Stress Testing During Cardiac Catheterization: Exercise and Pacing Tachycardia

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Patients with significant heart disease may have entirely normal hemodynamics when assessed in the resting state during cardiac catheterization. Because most cardiac symptoms are precipitated by exertion or some other stress, however, it also may be important to assess hemodynamic performance during some form of stress such as muscular exercise, pharmacologic intervention (e.g., dobutamine infusion), or pacing-induced tachycardia. Such an evaluation enables the physician to assess the cardiovascular reserve and the relationship (if any) between specific symptoms and hemodynamic impairment. Physiologic information so obtained is often valuable in prescribing specific medical therapy, selecting patients for corrective cardiac surgery, and estimating prognosis.

Muscular exercise, both dynamic and isometric, has been studied extensively in the cardiac catheterization laboratory, and the normal hemodynamic responses are reasonably well understood. There are major differences between the hemodynamic responses to dynamic exercise (done either in the supine or the erect position) and the responses to static, isometric exercise, and these two types of exercise are discussed separately.

DYNAMIC EXERCISE

During dynamic exertion, skeletal muscles are actively contracting and developing force that is translated into motion and work. This is accompanied by an increase in both carbon dioxide production and oxygen (O₂) consumption by skeletal muscle, and a corresponding increase in alveolar gas exchange needed to support the higher metabolic rate. In normal sedentary individuals, the level of O₂ consumption during maximal exercise (VO₂ max) can increase about 12-fold in comparison with that during the resting state (I). Age and fitness also modify VO₂ max. During aging, there is a decrease in VO₂ max of about 5% per decade. During athletic training, VO₂ max increases because of both cardiovascular and skeletal muscle adaptation. In marathon runners and Olympic-class athletes, VO₂ max may represent an 18-fold increase in O₂ consumption above the resting state. The increased oxygen requirements of muscular exercise are met by both an increase in the cardiac output and an increased extraction of oxygen from arterial blood by skeletal muscle, which causes widening of the arteriovenous oxygen difference (AV O₂ difference). The need for the heart to increase cardiac output appropriately for the increase in O₂ consumption resulting from exercise is met by an increase in heart rate and an increase in stroke volume.

The relative contributions of these increases to the rise in cardiac output depend on the type of exercise (supine versus upright), the intensity of exercise, the limitation of diastolic filling at high heart rates, and the response to sympathetic stimulation. Metabolic adaptations of exercising muscle include a switch from utilization of free fatty acids at rest to an accelerated breakdown of muscle glycogen stores and enhanced uptake of bloodborne glucose, which is supplied by increased hepatic gluconeogenesis. Because carbohydrate metabolism produces more carbon dioxide than fat metabolism does, the respiratory quotient (ratio of carbon dioxide production to O₂ consumption) rises from a resting value of 0.7 to 0.8 toward 1.0. The delivery of bloodborne oxygen and glucose to working skeletal muscle is enhanced in the presence of normal vasculature by a reduction in skeletal muscle vascular resistance mediated by metabolic byproducts and by sympathetically mediated vasoconstriction elsewhere, which causes a redistribution of blood away from the renal and splanchnic beds to exercising muscle.

Exercise depends on the adequacy of pulmonary function to increase oxygen supply. During progressive exercise, there is a linear increase in minute ventilation relative to the increase in O₂ consumption. When the intensity and duration of exercise are such that insufficient oxygen is delivered to exercising muscle, anaerobic metabolism of glucose develops, causing metabolic acidosis and an increase in respiratory quotient to values higher than 1.0; minute ventilation increases out of proportion to O₂ consumption. Beyond this anaerobic threshold the accumulation of hydrogen ions usually causes skeletal muscle weakness, pain, and severe breathlessness, followed by exhaustion and cessation of exercise. It is best to conduct exercise studies in the catheterization laboratory so that the patient reaches a steady-state level of submaximal exercise below the anaerobic threshold and exercise can be sustained for several minutes. This approach permits estimation of cardiovascular reserve and allows the physician to determine whether the increase in cardiac output is appropriate for the increase in O₂ consumption occurring at that particular level of exercise.
Oxygen Uptake and Cardiac Output

There is a linear relationship between \( O_2 \) consumption and increasing workload (Fig. 15.1). Oxygen uptake increases abruptly after initiation of dynamic exercise, reflecting additional work needed to overcome inertia of the legs, and then increases steadily over a few minutes to reach a new steady state that is directly related to the intensity or level of exercise (2–4). Simultaneously, the mixed venous blood oxygen saturation decreases to a lower steady level related to the intensity of exercise, producing an increase in the AV \( O_2 \) difference.

**FIG. 15.1.**

Oxygen consumption in normal subjects during exercise. Each group represents a different level of exercise, with the most intense exercise being performed by group 4. Note the prompt increase and establishment of a new steady state in oxygen uptake that is directly related to the intensity of the exercise. (From Donald KW, et al. The effect of exercise on the cardiac output and circulatory dynamics of normal subjects. *Clin Sci* 1955;14:37, with permission.)

The cardiac output increases linearly with increasing workload during both supine and upright exercise in normal subjects (2–5). As can be seen from the regression equation for this relationship (Fig. 15.2, for each increment of 100 mL/min/m\(^2\) of \( O_2 \) consumption during exercise there is an increase in cardiac output of 590 mL/min/m\(^2\).

**FIG. 15.2.**

The relationship between cardiac output and oxygen consumption (both indexed for body surface area) during supine dynamic exercise of varying intensity in normal subjects, based on the data of Dexter. As can be seen from the regression equation for this relationship (Fig. 15.2, for each increment of 100 mL/min/m\(^2\) of oxygen consumption, there is an increase in cardiac output of 0.59 L/min/m\(^2\) or 590 mL/min/m\(^2\). CI, cardiac index. (Data from Dexter L, et al. Effects of exercise on circulatory dynamics of normal individuals. *J Appl Physiol* 1951;3:439.)

**Exercise Index**

The linear relationship between oxygen uptake and cardiac output during exercise, illustrated in Fig. 15.2, may be used to assess whether the cardiac output response measured in an individual patient is appropriate to the level of exercise and increased oxygen uptake. The regression formula is \( CI = 0.0059X + 2.99 \), where \( CI \) is the cardiac index in liters per minute per square meter of body surface area (BSA) and \( X \) is the \( O_2 \) consumption in mL/min/m\(^2\) BSA. This formula may be used to calculate the predicted cardiac index for a given level of \( O_2 \) consumption (\( X \)), and the predicted cardiac index may then be compared with the measured cardiac index. Note that this assessment can be performed at any steady-state level of exercise and does not depend on achieving any specific “target” level of exertion. This equation can be used to calculate a predicted cardiac index by measuring \( O_2 \) consumption during dynamic exercise. The patient's actual measured cardiac index during exercise is then divided by the predicted cardiac index to determine the deviation from normal:

\[
\text{Exercise index} = \frac{\text{Measured cardiac index (L/min/m}^2\text{)}}{\text{Predicted cardiac index (L/min/m}^2\text{)}} \quad (15.1)
\]

We have termed this ratio the exercise index, since it allows expression of exercise capacity as a percentage of the normal response. An exercise index of 0.8 or higher indicates a normal cardiac output response to exercise.

**Exercise Factor**

Another way of using this same relationship between cardiac output and \( O_2 \) consumption involves calculation of the exercise factor, which is the increase in cardiac output with exercise divided by the corresponding increase in \( O_2 \)
A normal exercise factor would be an increase of \(600 \text{ mL/min in cardiac output per 100 mL/min increase in } O_2 \text{ consumption. An exercise factor less than 6.0 indicates a subnormal response in cardiac output; like an exercise index of less than 0.8, such a factor suggests some pathologic process limiting the heart's ability to meet the exercise-induced increase in } O_2 \text{ consumption with an appropriate increase in cardiac output, forcing an excessive reliance on oxygen extraction from arterial blood and widening of the AV } O_2 \text{ difference.}

**Systemic and Pulmonary Arterial Pressure and Heart Rate**

Systolic arterial pressure and mean arterial pressure also increase linearly in relation to \(O_2\) consumption during dynamic exercise in normal subjects, although the response is somewhat variable (4,6–8). Despite this increase in arterial pressure, systemic vascular resistance decreases substantially during dynamic exercise, indicating that the elevated arterial blood pressure is secondary to increased cardiac output. Patients who are unable to generate an adequate increase in cardiac output during dynamic exercise may also increase their arterial pressure, but in this circumstance systemic vascular resistance does not decline and may actually increase.

