Abnormalities of Left Ventricular Function
Associated with the Anginal State

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Although the clinical presentation of angina pectoris is familiar to most physicians, the pathophysiologic basis of this syndrome has only become evident within the last decade. Before this time there had been almost no hemodynamic and metabolic information regarding the anginal state. Today, by contrast, the number and variety of studies in this field have been great enough to create confusion regarding primary mechanisms. The purpose of the present review is to clarify some of the better documented aspects of this syndrome, as well as to indicate those areas requiring further elucidation. Discussion will be primarily concerned with abnormalities of ventricular pressure, volume, and wall motion associated with the anginal state. Cardiac performance will be considered in relation to heart rate, contractile state of the muscle, preload, and afterload.1 Preload can be defined as the resting fiber length as determined by end-diastolic volume, and is often expressed in terms of end-diastolic pressure. Afterload is the load that the ventricle must overcome during ejection; in the absence of aortic valve disease this is essentially a function of arterial pressure during systole. Only angina pectoris associated with coronary artery disease will be discussed.

Phenomenon of Myocardial Ischemia

The myocardial cell functions aerobically, with only a small capacity for high-energy phosphate generation by glycolytic processes. Under normal conditions the initial response to an increased myocardial demand for oxygen is an increase in coronary blood flow. However, if perfusion capacity is in any way limited, as by atherosclerotic obstruction of the coronary arteries, increased myocardial oxygen extraction becomes the primary compensatory response. Since the heart extracts nearly 75% of available oxygen in the resting state, little additional oxygen may be obtained by further passive diffusion. In such circumstances, the metabolism of the myocardial cell, and particularly the mitochondria, is altered. The cell is in a reduced state and cytoplasmic glycolysis ensues. This pathway generates a small amount of high-energy phosphate, but is at best a temporary stopgap measure. If hypoxia persists for 20 min or more, the cell undergoes irreversible injury.2 When a portion of left ventricular wall is ischemic for more than 1 min, it fails to contract properly. This observation, first reported by Tennant and Wiggers in animals,3 was initially thought to have its biochemical basis in depletion of ATP stores. However, the rapidity with which contraction ceases suggests defective ion transport across the cell membrane or sarcotubular structures, possibly due to accumulation of hydrogen ions.4 These alterations in ion transport may disrupt the excitation-contraction coupling mechanism.

In man, myocardial ischemia resulting from coronary artery disease is usually regional in nature. Electrocardiographic, metabolic, and arteriographic parameters reflect a segmental pattern,5 as do abnormalities of left ventricular wall motion demonstrated by cineventriculography.6 Hemodynamic function of the

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entire ventricle can become abnormal if the area of poor segmental contraction is sufficiently large. Dysfunction is most marked during anginal episodes. Whereas basal ventricular function may be normal even in the presence of extensive disease, once ischemia ensues the balance between poorly contracting and normally contracting segments is altered. Severe hemodynamic dysfunction may result and can be demonstrated by the traditional parameters of elevated left ventricular end-diastolic pressure and reduced cardiac output. Lesser degrees of dysfunction may be manifested only by a diminished ejection fraction. In some instances abnormalities may be noted only during isovolumic systole, in such calculated values as dP/dt or \( V_{\text{max}} \).

The study of myocardial blood flow in ischemic regions would be of obvious value. Unfortunately, most technics applicable to man are based on clearance principles and measure only “average” flow per unit mass. This obscures segmental abnormalities. Slower flow components derived from myocardium served by diseased vessels may be masked by the faster components from normally perfused areas. The development of radioisotope technics (including photoscintillation scanning) to study regional clearance may offer a solution to this problem. In addition, the role of coronary artery or arteriolar constriction in inducing angina may be clarified, especially in those situations in which there are no obvious preanginal increases in myocardial mechanical activity or energy requirements.

**Specific Types of Anginal States**

**Spontaneous Angina**

Elevation of blood pressure during spontaneous angina pectoris had been observed by several early investigators, but the first systematic study of this phenomenon was that of Roughgarden. Fifteen patients with a history of angina at rest were continuously monitored for changes in the electrocardiogram and systemic arterial blood pressure, with pulmonary artery pressure recorded in six. In most instances, heart rate and both systemic and pulmonary arterial blood pressure rose prior to the onset of anginal pain and often before S-T-segment depression was recorded on the electrocardiogram. Anginal episodes have also been studied during left heart catheterization. In a series of 18 patients from this laboratory, anginal episodes occurred most frequently in patients with extensive coronary artery disease and were associated with abnormal myocardial lactate metabolism. In addition, significant rises in left ventricular systolic and end-diastolic pressure were usually (but not invariably) present.

