CARDIOLOGY IN PRIMARY CARE

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Printed by The Byrd Press, Richmond, Virginia

MEDICAL COLLEGE OF VIRGINIA QUARTERLY
Published quarterly (Spring, Summer, Fall, Winter) by the Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University. The QUARTERLY publishes articles of original research and review in basic and clinical sciences. Contributions from outside the Medical College of Virginia faculty are invited. Manuscripts should be prepared according to recommendations in the Stylebook/Editorial Manual of the American Medical Association, Publishing Sciences Group, Inc., Sixth Edition, Littleton, (Mass), 1976. Correspondence: MEDICAL COLLEGE OF VIRGINIA QUARTERLY, Box 26, Medical College of Virginia, Richmond, Virginia 23298. Phone (804) 786-0460. Subscription rates (per year): U.S.A., Canada, and Mexico $10.00 (Individuals); $14.00 (Libraries and Institutions). All other countries $12.00 (Individuals); $15.00 (Libraries and Institutions). Interns, residents and students $4.00. Single copy $3.00. Third class postage paid at Richmond, Virginia.
TO OUR READERS

Appropriately, the MCV QUARTERLY begins a new volume for 1979 with a new format. Although the basic alterations of size and mailing method were dictated by a desire to reduce rising publication costs, we carried the impetus to change even further with the introduction of a new typeface and layout. For example, the table of contents will now be published on the outside back cover for easy reference. These and other modifications have streamlined our appearance and provided a few more pages for papers—papers which we hope will continue to be of high interest to practicing physicians as well as students of medicine.
INTRODUCTION

The McGuire Lecture Series honors Stuart McGuire, M.D., L.L.D. who served the Medical College of Virginia from 1913 to 1948 as Professor of Surgery, Dean, President, and Chairman of the Board of Visitors. His relentless dedication was a primary force in moving MCV into the national mainstream of medical education.

The 50th McGuire Lecture Series presented current reviews in clinical cardiology and hypertension for practicing physicians and medical students. Speakers were members of the faculty of the Divisions of Cardiology and Cardiovascular Surgery at the Medical College of Virginia, and Dean T. Mason, M.D., Chief of the Cardiovascular Section at the University of California at Davis. Dr. Mason, who is the outstanding authority on the management of congestive heart failure by reduction of the load against which the heart must pump, was the McGuire Lecturer.

The audience attending this lecture series came from several states and represented various medical disciplines. They entered freely into the discussion and thus contributed greatly to the value of the presentations. We offer thanks to them, to the lecturers whose talks are presented in this issue of the MCV QUARTERLY, to the Department of Continuing Medical Education whose planning for this symposium was both thorough and efficient, and especially to Dr. Mason, who gave a magnificent McGuire Lecture.

DAVID W. RICHARDSON, M.D.  
Chairman, Division of Cardiology
The Role of the Exercise Stress Test in the Adult

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The use, limitations, and value of the exercise stress test have been under debate in the recent cardiology literature.1-5 The purpose of this discussion is to examine the current role of the stress test.

Procedure

Common reasons for obtaining a stress test are:

1. Chest pain evaluation;
2. Screening for coronary heart disease in asymptomatic persons;
3. Post-myocardial infarction, including rehabilitation;
4. Angina pectoris evaluation;
5. Arrhythmia evaluation—complementary to Holter monitoring; this is less sensitive than the 24-hour Holter monitor but will detect arrhythmias not present on the Holter recording;
6. Functional capacity evaluation (also used in valvular heart disease and other types of heart disease);
7. Evaluation of therapy (coronary bypass surgery, antiarrhythmic agents, propranolol, rehabilitation programs).

Patients with the following problems are usually not exercised:

1. Recent myocardial infarction (although the test can be done at three weeks to a heart rate of 130 or symptoms, or at two to three months to 85% of predicted maximal heart rate); 2. Acute myocarditis or pericarditis;
3. Acute coronary insufficiency or unstable angina pectoris (since an exercise test can precipitate a myocardial infarction, it is preferable to wait two to three weeks until the patient’s condition is stable);
4. Rapid ventricular or atrial arrhythmias;
5. Second- or third-degree heart block;
6. Congestive heart failure;
7. Acutely ill patients (infections, hyperthyroidism);
8. Severe symptomatic aortic stenosis.

For practical purposes, ST-segment changes cannot be interpreted in the presence of digitalis, left bundle-branch block, left ventricular hypertrophy with the ST-T wave changes of the left ventricular strain pattern on the resting ECG, or the Wolff-Parkinson-White syndrome. The stress test is more difficult to interpret in patients with resting ST-T wave changes, particularly in women. If possible, cardiac medications should be discontinued prior to the test.

There are many different protocols for exercise tests. I prefer the submaximal graded treadmill exercise test, using the Bruce protocol.6 This is a continuous test with incremental increases in the elevation and speed of the treadmill every three minutes (Table 1). Patients are exercised to a target heart rate which is 90% of their age-predicted maximum heart rate (Table 2). The predicted maximum heart rate for untrained individuals is 205 - .41 (age, years) beats/minute and for athletically trained persons is 198 - .41 (age, years).7 Post-myocardial infarction patients are exercised to 85%
The major reasons for stopping an exercise test are as follows:

1. Target heart rate achieved;
2. Chest pain typical of angina pectoris;
3. Arrhythmias such as
   a. premature ventricular contractions—pairs, bigeminy, R on T, or increasing frequency,
   b. ventricular tachycardia (≥3 PVCs),
   c. atrial fibrillation, flutter, tachycardia,
   d. heart block—second- or third-degree;
4. Marked hypertension (>250 mm Hg systolic);
5. Hypotension with continuing exercise (>10 mm Hg fall in systolic pressure);
6. Fatigue, weakness, dyspnea;
7. Cerebral symptoms such as dizziness;
8. Intermittent claudication;
9. Decrease in heart rate with continuing exercise;
10. Marked ST-segment depression;

The interpretation of the exercise test is based on ST-segment changes, although there are other factors to be considered. The exercise test is considered positive when there is 1 mm of additional ST-segment depression which is horizontal or down-sloping for at least .08 seconds (Fig 1) or 1 mm of ST-segment elevation in an ECG lead without Q waves. When ST-segment elevation occurs with exercise in a lead without Q waves, there is usually a very critical narrowing of at least one of the coronary arteries. The following are other findings which should be considered in the interpretation of the exercise test:

1. Chest pain typical of angina pectoris during the test should be recorded in the interpretation.
2. An increase in R wave height with exercise in the left precordial leads is abnormal. Patients without coronary heart disease decrease their systolic and diastolic volume progressively with exercise which results in a decrease in R wave height; the ischemic ventricle is unable to decrease its volume and R wave height increases.
3. Inverted U waves in the absence of antiarrhythmic drugs or left ventricular hypertrophy; incidence is probably small.
4. Hypotensive response to exercise: A fall in systolic blood pressure of 10 mm Hg or more is abnormal; other etiologies of severe heart disease and vasovagal responses must be excluded.
5. Ventricular arrhythmias: Premature ventricular contractions at low heart rates (below 130) with exercise in patients who do not have PVCs at rest.
these are probably not specific for coronary heart disease.


The interpretation of the exercise test must be assessed in the clinical setting in which it occurs. The largest amount of information is available in patients with chest pain. A few years ago we evaluated the sensitivity and specificity of the exercise test in 124 patients with chest pain undergoing coronary arteriography. The criterion for a positive exercise test was 1 mm of additional ST-segment depression (or elevation) which was horizontal or down-sloping for .08 second. Sixty-five patients had greater than a 50% narrowing of one coronary artery; 49 (75%) of these had a positive exercise test; thus there were 25% false-negatives. Fifty-nine patients had less than a 50% narrowing in any coronary artery; 4 (7%) had a positive exercise test and were considered to be false-positives. This sensitivity of 75% and specificity of 93% is comparable to eight other studies where sensitivity ranged from 54% to 80% and specificity from 88% to 97%. The sensitivity of the exercise test will be higher in patients with three-vessel disease than in patients with single-vessel disease. The use of slowly up-sloping ST segments with ST-segment depression greater than or equal to 1.5 mm at 80 msec after the J point increased the sensitivity in one study from 64% to 76% but decreased specificity from 93% to 82%. It is important to realize that most false-negative calculations include only those patients who reach their target heart rate.

In general, patients with more severe coronary artery disease will have an exercise test which is positive at lower heart rates and during the early stages of the test. We compared the maximum heart rate achieved during an exercise test with the severity of coronary artery disease on angiography in 40 patients with a positive exercise test. There was a significant

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Fig 1—Example of positive exercise test. In the exercise tracing there is more than 1 mm of ST-segment depression which is horizontal and persists for more than .08 seconds.
inverse correlation \((p > .001, r = -0.62)\) between the severity of coronary artery disease and the maximum heart rate achieved (Fig 2). In a recent study patients who had a positive exercise test in stage I or II had: (1) greater than a 60% chance of having three-vessel disease, (2) greater than a 25% chance of having main left coronary artery disease, (3) greater than a 97% chance of having coronary heart disease, and (4) nonsurgical patients had a survival rate of 85% at one year and 63% at four years.\(^{19}\)

In post-myocardial infarction patients the diagnosis of coronary artery disease is established, but the exercise test may provide useful information. A recent study has shown that an exercise test to symptoms, or a heart rate of 130, is safe at three weeks post-infarction.\(^{20}\) Patients with a positive test based on ST-segment depression have a significantly higher incidence of cardiac events during the next eighteen months. At two or three months post-infarction patients who have additional ST-segment elevation in leads with a Q wave have a high incidence of either a ventricular aneurysm or a large infarction.\(^{21,22}\) Post-infarction patients\(^{22}\) with a positive exercise test based on ST-segment depression are likely to have multiple-vessel disease (87%) compared to patients with a negative test who are likely to have single-vessel disease (62%).

The assessment of the meaning of a positive exercise test is most difficult in the asymptomatic patient. It is difficult to determine the sensitivity and specificity in this population because coronary arteriograms are not routinely done. In selected populations where they have been done the incidence of false-positives has ranged from 36% to 69%\(^{23-25}\) and were lowest in the least selected population. The persistence of ST-segment depression for two minutes after termination of exercise may improve the specificity in asymptomatic patients.\(^{26}\) Despite the large percentage of false-positives, there is a significant increase in cardiac event rate (myocardial infarction and sudden death) in asymptomatic subjects with a positive test compared to those with a negative test.\(^{27}\) Also, it should be recognized that the significance of a positive exercise test is entirely different in an asymptomatic young woman who has 1 mm of horizontal ST-segment depression at the end of the tenth minute of exercise which lasts for 20 or 30 seconds compared to a middle-aged man with 2 or 3 mm of horizontal ST-segment depression in the fourth minute of exercise which persists for several minutes.