The behavior of the pulmonary circulation in response to dynamic exercise is different from that of the systemic circulation in normal individuals. Mean pulmonary artery pressure increases almost proportionally with cardiac output (pulmonary blood flow), so that there is only a slight decrease in pulmonary vascular resistance, in contrast to the normal substantial decrease in resistance of the systemic vasculature.

Heart rate increases consistently during both supine and upright dynamic exercise and tends to increase linearly in relation to \(O_2\) consumption. During dynamic supine exercise in the catheterization laboratory, tachycardia is the predominant factor in increasing cardiac output. Tachycardia exerts a positive inotropic effect (the so-called treppe phenomenon), but increased sympathetic nervous system activity appears to be the most significant factor leading to enhanced myocardial contractility. In most normal subjects, supine bicycle exercise is accompanied by an increase in ejection fraction, and other ejection indices of left ventricular (LV) systolic function with a decrease in LV end-systolic volume.

Several investigators (2,3,6–8) examined the responses of cardiac output, stroke volume, and heart rate to a given intensity of supine exercise in normal subjects and showed that the increase in cardiac output is caused primarily by an increase in heart rate with a negligible contribution by increased stroke volume. During repeat exercise when heart rate is held constant, there is a comparable increase in cardiac output caused by a marked increase in stroke volume (7). When heart rate is artificially increased by electrical pacing in the absence of dynamic exercise, however, cardiac output remains unchanged and a major fall in stroke volume occurs (7), indicating that further cardiovascular adjustments are required for an adequate hemodynamic response to dynamic exercise.

Therefore, to adequately interpret the response to supine exercise in the catheterization laboratory, it is important to recognize that the increase in cardiac output in normal young subjects is caused by a proportionate increase in heart rate. As discussed later, when chronotropic reserve is depressed, an appropriate increase in cardiac output relative to \(O_2\) consumption depends on the capacity to augment LV diastolic filling and end-diastolic fiber tension, leading to an increase in stroke volume by means of the Frank-Starling mechanism.

**Upright Versus Supine Exercise**

The contributions of heart rate and stroke volume to cardiac output differ in supine and upright bicycle exercise. End-diastolic volumes at rest are near maximum when normal subjects are supine, smaller when they are sitting, and smallest when they are standing (4). When subjects are in the upright position, LV end-diastolic volume, cardiac output, and stroke volume are lower than when they are in the supine position (6),(8). During erect bicycle exercise, most normal subjects
demonstrate an increase in ejection fraction and reduction in end-systolic volume, some enhancement of LV end-diastolic volume, and an increase in stroke volume as well as heart rate. LV end-diastolic volume and stroke volume tend to increase up to about 50% of peak O₂ consumption and then to plateau or actually decrease at high levels of exercise (4). At high levels of exercise and fast heart rates, recruitment of the Frank-Starling mechanism may be blunted by the effects of tachycardia and limitation of diastolic filling due to shortening of diastole. At high levels of upright exercise, stroke volume is preserved by a progressive decrease in end-systolic volume and increase in ejection fraction in the presence of a constant or decreased LV end-diastolic volume (4),(5).

Caution must be used in interpreting the relative contributions of inotropic reserve and utilization of the Frank-Starling mechanism in patients studied during dynamic exercise in the catheterization laboratory. The effects of advancing age profoundly alter the exercise response. In healthy subjects, there appear to be no age-related changes in resting cardiac output, ejection fraction, end-systolic volume, or end-diastolic volume (9). With age, there is a reduction in both peak O₂ consumption and cardiac output during exercise. Also, with advancing age there is a reduction in heart rate and contractility response during exercise, so that the increase in cardiac output at any level of exercise is accomplished by significant increases in end-diastolic volume and in stroke volume (9),(10). Therefore, as discussed earlier, studies of the effects of dynamic supine bicycle exercise in young adults have generally shown no change or a fall in LV end-diastolic pressure (LVEDP) and volume during exercise. In contrast, studies of older normal subjects or patients with atypical chest pain and normal coronary arteries have generally shown that both dynamic supine and upright bicycle exercise are associated with an increase in LVEDP (8),(11), which is consistent with an age-dependent reliance on an increase in preload during exercise. For example, in a group of 10 sedentary men whose average age was 46 years, there was a rise in LVEDP from 8 ± 1 to 16 ± 2 mm Hg during supine bicycle exercise, and a rise from 4 ± 1 to 11 ± 1 mm Hg during upright bicycle exercise (8). The diminished heart rate and contractility responses during exercise and resultant increased dependence on the Frank-Starling mechanism with aging may reflect an age-related decrease in responsiveness to beta-adrenergic stimulation (12). There are also gender-related differences in the normal response to exercise. Normal men and women can achieve comparable increases in weight-adjusted peak O₂ consumption, heart rate, and blood pressure. However, normal women generally achieve increases in stroke volume during upright exercise through an increase in end-diastolic volume without an increase in ejection fraction, whereas normal men exhibit a progressive increase in ejection fraction to peak exercise (13).

The interpretation of normal versus abnormal LV systolic performance during dynamic exercise may also be complicated by the effects of chronic BETA-adrenergic blockade. Studies of the hemodynamic effects of chronic BETA-adrenergic blockade on graded exercise in hypertensive but otherwise healthy young adults have shown that no impairment of maximal exercise capacity (maximal O₂ consumption) or cardiac output response occurs during chronic BETA-adrenergic blockade. BETA-Blockade, however, causes a reduction in heart rate at any level of exercise, and this relative reduction in heart rate is compensated for by both a widening of the AV O₂ difference and an increase in stroke volume, associated with an increased LV end-diastolic volume and a reduced arterial blood pressure (decreased impedance to ejection).

In normal BETA-blocked subjects, increases in cardiac output during exercise depends on increasing stroke volume by means of the Frank-Starling mechanism. Therefore, the dynamic exercise response of a patient receiving chronic BETA-adrenergic blocking therapy may be associated with an “inappropriately” low increase in cardiac output relative to O₂ consumption, accompanied by excessive widening of the AV O₂ difference with an increased reliance on an increase in LV end-diastolic volume. During dynamic supine exercise in the catheterization laboratory, the finding that an increase in cardiac output depends on an increase in LV end-diastolic volume (and pressure) could be caused by either BETA-adrenergic blockade per se or intrinsic impairment of LV systolic function. For these reasons, strong consideration should be given to discontinuation of BETA-adrenergic blocking drugs at least 24 hours before catheterization if analysis of the hemodynamic response to dynamic exercise is planned to assess the adequacy of cardiovascular reserve.

**Left Ventricular Diastolic Function**

Interpretation of the changes in LV diastolic pressure with exercise depends greatly on an appreciation of the adaptations in diastolic function that occur. In normal subjects, multiple adjustments occur to accommodate an increased transmitral flow into the left ventricle in the face of an abbreviated diastolic filling period and to maintain low pressures throughout diastole. Exercise is associated with a progressive acceleration of isovolumetric relaxation so that enhanced diastolic filling occurs with minimal change in mitral valve opening pressure (14). The exercise-induced enhancement of diastolic relaxation and filling is probably modulated by both BETA-adrenergic stimulation and increased heart rate.

In normal subjects, there is either no change or a downward shift in the LV diastolic pressure-volume relation during exercise (Fig. 15.3). In the presence of ischemia or cardiac hypertrophy, however, exercise may provoke an upward shift in
the LV diastolic pressure-volume relationship, so that any level of LV end-diastolic volume is associated with a much higher LVEDP. In such patients, the left ventricle may be regarded as exhibiting increased chamber stiffness (decreased distensibility) during exercise. In patients with coronary artery disease, a transient but striking upward shift in the LV diastolic pressure-volume relation is common during episodes of ischemia (15). Patients with coronary artery disease who develop angina during dynamic exercise in the catheterization laboratory commonly show a marked rise in LVEDP. A careful study of the dynamics of LV diastolic filling during exercise in patients with coronary artery disease has been reported by Carroll et al. (16). These authors studied LV diastolic pressure-volume relations in 34 patients with coronary disease who developed ischemia during exercise and compared the finding with those from 5 patients with minimal cardiovascular disease (control) and 5 patients with an akinetic area at rest from a prior infarction but no active ischemia during exercise (scar group). There was an upward shift in the LV diastolic pressure-volume relationship during exercise-induced ischemia, which was not seen in either the scar or the control group (Fig. 15.3). Therefore, interpretation of an exercise-induced rise in LVEDP in patients with coronary artery disease is complex and may be related to both a decrease in LV chamber distensibility and an increase in LV end-diastolic volume secondary to a reduction in ejection fraction (11), (16).

