Effects of Pharmacologically-Induced Hypertension on Myocardial Ischemia and Coronary Hemodynamics in Patients with Fixed Coronary Obstruction

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SUMMARY Twenty patients with fixed coronary artery obstruction were studied during rapid atrial pacing and methoxamine infusion. During pacing to heart rates of 142 ± 4 (mean ± SEM) beats per minute coronary sinus flow increased from 108 ± 8 to 187 ± 15 cc/min and myocardial oxygen consumption increased by + 80 ± 11%. During methoxamine infusion that raised arterial systolic pressure to 196 ± 5 mm Hg, similar increases in coronary sinus flow (to 179 ± 13 cc/min) and myocardial oxygen consumption (+ 77 ± 12%) occurred. Chest pain and ischemic ST segment changes developed in 17 and 14 patients respectively during atrial pacing, an incidence significantly greater (P < 0.05) than during infusion of methoxamine (6 and 3 patients). Myocardial lactate extraction which averaged 26 ± 4% during control was decreased to 10 ± 8% during pacing and to 24 ± 7% during methoxamine; the difference between decreases was not significant. The data show that at similar increases in myocardial oxygen consumption stress of increased heart rate results in more myocardial ischemia than stress of increased afterload.

ELEVATION OF ARTERIAL PRESSURE is frequently considered an important mechanism leading to myocardial ischemia in patients with coronary artery disease. For this reason acute reduction in arterial pressure to reduce myocardial oxygen needs has been recommended for hypertensive patients with unstable angina or acute myocardial infarction. However, since an elevated arterial pressure also may improve perfusion to areas supplied by partially obstructed vessels, it is difficult to predict the overall effects of altering arterial pressure on myocardial oxygen supply and demand. We have examined the effects of hypertension induced by methoxamine infusion on coronary hemodynamics, myocardial metabolism, and clinical signs of myocardial ischemia in 20 patients with significant coronary artery disease. For comparison, the effects of rapid
## Table 1. Patient Data and Clinical Findings during Control Period, Atrial Pacing, and Methoxamine Infusion

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*Statistical comparison between methoxamine and atrial pacing by Student's t-test.
†Statistical comparison between methoxamine and atrial pacing by Chi square analysis.

P < 0.05 was considered statistically significant.

Abbreviations: EF = ejection fraction; HR = heart rate; ASP = arterial systolic pressure; MAP = mean arterial pressure; CSF = coronary sinus flow; CVR = coronary vascular resistance; AOV2-CSO2 = arterial and coronary sinus blood oxygen in percent saturation; MVO2 = myocardial oxygen consumption; MLEx = myocardial lactate extraction; CP = chest pain; ST = ST-segment depression; C = control; AP = atrial pacing; M = methoxamine infusion; std = standard error of the mean.

Atrial pacing were also evaluated in each patient. The results suggest that hypertension, per se, may play a relatively minor role in precipitating myocardial ischemia in patients with fixed coronary artery obstruction.

### Methods

All patients had diagnostic coronary arteriography by Sones or Judkins technique, usually a few days before or following the study which was performed in a specially
equipped unit adjacent to the Coronary Care Unit. Informed consent was obtained prior to the study from each patient. The following procedure was utilized: Arterial systolic (ASP) and mean (MAP) pressures were measured by a Statham 23 DB transducer following percutaneous insertion of a cannula into the radial or brachial artery. Coronary sinus flow (CSF) was measured utilizing the continuous thermal dilution technique described by Ganz et al.1 In our laboratory flows determined in vitro utilizing this technique correlated well \( r = 0.949 \) with directly measured flows of 50 to 450 ml/min delivered by an adjustable sigma motor pump into a circuit of synthetic tubing. Following insertion of the thermistor catheter its position was verified by injecting contrast material to outline the coronary sinus. To maintain a stable catheter position, the external thermistor was positioned well beyond the mouth of the coronary sinus. In this location, flow measurement and blood sampling are primarily reflections of the anterior-lateral left ventricular blood supply. Coronary vascular resistance (CVR) was calculated as the ratio of CSF to MAP. Atrial pacing was performed from the same catheter which was equipped with bipolar pacing electrodes. A single calibrated ECG lead \( V_a \) was monitored throughout the study. Recordings were made on a Hewlett-Packard photographic recorder at variable paper speeds. Arterial (AL) and coronary sinus (CSL) lactates were measured by enzymatic techniques. Myocardial lactate extraction (MLEX) was calculated as 100 (AL-CSL)/AL. Arterial (AO2) and coronary sinus (CSO2) blood oxygen in percent saturation was measured with an American Optical oximeter. Myocardial oxygen consumption \( (MVO_2) \) was calculated as CSFx (AO2 - CSO2).