In summary, the exercise stress test can provide useful information in the diagnosis and prognosis of patients with heart disease or suspected heart disease when it is interpreted with the knowledge of the clinical findings.

**REFERENCES**

4. EPSTEIN SE: Value and limitations of the electrocardiographic response to exercise in the assess-


Thallium 201 Myocardial Imaging

MICHAEL J. COWLEY, M.D.

Assistant Professor of Medicine, Cardiovascular Disease, Medical College of Virginia, Health Sciences Division of Virginia Commonwealth University, Richmond, Virginia

In recent years technological advancements in nuclear medicine have resulted in increasing interest in the use of radioisotope techniques in the evaluation of cardiac disease, and cardiovascular nuclear medicine has developed into a useful noninvasive tool in clinical cardiology. Myocardial infarct imaging with technetium-99m pyrophosphate has been demonstrated to be a reliable method in the diagnosis of suspected myocardial infarction.\(^1\);\(^2\) Radioisotope cardiac flow studies are useful in the diagnosis and follow-up of congenital heart disease;\(^3\) and gated cardiac blood pool imaging is emerging as an important technique in the evaluation of left ventricular function and ejection fraction.\(^4\);\(^5\) One of the more promising recent applications of nuclear medicine in cardiology has been the development of myocardial perfusion imaging in the evaluation of coronary artery disease. Thallium 201 is the major radioisotope employed in myocardial perfusion imaging and this report will review its basic properties and its use in the diagnosis of ischemic heart disease.

Myocardial Perfusion Imaging

Myocardial perfusion imaging (MPI) refers to the use of certain radioisotope tracers which are rapidly and selectively concentrated in the heart. It is based on the principle that myocardial uptake of these isotopes occurs primarily as a function of myocardial blood flow and function. The resultant pattern of activity provides an assessment of regional myocardial blood flow by comparing the amount and distribution of activity in different areas of the heart. Regions of normal and abnormal myocardium are thereby distinguished by the presence and location of differences in myocardial radioactivity. Of the various radioisotopes which have been used for MPI, thallium 201 possesses the best radiation characteristics (Table 1) and has been the most widely investigated. Thallium 201 is an analogue of potassium and exhibits similar biologic and physical properties;\(^6\) it is a monovalent cation with a half-life of 73 hours and is readily concentrated in the myocardium by an active transport process involving membrane sodium-potassium adenosinetriphosphatase (ATPase). Thallium 201 emits low-energy photons which permit imaging with a scintillation camera and provide for high spatial resolution; it has a high myocardial extraction ratio, with 80% to 90% of an injected dose concentrated in the heart within the first few minutes, and exhibits a high myocardial-to-background ratio which contributes to improved image resolution. These features allow for prompt imaging following injection and a low patient radiation dose.

Myocardial activity with MPI is dependent on both the initial distribution of the radioisotope and its subsequent redistribution with time. The distribution phase is most important with early imaging and is determined both by isotope delivery to different regions of the heart and by myocardial extraction. Radioisotope delivery is a flow-dependent process and has been shown experimentally to be proportional to regional myocardial blood flow.\(^7\) Myocardial extraction of thallium 201 is a cell-dependent process requiring functioning myocardial cells. Distribution of thallium 201 occurs rapidly into normal areas.
of myocardium but may be significantly delayed to zones of diminished coronary blood flow and may be absent in regions of abnormal function which are unable to concentrate the isotope. Redistribution is homogeneous in normal hearts but is heterogeneous in zones of significantly diminished flow or function. Washout of thallium 201 begins early from normal areas and is detectable at one hour; while this is in process from normal areas, continuing uptake is often occurring into flow-limited areas which exhibit initially delayed myocardial uptake. These regions will eventually show normalization of activity if viable myocardium is present, and redistribution is usually complete within one to four hours. Areas of persistently diminished activity generally indicate impaired myocardial function and represent myocardial infarction.

**Technique**

Thallium 201 in a dose of 1 to 2 mCi is administered intravenously either at rest or at the peak of exercise when MPI is used in conjunction with treadmill exercise testing. Myocardial images are recorded using a stationary or portable scintillation camera. Early images are obtained 10 to 15 minutes after injection and reflect the status of myocardial perfusion at the time of injection. If the early image is abnormal, delayed imaging three to four hours later is performed to look for redistribution into ischemic areas. Multiple views are obtained to assess the different areas of myocardium with minimal superimposition and overlap. Interpretation is done by comparison of regional myocardial activity; a normal image will demonstrate a relatively homogeneous distribution of radioisotope within the left ventricle (Figs 1 and 2), and an abnormality is represented by diminished activity, appearing as a “cold” area (Fig 3). A defect which is persistent on late images indicates damaged myocardium or scar (Fig 4), and a transient defect which is present on early images but has resolved with delayed imaging represents an area of reversible ischemia (Fig 5). Difficulty with interpretation may occur when only small differences in regional activity are present, but this may be improved by use of computer processing techniques.

**Myocardial Infarction**

One area of clinical application of thallium 201 MPI is in the diagnosis of myocardial infarction. Several investigators have demonstrated a high sensitivity for thallium 201 in the detection of acute myocardial infarction. In these studies sensitivity was greater than 95% in patients with transmural infarction and from 80% to 85% for nontransmural infarction. Sensitivity is unaffected by location of infarction but is dependent on infarct size, with decreased

![Fig 1—Normal thallium 201 MPI in the anterior (ANT), left anterior oblique (LAO), and left lateral (LLATL) projections.](image)

**TABLE 1**

Myocardial Perfusion Imaging

<table>
<thead>
<tr>
<th>Radionuclides: K-43, Rb-81, Cs-129, TI-201</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Analogues of K+: physical and biologic</td>
</tr>
<tr>
<td>• TI-201 - best radiation characteristics</td>
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<tr>
<td>• t½ - 73 hours</td>
</tr>
<tr>
<td>• low-energy emission characteristics</td>
</tr>
<tr>
<td>• high myocardial extraction ratio (60%)</td>
</tr>
<tr>
<td>• high myocardial-to-background ratio</td>
</tr>
<tr>
<td>• low patient radiation dose (.07 rad/mCi)</td>
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<tr>
<td>• usual dose = 1 to 2 mCi</td>
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</table>

COWLEY: THALLIUM 201 MYOCARDIAL IMAGING / 9
Fig 2—Normal thallium 201 study with exercise (GXT) in the anterior (left), left anterior oblique (center), and left lateral (right) views. Activity in the left ventricle is homogeneous and intense, and there is activity seen in the right ventricle in the left and center panels. Right ventricular activity is often detectable with exercise. This patient had typical angina pectoris with normal coronary arteries on angiography and a false-positive exercise electrocardiogram.

Fig 3—Abnormal thallium 201 rest image in the anterior (ANT), left anterior oblique (LAO), and left lateral (LL) projections in a patient with acute anterior myocardial infarction. A large area of diminished activity is evident in the anterior and apical regions of the left ventricle in each projection.
Fig 4—Thallium 201 exercise MPI with early (left) and delayed (right) images in the left anterior oblique projection in a patient with atypical chest pain and history of previous myocardial infarction. The immediate image shows an anteroseptal defect and the delayed image recorded four hours later shows no redistribution into this area, indicating a fixed or irreversible defect from previous myocardial infarction.

Fig 5—Thallium 201 exercise (GXT) study in a patient with angina pectoris. The image at left was recorded immediately following completion of exercise and demonstrates a large area of markedly diminished activity in the anteroseptal region of the left ventricle. The image at right was obtained four hours later and shows redistribution of activity into the anteroseptal region with normalization of activity, indicating reversible, exercised-induced ischemia.
sensitivity in small infarctions. Sensitivity is also
dependent upon time, with rare false-negative
studies being obtained in the first 6 hours after
infarction and an increased incidence of false-
negative results observed after 24 hours.9 In ad-
dition, serial thallium 201 studies in the same
patient have also demonstrated that the size of
the defect often changes with time, usually
being largest during the first 24 hours and be-
coming smaller and more stable in size after 48
hours (Fig 6).9 This observation probably in-
dicates detection of zones of reversible peri-in-
farction ischemia in addition to acute infarction
in its early course which resolves with time,
leaving only the residual area of infarction ap-
parent on subsequent images. The size of the
defect with thallium 201 MPI also correlates
well with the size of the infarct as determined by
serum enzyme techniques,12 pathological anal-
ysis,11 and quantitative left ventricular angiogra-
phy.13 However, application of thallium 201 MPI
in suspected myocardial infarction is limited in
patients with previous myocardial infarction be-
cause of the isotope's inability to distinguish
new infarction from old infarctions or ventricular
aneurysm. There is also reduced specificity with
small infarctions (as with serum enzymes and
electrocardiographic diagnosis) because of the
limits of resolution of the technique.14 In ad-
dition, MPI at rest may be abnormal with early
imaging in some patients having unstable an-

**TABLE 2**

**Exercise Thallium Imaging**

<table>
<thead>
<tr>
<th>CLINICAL APPLICATIONS</th>
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<tr>
<td>Improved sensitivity over exercise testing alone</td>
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<td>Clarification of equivocal stress test</td>
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<td>Diagnosis when stress test uninterpretable</td>
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<tr>
<td>Conduction defect (LBBB)</td>
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<tr>
<td>Left ventricular hypertrophy</td>
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<tr>
<td>Resting ST-segment abnormality</td>
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<tr>
<td>Digitalis effect</td>
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<tr>
<td>Identification of false-positive stress test</td>
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<tr>
<td>Evaluation of coronary bypass graft function</td>
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</table>

Fig 6—Serial thallium 201 MPI in anterior (ANT), left ante-
rior oblique (LAO), and left lateral (LL) projections in a pa-
tient with posterior wall infarction. Arrows indicate a defect
at 4.5 hours after onset of chest pain. This defect is dimin-
ished on the repeated studies 24 hours and 8 days later,
especially in the LAO view.

