Myocardial Blood Flow in Coronary Artery Disease

Effect of Right Atrial Pacing and Nitroglycerin

SUZANNE B. KNOEBEL, M.D., PAUL L. MCHENRY, M.D., ANTHONY J. BONNER, M.D., AND JOHN F. PHILLIPS, M.D.

SUMMARY

Sixteen patients, 10 with significant three-vessel coronary artery disease (>50% occlusion of each vessel) and six without coronary disease, had nutrient myocardial blood flow, cardiac output, pressure time/min and arterial pressure determinations at rest, with atrial pacing and with right atrial pacing plus nitroglycerin. In the patients with coronary disease, nutrient myocardial blood decreased an average of 16% (P < 0.001) with pacing alone but increased by 22% (P < 0.001) from the pacing flows with the addition of 0.4 mg sublingual nitroglycerin at the same pacing rate. The directional changes in myocardial blood flow were unrelated to perfusion pressure or pressure work. In the patients without coronary disease, opposite effects were observed. With right atrial pacing, nutrient myocardial blood flow increased by 23% (P < 0.02). With the addition of nitroglycerin, myocardial blood flow decreased by 15% (P < 0.02). These changes were directionally related to changes in pressure-work of the heart.

It is suggested that the findings in this study are consistent with observations made in the experimental animal which indicate that the effect of nitroglycerin may be partly due to a redistribution of myocardial blood flow.

Additional Indexing Words:
Autoregulation Coincidence technic
*4Rubidium

Nutrient blood flow Perfusion pressure

In the past few years a number of studies have been reported utilizing acceleration of the heart rate by right atrial pacing as a stress intervention to study the hemodynamic, metabolic, and coronary flow characteristics in patients with coronary artery disease.1-14 The intervention has been of considerable interest because it is relatively safe, repeatable, and defines a threshold in terms of the tension-time index, pressure time/min, or triple product, having fewer independent variables than exercise or other forms of stress testing.4, 5, 9, 13 The studies have demonstrated manifestations of ischemia such as impaired left ventricular function, electrocardiographic alterations, and lactate production. More recently, demonstrations of coronary flow inadequacy with atrial pacing in coronary artery disease have also been reported.15, 16 In addition, nitroglycerin has been shown to increase the threshold to right atrial pacing in that indirect reflections of myocardial blood flow deficiency have been reversed at identical pacing rates through the concomitant use of nitroglycerin.4, 17, 18 Whether the effect of nitroglycerin in this situation is manifested by reducing myocardial oxygen requirement or by altering the distribution of myocardial blood flow is unresolved.19 Many of the problems concerning the effect of nitroglycerin are compounded by the varying methods used to determine myocardial blood flow. Some methods measure total coronary flow, not necessarily nutrient flow, some methods may be relatively insensitive to poorly perfused areas, some technics measure regional perfusion, and so forth.20-23 This study was designed to evaluate alteration in nutrient myocardial blood flow produced by sublingual nitroglycerin administered during right atrial pacing in patients with three-vessel coronary artery disease, as compared with patients without coronary artery disease. Nutrient myocardial blood
flow was measured utilizing a coincidence counting system and single bolus of $^{82}$Rb.24,28

**Material and Methods**

Sixteen patients undergoing selective coronary cinearteriographic studies for diagnosis or evaluation of the severity of coronary arteriosclerotic occlusive disease had myocardial blood flow determinations at rest, with right atrial pacing, and with right atrial pacing concomitant with the administration of sublingual nitroglycerin. The studies were performed just prior to the arteriographic evaluation.

All studies were performed in the morning with the patients in a fasting state and without sedation. Measurements were made with patients in the supine position.

A bipolar pacing catheter was passed through the basilic vein, positioned in the right atrium so that its tip was in contact with the high lateral wall, and connected to a battery-powered pacemaker (Medtronic). A short polyethylene catheter (approximately 18 gauge) was introduced percutaneously into the right femoral artery.