It is important to describe Prinzmetal’s variant angina or spontaneous angina associated with S-T-segment elevation. Guazzi et al. were able to observe 38 anginal episodes in four patients. They found that arterial pressure fell with the onset of chest pain and change in the electrocardiogram. In addition to the fall in blood pressure, cardiac function (as determined by measurement of cardiac output, isovolumic contraction time, and right atrial pressure) was severely impaired during the anginal attacks. These parameters reverted to normal only when S-T abnormalities disappeared, and the attacks ceased as spontaneously as they had begun.

Different mechanisms appear to be operative in spontaneous angina associated with S-T-segment depression as opposed to angina with S-T-segment elevation. In the former, a period of arterial hypertension usually exists before and during the pain; increased cardiac mechanical activity resulting from the increase in afterload, preload, and heart rate is usually the precipitating mechanism. In the latter, or Prinzmetal variant, however, there is no preceding arterial hypertension and hypotension actually occurs with the pain. To confuse the issue further, an occasional patient with coronary artery disease has been reported in whom coronary blood flow was decreased during spontaneous angina, irrespective of change in blood pressure.
Effort-Induced Angina

Physical exercise increases blood pressure, heart rate, and stroke volume. These occur through activation of cardiac adrenergic nerves, vagal inhibition, and augmented Starling effect. Cardiac energy consumption rises because these mechanisms increase systolic wall stress (a function of intraventricular pressure, volume, and wall thickness), contractile state, and cardiac rate, factors known to augment myocardial biochemical activity.17

Various indices have been used in the clinical setting to try to approximate changes in some of these variables. Heart rate and blood pressure in particular have been examined.18–20 Robinson21 studied angina induced by exercise and correlated the inception of pain with the product of directly recorded blood pressure and heart rate (fig. 1). Contrary to prior investigators, he made his measurements at the onset and not after the establishment of angina. A good correlation of the pressure-rate indices was found even though other unmeasured variables (contractile state and cardiac volume) change with exercise. This is so because contractility usually changes in the same direction as heart rate, and change in cardiac volume is small.

As cardiac mechanical activity increases, a point is reached at which myocardial perfusion distal to a major coronary arterial obstruction can no longer increase pari passu, and regional or segmental ischemia ensues. Although this has been demonstrated in animals with experimental coronary artery stenosis, a variety of studies in man has not recorded a diminution in the response of coronary blood flow at rest22, 23 or after exercise12, 24 in relation to normal subjects. This is most likely related to the fact that methodology available for human investigation involves a clearance of freely diffusible indicators in which flow through normally perfused vessels completely dominates the washout curve and calculated flow.

Impaired left ventricular function in patients with angina may be expressed through abnormal changes in cardiac output and left ventricular end-diastolic pressure. End-diastolic volume is somewhat increased during and immediately following supine exercise in
normal subjects as a result of the augmented venous return, but there are minimal, if any, increases in end-diastolic pressure.\textsuperscript{23, 26} In patients with coronary artery disease, however, supine exercise usually results in elevated end-diastolic pressure with a particularly prominent atrial filling wave.\textsuperscript{27–30} Furthermore, left ventricular stroke work,\textsuperscript{27, 30} stroke volume,\textsuperscript{29, 30} and systolic ejection rate\textsuperscript{12, 30} usually are either reduced or increase subsnormally. These findings often occur before the patient is aware of pain or S-T-segment depression develops.