Fig 7—False-negative stress electrocardiogram. Resting
(top) and stress (bottom) electrocardiogram and thallium
201 MPI in the anterior (ANT), left anterior oblique (LAO),
and left lateral (LLATL) projections in a patient whose coro-
nary angiograms (SCA) demonstrated significant left ante-
rior descending coronary artery stenosis. The resting scinti-
gram reveals homogeneous radioactivity. With stress, the
interventricular septum and anterior left ventricular walls (ar-
rows), the regions supplied by the stenotic vessel, are
barely visible. The electrocardiogram shows no ischemic
change on exercise.
Fig 8—Normal thallium 201 MPI and equivocal stress electrocardiogram in a patient with normal coronary arteries on angiography (SCA). Resting (top) and stress (bottom) electrocardiogram and stress imaging in the anterior (left), left anterior oblique (center) and left lateral (right) projections in a patient with troublesome atypical chest pain and a history of hypertension. The full resting electrocardiogram revealed left ventricular hypertrophy (LVH). The monitored lead showed ST-segment depression that deepened with stress and was difficult to interpret in view of the depression at rest. The perfusion image was normal and clarified the stress electrocardiogram.

gina without infarction owing to severely reduced flow, but this can usually be clarified if delayed images are also obtained. Thallium 201 studies may also be abnormal in certain forms of noncoronary heart disease, particularly cardiomyopathy. For these reasons, thallium 201 MPI appears to have limited general usefulness for the diagnosis of acute infarction but can be of value to confirm infarction in situations when standard criteria are not helpful. It has been useful in screening patients for coronary care unit admission.9

**Exercise Myocardial Imaging**

Thallium 201 MPI has its greatest application when used in combination with treadmill exercise testing for the evaluation of chest pain and transient myocardial ischemia, and it provides advantages over exercise testing alone.

Fig 9—False-positive stress electrocardiogram. Stress thallium 201 MPI in the anterior (ANT), left anterior oblique (LAO), and left lateral (LLATL) projections (top) and the resting and stress electrocardiograms (bottom) in a patient with normal coronary arteries on angiography (SCA). Radiouclide distribution was normal, but the stress electrocardiogram showed distinct and significant horizontal ST-segment depression. Scintigraphy proved to be the valid clinical indicator.

Fig 10—Preoperative (top) and post-operative (bottom) thallium 201 MPI in the 45-degree left anterior oblique (LAO) projection in a patient who underwent coronary bypass surgery. The preoperative rest image (top, left) is normal, but following exercise (ETT) there is an extensive defect in the anteroseptal region (top right) preoperatively. Postoperatively both rest (bottom, left) and exercise (bottom, right) are normal. The bypass graft was patent on angiography.
Thallium 201 is administered at the peak of exercise, and early images are obtained. If a normal image is recorded, further imaging is unnecessary (Fig 2). If an abnormality is present, delayed images are recorded to assess the redistribution into ischemic areas (Fig 5). When compared with standard exercise electrocardiography, thallium 201 MPI is significantly more sensitive than exercise testing in the detection of coronary artery disease. This improved sensitivity is present in patients with a normal resting electrocardiogram (ECG) in whom exercise testing is most reliable (Fig 7), and is found particularly in patients with an abnormal resting ECG, in whom ECG changes with exercise are often difficult to interpret or are uninterpretable. This is encountered in patients with intraventricular conduction defects, particularly left bundle-branch block; left ventricular hypertrophy (Fig 8); nonspecific resting ST-segment abnormalities; and in patients taking digitalis or other medications which may alter the resting and exercise ECG.

Thallium 201 also has a higher specificity in detection of coronary artery disease than standard treadmill exercise testing, as false-positive results with thallium 201 are infrequent (Fig 9).\(^1\)\(^7\)\(^,\)\(^1\)\(^9\) In contrast, the incidence of false-positive results with exercise electrocardiography may be as high as 30% in certain patient populations.\(^2\)\(^1\) Thallium 201 exercise imaging is complementary to exercise testing, and diagnostic accuracy is improved when they are used in combination. In several series, this accuracy exceeds 90% in the detection of significant coronary artery disease.\(^1\)\(^7\)\(^,\)\(^1\)\(^9\)

MPI with thallium 201 may also be of value in the postoperative evaluation of patients having coronary artery bypass graft surgery, as changes in regional myocardial perfusion with MPI have been shown to correlate well with bypass graft function,\(^2\)\(^2\) thereby providing a noninvasive method of determining graft patency or closure (Fig 10).

In summary, MPI with thallium 201 is a new and effective noninvasive technique in the diagnosis of ischemic heart disease. It can reliably detect myocardial infarction and may be useful when the diagnosis of acute infarction by other means is uncertain. Exercise thallium 201 imaging is the area of greatest clinical application of MPI, resulting in improved sensitivity and specificity over exercise testing alone, and in high diagnostic accuracy in the detection of coronary artery disease when used in combination with exercise electrocardiography. Thallium 201 MPI is also of value in the evaluation of coronary artery bypass graft function.

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Figure 6 is reproduced by permission from the New England Journal of Medicine (295:1–5, 1976).

Figure 10 is reproduced from Circulation (56:830–836, 1977) by permission of the American Heart Association, Inc.

REFERENCES


Indications for Cardiac Catheterization in the Diagnosis and Management of Coronary Artery Disease

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In 1979 coronary angiography remains the standard test for diagnosing the presence and extent of coronary artery disease. Non-invasive studies such as exercise testing are only relative predictors of coronary anatomy. Therefore, to define specifically whether or not coronary disease exists in a given patient and, if present, to delineate its location, severity and the potential for bypass surgery, a coronary angiogram is the test to obtain. The purpose of this paper is to discuss indications for coronary angiography in the management of patients with established or suspected coronary disease.

Figure 1 shows a schematic representation of the normal cardiac blood supply. The left and right coronaries exit directly from the aorta, and the left main coronary divides into two major branches, the left anterior descending and the circumflex vessels. It is important to note the extensive blood supply to the heart—mainly the left ventricle—through the left main coronary and its branches. Therefore, the left main coronary is frequently considered in a special class when discussing coronary artery disease. Other important vessels include the left anterior descending, the circumflex and the right coronary arteries. The term “single-”, “double-,” or “triple-vessel disease” refers to the number of these three important vessels involved with significant disease. Obstructive lesions of the coronaries represent the build-up of atherosclerotic material which decreases the vessel lumen and thereby decreases blood flow through the vessel. During coronary angiography, radiopaque dye is injected selectively into each coronary artery to allow visualization of each vessel and its major branches.

Figure 2 illustrates a single-frame cine from such a procedure; the significant atherosclerotic lesion is clearly demarcated. Therefore, using this technique, the extent and location of coronary artery lesions can be specifically identified.

Table 1 lists seven indications for coronary angiography. Considerable controversy continues to exist about the overall benefits of coronary bypass surgery and therefore it is extremely difficult to be unequivocal in listing one’s indications for coronary angiography. However, the general guidelines given here are thought to be the most reasonable, although clinical circumstances must be carefully analyzed for each patient prior to proceeding to coronary angiography.

Symptomatic Indications

The first and probably most frequent indication for coronary angiography is failure of a patient to respond to reasonable medical management; the term “reasonable medical management” is used because of the wide response of patients to medical treatment. Some patients’ response is less than ideal because of poor drug compliance while others have intoler-
able side effects to the medications such as severe protracted headaches associated with nitrate administration, or significant fatigue or bad dreams associated with propranolol. In addition, a prior history of asthma or congestive heart failure is a contraindication for the use of propranolol. Finally, despite adequate medical management, some patients remain incapacitated because of their chest pain. In any situation in which a patient fails to get adequate symptomatic benefit from medical treatment and/or has significant side effects associated with the treatment, coronary angiography should be considered to determine if he or she is a candidate for coronary bypass surgery. Clearly 80% to 90% of patients have a significant reduction in symptoms and medication requirements following coronary bypass surgery and many of them remain symptom-free.\(^1\) In a study of 100 patients randomly assigned to medical or surgical treatment, Mathur and Guinn\(^2\) documented significantly improved treadmill performance for post-bypass surgery patients when compared with their medically treated counterparts. Furthermore, subsequent to treadmill testing, 70% of the surgical patients had no angina while only 20% of the medical group were angina-free. These data emphasize the symptomatic benefits of coronary bypass surgery.

In addition to symptomatic benefits of coronary bypass surgery, certain subgroups of patients have improved longevity following this procedure. Ongoing studies will continue to better delineate these subgroups, but at present those patients with left main coronary artery disease appear to show improved function and prognosis as a result of the bypass operation. This fact is well illustrated by a three-year follow-up of the subgroup of patients with significant left main coronary artery disease from the VA Cooperative Study.\(^3\) In this study, 12 (29%) of 41 medically treated patients died in the three-year follow-up compared to only 3 (7%) of 42 patients in the surgically treated group; the difference was significant (\(p \leq 0.01\)). In addition, the ben-

Table 1: Indications for Coronary Angiography

<table>
<thead>
<tr>
<th>Indication</th>
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<tbody>
<tr>
<td>1. Angina inadequately responsive to reasonable medical management</td>
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<tr>
<td>2. Unstable angina</td>
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<tr>
<td>3. Atypical angina</td>
</tr>
<tr>
<td>4. “High-Risk” coronary patients</td>
</tr>
<tr>
<td>5. Undiagnosed chest pain</td>
</tr>
<tr>
<td>6. Heart failure post-myocardial infarction</td>
</tr>
<tr>
<td>7. Recurrent angina post-coronary bypass surgery</td>
</tr>
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\(\text{Fig 1} -\text{Schematic coronary anatomy. The right and left coronary arteries arise from the aorta. The short main left (LC) artery bifurcates into two large branches, the left anterior descending (LAD) artery and the circumflex (CX) artery supplying most of the anterior and lateral myocardial surface. The right coronary (RC) artery supplies the inferior myocardium through the posterior descending (PD) artery.}\)

\(\text{Fig 2} -\text{Left main coronary obstruction. The left coronary system seen in a lateral projection is filled with contrast medium during a contrast injection. Note critical left main artery stenosis (arrow).}\)
efit appeared to be greatest in those patients with associated right coronary disease.

Therefore, patients who do not respond well to reasonable medical treatment, and who are surgical candidates have an excellent prospect for improved functional status following bypass surgery. Furthermore, patients with left main vessel disease and perhaps yet-to-be-proven other subgroups have improved longevity following the bypass operation.

Unstable Angina Pectoris

A second major consideration for coronary angiography is patients who have unstable or rapidly worsening angina pectoris; in certain instances, these patients may even be classified as having pre-infarction angina. Most cardiologists feel that such patients should be stabilized first, if possible, with vigorous medical treatment. This philosophy is supported by studies suggesting that the risk of emergency coronary angiography and bypass surgery to patients with unstable angina is equal to the risk of initial medical management as far as morbidity and mortality are concerned; however, patients who do not respond to medical treatment are candidates for angiography and coronary bypass surgery to relieve their persistent symptoms. For those patients who do respond to medical treatment the question then arises as to whether they should be catheterized and, if so, when. Generally, it seems prudent to consider angiography for young, active patients with unstable angina even though they respond to medical treatment, as a review of the angiographic and historical data will show.