Blood pressure was measured via the indwelling catheter in the femoral artery, connected to a Statham P23D strain-gauge transducer and recorded on a Sanborn recorder (model 150). The mean arterial pressure was obtained by electrical integration and the mean systolic arterial pressure by planimetric integration. Pressure time/min, expressed in mm Hg-secs/min, was obtained as the product of systolic mean arterial pressure, heart rate, and systolic ejection period. Systolic ejection period, in seconds, was measured from the pressure records as the time interval between the onset of the femoral artery pulse and the dicrotic notch, and was expressed as the average figure of at least six beats taken at the extremes of respiratory fluctuation. Heart rate was measured from a simultaneously recorded electrocardiogram. The cardiac output was determined using $^{82}$RbCl as the indicator.26

Myocardial blood flow, in ml/min per total heart, was calculated using the formula: $MBF = q(t)/\int f^{\infty} \alpha_0(t)dt$ where $q(t)$ is the myocardial uptake of $^{82}$RbCl as measured by the coincidence counting system and $f^{\infty} \alpha_0(t)dt$ represents the concentration of the isotope in arterial blood during the first circulation, determined by extrapolation after recirculation begins. The theoretic basis of this formulation, experimental verification, and critique have been reported in detail.25,27

Control measurements were made during sinus rhythm, after which pacing was begun. The heart rate was gradually elevated to the point where 1:1 A-V conduction could just be maintained or angina intervened. The maximal heart rate achieved was maintained for 3 min before and during the taking of repeat measurements unless angina intervened. If angina intervened, the pacing was continued for the time period necessary to make the myocardial blood flow measurement (45 sec). Following a recovery period of 10 min, pacing was instituted at the same rate as on the previous determination and concomitantly 0.4 mg nitroglycerin was given sublingually. Repeat measurements were made at the precise time as the first stress measurement.

After completion of the myocardial blood flow and hemodynamic determinations coronary cineangiography was performed. Multiple oblique views were obtained using renographic contrast media. Injections were made before and after administration of sublingual nitrates. Recording was performed with 35-mm Double-X film developed in Ethol-90. A Phillips 6-in image intensifier was utilized with a 100-mm lens at 64 frames/sec.

Only patients whose cineangiograms were of good quality in multiple projections of all three major coronary vessels were included in this study. Coronary arterial lesions were classified as follows: Each of the three major coronary vessels (right, left anterior descending, and circumflex) was assigned a value of 100. A value of 200 was assigned to the left main stem coronary artery. The number of vessels involved was then determined and the percentage of each vessel which remained open was estimated in increments of 25%. In the case of branch stenosis, the degree of occlusion was estimated according to the technic of Rowe et al.29 For example, if the anterior descending artery bifurcated, giving off a branch about 50% of the size of the parent vessel and if this vessel was 50% occluded, the estimated occlusion of the anterior descending vessel would be equivalent to 25% occlusion of the anterior descending coronary artery. A final coronary artery index was then based on the estimated percentage of lumen of all three vessels remaining open (300 equaling no occlusive disease). The cineangiograms were interpreted independently by three investigators without availability of the physiologic data. Ten consecutive patients with coronary artery indices of 50 or less and six patients without coronary artery disease were included in this study. All data analyzed as the significances of the difference between the means of paired data.

**Results**

**Coronary Artery Disease Patients**

None of the 10 patients with coronary artery disease and coronary artery indices of 50 or less was able to increase myocardial blood flow significantly with pacing to an average rate of 131 beats/min (range 120–158) (table 1). Seven of the 10 experienced angina with pacing. All of these patients experienced pain after at least 2 min of pacing so that the disparity between pacing times for patients with and without angina was minimal. The average myocardial blood flow for the group changed from 207±53 ml/min, representing 4% of the cardiac output at rest, to 178±50 ml/min, 3.4% of the cardiac output, with atrial pacing ($P<0.001$). Pressure time/min rose 34% with pacing ($P<0.001$). Mean arterial blood pressure increased from an average of 98±14 to 107±22 mm Hg ($P<0.05$), and the diastolic pressure from 75±10 to 90±17 mm Hg ($P<0.01$). There was a

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Table 1
The Effects of Right Atrial Pacing and Pacing plus Nitroglycerin in Patients with Three-Vessel Coronary Artery Disease

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)/Sex</th>
<th>MBF (ml/min)</th>
<th>CO (liters/min)</th>
<th>PTM (mm Hg-sec/min)</th>
<th>HR (beats/min)</th>
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* +* = SD < 0.001 < 0.001 < 0.001 < 0.001 < 0.05 < 0.02 < 0.01 < 0.02

Abbreviations: MBF = myocardial blood flow; CO = cardiac output; PTM = pressure-time/min; HR = heart rate; BPM = mean systemic blood pressure; BPD = systemic diastolic pressure; C = control; P = right atrial pacing; PN = pacing and nitroglycerin.