The sharp rise in ventricular pressure at end-diastole has been attributed to a change in diastolic pressure-volume characteristics, i.e. compliance.\textsuperscript{31, 32} Cardiac size and wall thickness are usually normal in coronary artery disease in contrast to other disease states with decreased compliance (cardiomyopathy, aortic stenosis, etc.). It is probable that localized or segmental disease (fibrosis and/or ischemia) can so stiffen a region of left ventricle as to affect compliance of the ventricle as a whole.\textsuperscript{33}

**Pacing-Induced Angina**

There are several disadvantages to evaluating hemodynamic abnormalities during angina induced by exercise or drugs. Anginal pain may not be amenable to rapid induction and termination with these methods, important points to consider when human subjects are being studied. In addition, multiple variables may be difficult to measure and interpret in a rapidly changing and not easily controllable state. Perhaps most importantly, the metabolic and hemodynamic effects of the interventions, by obscuring the physiologic alterations due to the anginal state per se, may complicate any interpretation of data obtained during the anginal episode—especially the determination of myocardial lactate production. Lastly, there may be a considerable delay before hemodynamic measurements return to the preanginal state. Thus, if reevaluation of a patient is necessary, a lengthy period of recovery may be required. Even then, reproducibility of findings may not be achieved.

To circumvent some of these difficulties, Sowton et al. introduced the technic of pacing-induced tachycardia to bring on the anginal state.\textsuperscript{34} With a bipolar pacing catheter in the right atrium, heart rate was gradually increased until either angina resulted or a rate of 160 beats/min was achieved. Mean arterial pressure rose only slightly in the 22 studies, and left ventricular end-diastolic pressure usually fell or remained the same, in contrast to the increased end-diastolic pressure usually observed during effort-induced angina. Sowton's conclusions were very similar to those of Robinson's: in a given patient, a predictable value exists for the product of blood pressure and heart rate above which angina reproducibly occurs.

The obvious advantages of the pacing technic make it a more refined method for inducing anginal attacks without also affecting total-body work load, for permitting rapid termination of angina and ischemia, for reproducing this state with minimal delay, and for objectively testing the value of angina-relieving agents. In addition, there may be a psychic benefit as well.\textsuperscript{35} Patients are not asked to bring on their own attacks as with exercise; they are therefore less tense, and the excess catecholamine release associated with mental stress is not a further complicating factor in evaluating the hemodynamics of the anginal state within a laboratory setting.

A large number of studies followed Sowton's initial report. Lau et al. reported that the frequency of ischemic S-T-segment depression during atrial pacing at rates of 120–140 beats/min was similar to that following the two-step test.\textsuperscript{36} These findings were confirmed by Parker et al.\textsuperscript{37} In most of those patients with coronary artery disease who developed angina, not only did S-T changes precede the pain, but so did myocardial lactate production. This correlation between metabolic and electrocardiographic abnormalities was not as evident in the study of Helfant et al.\textsuperscript{38} Both
above-mentioned groups found atrial pacing to be an excellent method for evaluating the metabolic abnormalities associated with angina, in part because arterial lactate was constant and myocardial lactate production easy to detect. By contrast, the continuing rise in arterial lactate levels during physical exercise creates a transit time artifact for myocardium which makes interpretation of arterial-coronary sinus exchange of lactate difficult, if not impossible.

Asynergy of left ventricular contraction has been induced by pacing tachycardia, presumably due to segmental disease,39, 40 and this may lead to hemodynamic abnormalities. The effect of atrial pacing on hemodynamics is not uniform, however, particularly in relation to left ventricular end-diastolic pressure and cardiac output.38, 41-44 In the normal subject, and in patients with coronary artery disease who do not develop angina or ischemia, left ventricular end-diastolic pressure consistently decreases with increasing heart rate. When myocardial ischemia and/or angina occurs, however, left ventricular end-diastolic pressure may remain unchanged, rise slightly, or even decrease. Part of this variability is related to difficulties in measurement of end-diastolic pressure at high heart rates through fluid-filled catheter systems. In addition, the physiologic stress per se induces a reduction in end-diastolic pressure via reduced diastolic filling time. This tends to mask the rise in end-diastolic pressure usually seen with acute ischemia. These problems have been, in part, circumvented in two ways. First, when plasma volume is expanded with dextran before pacing, angina is precipitated earlier during the pacing stress and is frequently associated with elevations in left ventricular end-diastolic pressure, presumably via the Starling effect.43 Another approach is to measure end-diastolic pressure in the immediate postpacing beats. During these beats, end-diastolic pressure resets itself to meet the filling requirements of the ventricle. Usually in the first minute after the pacemaker has been turned off a significant but transient rise in left ventricular end-diastolic pressure has been noted in those patients with coronary artery disease who developed angina during pacing (fig. 2).

