Comparison of Metabolic and Vasoconstrictor Stimuli on Coronary Vascular Resistance in Man

GILBERT H. MUDGE, JR., M.D., SHELDON GOLDBERG, M.D., STEPHEN GUNTHER, M.D., TIFT MANN, M.D., AND WILLIAM GROSSMAN, M.D.

SUMMARY Coronary blood flow (CBF) is considered proportional to metabolic demand (MVO₂). However, recent studies have reported inappropriate vasoconstrictor response to α-adrenergic stimulation in patients with coronary artery disease (CAD). To assess the interaction of vasodilatory reserve and adrenergic vasoconstriction, we compared changes in coronary vascular resistance (CVR) during the metabolic stress of rapid atrial pacing and during the α-adrenergic stimulus of cutaneous cold (cold pressor test, CPT) in 13 control patients and 14 patients with CAD. Similar heart rates were achieved with pacing in both control and CAD patients, and both groups had a similar hypertensive response to CPT; thus, both pacing and CPT increased major determinants of MVO₂. In association with this increased MVO₂, CVR decreased with rapid pacing in control and CAD patients (−24% and −27%, respectively), but increased in CAD patients (+24%) during CPT. Seven of 13 CAD patients actually had a reduction in CBF, whereas CBF increased in all control patients in response to CPT. Compression of intramural coronary vessels by elevated left ventricular diastolic pressure was excluded as a pathogenic mechanism for increase in CVR in two CAD patients who showed marked reduction in CBF during CPT.

These data are further evidence that patients with CAD may have limited coronary vasodilatory mechanisms. Superimposed α-adrenergically mediated coronary vasoconstriction may contribute significantly to myocardial ischemia in patients with CAD.

ALTHOUGH CORONARY BLOOD FLOW (CBF) has been regarded as regulated primarily by the metabolic demands of the myocardium, extensive evidence indicates that such coronary autoregulation can be overridden at least partially by adrenergic vasoconstriction both clinically and experimentally. Enhanced myocardial oxygen demand would lead to myocardial ischemia unless increased perfusion pressure or a compensatory decrease in coronary vascular resistance (CVR) served to provide the required increase in CBF, and thus oxygen supply. In patients with coronary artery disease (CAD), angina pectoris is provoked when increased myocardial oxygen demand exceeds a limited supply. Coronary artery vasoconstriction has been documented in Prinzmetal’s variant angina and suggested as a possible pathogenic mechanism in patients with normal coronary anatomy who have sustained myocardial infarctions. Normal coronary vascular tone can respond to sympathetic and parasympathetic stimuli. Orlick and co-workers recently compared normal subjects with cardiac-denervated transplant patients and concluded that adrenergic tone accounts for about 12% of resting CVR in man. Withdrawal of this neural component was considered to be responsible for the initial vasodilatory response to a metabolic stimulus. Recent studies in patients with CAD have reported defective vasodilatory mechanisms. Patients with CAD demonstrated inappropriate coronary vasoconstrictor response to cutaneous cold, an α-adrenergic stimulus. Berndt et al. recently reported that spontaneous angina is associated with a significantly lower double product (heart rate × systolic blood pressure) and triple product (heart rate × systolic blood pressure × ejection time) than pacing-induced ischemia. They suggest that changes in CBF, rather than myocardial oxygen consumption, may cause spontaneous pain at rest in patients with the clinical syndrome of unstable angina. If such adrenergic mechanisms do play a role in ischemic heart disease, α-adrenergic blockade should be considered in the treatment of myocardial ischemia.

The present investigation compares the primary metabolic stimulus of pacing-induced tachycardia and the α-adrenergic stimulus of cutaneous cold on CBF and CVR both in subjects with normal coronary arteries and in subjects with obstructive CAD. Thus, we hope to clarify further the pathophysiologic mechanisms underlying transient myocardial ischemia.