**FIG. 15.3.**

Left ventricular (LV) diastolic pressure-volume relations at rest and during exercise in patients without heart disease (CONTROL), compared to patients with coronary disease who developed ischemia during exercise (ISCHEMIA), and patients with akinetic areas due to previous infarction but no active ischemia during exercise (SCAR). Pressure and volume are averaged at three diastolic points: early diastolic pressure nadir, mid-diastole, and end-diastole. The control group had a downward shift of the early diastolic pressure-volume relation, but the ischemia group showed an upward and rightward shift. (From Carroll JD, Hess OM, Hirzel HO, et al. Dynamics of left ventricular filling at rest and during exercise. *Circulation* 1983;68:59, with permission.)

The presence of cardiac hypertrophy is frequently characterized by depression of the rates of LV relaxation and diastolic filling at rest, and this depression profoundly impedes LV filling during exercise-induced tachycardia. In patients with conditions such as hypertrophic cardiomyopathy or hypertensive hypertrophic cardiomyopathy, in whom baseline LV end-systolic volumes are small, there is no reserve to further enhance systolic shortening, and abnormal diastolic properties limit the capacity to recruit the Frank-Starling mechanism during exercise. Furthermore, tachycardia may provoke ischemia (owing to impaired coronary vasodilator reserve), accompanied by an upward shift in the diastolic pressure-volume relationship. These findings with exercise-induced tachycardia in patients with coronary disease and/or advanced LV hypertrophy are remarkably similar to the changes in diastolic function seen during angina induced by pacing tachycardia, as described later in this chapter.

**FIG. 15.4.**

Seven patients with heart failure and normal left ventricular systolic function (*open symbols*) compared with 10 age- and gender-matched healthy volunteers (*solid symbols*) who served as controls. All subjects underwent upright bicycle exercise with hemodynamic evaluation. Cardiac output increased for the patients with heart failure as a result of an increase in heart rate, with fixed stroke volume. PT MAX, patient maximum exercise; NL MAX, normal subject maximum exercise. (From Kitzman D, et al. Exercise tolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 1991;17:1065, with permission.)

Marked abnormalities in LV diastolic function occur with exercise in patients with clinical evidence of heart failure but normal resting systolic function (so-called diastolic heart failure). Kitzman and Sullivan (17) studied seven patients with New York Heart Association (NYHA) class III or IV heart failure with one or more documented episodes of pulmonary edema and no significant coronary artery disease. All had LV ejection fractions of greater-than-or-equal-to 50%, without echocardiographic evidence of regional wall motion abnormalities or valvular or pericardial disease. Four of these patients were elderly with a medical history remarkable only for chronic hypertension. Most patients had increased LV wall thickness and mass. Patients were studied by symptom-limited upright exercise with simultaneous hemodynamic and radionuclide measurements, and data were compared to those seen in age- and sex-matched healthy volunteers who served as controls. As can be seen in Fig. 15.4, maximum exercise capacity was reduced, and the cardiac output increased primarily as a result of tachycardia, with no change in stroke volume. Fig. 15.5 shows that LV ejection fraction was normal at rest and with exercise for both patients and control subjects, but there was a striking rise in pulmonary capillary wedge pressure in those patients with diastolic heart failure, compared with the control subjects. Accordingly, these patients clearly
have “pure” diastolic heart failure: Efforts to treat their heart failure by improving systolic function (e.g., digoxin) will not be successful. As seen in Fig. 15.6, diastolic distensibility was markedly decreased with exercise in these patients.

**FIG. 15.5.**

Response of left ventricular function to upright bicycle exercise in the patients with diastolic heart failure (open squares) and healthy controls (solid squares) illustrated in Fig. 15.4. Pulmonary wedge pressure increases dramatically, but left ventricular end-diastolic volume fails to increase in the patients with heart failure, compared with healthy age- and gender-matched controls. LV ejection fraction remains normal. The intolerance to exercise is probably the result of increased pulmonary capillary wedge pressure and the resultant increased lung stiffness rather than decreased cardiac output or oxygen delivery to metabolizing tissues. PT MAX, patient maximum exercise; NL MAX, normal subject maximum exercise. (From Kitzman D, et al. Exercise tolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 1991;17:1065, with permission.)

**FIG. 15.6.**

Plot of the relationship between changes in pulmonary capillary wedge pressure and left ventricular end-diastolic volume in the patients illustrated in Figs. 15.4 and 15.5. In patients with diastolic heart failure, the stiff left ventricle cannot dilate normally (open squares) in response to the increased venous return of exercise, leading to a marked rise in left ventricular filling pressure, compared to normal controls (solid squares). (From Kitzman D, et al. Exercise tolerance in patients with heart failure and preserved left ventricular systolic function: failure of the Frank-Starling mechanism. *J Am Coll Cardiol* 1991;17:1065, with permission.)

**Examples of the Use of Exercise to Evaluate Left Ventricular Failure in the Cardiac Catheterization Laboratory**

Examples of the hemodynamic changes that can occur during supine bicycle exercise are shown in Tables 15.1 and 15.2. Table 15.1 illustrates the response to 6 minutes of supine bicycle exercise of a 36-year-old woman with an idiopathic dilated cardiomyopathy (ejection fraction, 40%) whose major symptom was exertional dyspnea. Because her ejection fraction was only moderately depressed and her hemodynamic values were almost normal at rest, resting hemodynamic data alone did not clarify whether her cardiovascular reserve was impaired and whether her exertional dyspnea was likely to be cardiac in origin. During exercise, the cardiac index increased appropriately in relation to the increase in $O_2$ consumption, yielding an exercise index of 1.1 and an exercise factor of 8.5:

\[
\frac{\Delta \text{ cardiac index}}{\Delta O_2 \text{ consumption}} = \frac{3,300}{387} = 8.5 \quad (15.3)
\]

The increase in cardiac output, however, was accomplished at the cost of a substantial increase in mean pulmonary capillary wedge pressure, which rose from 11 to 27 mm Hg. These data suggest that the patient had some limitation of inotropic reserve and that her ability to increase cardiac output depended heavily on utilization of the Frank-Starling mechanism. Therefore, her dyspnea can be considered to be of cardiac origin.

A patient with more severe impairment of cardiovascular reserve is illustrated in Table 15.2, which shows the response to 6 minutes of supine bicycle exercise of a 60-year-old man with idiopathic dilated cardiomyopathy and symptoms of marked fatigue and dyspnea with minimal exertion. His chest roentgenogram showed cardiomegaly with no evidence of pulmonary edema, and his rest hemodynamics were almost normal. Supine bicycle exercise was associated with a marked rise in both left and right heart filling pressures and a marginal ability to increase cardiac output appropriately in relation to his increase in $O_2$ consumption. His exercise index was 0.85, with a low exercise factor at 4.9:

\[
\frac{\Delta \text{ cardiac index}}{\Delta O_2 \text{ consumption}} = \frac{1,700}{341} = 4.9 \quad (15.4)
\]
The cause of exercise intolerance in some patients with LV failure is diminished cardiovascular reserve, so that inadequate oxygen is delivered to working skeletal muscle to meet the demands of aerobic metabolism. Other patients are not limited by the ability to deliver oxygen to working skeletal muscle but by the rise in pulmonary capillary wedge pressure associated with exercise (Table 15.1). As illustrated in these examples, the relative contributions of the inability of the heart to augment cardiac output versus an exercise-induced rise in pulmonary capillary wedge pressure that could impair gas exchange are controversial. Exercise tolerance in patients with congestive heart failure is highly variable and correlates poorly with ejection fraction. Studies of the hemodynamic and ventilatory response to exercise have shown that as the clinical severity of congestive heart failure worsens, there is a progressive decrease in maximal O\textsubscript{2} consumption, premature onset of the anaerobic threshold, and declines in both maximal cardiac output and the cardiac output achieved at levels of submaximal O\textsubscript{2} consumption (18),(19). Studies of brief exercise performed by patients with chronic congestive heart failure have shown that arterial oxygen saturation usually increases (presumably as a result of increased ventilation) despite elevation of the pulmonary capillary wedge pressure; maximal oxygen extraction is normal, and ventilatory mechanisms do not limit maximum O\textsubscript{2} consumption, so that both symptomatic limitation and the inability to normally increase oxygen delivery are caused by the failure to increase cardiac output adequately. Conversely, in patients with depressed LV ejection fraction who can achieve normal levels of exercise, factors that contribute to normal exercise capacity include normal augmentation of heart rate, the ability to increase cardiac output through further increases in LV end-diastolic volume and stroke volume, and tolerance of a high pulmonary venous pressure, possibly because of enhanced lymphatic drainage.