Some investigators report a fall in cardiac output during pacing in patients with angina,38 while others report no difference in output between control and pacing states in both anginal and nonanginal subjects.41, 42 The construction of curves relating left ventricular stroke work to end-diastolic pressure (modified ventricular function curves) has been of particular value in relating these varied responses in both stroke output and end-diastolic pressure. Normally, stroke work and/or volume falls in proportion to the fall in diastolic pressure (and volume), and these values may be plotted during pacing-induced tachycardia. A depressed curve may be seen in

![Figure 2](image_url)

**Figure 2**

Sequential changes in left ventricular end-diastolic pressure (LVEDP) following termination of a pacing study because of development of angina. In the first postpacing beat (lower arrow) the LVEDP is normal. In subsequent beats the LVEDP rises to almost 30 mm Hg as the R-R interval progressively lengthens. (Reproduced from O'Brien et al. by permission.48)
patients with coronary artery disease, both with and without angina (fig. 3). The depressed ventricular function curves and the postpacing elevations in left ventricular end-diastolic pressure have been interpreted as showing the development of transient left ventricular failure secondary to myocardial ischemia induced by the pacing tachycardia. These findings may also be explained by alteration in compliance, or delay in relaxation in such ventricles. Abnormalities of compliance and relaxation may result from segmental ischemia and may be difficult to differentiate from transient failure without simultaneous pressure-volume and wall-motion analysis.

In another approach to defining abnormalities induced by pacing tachycardia, Conti et al. have analyzed the isovolumic phase of systole. They reported calculated $V_{\text{max}}$ to be increased less during pacing in patients with coronary artery disease and myocardial ischemia than in normal subjects.

Several groups of investigators have compared the effects of atrial pacing and exercise in the same patients. Usually a similar anginal threshold (modified tension-time index) was present no matter which technic was used, but in one study angina occurred at a higher threshold and ventricular $dP/dt$ during effort than with pacing. Ventricular function curves are abnormal whenever ischemic symptoms or signs are precipitated by either technic. However, myocardial ischemia may occur without anginal pain, since the latter is determined by a series of neural, psychic, and possibly humoral factors. Thus, even in the absence of symptoms, ventricular function curves during exercise frequently show a flattened response. That this response is only rarely observed with pacing, but easily elicited by exercise, is most likely due to the fact that exercise increases venous return (Starling effect) and triggers sympathetic nerve activity, while pacing induces neither of these effects. Most investigators would therefore agree that exercise is a more useful stress for production of readily identifiable hemodynamic abnormalities than is pacing. Further studies of contractile element velocity ($V_{cE}$), as well as changes in compliance, are needed to clarify some of the differences between pacing and effort-induced angina.

Myocardial blood flow is increased in both normal subjects and patients with coronary disease during pacing, although there is a proportionately greater increase in normal individuals. Increased flow in patients with

![Figure 3]

Relationship between left ventricular end-diastolic pressure (LVEDP) and left ventricular stroke-work index (LVSWI) in three groups of patients studied during control (C), pacing (P), and postpacing (PP) periods. In normal controls, and in patients with coronary artery disease who did not develop angina during pacing, the decrease in LVSWI accompanying the increase in heart rate is associated with a decline in LVEDP (Starling effect). The patients in the angina group showed no change in LVEDP with the decrease in LVSWI. (In calculating LVSWI the assumption is made that cardiac output is similar in the pacing and postpacing periods.) This may be interpreted as reflecting a shift from a normal to an abnormal ventricular function curve when ischemia develops. (Reproduced from Parker et al. by permission.)

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coronary disease probably primarily reflects perfusion of normal areas, masking inadequate blood flow to ischemic areas. (This problem will be discussed further in reference to the effects of nitroglycerin on coronary blood flow). Similarly, average myocardial oxygen extraction does not increase with the observed increase in myocardial oxygen demand during pacing.49, 50 This may be due to admixture of venous inflows that would allow presumably subtle differences to be obscured by inflow into the coronary sinus from nonischemic regions.