Methods

The study population comprised 13 patients with normal coronary arteriograms and 14 patients with significant CAD involving one or both major divisions of the left coronary artery. Patients with normal coronary anatomy (control group) were studied to define the etiology of chest pain syndromes. No patients in the control group had electrocardiographic evidence of myocardial infarction or exercise tests positive for ischemic heart disease. The patients with significant CAD had 70% or greater obstruction in at least one of the major branches of the left coronary arteries. Seven
of the 13 patients with normal coronary anatomy and
nine of the 14 patients with obstructive CAD were on
propranolol therapy before cardiac catheterization;
propranolol, however, was discontinued 8 hours
before the study. Patients with isolated obstruction of
the right coronary artery were excluded from the
study. The protocol and consent forms were approved
by the Human Studies Committee of the Peter Bent
Brigham Hospital. Resting left ventricular end-
diastolic pressure was measured and left ven-
triculography and coronary arteriography performed
at either a previous catheterization or before this
study. If the research study was coincident with
diagnostic cardiac catheterization, sufficient time was
allowed after angiography for hemodynamics to
return to baseline values. An arterial catheter was in-
troduced percutaneously into either the femoral or
brachial artery and a thermodilution coronary sinus
catheter with a pacing tip was positioned in the cor-
onary sinus via a brachial vein cutdown. The position
of the catheter was confirmed angiographically and
rechecked frequently. Coronary sinus blood flow was
measured by the continuous thermodilution method of
Ganz et al.,20 as previously used in our laboratory.2
Electrocardiogram, arterial blood pressure, and cor-
onary sinus blood flows were simultaneously recorded
at rest, during rapid atrial pacing, and during the cold
pressor test.

After recordings at rest, heart rate was controlled
by pacing at a subthreshold rate of approximately 95
beats/min. With a steady state reestablished,
the patient’s hand was immersed in a mixture of water
and ice for 1 minute, and coronary sinus flow and
arterial pressure, mean and phasic, were continuously
recorded. Measurements were taken at peak mean
arterial pressure, which indicated maximum response
to the cutaneous cold stimulus. The cold stimulus was
removed, and basal conditions were reestablished.
Heart rate was then increased by 20 beats/min every 2
minutes until angina, atroventricular block, or a rate
of 150 beats/min was reached. Flow and pressure
recordings were taken at least 2 minutes after max-
imal heart rate was reached, and the pacing stimulus
was then stopped.

CVR was calculated as the quotient of mean
arterial pressure and coronary sinus flow,1,2,3,11,13,16,17
and the “double product” (a measure of myocardial
metabolic requirements) was calculated as the product
of mean arterial pressure and heart rate. Comparison
of heart rate, mean arterial pressure, coronary sinus
blood flow, and CVR was made between the resting
basal state and rapid atrial pacing, and the cutaneous
cold stimulation.

To determine if an increase in left ventricular end-
diastolic pressure might account for an increase in
CVR by decreasing left ventricular perfusion through
transmural compression of coronary vessels, left ven-
tricular diastolic pressure was recorded with a
micromanometer-tipped catheter during both cutaneous cold stimulation and rapid atrial pacing in
two patients with CAD who had a particularly marked
fall in CBF during the cold pressor test. In these two
patients, CVR was also calculated as the ratio of
[mean aortic diastolic pressure-mean left ventricular
diastolic pressure]/CBF.

Data were analyzed using the t test for paired and
unpaired variables, and differences were considered
significant when p < 0.05.

Results

Clinical Data

Clinical data are summarized in table 1. There were
more women in the control group, but there was no
significant difference in age between the two groups.
In the control group, resting hemodynamics were nor-
mal and no patient had ventricular dysfunction; left
ventricular end-diastolic pressure was 10 ± 1 mm Hg
(mean ± SEM) and left ventricular ejection fraction
0.65 ± 0.03.

Patients with CAD had slightly higher left ventricu-
lar end-diastolic pressures at rest (12 ± 1 mm Hg)
than patients in the control group. Six of the 14
patients with CAD had expected abnormalities in left
ventricular wall motion, and left ventricular ejection
fraction was lower than in the control group
(0.57 ± 0.03).