Therefore, in patients with severe depression of LV ejection fraction, the failure to increase cardiac output normally appears to be related both to the inability to increase stroke volume and to the inability to increase heart rate, compared with age-matched subjects (20). This impaired chronotropic response appears to be caused by an impaired postsynaptic response to \textit{BETA}-adrenergic stimulation that may be related to several defects, including a reduced cardiac \textit{BETA}-receptor density, “uncoupling” of the \textit{BETA}-receptor and adenylate cyclase activity, and deficient production of cyclic adenosine monophosphate (21).

### Evaluation of Valvular Heart Disease

#### Valvular Stenosis

Exercise may also be used in the cardiac catheterization laboratory to evaluate valvular heart disease. Gradients across the atrioventricular and semilunar valves may become apparent during exercise and may reach levels that account for the clinical symptoms of the patient. Exercise hemodynamics are especially useful when the resting transvalvular gradient or estimated valve area has borderline significance.

An example of the hemodynamic changes during supine dynamic exercise in a patient with moderate mitral stenosis is shown in Fig. 15.7 and Table 15.3. As the result of increased mitral valve flow and a decreased diastolic filling period, the pressure gradient increased significantly, producing left atrial pressures of sufficient magnitude to cause symptoms. Cardiac output increased normally, yielding an exercise index of 1.2 and an exercise factor of 5.8:

**FIG. 15.7.**

Simultaneous pressure recordings from left atrium and left ventricle at rest and at 5 minutes of bicycle ergometer exercise in a patient with mitral stenosis. The hemodynamic data for this patient are presented in Table 15.3. 

\[
\frac{\Delta \text{ cardiac output}}{\Delta \text{ O}_2 \text{ consumption}} = \frac{2,800}{481} = 5.8 \quad (15.5)
\]

These data are compatible with mild mitral stenosis and illustrate the changes in a diastolic pressure gradient across the mitral valve required to produce an increase in cardiac output appropriate to the increased oxygen requirements of strenuous exercise.

In evaluating hemodynamic changes across stenotic valves during exercise, it is often found that the calculated valve area during exercise varies somewhat from that calculated on the basis of resting data (it is usually slightly larger). This variance is usually small and may be related to actual changes in the degree of valvular obstruction (i.e., a higher gradient and
Valvular Insufficiency

The hemodynamic consequences of valvular insufficiency with ventricular volume overload may be subtle at rest. Dynamic exercise, by calling on the heart to substantially augment its forward cardiac output, may elicit changes in LVEDP and volume (preload) and in systemic vascular resistance (afterload) that are useful in assessing the cardiovascular limitations imposed by the valve lesion. Of particular importance here is the inability of many patients with valvular insufficiency to increase forward cardiac output in an appropriate manner, resulting in a low exercise index and an abnormal exercise factor. Dynamic exercise testing is especially valuable in such patients because the qualitative assessment of valvular insufficiency from angiograms may be unreliable and does not correlate well with the extent of functional impairment.

Figure 15.8 shows the hemodynamic response to dynamic bicycle exercise for a 55-year-old man with rheumatic heart disease and mitral regurgitation. The patient was able to increase cardiac output normally, but mean pulmonary capillary wedge pressure increased from 18 to 30 mm Hg, with V waves to 60 mm Hg, during 6 minutes of supine bicycle exercise. This patient had successful mitral valve replacement, with relief of symptoms.

FIG. 15.8.

Performing a Dynamic Exercise Test

Dynamic exercise during cardiac catheterization is easily performed with a bicycle ergometer while the patient is supine. A protocol detailing the exercise test should be prepared beforehand to ensure that all essential data are obtained. Pressures should be obtained so that the appropriate valve gradients can be evaluated, and LV pressure should be monitored if LV performance is in question.

Supine bicycle exercise tests are performed most easily when catheterization is done by the arm (e.g., brachial, radial) and/or neck (e.g., jugular vein) approach. However, supine bicycle exercise tests can also be done with safety when catheterization is by the femoral approach if care is taken to place the right and left heart manifolds and transducers in a stable and accessible position on the chest, away from leg motion artifact, and if the femoral venous and arterial sheaths are visualized and secured in place by the hand of one operator during exercise to ensure that catheters and sheaths are not displaced by leg movement.

We usually carry out a supine bicycle exercise test immediately after baseline hemodynamic values and cardiac output have been measured, before contrast angiography. The patient's feet are secured in the bicycle stirrups, and the right heart, left heart, and systemic arterial catheters and attached manifolds are positioned so that they are not kinked or under tension and will not be disturbed during the exercise. Next, the system for measuring $O_2$ consumption is put in place (see Chapter 8). Alternatively, cardiac output can be assessed with the use of an indicator-dilution technique (e.g., thermodilution), and $O_2$ consumption can be estimated as the quotient of cardiac output and AV $O_2$ difference.

Before beginning exercise, the patient is instructed that he or she will be coached to achieve a certain level of submaximal exercise over the first 1 minute that can be sustained for an additional 4 to 6 minutes. This detailed patient instruction is useful because some patients may be accustomed to the different format of progressively graded exercise aimed at achieving a transient level of maximal, exhaustion-limited exercise used in upright treadmill tests. A sufficient number of syringes for measuring systemic arterial and mixed venous (pulmonary artery) blood oxygen saturation content should be at hand.

With the patient resting quietly and feet positioned on the bicycle, all manometers are zeroed, phasic and mean pressures are recorded at 25 or 50 mm/sec paper speed (or electronic equivalent) and at the gain to be used during exercise, and cardiac output measurements are repeated to obtain an accurate preexercise baseline with legs elevated in the stirrups. Manometers are zeroed once again, all pressures are then redisplayed, and paper speed is slowed (to 5 to 10 mm/sec). Exercise is then begun with all pressures displayed continuously on the monitor and recorded at slow speed. We generally record LV phasic...
pressure, systemic arterial (e.g., radial or femoral artery) mean pressure, and pulmonary capillary mean pressure simultaneously. It is desirable to choose a gain setting on the recorder such that all pressures may be visualized simultaneously (as shown in Fig. 15.8). At each 1-minute interval, a brief recording of all three pressures on phasic at 25 to 50 mm/sec paper speed is accomplished, after which the pulmonary capillary and systemic arterial pressures are returned to “mean” and the paper speed is slowed to 5 to 10 mm/sec. The continuous observation and recording of pressures is important because it permits the accurate monitoring of any rise in filling pressure or fall in arterial pressure during exercise and ensures that catheters remain in correct position for measurements at peak exercise. After the patient has achieved a steady-state level of exercise for 4 minutes, simultaneous LV-systemic arterial, LV-PCW, and PCW-to-pulmonary artery pullback pressures are recorded during minutes 4 to 6, after increasing the recorder speed to 50 mm/sec without attempting to rezero the transducers. The right heart catheter is pulled back to the pulmonary artery, and exercise cardiac output is measured by the Fick or thermodilution technique, at which time systemic arterial and pulmonary artery blood samples are drawn for measurement of oxygen saturation.

Precautions should be taken during exercise to ensure patient safety. The duration and intensity of the exercise must be tailored to fit the needs of the individual patient. The electrocardiogram (ECG) should be monitored constantly to avoid serious arrhythmias, and exercise should be terminated if significant symptoms or greatly abnormal hemodynamic alterations occur. Little additional diagnostic information can be obtained by continuing the exercise to the point of producing pulmonary edema.