Pharmacologically Induced Angina

Isoproterenol, a powerful beta-adrenergic stimulating agent, is the drug most frequently used to precipitate angina in the catheterization laboratory.12, 51 Like atrial pacing, isoproterenol has a major advantage over exercise-induced angina: myocardial lactate production may be reliably demonstrated, since this drug has little effect on systemic arterial lactate levels. Angina is mostly likely precipitated by the profound increase in both myocardial contractile state and in heart rate52 and therefore in myocardial oxygen requirements. In patients who develop angina, cardiac output and systolic ejection rate rise, but to lesser degrees than in normal subjects. Because venous return is not affected, the Starling mechanism is not particularly tested; hence an abnormal relationship of end-diastolic pressure to stroke volume is not easily recognized.

The response of coronary blood flow to this stress has been reported to be normal in patients with coronary artery disease.12 Recently, however, Knoebel et al.53 have shown that the increase in blood flow induced by isoproterenol varied inversely with the degree of coronary artery disease.

Miscellaneous Causes of Angina

Patients with coronary artery disease who experience anginal episodes may do so on exposure to cold, during or after meals, with emotional stress, and during arrhythmias. The role of cold in precipitating anginal episodes were first studied by Freedberg et al.54 and recently by Epstein et al.55 Both groups concluded that a combination of acute systemic vasoconstriction, hypertension, and increased impedance to left ventricular ejection caused the ischemic state. The decrease in exercise capacity following meals has yet to be satisfactorily explained under laboratory conditions.56 The relationship of emotional stress and angina is best exemplified by a patient reported by Robinson.21 Heart rate and blood pressure increased while doing mental arithmetic and the patient developed chest pain. The mechanism of angina induced by arrhythmias is usually ascribed to increased heart rate with ensuing segmental or global subendocardial ischemia.

Patients both with and without coronary artery disease may experience angina in the presence of other disease entities: anemia, hyper- and hypothyroidism, or aortic stenosis. Occasionally chest pain, electrocardiographic changes, and even lactate abnormalities occur when no demonstrable cardiac (or other) disease is present.57

Hemodynamic Effects and Mechanism of Action of Agents that Relieve Anginal Symptoms

Nitroglycerin and Related Compounds

The mechanism of action of nitroglycerin in relieving the pain of myocardial ischemia is uncertain. Two theories have received widespread acceptance: relief of angina may be due either to increased coronary blood flow or to a reduction in the work of the heart. In the first instance, nitroglycerin is thought to increase perfusion to ischemic regions by altering regional blood flow. Its site of action may be in both large and small coronary arteries, as well as collateral vessels. In the second instance, extracardiac actions of the drug are considered most important: smooth muscle relaxation in the peripheral systemic small vessels (arteries, veins, or both) results in a reduction of intraventricular volume, pressure, and therefore myocardial wall tension in both systole and diastole.

In most normal individuals, coronary blood
flow increases following the sublingual administration of nitroglycerin,\textsuperscript{55-60} while in patients with coronary artery disease flow increases to a lesser degree if at all. Visible dilation of the large coronary arteries occurs following nitroglycerin administration,\textsuperscript{61} but this bears no relation to regulation of coronary blood flow which is dependent on the smaller resistance vessels. There is evidence, however, that \textit{regional} differences in flow do exist in patients with coronary artery disease.\textsuperscript{62} \textsuperscript{63, 64} and that improvement of flow in zones of potential ischemia occurs following sublingual administration of nitroglycerin.\textsuperscript{64} Whether or not nitroglycerin selectively dilates collateral vessels while leaving total coronary blood flow unchanged is uncertain in man, although there is experimental evidence in dogs to support this contention.\textsuperscript{63, 64} It is also possible that collateral flow is augmented by dilatation of the large artery distal to the obstruction with a fall in diastolic pressure and a subsequent increase in the pressure gradient across the stenotic area.

The effects of nitrites on the extracoronary circulation are much more obvious than those on the myocardial circulation. Following administration of nitroglycerin, systemic and pulmonary arterial pressures fall in both normal subjects and those with coronary artery disease. Both arterial and venous vasodilatation occur. The latter leads to peripheral pooling of blood\textsuperscript{65} in both the resting and exercise states.\textsuperscript{66} Lee et al.\textsuperscript{67} have demonstrated that these peripheral effects result in a reduction of venous return and end-diastolic volume (preload) as well as a reduction in resistance to left ventricular ejection (afterload) and a subsequent decrease in end-systolic volume. As expected with this reduction in both end-diastolic and end-systolic ventricular volume and pressure,\textsuperscript{68} cardiac oxygen consumption has been reported to decrease.\textsuperscript{60} Other workers, however, have not demonstrated a fall in oxygen consumption following change in dynamics with nitroglycerin.\textsuperscript{58, 69} Despite this discrepancy, most investigators support the thesis that the hemodynamic effects of the drug are in some way responsible for most of its ability to relieve angina.

