6 mg was given to produce approximately 10% decline in mean arterial pressure (MAP). When heart rate and arterial pressure stabilized (3–4 minutes after nitroglycerin administration), flow and pressure recordings were repeated.

**Calculations**

Both CSF and GCVF were calculated by a modification of the method of Ganz et al.\textsuperscript{11, 12} Venous flow was measured as room temperature saline solution (indicator) was infused by Harvard pump at a fixed rate. Temperatures of the indicator and venous blood were determined from catheter-mounted thermistors. The resultant temperature reduction of both the great cardiac vein and coronary sinus blood is inversely related to flow, which was calculated as described elsewhere.\textsuperscript{10–12}

The GCVF was taken as an index of flow draining from the anterior left ventricular region supplied predominantly by the anterior descending coronary artery and the CSF was used to represent the fraction of venous flow derived from the anterior region.

Indices of vascular resistance in each ventricular region were derived from the ratio of simultaneously measured MAP and the respective flow as:

\[
CR_{\text{ANT}} = \frac{\text{MAP}}{\text{GCVF}} \text{ mm Hg/ml/min}
\]

\[
CR_{\text{T}} = \frac{\text{MAP}}{\text{CSF}} \text{ mm Hg/ml/min}
\]

Where \( CR_{\text{ANT}} \) and \( CR_{\text{T}} \) = anterior regional and total left ventricular coronary resistance indices, respectively.

**Statistical analysis**

Mean values and SEM were determined before and after nitroglycerin. Data were compared using the \( t \) test for paired or unpaired analysis where appropriate. A \( P \) value <0.05 was considered significant.

**Results**

Regional coronary and left ventricular hemodynamic data before and after nitroglycerin are summarized for the NCA subjects in table 1. Data obtained in the CAD patients are summarized in table 2 according to the location of obstruction.

**Regional Hemodynamic Data at Rest Before Nitroglycerin**

**Regional flow**

In the NCA subject group, CSF averaged 149 ± 15 ml/min and GCVF 59 ± 9 ml/min (table 1). These values were not significantly different from those obtained in the CAD patients (121 ± 10 ml/min and 55 ± 10 ml/min, respectively) (table 2). In the subgroup of patients with obstruction limited to the anterior descending artery, GCVF (33 ± 6 ml/min) was lower than in the NCA group (\( P < 0.05 \)). However, CSF (109 ± 7 ml/min) was not significantly different. In contrast, in the other CAD patient subgroup with disease in the right and/or circumflex arteries but not the anterior descending, both CSF and GCVF (132 ± 20 ml/min and 77 ± 14 ml/min, respectively) were similar to those obtained in the NCA subjects. The GCVF/CSF ratio in NCA and CAD patients averaged 41 ± 5 and 45 ± 7%, respectively (\( P = \text{NS} \)). The GCVF/CSF in patients with anterior descending obstruction (31 ± 5%) was similar to that in NCA patients (41 ± 5%), but it was significantly (\( P < 0.02 \)) lower than that observed in the right and/or circumflex obstruction subgroup (60 ± 9%).

**Regional Coronary Resistance**

The resistance indices \( CR_{\text{T}} \) and \( CR_{\text{ANT}} \) were 0.71 ± 0.09 and 1.87 ± 0.25 mm Hg/ml/min, respectively, in NCA subjects, compared to 0.91 ± 0.08 and 2.54 ± 0.43 mm Hg/ml/min, respectively, in the CAD patients. Only \( CR_{\text{T}} \) was significantly higher (\( P < 0.05 \)) in CAD patients. However, \( CR_{\text{ANT}} \) (3.43 ± 0.66) was higher (\( P < 0.02 \)) in the CAD subgroup with anterior descending disease than that in the subjects with NCA.