**ISOMETRIC EXERCISE**

Sustained isometric contraction of the forearm flexor muscles produces a cardiovascular reflex consisting of increases in heart rate, arterial blood pressure, and cardiac output. The precise nature of this reflex is not completely understood, but it appears to require afferent neural impulses from the exercising extremity and may be related to inhibition of vagal activity. Although the cardiac output response may be blunted, the anticipated responses in heart rate and blood pressure are not blocked by administration of propranolol, indicating that more is involved than a simple increase in BETA-adrenergic stimulation.

**Hemodynamic Response**

The hemodynamic response to isometric handgrip exercise has been studied in a series of normal subjects and patients with heart disease (22). In normal adult subjects, heart rate, systemic arterial pressure, and cardiac output increase, whereas systemic vascular resistance shows no change, indicating that the increase in systemic arterial pressure is caused by the increased cardiac output rather than by a vasoconstrictor response. No significant or consistent change in LVEDP or stroke volume occurs, whereas stroke work, a function of both arterial pressure and stroke volume, usually increases. The augmentation of LV performance during isometric exercise may be caused by both increased LV myocardial contractility (22) and the Frank-Starling mechanism.

Patients with heart disease and decreased LV function or inotropic reserve commonly show an abnormal hemodynamic and contractile response to isometric exercise (22). Although the maximum rate of rise of LV pressure, peak dp/dt, may increase in diseased hearts, the change is of less magnitude than in normal subjects. LV stroke work may increase, remain unchanged, or decrease in response to isometric exercise in pathologic states. This may itself be evidence of compromised LV function but is more apparent when the change in stroke work is compared with the change in LVEDP. Significant increases in LVEDP are seen commonly in the abnormal response to isometric exercise (22) and indicate decreased inotropic reserve, dependence on the Frank-Starling mechanism to augment LV performance, and probably some component of diastolic dysfunction.

**Performing an Isometric Exercise Test**

Isometric exercise is most commonly performed as sustained hand grip. The subject is first tested to evaluate maximal voluntary contraction strength. A partially inflated sphygmomanometer cuff or a specially designed handgrip dynamometer may be used. This testing may be done before cardiac catheterization and should be done well before the actual handgrip test. The patient must be coached and encouraged to grip as hard as possible at the time maximal voluntary contraction strength is determined. Baseline resting hemodynamic data should include heart rate, systemic arterial pressure (phasic and mean), LV pressure, and cardiac output. Cardiac output is most easily determined for this form of exercise by the indicator dilution method (e.g., thermodilution) or by the Fick method with the continuous O₂ consumption measurement technique.
Once baseline data are collected, the subject is asked to grip the dynamometer at a level 30% to 50% of the previously determined maximal voluntary contraction. Some coaching is usually required to ensure that the patient sustains the grip. It is important that the patient not do a Valsalva maneuver during handgrip exercise, and the respiratory pattern should be closely observed. Valsalva maneuver may be avoided simply by engaging the patient in conversation during the test. We have used 50% maximal voluntary contraction for 3 minutes, with repeat measurements of pressures and cardiac output beginning at 2.5 minutes, so that measurements are completed by 3 minutes and the test may be terminated. The ECG should be monitored continuously to exclude the appearance of arrhythmias.

PACING TACHYCARDIA

Graded tachycardia induced by atrial pacing was first introduced in 1967 by Sowton et al. (23) as a stress test that could be used in the cardiac catheterization laboratory to evaluate patients with ischemic heart disease. They noted that artificially increasing the heart rate by pacing the right atrium usually could induce angina in patients with symptomatic coronary artery disease. Moreover, they found that the degree of pacing stress needed to produce ischemia, defined in terms of pacing rate and duration, was more or less reproducible in any given patient. Since this original report, numerous investigators have described characteristic pacing-induced ECG changes (24–30), alterations in adenosine production (31),(32) and myocardial lactate metabolism (25),(26), hemodynamic abnormalities (33–39), regional wall motion abnormalities (40),(41), and defects in thallium scintigraphy (42),(43). Although agreement on the overall usefulness of atrial pacing has not been universal, it is clear that the technique can safely and reliably induce ischemia in most patients with coronary artery disease and that information obtained during the pacing-induced ischemic state is often helpful in the diagnosis and treatment of the patient’s underlying disease.

Hemodynamic Effects of Pacing Tachycardia

The principal form of stress that accompanies pacing tachycardia is an increase in myocardial O₂ consumption secondary to the increased heart rate and an increase in myocardial contractility because of the treppe effect (44). Associated with this increase in myocardial O₂ consumption is a reflex coronary vasodilation with an increase in myocardial blood flow. Apart from these changes in oxygen demand and supply, pacing tachycardia appears to be associated with no major hemodynamic stress, at least in patients with normal coronary arteries. Artificially increasing the heart rate by pacing the right atrium is accompanied by a concomitant decrease in ventricular stroke volume, with little or no overall change in cardiac output. Moreover, there appears to be no significant change in ventricular afterload, venous return, or circulating catecholamines during pacing tachycardia.

Differences between Pacing Tachycardia and Exercise Stress

The physiology of pacing is distinctly different from that of dynamic or isometric exercise, in which there are not only increases in heart rate and myocardial contractility but also major changes in ventricular loading conditions and cardiac output in response to increased metabolic demands from the periphery.

Because of the differences in physiology between atrial pacing and exercise, each technique has relative advantages and disadvantages as a form of stress testing in the catheterization laboratory. Unlike pacing, exercise is associated with an increase in both heart rate and systolic blood pressure. As a result, exercise is usually capable of achieving a higher rate-pressure product (i.e., heart rate × peak systolic pressure) and represents a more severe form of stress with greater increases in myocardial O₂ consumption. On the other hand, pacing is not associated with exercise-induced changes in cardiac output or ventricular loading conditions, and, as a result, the characterization of ventricular function is easier. In addition, atrial pacing is superior to exercise for evaluating myocardial metabolic function because the rapid rise in arterial blood lactate and adenosine levels that accompanies exercise may obscure alterations of myocardial lactate metabolism and adenosine production. Finally, unlike exercise, with the termination of pacing and the rapid diminution of myocardial oxygen requirement, myocardial ischemia almost always resolves rapidly (i.e., within 1 to 2 minutes). As a result, the physician has more control over the amount of stress that the patient experiences, with very little prolonged ischemia occurring in the poststress period.

Pacing tachycardia has been used as a form of stress testing in patients with heart disease for more than 30 years. The technique has been most useful in the assessment of patients with coronary artery disease.

Method for a Pacing Stress Test
Atrial pacing protocols usually can be conducted in the cardiac catheterization laboratory without undue prolongation of the routine catheterization procedure or significant added risks to the patient. In our experience, pacing is best conducted after the routine diagnostic aspects of catheterization and usually extends the procedure by no more than 15 to 30 minutes, depending on the details of the protocol. It is important that detailed planning of the protocol be made before the catheterization is begun, to help incorporate the atrial pacing into the routine catheterization as much as possible without unnecessary repetition of maneuvers and excessive prolongation of arterial time.

The type of catheter used for the pacing protocol can vary depending on the type of information that is to be evaluated during the pacing procedure. In general, the pacing catheter can be either unipolar or bipolar. If pacing is to be conducted with simultaneous myocardial metabolic assessment, a Gorlin or Baim-Turi pacing catheter that allows simultaneous pacing and coronary sinus lactate sampling is ideal. Sampling of both coronary sinus lactate and adenosine has been accomplished with the use of a specially designed catheter placed in the coronary sinus. If assessment of myocardial O\textsubscript{2} consumption is to be made, a coronary sinus pacing catheter with the capability of measuring coronary blood flow, such as the Baim catheter (Elecath, Rahway, NJ), may be used. If pacing is to be conducted with simultaneous measurement of left heart filling pressures and cardiac output, then both a pacing catheter and a second right heart catheter (typically a thermodilution flow-directed catheter) may be inserted into the right side of the heart.

The pacing catheter may be inserted by either venous cutdown or percutaneous technique from the groin, the antecubital fossa, or the neck. Use of a coronary sinus pacing catheter usually requires a neck or arm approach for easier access into the coronary sinus.