Pacing Results

With pacing-induced tachycardia, heart rate in the
control group was increased from 79 ± 4 beats/min to
145 ± 6 beats/min (fig. 1). Mean arterial pressure
rose significantly during pacing (99 ± 4 mm Hg to
105 ± 4 mm Hg, p < 0.05), and the double product
(heart rate × mean arterial pressure) increased from
7818 ± 465 mm Hg/min to 15,428 ± 912 mm
Hg/min (p < 0.001), indicating a major increase in
myocardial oxygen demand. The increase in heart
rate, mean arterial pressure, and double product was
accompanied by an increase in coronary sinus blood
flow (125 ± 11 ml/min to 187 ± 18 ml/min,

<table>
<thead>
<tr>
<th>Table 1. Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group (n)</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Control (13)</td>
</tr>
<tr>
<td>CAD (14)</td>
</tr>
</tbody>
</table>

Abbreviations: LVEDP = left ventricular end-diastolic pressure; EF = ejection fraction by angiography; LVWM = left ventricular wall motion.
PACING

$P < 0.005$, and a decrease in CVR ($0.87 \pm 0.07$ to $0.64 \pm 0.06$ mm Hg/ml/min, $p < 0.05$), indicating vasodilation (fig. 2).

The effects of pacing-induced tachycardia in the CAD group are shown in figure 1. Patients with CAD had a slightly lower heart rate at rest ($73 \pm 4$ beats/min) and with maximum pacing ($135 \pm 4$ beats/min) than patients in the control group, but these differences were not significant. Mean arterial pressure rose significantly ($97 \pm 4$ to $111 \pm 5$ mm Hg) and the double product increased ($7212 \pm 676$ mm Hg/ml/min to $15,013 \pm 947$ mm Hg/minute, $p < 0.001$) as in the control group. As shown in figure 2, coronary sinus blood flow increased ($127 \pm 11$ ml/min to $215 \pm 21$ ml/min, $p < 0.01$) and CVR fell ($0.79 \pm 0.06$ to $0.57 \pm 0.06$ mm Hg/ml/min ($p < 0.005$), responses similar to those of the control group. Thus, patients with obstructive CAD and patients with normal coronary arteries both responded to the increased metabolic demand resulting from pacing-induced tachycardia with increased CBF and decreased CVR, suggesting coronary vasodilatation.

Cold Pressor Test

In patients with normal coronary anatomy, heart rate was maintained constant at $101 \pm 2$ beats/min (fig. 3). The cold pressor test elicited an increase in mean arterial pressure of $18$ mm Hg ($105 \pm 3$ mm Hg to $123 \pm 4$ mm Hg, $p < 0.01$), thus increasing the double product significantly ($10,715 \pm 426$ mm Hg/ml/min to $12,544 \pm 492$ mm Hg/min $p < 0.005$). As shown in figure 4, coronary sinus blood flow increased proportionally, from $149 \pm 13$ to $187 \pm 19$ ml/min, and CVR was unchanged ($0.73 \pm 0.07$ to $0.70 \pm 0.07$ mm Hg/ml/min).

The patients with obstructive CAD had a significantly different response. In this group, heart rate was controlled at $96 \pm 2$ beats/min. The cold pressor test elicited an increase in mean arterial pressure of $20$ mm Hg ($102 \pm 4$ mm Hg to $122 \pm 5$ mm Hg, $p < 0.01$), and the double product increased significantly ($9872 \pm 514$ mm Hg/min to $11,781 \pm 631$ mm Hg/min, $p < 0.05$) (fig. 3). In contrast to the control group (fig. 4), coronary sinus flow did not in-

**Figure 1.** Changes in heart rate, mean arterial pressure (MAP), and double product during pacing for both control patients (normals) and patients with coronary artery disease (CAD). The left bar indicates the control value for each group, and the right bar indicates the pacing result. Brackets indicate SEM.