**Regional Hemodynamic Data After Nitroglycerin**

**Regional Flow**

In the NCA group, nitroglycerin effected a decline (\( P < 0.02 \)) in both CSF (15%) and GCVF (17%) compared to control (table 1). In the CAD patients, nitroglycerin produced nonsignificant changes in CSF and
TABLE 1. Effect of Nitroglycerin on Left Ventricular and Coronary Hemodynamics in Subjects with Normal Coronary Angiograms

<table>
<thead>
<tr>
<th>Pt.</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>SAP × HR (units)</th>
<th>CSF (ml/min)</th>
<th>GCVF (ml/min)</th>
<th>GCVF/CSF (%)</th>
<th>CR(_T) (units)</th>
<th>CR(_{ANT}) (units)</th>
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<td>9450</td>
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</table>

Mean: 75 86* 96 86* 10 7* 9440 8380* 149 127† 59 49* 41 41 0.71 0.78 1.87 2.03†

± SEM: 4 5 4 3 0.7 0.3 463 598 15 17 9 7 5 5 0.09 0.11 0.25 0.26

*\(P < 0.01\) N vs C.
†\(P < 0.02\) N vs C.

Abbreviations: HR = heart rate; MAP = mean arterial pressure; LVEDP = left ventricular end-diastolic pressure; SAP × HR = systolic arterial pressure-heart rate product; CSF = coronary sinus blood flow; GCVF = great cardiac vein flow; CR\(_T\) = total left ventricular coronary resistance; CR\(_{ANT}\) = anterior regional coronary resistance; C = control, before nitroglycerin; N = after nitroglycerin.

TABLE 2. Effects of Nitroglycerin on Coronary and Left Ventricular Hemodynamics in Coronary Disease Patients

<table>
<thead>
<tr>
<th>Pt.</th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>SAP × HR (units)</th>
<th>CSF (ml/min)</th>
<th>GCVF (ml/min)</th>
<th>GCVF/CSF (%)</th>
<th>CR(_T) (units)</th>
<th>CR(_{ANT}) (units)</th>
</tr>
</thead>
</table>
| Patients with disease limited to the LAD
| 1   | 78             | 84          | 95            | 70               | 13            | 6             | 9282         | 7392           | 9282              | 7392              |
| 2   | 96             | 110         | 95            | 78               | 10            | 8             | 10560        | 10450          | 10560             | 10450             |
| 3   | 68             | 74          | 85            | 80               | 10            | 9             | 7480         | 7400           | 7480              | 7400              |
| 4   | 60             | 72          | 110           | 90               | 11            | 4             | 9300         | 7920           | 9300              | 7920              |
| 5   | 72             | 78          | 100           | 85               | 14            | 7             | 9360         | 8580           | 9360              | 8580              |
| 6   | 67             | 77          | 92            | 80               | 16            | 10            | 8576         | 7700           | 8576              | 7700              |

Mean: 74 83* 96 81† 12 7† 9093 8240† 109 96 33* 49† 31 53† 0.90 0.88 3.43† 1.77†

± SEM: 5 6 3 3 1 0.9 415 477 7 8 6 4 5 7 0.06 0.11 0.66 0.20

Patients with disease limited to RCA and/or LCX
| 1   | 72             | 78          | 120           | 115              | 23            | 10            | 11376        | 10080          | 11376             | 10080             |
| 2   | 72             | 78          | 92            | 85               | 15            | 10            | 10080        | 8424           | 10080             | 8424              |
| 3   | 150            | 150         | 118           | 87               | 14            | 8             | 23250        | 14700          | 23250             | 14700             |
| 4   | 72             | 78          | 105           | 87               | 18            | 10            | 9720         | 8190           | 9720              | 8190              |
| 5   | 84             | 96          | 105           | 90               | 35            | 12            | 10750        | 10722          | 10750             | 10722             |
| 6   | 80             | 85          | 110           | 105              | 13            | 8             | 12640        | 11650          | 12640             | 11650             |

Mean: 88† 108 95† 20 10† 12969 10533 132 153 77 52† 60* 39† 0.93 0.76§ 1.65 2.33

± SEM: 13 12 4 5 3 0.6 2099 980 20 32 14 12 9 9 0.16 0.16 0.26 0.49

All coronary patients (n = 12)

Mean: 81 88† 102 88† 16 9† 11031 9396† 121 125 55 50 45 46 0.91* 0.82 2.54 2.05

± SEM: 7 6 3 3 2 0.6 1176 626 10 18 10 6 7 6 0.08 0.09 0.43 0.26

*\(P < 0.05\) compared to normal coronary artery (NCA) group.
†\(P < 0.02\) compared to NCA group.
§\(P < 0.01\) N vs C.