Coronary angiography on large groups of patients who have had recent unstable angina have shown a 10% to 15% incidence of left main coronary disease. This finding is important because these patients have improved survival following bypass surgery. In addition, from 5% to 20% of patients may show normal coronary angiograms; variability of this number relates to the criteria used in any given study for the diagnosis of unstable angina. When accompanying electrocardiographic changes are required for the diagnosis of unstable angina, the incidence of normal coronaries associated with this chest pain syndrome is reduced. However, identifying normal coronaries is important as many patients are then found to have a non-cardiac cause for their chest pain. Rarely, individuals may have angina with normal coronaries, but generally these patients do well, with infrequent symptoms and a much lower risk of myocardial infarction than those patients with obstructive coronary disease. Therefore, the diagnosis of normal coronaries allows one to be much more positive in reassuring the patient about long-term survival. In addition to these subgroups, a majority of the remaining patients with unstable angina have significant three- vessel disease, a group that many feel may benefit from bypass surgery in terms of symptoms and prognosis.

One third or more of non-surgical patients who have unstable angina will have a subsequent unstable period within six months despite medical treatment. Excluding left main vessel disease, in randomized studies comparing medical versus surgical treatment for unstable angina, there was no significant difference in morbidity (subsequent myocardial infarctions) and mortality when the two groups were compared after four months or after 1½ years. However, these studies emphasize the improved functional performance seen in those patients who undergo surgery. Considering the higher incidence of left main vessel disease, the moderately frequent occurrence of normal coronaries and the significant subsequent disability of medically treated patients, coronary angiography is warranted in active individuals with unstable angina to better define the programs and appropriate treatment plan.

Atypical Angina Pectoris

A third consideration for coronary angiography is in those patients who demonstrate atypical or Prinzmetal type angina pectoris. This syndrome is characterized by chest pain at rest with associated significant ST-segment elevations which are transient in nature. These patients are often subject to significant rhythm disturbances and/or conduction abnormalities with the chest pain episodes. Anatomically, patients with atypical angina may have either high-grade fixed obstructive lesions or normal coronaries with intermittent vessel spasm producing the symptoms. These patients are frequently difficult to manage medically, thus the distinction between significant obstructive disease and spasm is important from the standpoint of therapeutic options, as patients with significant obstructive disease generally benefit from by-
pass surgery whereas patients with spasm do not.

High-Risk Patients

Symptoms of angina do not correlate well with the extent of disease. Ideally, one would like to have a simple noninvasive test that would identify those patients who have significant left main vessel disease which derives so much prognostic benefit from bypass surgery, but no such test is available. However, certain exercise test responses are considered suggestive of severe coronary artery disease which frequently includes left main vessel disease. Table 2 lists those high-risk abnormalities. Included in this group are patients who develop marked (2 mm or greater) ST-segment depression with exercise testing, particularly at low levels of exercise performance. In addition, the development of ST-segment elevation on treadmill testing in an area of the electrocardiogram not showing a prior myocardial infarction is a significant predictor of severe proximal coronary disease if not of left main vessel disease. Finally, patients who develop hypotension at nonmaximal exercise performance are again likely to have significant disease. Such hypotension suggests severe myocardial ischemia consistent with marked proximal coronary artery disease. In these high-risk patients coronary angiography is important to delineate this anatomic abnormality.

Other high-risk patients include those who have a history of prior myocardial infarction and significant symptomatology and/or poor exercise test responses, particularly if they are in the high-risk category listed above. Furthermore, subendocardial myocardial infarctions may represent another significant risk group. Fifty consecutive patients with a recent condition of this type at the Mayo Clinic showed a high frequency of symptomatic disability in a short-term ten-month follow-up. Fifteen patients (30%) had significant stable angina pectoris and nearly half, 23 (46%) of 50, developed unstable angina over the short time of the study; only 12 (24%) of the 50 remained angina-free. Considering the frequency of significantly limiting symptomatology in this study, early angiography in patients with a recent subendocardial myocardial infarction seems warranted to identify those patients who are candidates for bypass surgery, particularly in physically active individuals.

Chest Pain Diagnosis

To this point, the discussion has centered on the diagnosis of the extent of coronary disease. Another consideration for coronary angiography is specifically to exclude the existence of coronary disease. Not every patient with vague, intermittent or poorly defined chest discomfort is a candidate for a coronary angiogram; however, there are those in whom noninvasive studies, including exercise testing and perhaps thallium imaging, fail to demonstrate clearly whether or not coronary artery disease exists. Most of these patients have symptom complexes with components that are both typical and atypical of angina. In addition, the concern about the possibility of coronary disease may be limiting these patients' lifestyles. In such instances, coronary angiography is warranted to provide a definitive diagnosis.

Congestive Heart Failure

Congestive heart failure after a myocardial infarction can be a difficult management problem, particularly if it does not respond to routine medical treatment for heart failure. Left heart failure may be manifested either as a congested state with recurrent pulmonary edema and shortness of breath or as a low-output state in which the patient's major complaints relate to low forward cardiac output, that is, fatigue, weakness and exercise intolerance without chest pain. Clinical findings frequently include either a mitral regurgitation murmur, ventricular gallop rhythms and/or a contour on apex palpation, suggesting a left ventricular aneurysm. Anatomically, one wishes to know whether or not there is a localized aneurysm or significant mitral regurgitation. Cardiac catheterization of patients who fail to respond to routine treatment will delineate the severity and location of left ventricular wall motion abnormalities as well as whether or not there is significant valvular insufficiency. In addition, coronary angiograms identify obstructive vessels which may exist in the areas of remaining functional myocardium.

### TABLE 2

<table>
<thead>
<tr>
<th>Exercise Test Predictors of Potentially Severe Coronary Disease</th>
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<td>1. Marked ST-segment depression</td>
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<tr>
<td>2. ST-segment elevation in an area of noninfarction of the ECG</td>
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<tr>
<td>3. Hypotension at nonmaximal performance</td>
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VETROVEC: CARDIAC CATHETERIZATION / 19
Patients with severe diffuse non-localized left ventricular dysfunction are generally not candidates for bypass surgery, because in such instances the operative risk is increased and there is no benefit in terms of reducing heart failure. However, if a localized, correctable mechanical problem exists such as a left ventricular aneurysm or significant mitral regurgitation, the condition of these patients may be significantly improved by surgical correction of the appropriate defect with or without additional bypass surgery as dictated by the coronary anatomy.

**Recurrent Angina Pectoris Post-Bypass Surgery**

Finally, those patients who have previously undergone bypass surgery and who developed recurrent angina pectoris may need angiography; as the frequency of bypass surgery increases, so will the numbers of such patients. Two factors determine the need for repeat coronary post-bypass angiography. First, if the recurrent angina occurs within one to two months following bypass surgery, it is likely that one or more vein bypass grafts have occluded. In this event the preoperative angiograms should be reviewed and the anatomy discussed with the surgeon. If the distal vessels suggest poor distal runoff either angiographically and/or at the time of surgery and the post-bypass flows were poor, it is unlikely that reoperation will carry any better chance of maintaining a patent graft, and consideration of repeat catheterization should be postponed unless medical treatment fails to be effective. Conversely, if flows were good at the time of surgery and the distal runoff appeared adequate, graft failure might be caused by a technical problem resulting from surgery. Reoperation could conceivably benefit such a patient, thus a repeat angiogram is warranted; however, early recurrent angina is most often seen in patients with severe distal disease.

A further consideration for angiography is the patient who has experienced marked symptomatic improvement for a long time following the bypass operation. When recurrent angina occurs in such a patient, the anatomic problem is generally not in the graft but represents progression of the disease in the native circulation, either distal to the graft insertion or in other non-graftable vessels. Depending on the symptomatology and the state of the other vessels at the time of surgery, it is reasonable to consider a repeat study in these patients, looking for other potentially graftable vessels.

The foregoing discussion should provide a reasonable approach to the utilization of cardiac catheterization and coronary angiographic techniques in the diagnosis and management of patients with coronary artery disease. Combining the functional performance information derived from noninvasive tests with the anatomic abnormalities demonstrated with coronary angiography provides the most thorough evaluation of patients with coronary disease. The information derived from coronary angiography is frequently important in the prognostic and therapeutic decisions regarding patients with coronary disease.


**REFERENCES**


Afterload Reduction Therapy for Congestive Heart Failure

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The most important recent advance in the medical management of patients with acute and chronic congestive heart failure has been the application of systemic vasodilator drugs to reduce ventricular afterload, thereby improving low cardiac output and decreasing increased venous pressure. Although such drugs have been employed for several years to treat essential hypertension, hypertensive heart failure, acute hypertensive crises, and angina pectoris, only in the past five years has their use become widely popular in the therapy of normotensive heart failure.\(^1\) While it can be reasoned that the vasodilator approach is a logical therapeutic extension of fundamental determinants regulating cardiac function known for many years, it is nevertheless intriguing that consideration has been delayed until the present time of such a useful concept as afterload reduction therapy in heart failure.