Perhaps the most critical part of the atrial pacing technique is proper placement of the pacing lead, because accidental displacement of the pacing tip during pacing can disrupt the protocol. The pacing lead can be placed at the junction of the superior vena cava and right atrium, at the lateral right atrial wall, or in the coronary sinus. Placement of the pacing lead is most stable at either the first or last of these positions, because displacement of the lead commonly occurs from the lateral atrial wall during respiration. Stimulation of the phrenic nerve with subsequent diaphragmatic stimulation also occurs commonly with placement of the catheter against the lateral atrial wall. To avoid problems with displacement of the pacing tip, we have used a bipolar flared pacing catheter (Atri-Pace I, Mansfield Scientific, Mansfield, MA).

Once the pacing catheter is positioned in the right atrium, it is connected to the pulse generator unit. This unit should be equipped with a fixed-rate mode, pacing at least to 170 beats per minute (bpm), and a variable output from 0.5 to 10 mA. Bipolar pacing catheters may be connected directly to the pacemaker unit or attached through extension wires with alligator clamps. Unipolar catheters should have their negative pole grounded to the skin via either a needle electrode or standard ECG plates. Once the pacing catheter has been positioned properly and connected to the pulse generator, the ability of the pacemaker to stimulate the atrium, and to control ventricular rate should be assessed. Initially, the output of the generator is set at 2 to 3 mA, and the pacing rate is adjusted to 10 bpm faster than the sinus rate. Pacing is then begun, and if there is atrial and ventricular capture, the pacing rate is increased by 10 bpm every 5 seconds until a rate of 150 to 160 bpm is reached. Inadequate pacing may occur secondary to an inadequate output of the pulse generator, improper lead positioning, or the development of atrioventricular block. The output of the pulse generator may be increased, but, in general, stimulating energies in excess of 7 to 8 mA frequently result in painful phrenic nerve stimulation. If excessively high energies are required for capture, the electrode lead should be repositioned. If atrioventricular block develops at high stimulatory rates, 1 mg atropine may be administered intravenously: this usually ensures adequate atrioventricular conduction up to rates of 140 bpm or more.

After the lead has been properly positioned and an adequate trial of pacing to assess capture has been performed, the actual pacing protocol may be done. A pacing stress test usually begins with pacing at approximately 20 bpm above the baseline rate, with increases of 20 bpm every 2 minutes, until angina pectoris or characteristic hemodynamic alterations occur, or until 85% of maximum age-predicted heart rate is achieved. Placement of a thermodilution balloon-tip flow-directed catheter, a left heart catheter, and a radial arterial cannula (or femoral arterial sheath sidearm) before pacing allows simultaneous assessment of right- and left-sided heart pressures, cardiac output measurement by thermodilution and/or Fick method, and determination of systemic and pulmonary vascular resistances. Assessment of LV volumes also may be accomplished with standard angiographic, echocardiographic, or radionuclide techniques.

Following the induction of chest pain during pacing tachycardia, pacing may be continued at the same heart rate safely for up to 3 to 5 minutes, during which hemodynamic, metabolic, and ECG data may be obtained. After cessation of pacing, chest pain usually resolves quickly, but it may occasionally persist for up to 1 to 2 minutes after the return to sinus rhythm.

**Pacing-induced Angina**
Electrocardiographic Changes in Response to a Pacing Stress Test

Like pacing-induced angina, the presence of ischemic ST-segment depression during pacing tachycardia has not been regarded previously as a sensitive or specific marker for the presence of coronary artery disease. For example, in terms of sensitivity, Rios and Hurwitz (27) compared pacing tachycardia and exercise in 50 patients and found diagnostic ECG changes with pacing in only 20% with pacing tachycardia, compared with 83% with exercise. Similarly, in terms of specificity, Robson et al. (28) reported ST-segment depression of 1.5 mm or more during pacing tachycardia in as many as 80% of patients with normal coronary arteries. In addition to poor overall sensitivity and specificity, pacing tachycardia is associated with certain distortions of the ECG that sometimes make interpretation of ischemic ST-segment changes difficult or impossible. Pacing is associated with prolongation of the PR interval in most patients, and extreme prolongation of this interval can cause the pacemaker spike to fall within the ST segment of the preceding paced complex, thereby obscuring potential ST-segment changes.

Despite the previously reported poor utility of pacing-induced ECG changes, work from our laboratory (29) has suggested an improved sensitivity and specificity of ischemic ST-segment depression during pacing tachycardia if certain technical guidelines of the pacing protocol are followed. Several earlier pacing trials that reported a low sensitivity of pacing ECG changes used only limited three-lead recording, and it is clear, at least with standard exercise testing, that sensitivity can be improved substantially with full 12-lead monitoring.

To maximize the utility of pacing-induced ECG changes, pacing trials should be conducted with the use of the following guidelines. First, a 12-lead ECG is used for monitoring, and the ECG is regarded as positive for myocardial ischemia if at least 1 mm or more of horizontal or downsloping ST-segment depression is produced. Second, pacing tachycardia is terminated when 85% of maximal age-predicted heart rate is achieved or when typical ischemic chest pain is accompanied by diagnostic ECG changes. Finally, if marked prolongation of the PR interval distorts the preceding ST-segment changes, the ECG is considered positive for ischemia only if there is ST-segment depression in the first five beats after the discontinuation of the pacing stimulus.

Using these guidelines, actual pacing protocols conducted in our experience had an overall sensitivity and specificity of 94% and 83%, respectively, with regard to pacing-induced ECG changes. In addition, distortion of the ST segment by the pacing stimulus because of marked prolongation of the PR interval appeared to occur infrequently when the peak pacing rate was no higher than 85% of the maximum age-predicted heart rate. Moreover, in at least one subgroup of patients who were tested with both atrial pacing and standard treadmill exercise (29), the concordance between pacing-induced and exercise-induced ECG changes was 90%. Examples of pacing-induced and exercise-induced ECG changes are shown for a patient with normal coronary arteries in Fig. 15.9A and for a patient with coronary artery disease in Fig. 15.9B.

FIG. 15.9.

A: Electrocardiographic (ECG) response to atrial pacing and exercise stress in a man with normal coronary arteries. From top to bottom, leads V4, V5, and V6 are monitored. B: Comparison of ECG response to atrial pacing and exercise stress in a man with severe three-vessel coronary artery disease. Leads V4, V5, and V6 are monitored (top to bottom) as in A. ST depression occurs to the same degree with both types of stress. (From Heller GV, et al. The pacing stress test: a reexamination of the relation between coronary artery disease and pacing-induced electrocardiographic changes. Am J Cardiol 1984;54:50, with permission.)
The sensitivity of pacing-induced ECG changes may be further improved with the use of endocardial electrograms obtained during the pacing stress test. Nabel et al. (30) reported on the use of local unipolar electrograms recorded from the tip of a 0.064-cm-diameter guidewire positioned against the endocardial surface of potentially ischemic regions. Endocardial electrograms, LVEDP, and multiple surface ECG leads were recorded before, during, and after rapid atrial pacing in 21 patients with coronary artery disease. Before pacing, endocardial electrograms in all 21 patients were free of ST-segment elevation. After rapid atrial pacing, marked ST-segment elevation was apparent in 17 of the 21 patients. This ST-segment elevation could be abolished in all patients with the use of nitroglycerin. Moreover, in several patients, endocardial ST-segment elevation after pacing was abolished by successful percutaneous coronary angioplasty of the critically stenosed artery supplying the ischemic region of myocardium. The authors concluded that endocardial electrographic changes are a reliable marker of pacing-induced myocardial ischemia and may be more sensitive than angina, pacing-induced hemodynamic changes, or ST-segment depression on the surface ECG.

Myocardial Metabolic Changes Induced by a Pacing Stress Test

Abnormal myocardial metabolism has been documented during pacing-induced ischemia by means of coronary sinus sampling and the subsequent measurement of coronary arterial and venous blood lactate. Because lactate production is a byproduct of anaerobic glycolysis, its production by the heart and appearance within the coronary sinus is a sign of myocardial ischemia. Previous investigators have noted rapid increases in coronary sinus lactate levels during pacing tachycardia in patients with coronary artery disease, often before the appearance of angina (25),(26). With cessation of pacing, the elevated coronary sinus lactate concentrations fall rapidly, representing a washout of the accumulated myocardial lactate and diminished lactate production as normal oxygenation is restored. Monitoring of arterial lactate levels while coronary sinus lactate levels are rising usually shows little or no elevation, in marked contrast to arterial lactate levels during exercise. As a result, atrial pacing tachycardia is superior to exercise for evaluating abnormal myocardial metabolic function, because rapidly rising arterial lactate levels during exercise may obscure abnormal patterns of myocardial lactate metabolism.