Abbreviations: HR = heart rate; MAP = mean arterial pressure; LVEDP = left ventricular end-diastolic pressure; SAP × HR = systolic arterial pressure-heart rate product; CSF = coronary sinus blood flow; GCVF = great cardiac vein flow; CR\(_T\) = total left ventricular coronary resistance; CR\(_{ANT}\) = anterior regional coronary resistance; C = control, before nitroglycerin; N = after nitroglycerin; LAD = left anterior descending artery; RCA = right coronary artery; LCX = left circumflex artery.
GCVF (table 2). In the CAD subgroup with disease limited to the anterior descending, GCVF increased (48%, \( P < 0.02 \)), while CSF fell (10%, \( P = \text{NS} \)). In the patient subgroup with right and/or circumflex CAD, CSF was not significantly increased (15%, \( P = \text{NS} \)) while GCVF declined (32%, \( P < 0.01 \)). In subjects with and without coronary disease, GCVF/CSF was unchanged (table 1 and 2) with nitroglycerin. However, in the CAD patient subgroup with anterior descending disease, GCVF/CSF increased (66%, \( P < 0.01 \)), whereas in the subgroup with right and/or circumflex disease, it declined (36%, \( P < 0.01 \)).

Regional Coronary Resistance

In the NCA subjects, CR\(_{\text{T}}\) was not significantly altered, but CR\(_{\text{ANT}}\) increased (9%, \( P < 0.02 \)). In the CAD patients, both CR\(_{\text{T}}\) and CR\(_{\text{ANT}}\) declined, but the change was not significant. The patient subgroup with CAD localized to the anterior descending had a CR\(_{\text{ANT}}\) decline (48%, \( P < 0.02 \)), whereas in the subgroup with right and/or circumflex obstruction, CR\(_{\text{T}}\) declined (18%, \( P < 0.02 \)).

Systemic Hemodynamic Effects of Nitroglycerin (tables 1 and 2)

Nitroglycerin increased heart rate (14%) and decreased MAP (10%) in the NCA group and 9% and 14%, respectively, in the CAD group (all \( P < 0.01 \)). The systolic pressure-heart rate product declined (\( P < 0.01 \)) in both groups. One patient (number 3) in the CAD subgroup with right and/or circumflex artery disease had persistent atrial tachycardia unaltered by nitroglycerin. Otherwise, similar changes in heart rate, MAP and systolic pressure-heart rate product were seen in the two CAD subgroups. Left ventricular end-diastolic pressure declined (10 ± 0.7 to 7 ± 0.3 mm Hg, \( P < 0.01 \)) in the NCA and (16 ± 2 to 9 ± 0.6 mm Hg, \( P < 0.01 \)) in the CAD patient groups.

Discussion

Resting total and anterior regional left ventricular blood flow values found in this study are similar to those reported by others using the same\(^{11,14}\) or different techniques.\(^{15,16}\) Coronary flows at rest in coronary disease patients were not significantly different than in subjects with normal coronary arteries, supporting observations in other patient groups.\(^{11,14}\) Indices of coronary resistance were slightly higher in the coronary disease patients than in normal coronary subjects, as expected.\(^{15}\)

In the patient subgroup with angiographic evidence of obstruction limited to the anterior descending, anterior regional flow was lower and resistance index higher than in the patients with right and/or circumflex obstruction. Similarly, these anterior regional hemodynamic values found in the anterior descending obstruction subgroup were altered significantly from NCA subjects. The fraction of total left ventricular flow derived from the anterior regional flow was also reduced compared to the other CAD subgroup or patients with NCA. In contrast, patients with obstruction limited to the right and/or circumflex arteries had anterior regional flow and resistance indices similar to normal coronary subjects. These observations suggest that measurements of regional venous flow provide the potential for functional evaluation of the significance of regional coronary artery obstructive disease. This type of functional evaluation is not necessarily apparent from the arteriogram alone.