**Regulation of Cardiac Function**

The intact heart is normally governed by the intimate integration of four principal determinants regulating stroke volume and cardiac output (Fig 1): 1) preload (ventricular end-diastolic volume), 2) contractility (variable force of ventricular contraction independent of loading), 3) afterload (ventricular systolic tension during ejection), and 4) heart rate.\(^2\) The terms "cardiac function" and "ventricular performance" are used in the general sense to refer to the combined action of these four determinants of cardiac output, and not necessarily to the single determinant of contractility. The disturbed mechanisms operative in all types of clinical heart disease can be evaluated and accurately measured within the framework of isolated or composite disorders of these four major determinants of cardiac performance.\(^3\) Besides affording a better understanding of the manner in which various types of heart disease lead to disturbed pump performance, appreciation of the determinants of cardiac function (Fig 1) provides the rationale for an organized approach to the integration of therapy in the management of congestive heart failure.\(^4\)

**Rationale of Afterload Reduction Therapy**

Facilitation of ventricular emptying leading to increasing lowered stroke volume is the fundamental objective of therapy for heart failure. Conventional treatment of congestive heart failure has focused primarily on increasing ventricular stroke volume and cardiac output through the use of direct positive inotropic agents and concomitant diuretic therapy. In the case of patients with coronary heart disease in whom acute and chronic pump failure results principally from the impairment and loss of myocardial contractile units, an increase in the inotropic state of the remaining functioning heart muscle may insufficiently augment cardiac per-
performance. The powerful inotropic stimulus of cardiotonic agents may also increase overall myocardial oxygen demand (MV\textsubscript{O2}), which is potentially detrimental in acute ischemic heart disease. In contrast to elevating low stroke output by direct inotropic stimulation in heart failure, reducing impedance to left ventricular ejection by administration of systemic arteriolar dilator drugs provides a unique therapeutic mechanism for the augmentation of pump performance by increasing ventricular emptying, while also diminishing MV\textsubscript{O2}.\textsuperscript{5}

**Determinants of Ventricular Afterload**

As with ventricular filling (preload), several factors influence afterload and impedance to left ventricular outflow. The load or tension that the left ventricle must develop to eject stroke volume constitutes ventricular afterload. Afterload is defined as the wall tension during left ventricular ejection.\textsuperscript{5} The two principal determinants of afterload are systolic pressure and radius of the ventricle, according to the Laplace formula. In turn, systolic pressure is related to impedance to blood flow in the aorta, and the radius of the ventricular chamber is related to left ventricular volume (preload).

**Determinants of Aortic Impedance**

Impedance to left ventricular ejection is the instantaneous relation between the rate of change in aortic pressure and aortic flow.\textsuperscript{5} Left ventricular outflow impedance is governed primarily by two factors: 1) the compliance (relation of pressure to flow) in the large arteries; and 2) the total peripheral vascular resistance (the rate of runoff from the systemic arterial tree) which is determined principally by the radius or cross-sectional area of the systemic arteriolar beds. Of these factors regulating impedance, systemic arteriolar resistance is the most important and the variable most subject to modification by pharmacologic vasodilation.

**Determinants of Left Ventricular Energetics**

In the setting of impaired ventricular performance, elevation of outflow impedance results in declines of the extent and rate of fiber shortening and reduction in the ejection fraction with the consequent elevation of left ventricular filling pressure (preload). Thus stroke volume must be maintained at increased energy costs related to the increase in intramyocardial wall tension (afterload) (Fig 2).\textsuperscript{5} In severe pump failure, elevations of impedance and preload (afterload product), which are inherent consequences of the heart failure state, result in the rise of MV\textsubscript{O2}. This rise in MV\textsubscript{O2} leads to potential myocardial ischemia and continued impairment of pump function, causing greater sympathetic-induced rise of peripheral vascular resistance with resultant increases in ventricular afterload and preload. Thus a progressively deleterious cycle adversely affecting MV\textsubscript{O2} and pump performance is set in motion by the operation of compensatory mechanisms attempting to maintain cardiocirculatory integrity. Systemic vasodilator therapy, which produces reductions in both impedance and preload, interrupts this harmful chain of events while augmenting cardiac output, diminishing pulmonary congestion and improving myocardial energetics.\textsuperscript{5}

**Clinical Use of Systemic Vasodilators**

While it has been two decades since Burch produced ganglionic blockade with the intravenous vasodilator, hexamethonium, in the relief of intractable pulmonary congestion due to left heart failure and Johnson diminished acute pulmonary edema by sublingual nitroglycerin in left ventricular dysfunction,\textsuperscript{7} the expressed purpose of those two isolated reports was clearly the reduction of increased left ventricular preload and elevated systemic venous tone in the amelioration of backward failure (pulmonary congestion) via peripheral venodilation. That vasodilators might be useful in decreasing raised peripheral arterial resistance to diminish
pump outflow impedance with improvement in forward failure (low cardiac output) was not appreciated at that time.

The pharmacologic approach of vasodilator therapy for impedance reduction was first employed clinically in normotensive severe heart failure by Majid and associates in 1971. Thus, infusion of the alpha-adrenergic blocking agent, phentolamine, in acute myocardial infarction was observed to result in the decline of elevated systemic vascular resistance, accompanied by the rise of low cardiac output and the fall of elevated pulmonary artery pressure, without substantial alterations in systemic arterial pressure and heart rate. The modern era of afterload reduction gained momentum following reports of similar hemodynamic benefits achieved by intravenous nitroprusside in acute myocardial infarction patients. The vasodilator concept spread rapidly and has now been extended to the management of severe chronic cardiac dysfunction of various types.

As to why the idea of afterload reduction therapy of heart failure was not recognized sooner, it seems to me that this delay has been largely the result of a lack of understanding, until recently, of the critical relationships between peripheral circulatory dynamics and cardiac performance. Furthermore, the relation of cardiac output to peripheral vascular activity is dependent upon left ventricular contractility. When the heart is normal, cardiac output is principally governed by systemic venous tone with the left ventricle operating on the steep ascending limb of its Frank-Starling curve (outflow-preload relation) (Fig 3); aortic impedance reduction is of little importance. In contrast, in the presence of left ventricular dysfunction, arterial resistance is elevated and cardiac output becomes strongly dependent on outflow resistance (Fig 4). Thus, the interplay between impedance (arterial resistance bed) and preload (venous capacitance bed) reductions is that preload is more important than impedance in the normal heart (cardiac output declines) (Fig 3), while in the failing heart, impedance reduction predominates over preload decline (cardiac output rises) (Fig 4).

While profound peripheral arterial and venous constriction accompanies chronic heart failure, only recently has it become appreciated that the heightened adrenergic activity in response to lowered cardiac output, while seemingly useful in maintaining blood pressure, may result in a greater level of increased systemic vascular resistance than is required to sustain arterial pressure, and thus this reflex adaptive mechanism may actually further decrease cardiac output (Fig 4). A harmful cycle is thereby provoked in which the heart failure patient reaches a greater depression of hemodynamics than is really optimal, systemic vascul-
lary resistance being higher and cardiac output lower than are salutary. In addition, systemic venoconstriction may also become excessive in chronic heart failure. Consequently, there occurs greater elevation of left ventricular end-diastolic pressure than is required relative to the lowered cardiac output on the depressed and flattened ventricular function curve characteristic of impaired contractility. Importantly, vasodilator therapy possesses the ability to interrupt this deleterious sequence of events by partially counteracting the compensatory sympathetic reflex mechanism.1

**Spectrum of Systemic Vasodilator Drugs**

A variety of intravenous, oral, sublingual and cutaneous agents are now readily available which provide a spectrum of actions which result in the elevation of lowered cardiac output by reducing peripheral vascular resistance and/or decline of increased ventricular end-diastolic volume (ventricular preload) by lowering venous tone. These drugs produce disparate modifications of cardiac function by their differing alterations of preload versus impedance, which are dependent upon their relative effects on systemic arteriolar resistance and venous capacitance vessels characteristic of each agent (Fig 5).20 In addition, these drugs cause concomitant reduction in MVO₂ which is of special importance in ischemic heart disease.

Therefore, modulation of cardiac function by the vasodilators is determined by their relative preload and impedance effects (Fig 6). Thus, the nitrates15 principally cause venodilation (decrease elevated left ventricular end-diastolic pressure); nitroprusside,21 phentolamine,20 and prazosin21 produce balanced arterial and venous dilation (decrease elevated left ventricular end-diastolic pressure and increase lowered cardiac output) provided left ventricular filling pressure is maintained at the upper limit of normal12; while hydralazine13 predominantly effects arteriolar dilation (increases lowered cardiac output). With depressed cardiac output plus highly elevated left ventricular end-diastolic pressure and elevated peripheral vascular resistance, nitrates15 also achieve some increase of lowered cardiac output by markedly reducing increased peripheral vascular resistance. Combined nitroprusside and dopamine22 or dobutamine synergistically increase low cardiac output and decrease raised left ventricular end-dias-

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**Diagram of the spectrum of actions of systemic vasodilators on the peripheral arterial tree and systemic venous bed. CO = cardiac output; EDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; MVO₂ = myocardial oxygen consumption; IV = intravenous; SL = sublingual; H = hydralazine.**

**Relationship between cardiac output (CO) and left ventricular end-diastolic pressure (LVEDP) in a normal subject (left curve) and a patient with congestive heart failure (CHF) (right curve). Point A indicates the point of operation of the dysfunctioning left ventricle in CHF. The intermediate curve (1) is the improved relation between CO and LVEDP after the administration of digitalis (Point E), nitroprusside (NP) to above LVEDP of 12 mm Hg (Point B), and NP to below LVEDP of 12 mm Hg (Point C) with the addition of dextran (Point B). Prazosin and combined hydralazine-nitrate therapy are the same as NP from Point A to Point B. The enhanced CO and reduced LVEDP following the administration of phentolamine (PT) are shown by Point F. Hydralazine therapy can be represented from Point A to Point E. It is instructive that the improvements from Point A on the lowest ventricular function curve to Point B on the intermediate function curve (1) after NP administration and to Point F after PT was given are not the result of increased contractility; rather, they are due to the enhanced relation between CO and LVEDP that the reduction of impedance to left ventricular ejection NP and PT allow. Point D on the CHF curve is the LVEDP after diuretic or nitrate therapy. The intermediate curve (2) demonstrates the improvement in CO and decrease of LVEDP achieved with combined NP and dopamine therapy (Point G). The horizontal broken line indicates the lower limit of normal for CO and the vertical broken line indicates the upper limit of normal of LVEDP. Congestion = pulmonary congestion.**

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**FIG 5—Diagram of the spectrum of actions of systemic vasodilators on the peripheral arterial tree and systemic venous bed. CO = cardiac output; EDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; MVO₂ = myocardial oxygen consumption; IV = intravenous; SL = sublingual; H = hydralazine.**

**FIG 6—Relationship between cardiac output (CO) and left ventricular end-diastolic pressure (LVEDP) in a normal subject (left curve) and a patient with congestive heart failure (CHF) (right curve). Point A indicates the point of operation of the dysfunctioning left ventricle in CHF. The intermediate curve (1) is the improved relation between CO and LVEDP after the administration of digitalis (Point E), nitroprusside (NP) to above LVEDP of 12 mm Hg (Point B), and NP to below LVEDP of 12 mm Hg (Point C) with the addition of dextran (Point B). Prazosin and combined hydralazine-nitrate therapy are the same as NP from Point A to Point B. The enhanced CO and reduced LVEDP following the administration of phentolamine (PT) are shown by Point F. Hydralazine therapy can be represented from Point A to Point E. It is instructive that the improvements from Point A on the lowest ventricular function curve to Point B on the intermediate function curve (1) after NP administration and to Point F after PT was given are not the result of increased contractility; rather, they are due to the enhanced relation between CO and LVEDP that the reduction of impedance to left ventricular ejection NP and PT allow. Point D on the CHF curve is the LVEDP after diuretic or nitrate therapy. The intermediate curve (2) demonstrates the improvement in CO and decrease of LVEDP achieved with combined NP and dopamine therapy (Point G). The horizontal broken line indicates the lower limit of normal for CO and the vertical broken line indicates the upper limit of normal of LVEDP. Congestion = pulmonary congestion.**

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**MASON: AFTERLOAD REDUCTION THERAPY / 25**
tolic pressure. Mechanical counterpulsation aids nitroprusside in acute myocardial infarction. The 30-minute venodilator action of sublingual nitroglycerin\(^{23,24}\) is extended by 4 to 6 hours by cutaneous nitroglycerin ointment,\(^{25}\) oral isosorbide dinitrate,\(^{15}\) oral pentaerythritol tetranitrate,\(^{26}\) and by sustained-release nitroglycerin capsules.\(^{27}\) Ambulatory oral vasodilator therapy is provided by long-acting nitrates\(^{15}\) (relieve pulmonary congestion); hydralazine\(^{13}\) (improves fatigue); and prazosin alone,\(^{16,28}\) combined nitrate-hydralazine,\(^{29}\) and combined prazosin-hydralazine\(^{5}\) (improve both dyspnea and fatigue).