The elevated pulmonary capillary, left atrial, and left ventricular end-diastolic pressures usually observed with the anginal episode can rapidly be reversed by nitroglycerin.\textsuperscript{70, 71} This reduction in left ventricular end-diastolic pressure can also be detected by a noninvasive method, i.e., the disappearance of the fourth heart sound and abnormally large A wave on the apexcardiogram.\textsuperscript{71} Posture is important when the effects of nitroglycerin (or any of the nitrites) are evaluated. In the supine position peripheral pooling is less pronounced, venous return is greater, and exercise tolerance lower.\textsuperscript{72-74} A common example is the development of angina in previously exercised patients \textit{after} they assume a recumbent position. By reducing the mechanical activity of the heart, nitroglycerin also increases exercise capacity in patients with coronary artery disease.\textsuperscript{75-79} This occurs at least in part because the increase in cardiac mechanical activity, particularly blood pressure, is attenuated during exercise. Anginal threshold has been correlated with a consistent level of cardiac performance. Therefore, after administration of nitroglycerin, a greater total-body workload can be performed before the anginal threshold is reached.

With the adoption of the atrial-pacing technic, repeat studies are more easily performed in the same patients, and the action of drugs can be evaluated in a more objective manner. Results of such studies during pacing reinforce the conclusions derived from investigations into effort-induced angina. After nitroglycerin is administered, hemodynamic and metabolic abnormalities are not as readily manifested, and the heart can be paced at faster rates without development of chest pain.\textsuperscript{80, 81} Whether or not nitroglycerin can improve resting or stress-induced abnormalities of ventricular wall motion remains to be demonstrated.

The mode of action of longer acting nitrite preparations is similar to that of nitroglycerin, but the therapeutic advantages of these
preparations, compared to nitroglycerin, are still largely unproven.\textsuperscript{79, 82}

**Beta-Adrenergic Blocking Agents**

The cardiac excitatory effects produced by sympathomimetic amines are mediated mainly by beta-adrenergic receptors.\textsuperscript{83} Following extensive studies of the pharmacology of beta-adrenergic blocking agents, Hamer et al.\textsuperscript{84, 85} used propranolol in the clinical treatment of angina pectoris. Elliott and Stone\textsuperscript{86} have reviewed the majority of subsequent studies confirming the efficacy of this form of therapy. Propranolol, the most widely used of these agents, has been shown by Wolfson and Gorlin\textsuperscript{87} to reduce both myocardial oxygen requirements and coronary blood flow pari passu with a decrease in heart rate and myocardial contractile state. The drug's clinical effectiveness in relieving angina is further demonstrated by an improved exercise tolerance in patients with effort-induced angina. When a selected group of patients was exercised before and after intravenous administration of propranolol, Dwyer et al.\textsuperscript{88} reported a decrease in the response of cardiac output, left ventricular stroke work, and dP/dt. Despite a similar total-body work load, anginal pain either did not develop or was not as intense and of shorter duration. These results are consistent with the observations of Wolfson and Gorlin\textsuperscript{87} that for the same total-body work load during supine leg exercise propranolol attenuated the rise in myocardial oxygen consumption in direct proportion to the reduced cardiac effort. The hemodynamic effects of propranolol are different from those of nitroglycerin. Left ventricular end-diastolic pressure is either unchanged or may actually increase after administration of propranolol.\textsuperscript{87–89} In addition, heart size may be somewhat increased,\textsuperscript{90} and left ventricular asynergy may develop.\textsuperscript{91} Despite differences in mode of action, both propranolol and nitroglycerin relieve the subjective sensation of angina equally well when they are compared in the same group of patients.\textsuperscript{92–97} Under laboratory conditions several groups of investigators\textsuperscript{93, 94, 97} reported that the effects of the two drugs are additive in increasing exercise tolerance (fig. 4), although this has not been confirmed by other workers.\textsuperscript{92, 96} There is little doubt, however, that the reflex tachycardia which accompanies nitrite-induced peripheral vasodilatation and