Nitroglycerin was administered in a dose sufficient to evoke a comparable change in arterial pressure and heart rate in the patient groups studied. This approach resulted in a similar systolic arterial pressure-heart rate product and left ventricular end-diastolic pressure reduction in these patients. Alterations in coronary blood flow and resistance patterns, however, were strikingly different. In patients with normal coronary angiograms, both total and anterior regional flow declined and resistance increased as indices of myocardial oxygen demand fell. These observations are similar to those reported by Cohn et al.\(^{15}\) In contrast, both coronary flow and resistance were unaltered considering all the coronary disease patients together. But in those with obstruction limited to the anterior descending, there was a significant increase in anterior regional flow associated with a reduction in the index of anterior coronary resistance. Total coronary blood flow, however, was unchanged, suggesting redistribution of flow from areas supplied by the right and/or circumflex arteries to the region supplied by the anterior descending. Similarly, in the subgroup with disease limited to the right and/or circumflex arteries, nitroglycerin produced a decline in flow and an increase in resistance indices related to the anterior region without changing total left ventricular flow. These alterations again suggest redistribution of blood flow from areas perfused by the nonobstructed anterior descending to the hypoperfused region supplied by the right or circumflex arteries.

Redistribution of blood flow from nonischemic to ischemic zones appears related to the effects of nitroglycerin on the large coronary arteries.\(^{5,17-19}\) Our observations also support other patient studies suggesting redistribution of blood flow to a hypoperfused area.\(^{6,15,16}\) Although intracoronary nitroglycerin can increase total left ventricular blood flow\(^{7,12}\) without changing systemic arterial pressure, a beneficial effect on pacing-induced angina was not demonstrated by Ganz and Marcus.\(^{12}\) Intravenous nitroglycerin in the latter study, however, reduced myocardial oxygen demand indices and relieved angina. Regional blood flow responses were not reported by these investigators. In our patients, sublingual nitroglycerin decreased systolic arterial pressure-heart rate product and was associated with apparent redistribution in left ventricular blood flow. The decrease in left ventricular end-diastolic pressure with nitroglycerin could contribute to increased blood flow to regions with obstructed vessels. This increase in blood flow to potentially ischemic areas induced by sublingual nitroglycerin may complement the reduc-
tion in myocardial oxygen demand, providing additional beneficial actions.

Bache et al. suggested that nitroglycerin improves perfusion of ischemic subendocardium by dilating penetrating arteries. This would deliver blood from epicardial to subendocardial layers. In contrast, Forman et al. indicated that nitroglycerin may not dilate subendocardial vessels that are already "fully dilated" during ischemia. This dilation of vessels in non-ischemic subepicardial layers may result in hemodynamic conditions that favor a "steal" of blood flow from ischemic regions. The thermodilution technique used in our study cannot differentiate between flow in subepicardial and subendocardial layers. Our study was not designed to examine the coronary flow effects of nitroglycerin during acute ischemia when the hypothesis of "fully dilated collaterals and fixed blood flow" may be operative. However, the flow increase and resistance decrease in zones supplied by obstructed vessels was striking in selected CAD patients who were probably not ischemic at rest or during nitroglycerin study. These observations demonstrate the presence of flow reserve in potentially ischemic regions, and raise the possibility that some degree of ischemia may have been present at rest.

In summary, our study implies that sublingual nitroglycerin decreases coronary flow in subjects with normal coronary arteries as oxygen demands decline. In selected patients with coronary disease, nitroglycerin appears to produce a redistribution of coronary flow manifested by an increase in venous blood flow from hypoperfused regions. This is interpreted as an increase in flow to potentially ischemic zones associated with a reduction in determinants of oxygen demand. The change in coronary flow distribution may be related to alterations in regional resistance and could contribute to nitroglycerin's beneficial action in patients with coronary disease. Although the data indicate that sublingual nitroglycerin may redistribute flow to hypoperfused areas, further studies are warranted. These studies should define: 1) the normal ratio limits of GCVF to CSF in larger numbers of CAD patients; 2) the ratio limits in patients with varying CAD patterns at rest and with stress; and 3) possible errors in measuring total and regional coronary flows.

References

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