**Conclusions and Future Directions**

Since activity of the renin-angiotensin system is increased in cardiac dysfunction,\(^{2}\) angiotension II contributes in part to the increase of total peripheral vascular resistance characteristic of the heart failure state. Furthermore, this renin mechanism is stimulated in most instances of chronic systemic vasodilator therapy which attenuates systemic arteriolodilation produced by such treatment. Because recent evidence has been provided that administration of angiotensin-converting enzyme inhibitor in patients with heart failure results in dilation of the peripheral arterial bed with an increase in cardiac output and decrease in left ventricular filling pressure, considerable attention is now being focused on the efficacy of oral and intravenous converting enzyme inhibitors alone and in combination with conventional systemic vasodilators in clinical heart failure.\(^{30}\) In addition, the vasodilator properties of the prostaglandins are also under evaluation in heart failure therapy.

The initial administration of the vasodilators to congestive heart failure patients is usually accompanied by a favorable diuresis. However, with prolonged use of the agents, body fluid accumulation often takes place, requiring greater dosage of concomitant diuretics. While oral furosemide is generally useful in this respect, the administration of spironolactone has been particularly beneficial in effecting diuresis,\(^{31}\) probably caused by vasodilator-stimulation of the renin axis, resulting in increased aldosterone secretion.

With the prolonged use of each of the oral vasodilators in the ambulatory treatment of severe congestive heart failure, tolerance to the agents may develop in some individuals after several months. In the case of prazosin, tolerance can occur in approximately one third of patients after six months of effective therapy.\(^{32}\) This tolerance is surmountable with a return of prazosin efficacy by increasing the dose of the drug, or by the brief discontinuation of the agent for a few weeks, or by switching for a short period to another vasodilator regimen such as trimazosin\(^{33}\) or combined nitrate-hydralazine. Not a single instance of tachyphylaxis with repeated prazosin administration has been observed in over 150 heart failure patients to whom the agent has been given for either investigational or therapeutic purposes at our institution. The few reports of apparent prazosin tachyphylaxis can each be readily attributed to faulty study design and/or incorrect interpretation such as those by Chatterjee,\(^{34}\) Packer et al,\(^{34}\) and Elkayam et al.\(^{36}\) In contrast, the chronic use of hydralazine in heart failure, besides possible tolerance and the occasional side effects of the lupus erythematosus syndrome and peripheral neuropathy, may cause hydralazine-induced tachycardia, a frequent and serious complication,\(^{37}\) leading to potentially lethal dysrhythmias, angina pectoris, and left ventricular pump deterioration.

The most important question as yet unanswered is the effectiveness of vasodilator therapy in acute and chronic refractory heart failure and in reducing complications and mortality. Although some preliminary studies have been encouraging, the definitive answers have not yet been established. If myocardial ischemia plays an important role in essential hypertension, cardiomyopathies and chronic coronary heart disease, then the increased ventricular filling pressures in these conditions probably contribute to sustained subendocardial ischemia with resultant progression of cardiac dysfunction.\(^{1}\) Provided this mechanism is operative, then reduction of increased filling pressure by vasodilators should improve subendocardial perfusion and thereby diminish morbidity and extend longevity.

It is remarkable how quickly systemic vasodilator therapy has become established as an important new medical treatment for both acute and chronic heart failure.\(^{19}\) Perhaps no other recent therapeutic concept in cardiovascular medicine has been so rapidly translated into practical clinical management as that of reducing left ventricular afterload by means of
vasodilator drugs. In our thinking about the management of congestive heart failure, it is apparent that a change of focus has occurred from emphasis on contractility prevalent in the past decade to innovative considerations of cardiac unloading by agents that primarily relax vascular smooth muscle without direct actions on the heart.¹ In consort, reexamination of the proper role of the digitalis glycosides is taking place.

Some clinicians maintain that the vasodilators are important as adjuncts in severe heart failure for use when traditional means are inadequate, to be added only in combination with digitalis and diuretics; others already view the vasodilators as equal or even better alternatives than the conventional agents. In the difficult circumstance of refractory acute or chronic heart failure, the combination of vasodilators and powerful cardiotonics such as dopamine (Fig 6) or dobutamine in hospital situations,² and digitalis³⁶ or promising new oral positive inotropics on the horizon in outpatient settings,¹ provide the most potent pharmacologic augmentation of pump function possible. It is probable in the future that as more experience is gained with the vasodilators and as newer agents become available, the systemic vasodilators will be utilized as frequently as digitalis in the standard treatment of congestive heart failure.

Acknowledgment: The author gratefully acknowledges the professional collaboration of Drs. N. Awan, A. DeMaria, E. Amsterdam, D. Williams, R. Miller, E. Braunwald, L. Laslett, R. Klein, J. Joye, G. Lee, W. Bommer, J. Hermanovich, C. Taylor and Ms. L. Silvernail throughout the course of these investigations.

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Figures 3 and 4 are reproduced with permission from Drugs (16:506–521, 1978).

REFERENCES


18. MILLER RR, AWAN NA, MASON DT: Nitroprusside ther­


32. **AWAN NA, HERMANOVICH J, MASON DT, ET AL:** Ambulatory prazosin treatment of chronic congestive heart failure: Development of tolerance and maintenance of salutary vasorelaxant actions by higher dosage, substitution and interrupted therapy. *Am J Cardiol*, in press.


Evaluation of medical therapy of angina pectoris can be approached in many ways, but the objectives remain the same: (1) to relieve the acute attack of angina pectoris, (2) to prevent its recurrence, (3) to allow the patient to lead a normal lifestyle or, at least, one that is acceptable to him or her, and (4) to prevent myocardial infarction.

Major problems are incurred when one attempts to evaluate the natural history of angina pectoris with the effects of various treatments. Angina pectoris is a subjective complaint and therefore the response to therapy is also subjective. As angina frequently waxes and wanes, improvement of the patient’s condition does not necessarily indicate a direct correlation with treatment, nor does the fact that a patient has angiographically proven coronary artery disease and chest pain mean that the coronary lesion is causing the patient’s complaint. Furthermore, many patients treated for angina pectoris who were later catheterized demonstrated that, despite the fact that they had classical angina, upwards of 10% to 20% of them had insignificant coronary artery disease.\footnote{Correspondence and reprint requests to Dr. Andrea Hastillo, Box 83, Medical College of Virginia, Richmond, VA 23298.}

Thus there are problems in defining the criteria by which to judge the patient’s response to medical therapy. Electrocardiograms as well as exercise stress testing may show false-positive as well as false-negative patterns. Despite the fact that not all angiographically demonstrated lesions cause symptoms, coronary angiography remains the best method by which to judge the etiology of the patient’s complaint. In serving as the standard by which to define the presence of coronary artery disease it also provides a basis for the determination of the effectiveness of both medical and surgical interventions.

When correlating the natural history of angina pectoris and its treatment to this standard, one should remember that there are different types of angina. Basically, patients demonstrate either simple stable angina or unstable angina—the latter often being termed “pre-infarction angina” or intermediate syndrome. After reviewing a number of clinical studies, it becomes apparent that different investigators have different definitions of the forms of the angina they describe and hence these studies are not always comparable. The prognosis of angina varies with the form of angina being considered. In addition, when the true natural history of angina pectoris could have been studied—that is, before medical or surgical intervention was possible—angiography was not available. All of these factors have precluded the exact determination of the effectiveness of medical therapy based on the true natural history of angina pectoris. At the present time, there is no means by which such a study could be done. Despite all the problems and lack of exactitude, one can evaluate, to some extent, how modern medical therapy may or may not help the patient reach the therapeutic goals outlined above.

In approaching the medical management of angina, one must be aware that not all angina is the result primarily of coronary artery disease. As mentioned earlier, there are other causes of angina such as arrhythmias, severe anemias, aortic valve disease, hypertensive cardiovascular disease, and idiopathic hypertrophic subvalvular aortic stenosis which need to be ex-
cluded or, if included, to be treated. In many instances therapy (which may include surgery) aimed at these particular abnormalities may alleviate the patient’s angina and make the use of specific antianginal drugs unnecessary.

The physician should first try to remove any recognized cause of the angina. The next step should be an attempt to change the patient’s lifestyle without turning the individual into a cardiac cripple. The physician should advise the patient to stop smoking, avoid situations which might precipitate angina, avoid extreme environmental hazards, lose weight if necessary, and switch to an appropriate diet to decrease, or possibly reverse the progression of the atherosclerotic process. Participation in physician-approved exercise programs may allow the patient to maintain an acceptable lifestyle with a minimum of pain. If the patient is unhappy with the changes in lifestyle or if the angina persists, the physician must employ additional medical (nitroglycerin may have already been prescribed) or surgical therapy.

To understand why certain drugs are used for the relief of angina, one needs to understand the pathophysiology of ischemia (Fig 1). An individual develops angina or ischemic pain (which may be manifested by sudden death, angina pectoris, myocardial infarction, or the intermediate syndrome) when the myocardial oxygen demand exceeds the myocardial oxygen supply. Basically, medical therapy attempts to decrease oxygen demand whereas surgical therapy attempts to improve oxygen supply.