![Figure 4](http://circ.ahajournals.org/)

*Effects of propranolol and the combination of propranolol and nitroglycerin (TNG), on the product of heart rate and mean systemic arterial pressure at rest and during exercise. In this patient the angina threshold is approximately 1000 rate-pressure units. Without medication a work load of 40 watts results in chest pain; with propranolol the minimal angina-producing work load is 60 watts; with propranolol and TNG a work load of 80 watts is necessary to produce pain. (Reproduced from Epstein and Braunwald by permission.\textsuperscript{97})*
hypotension is blocked by propranolol. Although this agent also causes venodilation\textsuperscript{87} and decreased venous return, its therapeutic usefulness appears to be related mainly to reduced myocardial contractility and heart rate under all conditions studied. The resulting reduction in myocardial oxygen requirements more than offsets the possible adverse effects on left ventricular function (asynery, and elevated diastolic pressure and volume). For a more detailed study of the pharmacology of beta-adrenergic blocking agents, the reader is referred to the recent review by Lucchesi and Whitsitt.\textsuperscript{98}

**Other Angina-Relieving Agents**

Digitalization of anginal patients with ventricular dilatation or heart failure may lead to a reduction in ischemic pain. Digitalization causes a reduction in heart rate, size, and developed tension in such individuals. These decreases may effectively counteract the increase in myocardial oxygen consumption caused by the drug's enhancement of contractile state.\textsuperscript{99} Since many patients with angina pectoris do not have cardiomegaly or congestive failure, it is not surprising that variable responses in exercise tolerance are observed following digitalization.\textsuperscript{100-104}

Stimulation of the carotid sinus nerves has proved useful in the treatment of incapacitating angina in selected patients.\textsuperscript{105} Carotid sinus nerve stimulation reduces myocardial oxygen requirements by a reflex decrease in sympathetic nerve activity. A fall in heart rate and systemic blood pressure occurs, modifying the anginal threshold accordingly.\textsuperscript{106}

Phlebotomy of patients during an anginal episode (provoked by atrial pacing) has been shown by Parker et al.\textsuperscript{107} to be of benefit in ameliorating pain. When the blood was reinfused, angina returned. Reduction in left ventricular volume (and stroke work) was the postulated mode of action.

**Conclusions**

The advent of cardiac catheterization has added considerably to our knowledge of the anginal state, but there are still areas that require further elucidation.

1. There are abundant data to indicate that increased cardiac mechanical activity is the major precipitating mechanism in effort- and pacing-induced angina. The etiology of spontaneous angina is less certain. With the exception of Prinzmetal's variant it is probably most often related to acute hypertension and/or tachycardia. These mechanical stresses augment myocardial energy demands. Eventually the capacity of segments of the coronary circulation to supply additional blood is exceeded. Whether primary reduction in coronary blood flow can occur either in global or regional fashion, and therefore precipitate angina, is currently not known.

2. Evidence of left ventricular dysfunction is often present during an anginal episode even though myocardial ischemia usually involves segments of ventricular wall, rather than the chamber as a whole. However, no consistent hemodynamic pattern characterizes all anginal episodes even when the same stress is utilized. For example, not all patients undergoing exercise experience preanginal elevations of ventricular pressure, and not all patients develop angiographic evidence of left ventricular asynery during pacing tachycardia. In addition, there is a lack of agreement as to whether transient left heart failure or reduced ventricular compliance is the primary hemodynamic abnormality during the anginal state.

3. Relief of angina can be achieved by a variety of drugs, as well as by carotid sinus nerve stimulation and by phlebotomy. All of these methods have in common reduction of myocardial oxygen requirements secondary to decreased cardiac mechanical activity, i.e. heart rate, blood pressure, left ventricular volume, and contractile state, or a combination of these factors. The primary effects of many pharmacodynamic agents on the coronary circulation are not as well understood as are the actions on the extracoronary circulation. To fill this gap in our knowledge of angina pectoris may well represent the immediate challenge in the continuing study of this syndrome.  

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