**Figure 2.** Changes in coronary blood flow (CBF) and coronary vascular resistance (CVR) during pacing for both groups. The left bar indicates the control value for each group, and the right bar indicates the pacing result.
Increase proportionally with pressure in the CAD group (151 ± 9 ml/min to 147 ± 11 ml/min), and in eight of the CAD patients, coronary sinus flow decreased. Calculated CVR increased 24% in the CAD group, (0.69 ± 0.04 to 0.86 ± 0.05 mm Hg/ml/min, p < 0.05). Thus, despite similar increases in an index of myocardial oxygen demand (the double product), patients in the control group and patients in the CAD group exhibited disparate responses in CBF to the cold pressor test.

Role of Left Ventricular Diastolic Pressure

The CAD patients exhibited altered left ventricular function on angiogram, and had a slightly higher resting left ventricular diastolic pressure than the control patients. To assess whether the increase in CVR in CAD patients in response to cutaneous cold might be caused by an increase in left ventricular diastolic pressure and concomitant transmural compression of the distal resistance vessels, left ventricular diastolic pressure was measured in two CAD patients whose response to the cold pressor test was a marked reduction in coronary sinus flow (table 2). CVR (quotient of mean arterial pressure and coronary sinus flow) increased from 0.80 to 1.01 mm Hg/ml/min in patient A, and from 0.81 to 1.10 mm Hg/ml/min in patient B. When CVR was calculated as the ratio of [mean arterial diastolic pressure-mean left ventricular diastolic pressure]/CBF, a significant rise in CVR was still noted. Thus, the reduction in coronary sinus flow and increase in CVR in response to cutaneous cold cannot be explained by extrinsic compression of intramural coronary vessels in these patients.

Angina with Pacing and Cold Pressor Test

Three patients with CAD developed angina during both pacing and the cold pressor test. As shown in table 3, the double product was lower with angina induced by the cold pressor test than with angina induced by pacing, and CVR was higher during angina with the former stimulus than the latter. This suggests that ischemic pain in these patients occurred at a
Table 2. Response to CPT in Two Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Control CPT</th>
<th>Patient B</th>
<th>Control CPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (ml/min)</td>
<td>156</td>
<td>143</td>
<td>113</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>125</td>
<td>145</td>
<td>92</td>
</tr>
<tr>
<td>LVDP (mm Hg)</td>
<td>12</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Coronary vascular resistance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP/CBF (mm Hg/ml/min)</td>
<td>0.80</td>
<td>1.01</td>
<td>0.81</td>
</tr>
<tr>
<td>ADP-LVDP/CBF (mm Hg/ml/min)</td>
<td>0.72</td>
<td>0.84</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Abbreviations: CBF = coronary blood flow measured by thermodilution technique; MAP = mean arterial pressure; LVDP = mean left ventricular diastolic pressure; ADP = mean aortic diastolic pressure; CPT = cold pressor test.

Transplanted heart and normal hearts have provided physiological evidence for important tonic α-adrenergic coronary vasoconstrictor activity in man. Measuring CVR by coronary sinus thermodilution technique, Orlick and colleagues showed that the two patient populations had significantly different hemodynamic responses to intravenous administration of phentolamine. Normal subjects had a 20% decrease in CVR after α-adrenergic blockade, while cardiac transplant patients had a 9% diminution in CVR. There was no significant difference in metabolic demand, reflected as the product of systolic arterial pressure and heart rate, between the two groups. These results were interpreted to suggest that α-adrenergic tone accounts for approximately 12% of resting CVR in man. These investigators also compared the response of the same groups to the metabolic stimulus of rapid atrial pacing. Normal subjects exhibited a rapid rise in CBF to metabolic demand that was not seen in transplanted hearts or in those normal subjects pretreated with the α-adrenergic blocking agent, phentolamine. After 20 seconds of atrial pacing, coronary vasodilation and CVR were comparable in the two groups. This suggested to the authors that initial coronary vasodilation to metabolic stimulation may be mediated by withdrawal of α-adrenergic constrictor tone.