Prior to atrial pacing or infusion of methoxamine two sets of control measurements were obtained 10 min apart and averaged to yield a single control value. Differences between the two control measurements \( (\text{mean } \pm \text{SEM}) \) were 3.4 \( \pm \) 3.5 cc/min for CSF (NS); 1.2 \( \pm \) 6.8% for MLEX (NS); and 0.3 \( \pm \) 0.7% for AO2 - CSO2 (NS). Following control measurements atrial pacing was started and the pacing rate increased every few minutes until chest pain developed. In the three patients who did not have chest pain during pacing, the maximum heart rates achieved were 134, 140, and 146 beats per minute. Measurements were repeated in duplicate at the peak pacing rate and pacing was then discontinued. In order to avoid baseline shift due to atrial depolarization during pacing, measurement of ST-segment change was made from the first few sinus beats following termination of pacing. A flat or downward sloping ST depression of one mV or greater was considered "ischemic." In nine patients, pacing was repeated a second time, but only data obtained during the first pacing period will be presented. When necessary, atropine \( (0.5 - 1.0 \text{ mg}) \) was given intravenously to achieve an adequate ventricular rate during atrial pacing. After completion of the pacing part of the study, the patient was allowed to return to a basal state for approximately 30 minutes. Methoxamine infusion was then started at a dosage of 2 mg/min and measurements were repeated when arterial pressure stabilized at hypertensive levels. To avoid reflex bradycardia during infusion of methoxamine the atrium was paced at or near the sinus rate present just prior to methoxamine infusion.

Statistical significance was determined by the Student's \( t \)-test for paired numerical data and by Chi square analysis. \( P \) values above 0.05 were considered not significant (NS).

**Results**

**Clinical and Catheterization Features**

All patients were male, ranging in age from 46 to 67 years (average 54 years) (table 1). At the time of study, all had stable angina and none had severe heart failure or recent (within 4 weeks) myocardial infarction. Diagnostic cardiac catheterization showed left ventricular function to be normal or only mildly impaired (ejection fraction \( \geq 50\% \) or estimated normal) in 14 patients. In six patients, left ventricular ejection fraction was low, ranging between 27% and 40%.

All patients had coronary arteriography showing significant \( (\geq 70\%) \) obstruction in a major coronary artery. Seven patients had single, nine had double, and four had triple vessel disease.

**Hemodynamics**

Prior to atrial pacing, heart rate (HR) averaged 74 \( \pm \) 2 beats/min (mean \( \pm \) SEM). With rapid atrial pacing, HR increased to an average of 142 \( \pm \) 4 beats/min. During infusion of methoxamine, HR averaged 81 \( \pm \) 2 beats/min. During the control period, ASP averaged 130 \( \pm \) 3 mm Hg and MAP averaged 90 \( \pm \) 2 mm Hg. With atrial pacing, ASP averaged 142 \( \pm \) 6 mm Hg and MAP averaged 107 \( \pm \) 4 mm Hg. During methoxamine infusion, ASP was increased to an average of 196 \( \pm \) 5 mm Hg and exceeded 170 mm Hg in all but two patients while MAP increased to an average of 140 \( \pm \) 4 mm Hg.

**Coronary Sinus Flow**

During the control period, CSF was 108 \( \pm \) 8 cc/min. With atrial pacing, CSF increased to 187 \( \pm \) 15 cc/min which was not significantly different from the CSF during infusion of methoxamine which averaged 179 \( \pm \) 13 cc/min (fig. 1).