Monitoring of coronary sinus lactate during pacing protocols is most easily accomplished with a Gorlin pacing catheter. Placement of the Gorlin catheter in the coronary sinus usually can be confirmed by injection of a small amount of contrast medium. Care must be taken not to perforate either the coronary sinus or the great cardiac vein, and not to place the pacing tip of the catheter too distally, because placement of the distal catheter into the great cardiac vein may result in ventricular rather than atrial pacing.

Arterial and coronary venous blood lactate concentrations in response to a pacing stress test are illustrated in Fig. 15.10. In the control state, the concentration of coronary sinus blood lactate is lower than lactate concentration in arterial blood, reflecting the fact that the heart normally consumes lactate as a fuel. During pacing tachycardia, coronary sinus blood lactate concentration rises progressively and exceeds arterial blood lactate concentration, reflecting a shift to anaerobic metabolism of the ischemic myocardium. The lactate falls rapidly after discontinuation of pacing because the heart rate returns to control immediately.

FIG. 15.10.

Mean values for arterial (ART.) and coronary sinus (C.S.) blood lactate concentration before (CONTROL), during (PACING) and after (RECOVERY) tachycardia in 17 patients with coronary artery disease. Left ventricular end-diastolic pressure (LVEDP) changed little during pacing tachycardia but was elevated during brief periods of interruption of pacing (values in parentheses). ST-segment depression developed progressively during pacing tachycardia and resolved in recovery. Lactate extraction shifted to lactate production during ischemia, and this persisted into recovery for a brief period. (From Parker JO, Chiong MA, West RO, et al. Sequential alterations in myocardial lactate metabolism. S-T segments, and left ventricular function during angina induced by atrial pacing. Circulation 1969;40:113, with permission.)

There has been renewed interest in using coronary sinus adenosine as a marker of myocardial ischemia. Adenosine, a metabolite released by ischemic myocardium, elicits an increase in coronary artery blood flow in response to a decrease in the ratio of myocardial oxygen supply to demand. As a result, adenosine should be a more sensitive marker of myocardial ischemia than lactate, which requires anaerobic glycolysis. An early report demonstrated that adenosine is increased in the coronary sinus blood of patients with ischemic heart disease during pacing tachycardia (31), and later Feldman et al. (32) made several methodologic improvements regarding adenosine measurements. A double-lumen “metabolic” catheter was used that allowed the addition and mixing of a solution to stop adenosine metabolism at the tip of the catheter. Adenosine has a half-life of less than 1.5 second in human blood. Furthermore, there are numerous sources of artifactual adenosine
production in human blood. It is therefore essential that a solution that inhibits both the breakdown and the production of adenosine be mixed with human blood at the site of collection. Using this technique, adenosine was demonstrated to be a more sensitive marker of myocardial ischemia than lactate (32). Each patient with coronary artery disease (n = 9) atrially paced to ischemia demonstrated at least a 1.5-fold increase in coronary sinus adenosine. In contrast, only three of these nine patients had lactate production. In a subsequent study with improved methodology (48), patients with coronary artery disease (n = 17) were found to have higher coronary sinus adenosine concentrations than a control group of patients (n = 6) at rest. This finding provides evidence that release of endogenous adenosine may be an intrinsic homeostatic mechanism to maintain resting flow distal to a stenotic coronary artery.

**Hemodynamic Changes During a Pacing Stress Test**

Patients without ischemic heart disease who are stressed by atrial-paced tachycardia generally demonstrate no significant change in cardiac output, mean arterial pressure, AV O₂ difference, or systemic vascular resistance. LVEDP and pulmonary capillary wedge pressure usually fall during pacing tachycardia and then return to prepacing baseline levels in the immediate postpacing period. LV end-diastolic and end-systolic volumes fall during pacing tachycardia, with a decrease in stroke volume and no significant change in ejection fraction.

Patients with coronary artery disease who are paced to ischemia likewise manifest no significant change in cardiac output, mean arterial pressure, AV O₂ difference, or systemic vascular resistance. Some investigators have documented slight decreases in cardiac output with slight increases in mean arterial pressure, AV O₂ difference, and systemic resistance. However, these differences are probably related to the intensity of pacing-induced ischemia, its duration before the measurement of hemodynamic variables, and the amount of myocardium that has become ischemic, with more extensive hemodynamic abnormalities occurring in the setting of more extensive myocardial ischemia. The most dramatic differences in pacing hemodynamics between patients with normal coronary arteries and those with coronary artery disease are seen in terms of LV pressure-volume relationships during pacing tachycardia and in the immediate postpacing period. Of note, LV filling pressures do not show the progressive decrease seen in nonischemic patients, and elevations in pulmonary capillary wedge, mean pulmonary artery, and occasionally LV end-diastolic pressures occur at maximum pacing. Most important, there is a marked rise in LVEDP in the immediate postpacing period. Similarly, LV end-diastolic and end-systolic volumes decrease less during pacing-induced tachycardia in patients with ischemic heart disease compared with normal subjects, and there is often a significant decrease in LV ejection fraction.

A study looking at pressure-volume relationships during pacing tachycardia conducted by us (49) illustrates well the differences between nonischemic and ischemic hemodynamic responses to pacing. In this study, 22 patients, including 11 patients with normal coronary arteries and 11 with significant coronary artery disease, underwent sequential atrial pacing with simultaneous monitoring of LV pressure and ventricular volume measured by gated radionuclide ventriculography. Using synchronized LV pressure tracings and radionuclide time-activity volume curves, three sequential pressure-volume diagrams were constructed for each patient, corresponding to baseline, intermediate, and maximum pacing levels. All 11 patients with coronary artery disease demonstrated angina and significant ST-segment depression at maximum pacing, but none of the 11 patients with normal coronary arteries showed any evidence of pacing-induced ischemia.

Figure 15.11 shows typical LV pressure-volume curves for a patient with normal coronary arteries stressed with pacing tachycardia. Notably, there is a progressive leftward shift for the loop, with an increased heart rate and a progressive downward shift in the LV diastolic pressure-volume limb of each pressure-volume curve. It is clear that changes in both systolic and diastolic function have occurred in these patients during pacing tachycardia. In terms of systolic function, the progressive leftward shift of the end-systolic portion of the loop presumably represents increased contractility secondary to a terep effect. Other investigators (44) have likewise demonstrated a positive inotropic stimulus in response to increased heart rate, with increases in isovolumetric contraction indices (e.g., dP/dt) and ejection-phase indices (e.g., circumferential fiber shortening) during pacing tachycardia. With respect to diastolic function, the progressive downward shift of the diastolic limbs seen in Fig. 15.11 suggests that LV distensibility has increased slightly during pacing tachycardia. Whether this downward shift is an increase in myocardial relaxation, an alteration in viscoelastic properties, or a change in factors extrinsic to the myocardium (e.g., right ventricle, pericardium) is not known. It is notable that some investigators have documented small increases in markers of diastolic relaxation during pacing-induced tachycardia, such as peak negative dP/dt (50) and the time constant tau (51) in normal animals and the peak rate of posterior wall thinning (52) and LV internal dimension changes in humans.

**FIG. 15.11.**
Sequential left ventricular pressure-volume diagrams for a patient with normal coronary arteries in response to atrial pacing tachycardia at three increasing heart rates. (See text for discussion.) (From Aroesty JM, et al. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. *Circulation* 1985;71:889, with permission.)

Figure 15.12 shows sequential LV pressure-volume diagrams for a patient with coronary artery disease whose heart rate was increased progressively by atrial pacing. All patients in our study who developed chest pain and ischemic ECG changes demonstrated a similar pressure-volume pattern with an initial shift of the pressure-volume loop to the left at an intermediate heart rate, followed by a rightward shift at peak pacing when ischemia developed. In terms of systolic function, it is clear that pacing resulted in an initial treppe effect with a leftward shift of the end-systolic portion of the diagram at intermediate pacing, followed by systolic failure at peak pacing with an increase in ventricular volumes and a rightward shift in the end-systolic portion of the curve. Similarly, in terms of diastolic function, it is evident that the patient did not show a progressive downward shift of the diastolic limb of the LV pressure-volume curve but actually experienced an upward shift at intermediate and peak pacing. In part, the increase in LVEDP at peak pacing is related to systolic failure with an increase in ventricular volume. Because the patient did not experience evidence of systolic failure at the intermediate pacing level, however, it is also clear that this patient has experienced a primary decrease in LV diastolic distensibility so that pressure is higher at any given chamber volume throughout diastole.