Such competition between α-adrenergic vasoconstricting influences and metabolically induced vasodilation has been more recently demonstrated by Mohrman and Feigl, who reported definite competition between sympathetic vasoconstriction and metabolic vasodilatation in the canine coronary circulation. Using a closed-chest dog anesthetized with chloralose, they showed that α-adrenergic vasoconstrictor tone restricted metabolically induced coronary vasodilation by 30%. In a previous study they found a 27% rise in CVR during the application of cutaneous cold in patients with CAD. In three patients, CBF actually fell, despite a rise in arterial blood pressure, and angina pectoris developed. Alpha-adrenergic blockage with phentolamine prevented increases in arterial blood pressure or CVR in response to the cutaneous cold stimulus. In the present investigation, we have compared changes in the coronary vascular tone of control and CAD patients to two different stimuli, rapid atrial pacing and application of cutaneous cold. Each stimulus increased the major determinants of metabolic demand for both groups. The results show that the α-adrenergically

Table 3. CVR and Double Product During Angina

<table>
<thead>
<tr>
<th>Patient</th>
<th>CPT</th>
<th>Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CVR (mm Hg/ml/min)</td>
<td>HR × MAP (mm Hg/min)</td>
</tr>
<tr>
<td>D</td>
<td>0.64</td>
<td>9770</td>
</tr>
<tr>
<td>E</td>
<td>1.01</td>
<td>14970</td>
</tr>
<tr>
<td>F</td>
<td>0.66</td>
<td>15300</td>
</tr>
</tbody>
</table>

Abbreviations: CVR = coronary vascular resistance; CPT = cold pressor test; HR = heart rate; MAP = mean arterial pressure.
mediated reflex stimulus of cutaneous cold caused a significant increase in CVR in patients with CAD. This response differed qualitatively from that seen with rapid atrial pacing, where coronary vasodilation accompanied the enhanced metabolic demand.

The double product is proportional to myocardial oxygen consumption, and increased significantly with both pacing and adrenergic stimuli. Other determinants of myocardial oxygen consumption which affect wall stress — systolic ejection time, contractility, and left ventricular size — were not readily measured in this study but might be significant. Cold CBF in patients in both groups increased with rapid atrial pacing, as reported by other investigators using similar methods, and indicated a competent response of vasodilatory mechanisms in normal and diseased coronary arteries to a purely metabolic stimulus. However, with α-adrenergic stimulation and subsequent enhanced metabolic demand, control patients failed to show vasodilatation, while patients with significant CAD showed paradoxical vasoconstriction.

Three of the patients with CAD had angina during both pacing and cutaneous cold. In each instance, the double product was lower at the time of angina during cutaneous cold than at the time of angina during rapid atrial pacing. Corresponding CVR was higher in each case of cold-induced angina. This observation suggests that actual vasoconstriction may have precipitated transient ischemia, and is in agreement with the recent observations of Berndt et al., who report seven patients with CAD whose double product (heart rate × systolic pressure) and triple product (heart rate × systolic pressure × ejection time) were significantly lower at the onset of spontaneous angina than during pacing-induced angina. Hattenhauer and Neill reported four patients who developed angina in response to cold air inhalation at a lower double product than in response to pacing-induced angina. Both studies concluded that changes in CBF rather than myocardial oxygen consumption might be responsible for angina in certain patients with CAD. Such a hypothesis has recently been supported by Raizner and co-workers, who reported angiographic evidence for vasoospasm during the cold pressor test in patients with CAD not suspected of having Prinzmetal's variant angina.

It seems unlikely that the increases in CVR in CAD patients we report are mediated by extrinsic compression of the distal coronary vasculature by increased left ventricular diastolic pressure, with a resulting decrease in coronary perfusion pressure. In two patients, there was still a significant increase in CVR when left ventricular diastolic pressure was incorporated into the numerator. Active coronary vasoconstriction is a probable pathogenic mechanism in these two patients.