Medical therapy for noncoronary-artery-disease-induced angina pectoris may also involve changes in the myocardial oxygen demand. For instance, treatment of hypertension reduces intramyocardial tension and thus decreases oxygen demand. Treatment with digoxis of heart failure associated with angina may decrease angina by lowering both the ventricular volume and the heart rate, and this, too, reduces oxygen demand; also, by lowering the left ventricular end-diastolic pressure, coronary vascular resistance is theoretically decreased and the subendocardial oxygen supply improved. Although digoxis increases the contractile state, thus increasing oxygen demand, it is hoped that the abatement in heart rate and ventricular volume will produce a greater decrease in oxygen demand, thereby relieving the angina.

Cigarette smoking causes undesirable effects on both oxygen supply and oxygen demand; it increases the heart rate and causes vasoconstriction, both of which increase oxygen demand, and it also decreases the oxygen supply by shifting the oxygen hemoglobin dissociation curve so that hemoglobin releases oxygen less readily to the tissues. In addition, smoking increases the carbon monoxide content of the blood, which is bound by hemoglobin in preference to oxygen; this, too, decreases the oxygen supply.

Treatment with certain drugs which can reduce or alleviate the angina may be indicated. Specific antianginal drugs include nitroglycerin, isosorbide dinitrate, topical nitroglycerin, propranolol and metoprolol.

The various nitrates decrease angina by causing peripheral venous pooling, thus lowering the intraventricular volume which lessens oxygen requirements. Intraventricular pressure may also abate, thereby decreasing coronary vascular resistance and theoretically improving subendocardial blood flow. Nitrates may also lower arterial blood pressure and, as a result, effect a decrease in impedance to blood flow; hence, less intraventricular tension will be necessary for blood to be ejected. Problems occasionally arise if a decrease in blood pressure caused by nitrates produces reflex tachycardia which in turn causes an increase in the contractile state of the myocardium. Both the increased heart rate and the increased contractility will increase oxygen demand and may cause angina. Furthermore, marked hypotension may develop with the administration of sublingual nitroglycerin which may decrease oxygen supply. However, these problems are infrequent.

The broad beta-blocker, propranolol, and the more specific beta-one-blocker, metoprolol, both decrease oxygen demand2 by decreasing the heart rate, the force of myocardial contractility, and the systolic blood pressure. The theoretical problems of beta-blockers causing increased ventricular volume which in turn increases oxygen demand and left ventricular end-diastolic pressure, thus producing increasing coronary resistance and decreasing oxygen supply, is usually not of clinical significance. Contraindications for the use of these drugs, however, are very important. If the patient’s heart rate prior to institution of therapy is 45 or
50, beta-blockers should not be used or else used with extreme caution. Insulin-dependent diabetics who are poorly controlled or who are unreliable, in general, are not candidates for beta-blocking drugs. Propranolol should not be used on patients with severe bronchospastic disease. Metoprolol, being a more specific beta-one-blocker, theoretically should not cause as many problems as propranolol, especially with bronchospastic disease; however, it may be desirable to have these patients on a beta-one agonist prior to the institution of metoprolol.

Though the dose of these various antianginal drugs will vary from individual to individual, a few broad guidelines can be set (Fig 2). Nitroglycerin is usually the first anti-anginal drug utilized. Sublingual nitroglycerin should be begun in the lowest dose possible and the first dose should be given in the physician’s office while the patient is seated to observe any untoward reactions. Some patients complain of severe headaches and a few may be intolerant of the drug for this reason. The dose of nitroglycerin should be increased as necessary to achieve control of the patient’s angina. Sublingual nitroglycerin is not solely used for acute anginal attacks but may also be given prophylactically to patients who routinely develop angina with certain situations such as climbing or engaging in anxiety-producing confrontations.

If angina is frequent, if the patient cannot tolerate the nitroglycerin or if it is advisable to avoid using prophylactic nitroglycerin, then either the long-acting nitrates or propranolol should be used. Neither the long-acting nitrates nor propranolol are effective in terminating the acute anginal attack; Isordil’s effect lasts longer than the 15-minute changes induced by nitroglycerin and is often better tolerated by the patient. However, the duration of Isordil’s action is variable, and is partially determined by the route of administration. Sublingual Isordil has a shorter onset of action than the oral form, but its effect lasts only 3 to 4 hours whereas oral Isordil may be given at 4- to 6-hour intervals. Topical nitroglycerin action lasts for from 4 to 6 hours.

The dose of sublingual Isordil may vary from 2.5 mg up to 20 mg every 3 to 4 hours, depending on the patient’s response. If one uses oral Isordil, it is important to realize that higher dosages must be used compared to sublingual Isordil to produce the same hemodynamic effects; however, the use of oral Isordil may be preferred, as it is often better tolerated by the patient. Though one often starts with at least 10 mg of oral Isordil every 6 hours, usually at least 20 mg every 6 hours is necessary to achieve improvement. The dosage of topical nitroglycerin, like Isordil, must be titrated by the patient’s response. Its advantage is that a single evening application may prevent nocturnal angina and permit the patient to sleep through the night; a major disadvantage is that, as a paste, it may be aesthetically unpleasing. Topical nitroglycerin is usually applied in terms of inches or fractions of an inch and its efficacy is partially dependent upon the site of application—better absorption obtained when it is applied above the waist—and the area over which the paste is applied—the greater the area, the better the absorption.

All nitrates have the potential problem of decreasing blood pressure and causing reflex tachycardia. Patients can usually tolerate headache, although aspirin or acetaminophen may have to be added to the regimen.

Propranolol is an effective drug for treat-
Nitroglycerin SL, PRN

Isordil, SL 2.5 - 10 mg. q4h  Tachycardia
Isordil, PO 20 - 40 mg. q4-6h  Hypotension
Topical Nitroglycerin 1/2 - 2" q4-6h  Headache

Propranolol 40 - 80 mg. q6h  Bradycardia
Brachyconstriction
Congestive Heart Failure
Rebound Angina
Block Hypoglycemic Symptoms

Fig 2—Commonly used anti-anginal drugs.

ing angina and the best results appear to occur in patients who have either an elevated blood pressure or an increased heart rate prior to institution of the drug. In treating angina, one usually prescribes propranolol every 6 hours and the total daily dose is at least 160 mg. The drug is begun at a lower dose of 10 to 20 mg every 6 hours and increased every 2 to 3 days, depending on the patient’s response in terms of blood pressure, heart rate and symptoms. One should carefully evaluate the patient for the appearance of peripheral edema, rales, weight gain or other evidence of heart failure. The end point for increasing the propranolol varies: precipitation of congestive heart failure, alleviation of symptoms, or a decrease in heart rate to less than 50 beats per minute. In some patients, one may have to stop the drug because of bronchospasm.

Metoprolol was recently introduced in the United States but has been used in Europe for a long time. It is quite similar to propranolol but has less effect on beta-two receptors. It is therefore preferable for patients with lung disease. Otherwise, the many side effects are similar to those of propranolol. One must remember that both propranolol and metoprolol are associated with rebound angina if the drug is rapidly withdrawn from patients who have responded. Equipotent dosages of propranolol and metoprolol are about 40 mg of propranolol and 50 mg metoprolol and appear to produce the same decrease in heart rate, reduction of angina pectoris, reduction of nitroglycerin consumption and improvement in exercise tolerance testing. In European studies, propranolol and metoprolol were given every eight hours, but in the United States, administration of propranolol every six hours is more common.

Specific studies with Isordil®, in which the drug was continued for up to 5 to 6 months, have shown sustained symptomatic relief in terms of the decreased frequency of anginal attacks, the number of nitroglycerin tablets used by the patient, and improved exercise tolerance. Other studies have shown that continued administration of Isordil® does not interfere with the patient’s usual response to sublingual nitroglycerin: it does not blunt hemodynamic effects induced by nitroglycerin or the relief of angina. Similar results have been obtained with long-term studies of nitroglycerin ointment. One can therefore conclude that there is good evidence that Isordil® and topical nitroglycerin do cause improvement in the patient’s symptoms and functional status both subjectively and objectively, possibly for several months. However, none of these studies answer the question “will they prevent myocardial infarction and sudden death?”

Propranolol and metoprolol have been studied in a similar manner. In 1969,9 patients clinically defined as having angina pectoris were further subdivided into those having coro-
nary artery disease as judged by coronary arteriography (50% occlusion of at least one coronary artery) or a demonstrated transmural infarction, and a second group of patients with clinical angina but negative coronary arteriograms. Successful response to propranolol was defined by at least a 50% decrease in incidence of angina, a 50% decrease in the number of nitroglycerin tablets used, or loss of one or more provoking factors of angina. Only 23% of patients with clinical angina but without proven coronary artery disease responded to the drug; the patients with proven coronary artery disease responded 86% of the time. Thus, without employing coronary arteriography one could have concluded that propranolol was less successful in the treatment of angina pectoris than it really is. This study showed that the dose of propranolol required for a favorable response was 160 to 240 mg a day and that the response to the drug did not correlate with the number of vessels involved or the severity of the patient’s pretreatment angina.

In 1976 another study attempted to show that the patient’s response to propranolol appeared to affect mortality. Despite some loopholes the study did clearly indicate that patients who failed to respond to medical management appeared to have a worse prognosis than the responders; these nonresponders are therefore the patients who are usually referred for surgery.

Most studies conclude that high doses of propranolol clearly decrease the incidence of angina and allow the patients to lead more normal lives. Other evidence has shown that exercise tolerance also improves, although if metoprolol and propranolol are used, it is often not angina that curtails the patient’s activity but frequently a fatigue-like syndrome; some studies have shown that if the patient is maintained on a combination of propranolol and isosorbide dinitrate, exercise tolerance improves even more. It would seem logical that as these two drugs affect different determinants of oxygen demand, a combination of the two might be more effective than either one used singly.

In summary, one can clearly state that the medical therapy of angina pectoris is better than no therapy at all and that some patients clearly do obtain subjective as well as objective improvement. However, one still cannot determine whether or not there is clear improvement utilizing medical therapy in terms of mortality relative to the natural history of the disease. There are also limitations to the use of the drugs and there are clearly failures; these drugs do not halt progression of the underlying atherosclerotic process and therefore do not cure. The choice between medical or surgical therapy depends on many factors which are often defined by angiography, determined by the failure of whatever the physician believes to be maximum medical therapy, and commonly influenced by the local surgeon’s skills. The patient as well as the physician has a profound influence on whether medical or surgical therapy is ultimately used.

