Myocardial Blood Flow in Coronary Artery Disease

Effect of Right Atrial Pacing and Nitroglycerin

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SUMMARY
Sixteen patients, 10 with significant three-vessel coronary artery disease (>50% occlusion of each
divid) 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, nutri-
tent 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 sub-
lingual 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 dis-
 ease, opposite effects were observed. With right atrial pacing, nutrient myocardial blood flow in-
creased 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 redis-
tribution of myocardial blood flow.

Additional Indexing Words:
Autoregulation Coincidence technic
"Rubidium
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. 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. The
studies have demonstrated manifestations of ische-
mia such as impaired left ventricular function,
electrocardiographic alterations, and lactate pro-
duction. More recently, demonstrations of coronary
flow inadequacy with atrial pacing in coronary
artery disease have also been reported.

In addition, nitroglycerin has been shown to
increase the threshold to right atrial pacing in that
indirect reflections of myocardial blood flow defi-
ciency have been reversed at identical pacing rates
through the concomitant use of nitroglycerin. 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. 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 nutri-
ent flow, some methods may be relatively insensitive
to poorly perfused areas, some technics
measure regional perfusion, and so forth. 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

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flow was measured utilizing a coincidence counting
system and single bolus of $^{82}$Rb.24,26

Material and Methods

Sixteen patients undergoing selective coronary cine-
arteriographic 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 nitrates. 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 to 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 electric integration and the
mean systolic arterial pressure by planimetric integra-
tion. 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: \( \text{MBF} = q(t)/\int \frac{dA_0}{dt} \) where \( q(t) \) is the myocardial uptake of $^{82}$RbCl
as measured by the coincidence counting system and
\( \int \frac{dA_0}{dt} \) 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.26,27

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 coro-
nary vessels were included in this study. Coronary ar-
terial lesions were classified as follows: Each of the
three major coronary vessels (right, left anterior des-
cending, and circumflex) was assigned a value of 100.
A value of 200 was assigned to the left mainstem coro-
nary artery. The number of vessels involved was then
determined and the percentage of each vessel which re-
mained 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.20 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 were 50% occluded, the esti-
imated occlusion of the anterior descending vessel would
be equivalent to 25% occlusion of the anterior des-
cending 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 inde-
pendently 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
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>MBBF (ml/min)</th>
<th>CO (liters/min)</th>
<th>PTM (min Hg-sec/min)</th>
<th>HR (beats/min)</th>
<th>BPM (min Hg)</th>
<th>BPD (min Hg)</th>
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<td>C</td>
<td>P</td>
<td>PN</td>
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Abbreviations: MBBF = 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.

There were no significant changes in myocardial blood flow in both groups. A graphic presentation of the changes in myocardial blood flow with pacing plus nitroglycerin is shown in figure 1.

Patients without Coronary Disease

In the six patients without coronary obstruction, pacing with nitroglycerin had no significant effect on myocardial blood flow, but significantly increased the mean arterial pressure by 5% (P < 0.01). There were no significant changes in cardiac output with pacing or pacing plus nitroglycerin.

Patients with Coronary Disease

In the six patients with coronary obstruction, pacing with nitroglycerin had no significant effect on myocardial blood flow, but significantly increased the mean arterial pressure by 4% (P < 0.01). There were no significant changes in cardiac output with pacing or pacing plus nitroglycerin.

There were no significant changes in myocardial blood flow, cardiac output, or mean arterial pressure in any group.

With pacing to the same rate but with 0.4 mg sublingual nitroglycerin administered at the onset of pacing, myocardial blood flow increased significantly (P < 0.001), and mean blood pressure significantly increased (P < 0.001). The difference in the pacing plus nitroglycerin and pacing alone groups was statistically significant (P < 0.001), and the difference in mean blood pressure was also significant (P < 0.001).

With pacing to the same rate but without nitroglycerin, myocardial blood flow and diastolic blood pressure showed a significant negative correlation between the change in myocardial blood flow and diastolic blood pressure.
Table 2

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

<table>
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<tr>
<th>Case</th>
<th>Age (yr)/Sex</th>
<th>MBF (ml/min)</th>
<th>CO (liters/min)</th>
<th>PTM (mm Hg·sec/mm)</th>
<th>HR (beats/min)</th>
<th>BPM (mm Hg)</th>
<th>BPD (mm Hg)</th>
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*sd for change from preceding column: <0.05 <0.01 ns <0.02 <0.01 <0.05

Abbreviations: see Table 1.

Discussion

The hemodynamic data from this study is similar to those reported in a number of other studies. Right atrial pacing has been demonstrated to increase systemic cardiac output. However, nitroglycerin decreases myocardial blood flow. As nitroglycerin decreases myocardial blood flow, the coincidental increase in coronary artery blood flow, if significant, could increase myocardial uptake of isotope. If of sufficient size, it is possible that increased myocardial perfusion, leading to a decrease in regional perfusion, is of sufficient size, it is possible that increased myocardial uptake of isotope is increased by pacing, but not by nitroglycerin. The coincidence of increased myocardial uptake of isotope and decreased pressure gradients may be present only in this study.

Further comparison with previous studies is probably not warranted as there is great variation in experimental design, animal preparation, and method of data collection. In the current study, the presence of nitroglycerin was taken into account, and the coincident increase in myocardial uptake of isotope is possible only in this study.
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

\textbf{Figure 1}

(Left) The percent change in myocardial blood flow with right atrial pacing, and pacing and nitroglycerin, in patients with three-vessel coronary artery disease. (Right) The changes induced by the same interventions in patients without coronary artery disease.
effects as proposed by Becker and Pitt or “coronary steal” as proposed by McGregor and Fam, is operative in patients with coronary disease, nitroglycerin could result in a redistribution of flow into an ischemic area as has been shown in the experimental animal. 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. Nitroglycerin has been shown to dilate collateral vessels and increase flow to areas supplied by such vessels. 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 resume and, perhaps, be augmented.

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. Elevation of arterial blood pressure designed to increase coronary perfusion pressure might rather increase pressure work and myocardial consumption to the point where coronary reserve would be exceeded. These considerations are of particular importance in dealing with patients with myocardial 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. The relationship between myocardial oxygen demand induced by any particular 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.

References


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