P for change from preceding column

A graphic presentation of the changes in myocardial blood flow with pacing plus nitroglycerin in both groups is shown in figure 1.

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- The cardiac output decreased from 5.7 liters/min to 2.4 liters/min, which was a change from 0.4 liters/min to 0.2 liters/min.
- With pacing alone, the cardiac output increased from 2.4 liters/min to 3.0 liters/min, which was a change from 0.2 liters/min to 0.4 liters/min.
- In the six patients without coronary occlusive disease, the cardiac output increased from 2.4 liters/min to 3.0 liters/min, representing a 25% increase.
- In the group with nitroglycerin, the cardiac output increased from 2.4 liters/min to 3.0 liters/min, representing a 25% increase.

- The mean arterial and myocardial blood pressure increased significantly with pacing plus nitroglycerin from 128 mm Hg to 133 mm Hg (P < 0.01).
- The mean arterial and myocardial blood pressure increased significantly with pacing plus nitroglycerin from 128 mm Hg to 133 mm Hg (P < 0.01).

- There were no significant changes in blood pressure.
- There were no significant changes in blood pressure.

- Five patients with three-vessel coronary artery disease had previously been studied with pacing alone and pacing plus nitroglycerin, respectively. The pacing plus nitroglycerin increased the cardiac output from an average of 10 liters/min to 12 liters/min, representing a 25% increase.
- Five patients with three-vessel coronary artery disease had previously been studied with pacing alone and pacing plus nitroglycerin, respectively. The pacing plus nitroglycerin increased the cardiac output from an average of 10 liters/min to 12 liters/min, representing a 25% increase.

- With pacing to the same rate but with 0.4 mg of sublingual nitroglycerin administered at the onset of pacing, myocardial blood flow increased by 25% (P < 0.001), compared with pacing alone.
- With pacing to the same rate but with 0.4 mg of sublingual nitroglycerin administered at the onset of pacing, myocardial blood flow increased by 25% (P < 0.001), compared with pacing alone.

- The pacing plus nitroglycerin increased the cardiac output by 25% (P < 0.001), compared with pacing alone.
- The pacing plus nitroglycerin increased the cardiac output by 25% (P < 0.001), compared with pacing alone.
Table 2

The Effects of Right Atrial Pacing and Pacing plus Nitroglycerin in Patients without Coronary Occlusive Disease

<table>
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<th>CO (liters/min)</th>
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<th>BPD (mm Hg)</th>
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* SD

P for change from preceding column

Abbreviations: see table 1.

Discussion

The hemodynamic data from this study are similar to those reported in a number of other studies. Right atrial pacing has been demonstrated to increase pressure time/min, and not to affect cardiac output significantly.2,4,5 Nitroglycerin decreases myocardial blood flow, and probably results in decreased ventricular dimensions,2,11,29 Nitroglycerin seems to decrease myocardial blood flow and decreases myocardial blood flow, and probably results in decreased ventricular dimensions.2,11,29
decreases.\textsuperscript{15, 32} Thus, the coincidence system may reflect alterations in regional perfusion. Other technics measuring single-vessel flow or dominated by single-vessel flow might register no increase (fixed flow) with an intervention which acts primarily by redistribution of flow or an actual increase in flow through nonoccluded vessels.\textsuperscript{15, 23} With these considerations in mind, we propose that our data support the concept that, in the patient with coronary artery disease, when ischemia is caused by an increase in myocardial oxygen requirement with atrial pacing, a redistribution of blood flow occurs, the nutritional flow to the endocardium being limited by flow in the large conducting vessels.\textsuperscript{33} The decreased nutritional flow to the endocardium, by adding a zero count to the myocardial uptake of rubidium, results in the coincidence system measuring a decreased flow. Nitroglycerin, in addition to reducing cardiac work so that a better ratio exists between nutritional circulation to the endocardium and requirement, also results in a redistribution of nutritional blood supply,\textsuperscript{33} reflected by an increased flow measured by the coincidence system.