REFERENCES


General Review
The Management of Patients with Premature Ventricular Contractions

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Premature ventricular contractions (PVCs) occur frequently in patients with virtually all types of cardiac disease and in persons without evidence of cardiac disease. Since PVCs and advanced grades of PVCs are known to be predictors for ventricular fibrillation, increased mortality, and sudden death in certain clinical settings, the management of patients with PVCs is frequently based on the clinical setting in which they occur. For the purpose of this talk we will discuss the treatment of PVCs in the following three instances: acute myocardial infarction in the coronary care unit, post-myocardial infarction patients, and persons without any evidence of organic heart disease.

Acute Myocardial Infarction

Almost all patients with acute myocardial infarction have PVCs during the first few days. The frequency of PVCs is greatest in the first hours after infarction and decreases gradually and progressively during the next several hours and days. In acute myocardial infarction, Lown and co-workers described certain types of PVCs that commonly preceded ventricular fibrillation. They applied the term "serious ventricular arrhythmias" to the following types of PVCs: (1) occurrence at a rate of five or more per minute, (2) "R on T" phenomenon, (3) multiform PVCs, (4) paired PVCs, and (5) ventricular tachycardia. When observed on routine monitoring, these premonitory ventricular arrhythmias were treated with lidocaine, and Lown and associates reported less than a 2% incidence of primary cardiac arrest in 300 patients with acute myocardial infarction. The detection of serious ventricular arrhythmias from the cardiac monitor followed by suppression with anti-arrhythmic drugs is the approach in many coronary care units today.

There are two problems with this approach. First, the serious ventricular arrhythmias appear to be neither very sensitive nor very specific for the subsequent development of ventricular fibrillation. El-Sherif and associates found that only 11 (58%) of 19 patients with an acute myocardial infarction who developed ventricular fibrillation had premonitory arrhythmias. In the 17 patients where ventricular fibrillation was preceded by a single PVC, 10 had early PVCs or "R on T" phenomenon. Of the 430 patients without ventricular fibrillation in this series, 236 (55%) had premonitory ventricular arrhythmias and 194 (45%) did not. A second study reported similar findings.

The second problem is the adequacy of the detection system for arrhythmias as it is routinely employed in the coronary care unit. We compared the recognition of arrhythmias in 31 patients with acute myocardial infarction by the nurses and by rate-alarm signals in the coronary care unit with a continuous five-day tape recording that was subsequently processed through an automated Hewlett-Packard arrhythmia detection system. The Hewlett-Packard system printed out all arrhythmias for verification and quantification by the investigators. The observation of conventional monitors by coronary
care unit personnel in conjunction with rate-alarm systems resulted in an inadequate detection rate of PVCs and serious ventricular arrhythmias compared to the subsequent analysis of the tape recording (Table). In addition, there was a considerable time delay between the initial occurrence of PVCs and serious ventricular arrhythmias on the tape and their recognition by coronary care unit personnel. Arrhythmia recognition in coronary care units has improved and computer systems are available which can be used on line to improve the detection rate for PVCs; however, most coronary care units continue to rely on trained personnel for arrhythmia recognition.

Since there is such a high incidence of PVCs in patients with acute myocardial infarction, the prophylactic administration of anti-arrhythmic drugs has been evaluated extensively. Initially quinidine, procaïnamide, lidocaine, and phenytoin were reported to reduce significantly PVCs and serious ventricular arrhythmias, without reducing mortality. The patients in these studies were always a good-risk population with a low mortality in the control groups. In addition, when arrhythmias were recognized in the control groups, they were treated. More recently, Lie and co-workers in a double-blind randomized study demonstrated that lidocaine given prophylactically as an initial 100 mg bolus followed by an infusion rate of three mg/min significantly decreased the incidence of primary ventricular fibrillation, but mortality was not effected since all but one patient with ventricular fibrillation was resuscitated. The frequency of side effects at this infusion rate was 15% and was higher in the 60- to 70-year age group than in patients below the age of 60.

Since the PVC predictors for ventricular fibrillation are less reliable than indicated in initial reports, and PVC detection by conventional monitoring in the coronary care unit is not optimal, there is evidence available to recommend the prophylactic administration of lidocaine to patients during the first 48 to 72 hours of an acute myocardial infarction for the prevention of primary ventricular fibrillation. Patients with evidence of heart block, cardiogenic shock, severe congestive heart failure, and sinus bradycardia (below the rate of 50) probably should be excluded from this recommendation. Since patients above the age of 70 apparently have a low incidence of primary ventricular fibrillation in the coronary care unit and a higher incidence of adverse reactions to lidocaine, they also should probably be excluded from this recommendation.

The dosage of intravenous lidocaine used for prophylaxis is important. When a loading dose of 50 to 100 mg followed by a 2 mg/min infusion rate is used, there is an initial period of six to seven hours when plasma levels are suboptimal. In an effort to avoid this dip in plasma levels it is necessary to give about 200 mg of lidocaine in the first 20 minutes. There are several ways to give this loading dose: (1) 100 mg given twice at ten-minute intervals; (2) 50 mg given four times at five-minute intervals; (3) infusion of 20 mg/min for ten minutes; and (4) 100 mg bolus followed by infusion of 6 to 7 mg/min for 15 minutes. I prefer the last method followed by the continuous administration at an infusion rate of 2 to 4 mg/min, preferably 3 mg/min. In patients with shock, congestive heart failure, or hepatocellular disease, the loading dose and infusion rates should be decreased by about 50%. This may also apply to patients over the age of 70. If PVCs occur, the plasma concentration of lidocaine can be raised rapidly with a 25 to 50 mg bolus and an increase in the infusion rate. There is some evidence that the plasma half-life of lidocaine increases by a factor of about two after 24 hours.

### TABLE

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<th>Arrhythmia Recognition in Acute Infarction (31 Patients)</th>
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<td><strong>Monitor</strong></td>
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ROMHILT: VENTRICULAR PVC’S / 35
in patients with acute myocardial infarction, thus the infusion rate may have to be decreased at this time.\textsuperscript{13}

**Post-Myocardial Infarction**

In patients with a previous myocardial infarction many studies have reported an increased mortality and/or an increased frequency of sudden death in patients with PVCs or advanced grades of PVCs.\textsuperscript{14-18} Although there is some variability in the reported studies, the increased mortality appears to be true for the presence of PVCs on a routine electrocardiogram as in the Coronary Drug Project,\textsuperscript{14} and for an increased frequency of PVCs (>10 per hour or >20 per hour) or advanced grades of PVCs both during monitoring studies. In contrast to these studies, the work of Moss and co-workers,\textsuperscript{18,19} has indicated that PVCs and advanced grades of PVCs have limited use in predicting subsequent cardiac events and a similar study has been reported by de Soyza and associates.\textsuperscript{20} It is likely that PVCs and advanced grades of PVCs will be neither sensitive nor specific for the prediction of subsequent mortality in post-myocardial infarction patients similar to the findings in patients with acute myocardial infarction. There may be two exceptions to this. The first exception may be those patients with a low-ejection fraction (less than 40%) and advanced grades of PVCs who have an increased incidence of sudden death compared to patients with a low-ejection fraction without advanced grades of PVCs.\textsuperscript{21} The second exception may be those patients who develop ventricular arrhythmias with low-level exercise tests to a heart rate of 130 beats per minute or symptoms at three weeks post-infarction.\textsuperscript{22}

There are three controlled clinical trials that have been carried out in Europe, evaluating the prophylactic administration of beta adrenergic-blocking drugs in postinfarction patients. The first trial, in Sweden, using alprenolol in 230 patients demonstrated a significant reduction in sudden death, but not in total mortality or recurrent infarction.\textsuperscript{23} The second study, also in Sweden and also using alprenolol, reported a significant reduction in sudden death and recurrent infarction but not in total mortality.\textsuperscript{24} A large multicenter trial in England with practolol demonstrated a significant reduction in cardiac death and sudden death, particularly after anterior infarctions.\textsuperscript{25} In this trial the rate of recurrent infarction was reduced but was not statistically significant. The trial had to be terminated because of the ocular complications associated with long-term practolol administration. Since the incidence of recurrent infarction was shown to be reduced, the mechanism of the beneficial effect of beta adrenergic-blocking drugs may not be entirely related to their antiarrhythmic properties. In June 1978 a large multicenter trial was started in the United States, using propranolol in post-infarction patients, and the Medical College of Virginia is one of the clinical centers.

It is possible that oral antiarrhythmic drugs (quinidine, procainamide, disopyramide, phenytoin, or propranolol) on a long-term basis may be beneficial in postinfarction patients, but the results of additional clinical trials with drugs available in the United States are needed. At the present time postinfarction patients with frequent or advanced grades of PVCs may benefit from antiarrhythmic drugs, particularly when the PVCs are associated with a low-ejection fraction, angina pectoris, or a positive exercise test. It is essential that patients have a baseline monitoring or exercise study (whichever demonstrated the PVCs) prior to therapy and again after institution of therapy in conjunction with blood levels of the drug, when available, to evaluate the effectiveness of the antiarrhythmic therapy. It also should be remembered that we do not really have a good oral antiarrhythmic drug approved for use in the United States.

**Without Organic Heart Disease**

The significance of PVCs in persons without evidence of organic heart disease is less clear and can be a difficult problem with respect to treatment. Hinkle and co-workers reported that 62% of middle-aged American men had PVCs during a six-hour recording.\textsuperscript{26} The presence of PVCs or more than 10 PVCs per 1000 beats correlated with an increased risk of sudden death. In the Tecumseh Study there was a significant increase in mortality in persons over the age of 30 with PVCs on an electrocardiogram compared to those without PVCs.\textsuperscript{27} However, in both of these studies there was also a correlation between PVCs and the presence of coronary artery disease. Thus, PVCs appear to be only a marker for coronary artery disease in these studies, but are not spe-
cific enough for coronary artery disease to be useful in individual patients. Fifty percent of male medical students had PVCs during a 24-hour period, but only 2% had more than 50 PVCs during the 24 hours.28 In persons without organic heart disease PVCs are frequently associated with fatigue, anxiety, or use of coffee, tobacco, tea or alcohol.29 Removal of these factors will often decrease or eliminate the PVCs. In general the use of antiarrhythmic drugs should be avoided in individuals who have PVCs without evidence of organic heart disease.

REFERENCES


Program for the 50th Annual McGuire Lecture Series

**Cardiology in Primary Care**

Presented by

the Division of Cardiovascular Disease and the Department of Continuing Education

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**DONALD W. ROMHILT, M.D.**

Thallium Myocardial Scanning
**MICHAEL J. COWLEY, M.D.**

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