**FIG. 15.12.**

Sequential left ventricular pressure-volume diagrams in a patient with three-vessel coronary artery disease who was paced at three increasing heart rates. The patient developed angina and ischemic ST depression at peak pacing. (See text for discussion.) (From Aroesty JM, et al. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. *Circulation* 1985;71:889, with permission.)

Speculation has continued over the last three decades as to whether the increase in diastolic pressures during pacing-induced ischemia is related to a primary decrease in distensibility or is secondary to systolic failure with increases in ventricular volume. At present, it seems clear that both mechanisms play some role in creating the elevated diastolic pressures. The evidence, however, suggests that changes in diastolic distensibility actually precede altered systolic function (49).

The cause of the altered diastolic distensibility during pacing-induced ischemia has been debated, and a number of different mechanisms (35–38,53,54) have been proposed, including incomplete myocardial relaxation, altered diastolic tone, partial ischemic contracture of some myofibrils within the distribution of the stenotic or occluded coronary artery, altered right ventricular loading, and influence of the pericardium. At present, it seems likely that relaxation of myocardial cells within the reversibly ischemic region is slowed and does not proceed to completion by end-diastole (53),(54). This may be related to impaired diastolic calcium sequestration by sarcoplasmic reticulum, but data are insufficient to permit a firm conclusion.

The postpacing rise in LVEDP is perhaps the most concrete evidence of pacing-induced ischemia during atrial pacing protocols. In our protocols, this postpacing rise has been calculated on beats 5 through 15 after discontinuation of pacing, with greater than a 5 mm Hg increase in LVEDP in comparison with the prepacing baseline being considered abnormal. Figures 15.13 and 15.14 summarize hemodynamic changes in patients with normal coronary arteries and in those with ischemic heart disease in response to a pacing stress test.

**FIG. 15.13.**

Changes in cardiac index, systemic vascular resistance (SVR), and arteriovenous oxygen (AV O₂) difference in 5 patients with normal coronary arteries and 20 patients with coronary artery disease (CAD) during pacing tachycardia. Patients with CAD showed a significant decrease in cardiac index and increases in SVR and AV O₂ difference during maximum pacing tachycardia. (From McKay RG, et al. The pacing stress test reexamined: correlation of pacing-induced hemodynamic changes with the amount of myocardium at risk. *J Am Coll Cardiol* 1984;3:1469, with permission.)

**FIG. 15.14.**

Changes in left ventricular end diastolic pressure (LVEDP), mean pulmonary capillary wedge pressure (PCW), and mean
Quantification of the hemodynamic alterations induced by pacing tachycardia may also be useful in assessing myocardial performance in patients with other forms of cardiac disease. Feldman et al. (55) used atrial pacing tachycardia to evaluate the systolic and diastolic myocardial reserve of patients with dilated cardiomyopathy. PACing-induced changes in LV pressure and volume in seven patients with dilated cardiomyopathy (mean LV ejection fraction, 19%) were compared with findings in six patients with normal coronary arteries and normal LV function (mean LV ejection fraction, 69%). The patients with normal LV function demonstrated significant increases in LV peak positive dP/dt, LV end-systolic pressure-volume ratio, and LV peak filling rate during graded increases in heart rate with atrial pacing. They also exhibited a progressive leftward and downward shift of their pressure-volume diagrams, compatible with increased contractility and enhanced diastolic distensibility in response to pacing tachycardia. In contrast, patients with dilated cardiomyopathy demonstrated no increase in either LV peak positive dP/dt or the end-systolic pressure-volume ratio and absence of a progressive leftward shift of their pressure-volume diagrams. Moreover, patients with dilated cardiomyopathy demonstrated no increase in LV peak filling rate and a blunted downward shift of the diastolic limb of their pressure-volume diagrams. These data suggest that patients with dilated cardiomyopathy demonstrate little or no enhancement of systolic and diastolic function during atrial pacing tachycardia, indicating a depression of both inotropic and lusitropic reserve.

Regional Wall Motion Abnormalities During a Pacing Stress Test

Regional wall motion abnormalities during pacing-induced ischemia have been noted with contrast ventriculography, gated radionuclide ventriculography, and transesophageal echocardiography. Using contrast ventriculography, Dwyer (40) studied eight patients with coronary artery disease who were paced to angina and found that three developed regional hypokinesia in one area, while the remaining five developed at least two separate areas of hypokinesia or akinesis. In all cases, an associated coronary artery lesion could be identified in the vessel that supplied the area of the new regional wall motion abnormality. Similarly, Tzivoni et al. (41), using radionuclide ventriculography, found that 9 of 11 patients developed new regional wall motion abnormalities in response to pacing-induced ischemia.

The overall specificity and sensitivity of pacing-induced regional wall motion abnormalities have been defined with the development of simultaneous transesophageal two-dimensional echocardiography and atrial pacing. Lambertz et al. (56) first developed an ultrasound system in which an atrial pacing facility was incorporated. Fifty patients were evaluated prospectively by cardiac catheterization and pacing echocardiography; 44 had correlative exercise testing. Nine patients were found to have normal epicardial coronary arteries and normal pacing results (100% specificity). Thirty-eight of the 41 patients with significant coronary artery disease developed regional wall motion abnormalities with pacing (93% sensitivity). In contrast, the specificity and sensitivity for exercise testing were 50% and 53%, respectively.

Thallium Scintigraphy and the Pacing Stress Test

The incorporation of thallium scintigraphy into pacing protocols has improved the overall utility of atrial pacing as a stress test. In patients with normal coronary arteries, pacing tachycardia is associated with a homogeneous increase in myocardial O	extsubscript{2} consumption and a secondary increase in coronary blood flow. In patients with coronary artery disease, however, regional increases in myocardial blood flow may be limited by critical coronary stenoses. Because initial myocardial uptake of thallium 201 has been shown to reflect myocardial perfusion and viability, myocardial ischemia induced by pacing tachycardia theoretically should be detectable by thallium scintigraphy. Although early reports on the simultaneous use of atrial pacing and thallium scintigraphy suggested serious limitations (41), studies with improved methodology indicate that this approach is successful in detecting both reversible ischemia and infarcted myocardium (42),(43).

To assess the utility of combined atrial pacing and thallium scintigraphy, our laboratory researchers (42) examined the correlation between pacing-induced and exercise-induced thallium defects in patients referred for evaluation of chest pain. The overall sensitivity and specificity of thallium imaging after atrial pacing were excellent. Moreover, segment-by-segment comparison of the thallium scans after either pacing or exercise stress testing revealed a correlation of 83%.

Simultaneous use of thallium scintigraphy and atrial pacing tachycardia can be accomplished by injection of 1.5 to 2.0 mCi of thallium 201 intravenously at peak pacing, followed by continued pacing for at least an additional 5 minutes. In routine
thallium exercise testing, exercise is maintained for only 30 to 60 seconds after injection of the radionuclide to allow the thallium to reach the myocardium. However, because of the rapid decrease in heart rate after discontinuation of pacing and the subsequent rapid diminution of myocardial oxygen requirements, pacing is extended to 5 minutes. After discontinuation of the pacing stimulus, while the patient is in the supine position, standard anterior, 40°, and 70° left anterior oblique views are obtained immediately in the catheterization laboratory with a mobile scintillation camera. Repeat standard views are obtained 4 hours after termination of the pacing protocol.

Clinical Uses of Atrial Pacing

The complete evaluation of a patient's cardiac function in the catheterization laboratory often requires an examination of the patient's performance under stressed conditions, when ECG, metabolic, and hemodynamic abnormalities may manifest themselves fully. The role of stress testing is particularly important in the evaluation of patients with ischemic heart disease, in whom, for example, it may be useful to determine the anginal threshold, the magnitude of hemodynamic impairment during ischemia, and the efficacy of antianginal therapy and to establish a need for coronary revascularization. Although standard dynamic and isometric exercise may serve as a form of stress for many patients, not all patients are able to exercise because of physical disabilities, old age, pulmonary disease, peripheral vascular disease, and possibly BETA-blockade. In each of these situations, atrial pacing may be used as a suitable form of stress.

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