**FIGURE 1.** Coronary sinus flow during control, atrial pacing and methoxamine infusion in each of the twenty patients.
Coronary Vascular Resistance

Prior to pacing, CVR averaged 0.93 ± 0.07 mm Hg/cc/min. During atrial pacing, CVR fell to an average of 0.63 ± 0.04 mm Hg/cc/min. During methoxamine infusion, CVR was significantly higher (P < 0.001) than during pacing averaging 0.87 ± 0.06 mm Hg/cc/min (fig. 2).

Oxygen Saturations

(AO₂ - CSO₂) difference was determined in 15 patients and averaged 64 ± 2% during the control period with essentially no change during either atrial pacing or methoxamine infusion, averaging 63 ± 2% and 64 ± 2% respectively (fig. 3).

Myocardial Oxygen Consumption

Because CSF measurements reflect subtotal myocardial blood flow, values for MVO₂ during pacing and methoxamine infusion are presented as the percent change from control for the 15 patients in whom this calculation could be made (fig. 4). During atrial pacing, MVO₂ increased by an average of 80 ± 11% which was not significantly different from the increase in MVO₂ of 77 ± 12% present during infusion of methoxamine.

Myocardial Lactate Extraction

Prior to atrial pacing, MLEx (measured in 18 patients) averaged 26 ± 4% and was 10% or above in all but two patients (fig. 5). During atrial pacing, lactate production was present in five of the 18 pts. During infusion of methoxamine, lactate extraction was restored in four of the five patients who had lactate production with pacing. However, two patients had lactate production during methoxamine infusion, one of whom had lactate extraction during pacing. The difference in mean MLEx during pacing (10 ± 8%) and infusion of methoxamine (24 ± 7%) was not significant.

Clinical Evidence of Myocardial Ischemia

Chest pain or discomfort occurred in 17 patients (85%) during atrial pacing but in only six patients (30%) during infusion of methoxamine (P < 0.05). Similarly, ischemic ST-segment changes were seen in 14 patients (70%) during pacing, but in only three patients (15%) during methoxamine infusion (P < 0.05). There was no apparent relationship between clinical signs of ischemia and other measured parameters during either pacing or infusion of methoxamine.

Discussion

The present study was undertaken to examine the role played by hypertension on the development of myocardial ischemia in patients with fixed coronary artery obstruction. In order to avoid the effects of altered contractility and heart rate on myocardial oxygen demand, we used the alpha-adrenergic drug methoxamine (a vasoconstrictor) to increase blood pressure while we maintained heart rate at near control values with atrial pacing. Under these conditions, myocardial oxygen consumption was increased by an average of 77%. In spite of this increase in oxygen consumption, clinical, electrocardiographic, and metabolic evidence of myocardial ischemia did not develop in most patients and was significantly less frequent than when similar increases in myocardial oxygen consumption (average 80%) had been induced by rapid atrial pacing.

The relationship between systemic arterial pressure and myocardial ischemia in patients with coronary artery disease is currently under investigation. Systolic hypertension during the early phases of acute myocardial infarction is not uncommon, and in the absence of clinical heart failure, does not seem to indicate a poor prognosis for these patients. Use of aggressive antihypertensive therapy in such patients has been questioned. Shell and Sobel, who used early CPK
values to predict infarct size, administered trimethaphan to 14 patients with AMI whose arterial pressures on admission were above 145/90 mm Hg and reported actual infarct size (estimated by subsequent CPK measurements) to be significantly less than had been predicted. In contrast, Magnusson et al. using similar techniques reported increased CPK release in four patients with AMI when systolic pressures were reduced from 144 mm Hg to 128 mm Hg with nitroprusside. In addition to hypertensive patients, normotensive patients with AMI have also been considered candidates for vasodilator therapy in an effort to limit ischemic damage. Improved left ventricular function has been reported in such patients during treatment with nitroglycerin, nitroprusside, and phentolamine and is particularly apparent when left ventricular filling pressure is elevated. The effects of afterload reduction on myocardial ischemia is somewhat less clear, however.

The presence or absence of heart failure appears to be an important factor in determining what effect altering blood pressure will have on myocardial ischemia. With heart failure, myocardial wall tension (a determinant of MVO₂) may be markedly increased even when arterial pressure is normal. Significant reduction in wall tension and MVO₂ can be expected as arteriolar resistance is reduced and venous capacitance is increased with vasodilators.