Data from experimental animal studies utilizing microsphere injection technics and intramyocardial oxygen tension measurements\textsuperscript{34-37} are in accord with the concepts outlined above. It has been demonstrated that, in addition to a reduction in total blood flow following acute experimental coronary artery occlusion, there is also a disproportionate reduction in subendocardial flow within the ischemic area.\textsuperscript{34} The possible mechanisms for this altered flow pattern have been discussed by Becker and Pitt,\textsuperscript{35} including a change in resistance gradient between endo- and epicardium, a possible perfusion pressure drop in perforating vessels, and an increase in extravascular compressive forces, all essentially mechanical effects following ischemia. Another model proposed by McGregor and Fam\textsuperscript{31} also warrants consideration and is, perhaps, more appropriate for the chronic state. In their model, a decrease in resistance at the arteriolar level of nonoccluded vessels when oxygen requirement is increased, might result in a decrease in blood flow to a portion of the myocardium previously supplied by that artery through collaterals, a "coronary steal" syndrome. Whichever mechanism, i.e., mechanical...
effects as proposed by Becker and Pitt or "coronary
steal" as proposed by McGregor and Fam, is
operative in patients with coronary disease, nitro-
glycerin could result in a redistribution of flow into
an ischemic area as has been shown in the
experimental animal.84–87 By decreasing myocardial
oxygen demands through reduction in arterial
pressures, wall tension, and ventricular volume, the
increased extravascular compressive forces caused
by ischemia could be reversed and flow reestablished.
Or, by allowing vasoconstriction to again
maintain in nonoccluded vessels, the "steal"
might be eliminated by reestablishing resting pressure
relationships.

Another possibility is that nitroglycerin may
dilate collateral vessels in coronary patients and,
thus, partially decrease the resistance quantum of
the proximal occlusive lesions, effectively allowing a
greater coronary reserve.19,38 Nitroglycerin has been
shown to dilate collateral vessels and increase
flow to areas supplied by such vessels.38 However, it
would seem that if the arteriolar bed were fully
dilated because of increased oxygen demand by
right atrial pacing, or if extravascular resistance
were increased in an ischemic area, an increased
volume of flow through collaterals would simply
continue to traverse the path of least resistance and
would not necessarily become nutrient flow. It is
possible, however, that nitroglycerin by decreasing
wall tension could permit collateral flow, which had
been prevented by the ischemic changes, to
resume35 and, perhaps, be augmented.59

The questions raised may prove to have some
clinical relevance. Regardless of the mechanisms
involved, the diseased coronary circulation does not
appear to be entirely a passive one. It is not a
perfusion pressure-dependent system, in the sense
of epicardial vessel perfusion pressure, within
normal ranges of blood pressure. The nutrient
myocardial blood flow can be manipulated through
the use of drugs which either decrease the pressure
time/min, redistribute myocardial blood flow, or,
perhaps, increase collateral flow. If, for example, it
were necessary to artificially increase heart rate in
patients with coronary artery disease for the control
of ventricular tachycardia or other tachyarrhythmia,
it might be possible to "protect" the blood supply to
the myocardium through the concomitant use of an
agent such as nitroglycerin. Other combinations of
interventions could be similarly considered. Elev-
ation of arterial blood pressure designed to
increase coronary perfusion pressure might rather
increase pressure work and myocardial consump-
tion to the point where coronary reserve would be
exceeded. These considerations are of particular
importance in dealing with patients with myocar-
dial infarction or impending infarction where a
prime concern is in preserving as much myocardial
blood flow as possible in order to reduce to a
minimum the area of myocardial ischemia. Each
patient, however, should be assessed individually.
Not all of our patients had angina induced by
pacing nor did nitroglycerin consistently relieve
induced angina. Other investigators have observed
similar variability.12 The relationship between
myocardial oxygen demand induced by any particu-
lar stress, the mechanisms by which various agents
exert influence on collateral vessels, and work of the
heart may vary considerably from patient to
patient. It is the algebraic sum of all effects that is
probably important and may account for differing
clinical responses.

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