Certain limitations of this study should be emphasized. First, while the accuracy of the thermodilution technique for coronary sinus blood flow measurement is suggested by animal studies reported by Ganz et al. and VanDevanter et al., the method measures combined flow in all areas of myocardium which drain to the coronary sinus. Thus, no changes in flow might be detected if equal and opposite flow changes occurred in regional beds within the drainage area. For example, the opening (or closing) of large, collateral channels between normally perfused and ischemic regions could result in substantial redistribution of flow with no change in net flow. Thus, CVR might have decreased in certain regional beds during the cold pressor test despite a calculated increase in resistance for the entire coronary sinus drainage area.

Second, small shifts in the coronary sinus catheter tip position can potentially result in changes in measured flow by including or excluding venous drainage branches. In addition, atrial pacing could potentially alter geometric relations of the right atrium and coronary sinus, and has been implicated as causing reflux of right atrial blood into the coronary sinus. While such considerations may have introduced into our results an error of unknown magnitude, it seems unlikely that such an error would systematically influence the results in the CAD group differently from the results in the control group. In the report by Mathey and co-workers, a reflux of blood from the right atrium to the coronary sinus occurred in dogs during interventions which raised right atrial pressure. This reflux caused falsely high estimations of CBF by the thermodilution technique, compared with electromagnetic measurement of CBF, which served as a control. If a similar artifact were introduced into this study during pacing-induced tachycardia, true flows might have been lower, and the fall in resistance might have been less than that observed. With the cold pressor studies, if true flow were lower, the increases in CVR would be even greater than reported. Substantial increases in coronary flow with rapid atrial pacing in this study are similar to the findings of others, who used different methods to measure CBF.

Third, the increased calculated coronary resistance found in this study may in part have been due to factors other than adrenergically mediated coronary vasoconstriction. Ellis and Klocke reported that increased preload produced by elevation of mean left atrial pressure from 5 mm Hg to 20 mm Hg led to increased resistance to myocardial blood flow, particularly in the subendocardium, presumably due to the transmural compressive force of the increased left ventricular diastolic pressure. We have tried to analyze for this effect in two patients with CAD in whom total coronary sinus flow fell during the cold pressor test and in whom left ventricular diastolic pressures were simultaneously recorded. In these two patients, calculated CVR rose, even when corrected for preload. Nevertheless, this factor might have played some part in causing the observed changes in resistance. We could not distinguish subendocardial from subepicardial flow and resistance in our patients, and cannot estimate the potential magnitude of this important effect.

We present the following hypothesis to explain the data of this study. With a primary metabolic stimulus, both control patients and patients with CAD are able
to respond to depressed local oxygen tension, increased adenosine concentration, and parasympathetic and β-adrenergic mechanisms with coronary vasodilation. Hence, CVR falls. When heart rate is increased to 100 beats/min, and an α-adrenergic stimulus is superimposed, the control patients can offset the vasoconstrictor stimulation because of substantial vasodilatory reserve, so that no change occurs in calculated CVR. However, when patients with CAD are paced to a similar subendocardial rate, lesions in the proximal conductance vessels have resulted in near-maximal metabolic vasodilation in the more distal resistance vessels. In this instance, when a competitive α-adrenergic vasoconstrictor influence is superimposed, vasoconstriction predominates. CBF fails to rise, or even falls, despite elevated coronary perfusion pressure, and hence calculated CVR rises.

Myocardial ischemia may therefore result from an imbalance between myocardial oxygen supply and demand, caused by primary changes in either variable. Various stresses in patients with CAD, such as cold exposure or emotional excitement, may exert a pathophysiologic effect through both mechanisms. Chronic α-adrenergic blocking drugs, particularly those which are cardioselective, may have a role in the management of certain patients with chronic angina pectoris and ischemic heart disease.

References

Comparison of metabolic and vasoconstrictor stimuli on coronary vascular resistance in man.

G H Mudge, Jr, S Goldberg, S Gunther, T Mann and W Grossman

Circulation. 1979;59:544-550
doi: 10.1161/01.CIR.59.3.544

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/59/3/544.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/