At the same time, vasodilator-induced reflex tachycardia and increased contractility tend to be attenuated in the presence of heart failure. An independent effect of vasodilator therapy on subendocardial perfusion and collateral coronary flow may also result in a favorable net effect on the balance between myocardial oxygen supply and demand.

In the absence of heart failure, reduction of arterial pressure using vasodilator drugs often results in reflex increases in heart rate and contractility which could offset the benefit on MVO₂ derived from decreased myocardial wall tension.

Under normal circumstances, alterations of arterial pressure over the physiologic range result in changes in myocardial blood flow similar in magnitude to changes in myocardial oxygen needs. In the presence of severe coronary artery obstruction, however, perfusion pressure proximal to the site of an obstruction may become a dominant factor in determining the adequacy of perfusion distal to it.

Although we were unable to measure regional blood flow directly, the fact that ischemia occurred significantly less during methoxamine than during pacing, while MVO₂ and CSF increased similarly, suggests that these two interventions differed with regard to their effects on regional myocardial perfusion. During rapid atrial pacing the diastolic period is considerably reduced. Since subendocardial perfusion, particularly in areas supplied by partially obstructed vessels, may be largely dependent upon the product of diastolic perfusion time and pressure, it is not surprising that ischemia occurred when myocardial oxygen needs were increased by pacing. On the other hand, during methoxamine infusion heart rate was not altered and arterial diastolic as well as systolic pressure was substantially increased. Under these conditions, the increased myocardial oxygen needs appeared to have been met even in areas supplied by diseased arteries, presumably because the higher diastolic time-pressure product enhanced blood flow over partially obstructed vessels and/or through collateral channels.

In the above discussion, we have not considered the direct...
effects methoxamine may have had on coronary vasomotor tone. The ability of coronary vascular smooth muscle to respond to various stimuli other than the metabolic needs of the myocardium is well established. Methoxamine has been reported to augment subendocardial blood flow by causing alpha-adrenergic mediated vasoconstriction of subepicardial vessels. In our patients, CVR was significantly lower during pacing than during methoxamine infusion, suggesting a coronary vasoconstricting effect from methoxamine. It is impossible, however, to know if or how the direct coronary vascular effects of methoxamine influenced our results.

Hypertension frequently precedes the pain of angina pectoris and it has been postulated that elevated blood pressure per se plays a causative role in the development of myocardial ischemia. Under these circumstances however, heart rate and contractility may also be increased in response to increased adrenergic activity and the contribution made by elevation of arterial pressure to the total rise in myocardial oxygen requirement is difficult to assess. We have recently reported 18 patients with significant coronary artery disease who developed 25% or greater increases in arterial systolic pressure during rapid atrial pacing. Each of these patients had chest pain and ECG changes during pacing and 16 had myocardial lactate extraction of less than 10%. During pacing, the increase in arterial pressure appeared to parallel the other manifestations of myocardial ischemia. We have never observed such increases in arterial pressure during rapid atrial pacing in patients without significant coronary obstruction (regardless of whether or not chest pain has been provoked). These observations have led us to consider the possibility that in some patients myocardial ischemia may be the cause rather than the result of acute hypertension. James, Isobe and Urrthaler have investigated a cardiogenic hypertensive chemoreflex in the dog. Increases in arterial pressure can be induced by injection of serotonin into or around the proximal left coronary artery and blocked by infiltration of xylocaine in this region. Histologic examination of tissue adjacent to the main left coronary artery from both dog and human hearts revealed a structure resembling a chemoreceptor with a blood supply originating from the left coronary artery. Whether or not such a cardiogenic hypertensive reflex occurs in man remains to be shown.

The clinical implications that can be drawn from this study deserve comment. Hemodynamic parameters in patients with various manifestations of coronary artery disease can be altered by pharmacological interventions currently available. However, the net effect these interventions have on the balance between myocardial oxygen supply and demand must be determined by carefully controlled clinical trials before their use can be recommended.

References

Effects of pharmacologically-induced hypertension on myocardial ischemia and coronary hemodynamics in patients with fixed coronary obstruction.
H S Loeb, A Saudye, R P Croke, J V Talano, M L Klodnycky and R M Gunnar

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