Mechanical Function of the Heart and Its Alteration During Myocardial Ischemia and Infarction
Specific Reference to Coronary Atherosclerosis

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SUMMARY Altered regional mechanical myocardial performance is an early, sensitive marker of myocardial ischemia, and can be estimated in man with reasonable accuracy. Identification, localization and quantification of abnormalities in mechanical performance can be used to predict the presence of coronary artery disease. Testing techniques that have little or no effect on diagnostic efficiency must be replaced with more sensitive indicators of ischemia. If experimental data are validated by findings in human subjects, accurate identification of regional wall motion changes during test conditions should prove to be a powerful marker of ischemia. To be of value, a diagnostic test must strongly increase the frequency of identification of subjects with a high probability for the presence of coronary artery disease in an otherwise low-prevalence population, and of those with known disease who are at the highest risk for complications including myocardial infarction or death.

THE CLINICAL CONSEQUENCES of atherosclerosis of the coronary arteries are primarily the result of alterations in myocardial blood flow or distribution and the effects on the mechanical and electrical properties of the heart. Important anatomic coronary artery disease may be present and readily identified by coronary arteriography or at autopsy without the manifestations of significant adverse effects in the patient during his lifetime. Ischemic heart disease is the proper term when coronary artery narrowing is severe enough to cause a reduction or redistribution of blood supply under conditions of stress or even at rest. Luminal alteration also may result from changes of vasomotor tone or from the adherence of formed elements of the blood to normal or abnormal intimal surfaces. Hence, the degree and location of luminal wall narrowing are as critical in ischemic heart disease as the presence of intraluminal coronary atherosclerosis.

While a reasonable measure of the degree of narrowing necessary to cause reduction of coronary blood flow is possible in the experimental animal, its quantification by coronary arteriography in man is still open to considerable error; this is particularly true at intermediate degrees of coronary arterial narrowing. For example, few coronary arteriographers would disagree about angiograms demonstrating normality or minimal (≤ 20%) luminal restriction on the one hand, or 90–99% narrowing on the other. The 40–70% range of diameter reduction is where the greatest variability appears to exist. The data of Gould indicate that the critical degree of narrowing is at about 80% diameter reduction. Values above this level are consistently associated with limitation of blood flow and values below it cause flow limitation only under conditions of increased demand. Coronary vasomotor tone and coronary spasm are of increasing interest as potentially important factors in the modulation of the degree of narrowing in some patients with 60–75% organic obstruction. Spasm alone is a primary factor in a minority of patients. There is increasing speculation that permanent or

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transient occlusion of a vessel with a critical or subcritical atherosclerotic narrowing may be precipitated by the formation of platelet or whole blood thrombus. This may be of decisive importance in many patients who develop acute myocardial infarction. Vasomotion and thrombosis usually appear in addition to preexisting coronary stenosis of intermediate or subcritical degree. Thrombosis alone only rarely appears to be a cause of myocardial infarction in patients with normal coronary vessels. Spontaneous lysis of platelet thrombi may explain the prevalent opinion that thrombotic mechanisms are not primary in most cases of myocardial infarction. However, recognition of the critical reduction in blood flow between an atherosclerotic lesion that obstructs 60–80% of luminal diameter and an acute increase in that narrowing to 90–100% by vasoconstriction or the addition of a relatively small thrombus underscores the need for a prompt reevaluation of the potential significance of these mechanisms.

The purpose of this report is to present evidence that altered regional mechanical performance is an early and highly sensitive marker of myocardial ischemia; that mechanical performance can be estimated in man with reasonable accuracy; and that such changes can be used to improve the predictive accuracy for or against important coronary artery disease in patients with or without symptoms of cardiac ischemia and/or to evaluate the functional significance of ischemia in patients with anatomic coronary artery disease.

**Animal Studies**

Experimental observations on the acute effects of ligation of a coronary artery have been reported for over 100 years. The classic description of Sir Thomas Lewis in 1909 bears repeating:

In the case of the descending branch of the left vessel, a patch of muscle which lies entirely in the ventricular muscle is damaged and . . . a narrow strip of healthy muscle remains in the right ventricle directly to the right of the intraventricular groove. When the ligation is tightened, an immediate change in the color of the implicated muscle is seen as a result of the obstruction to its blood supply. From a slightly cyanotic tinge, the color passes rapidly to a lividity which is maintained during the remainder of the experiment (the accompanying veins are usually included in the ligation). Within a few minutes, the damaged ventricle dilates and is ballooned with each contraction of the heart. It becomes more swollen until eventually no visible contraction is present.

However, Tennant and Wiggers in 1935 were the first to measure formally the changes in cardiac dynamics caused by ligation of a coronary artery.

In the past decade, animal models have been used to describe the acute effects of coronary narrowing as a result of the new interest in the management of ischemic heart disease. This enormous literature reveals:

1) Total occlusion of the proximal portion of a coronary artery will ordinarily cause an immediate (< 2 seconds) reduction of contraction in the territory supplied by the occluded artery. Contraction ceases in 30–90 seconds and may or may not be followed by systolic expansion. Systolic stretch is due to the failure of the ischemic myocardium to resist the increase in intracavitary tension associated with the effective contraction of the nonischemic myocardium. If the arterial occlusion is partial (70–90%), the magnitude of reduction and the extent of territory affected is reduced. Factors that apparently increase myocardial oxygen consumption in the presence of a partial occlusion of high grade will usually increase the degree and extent of dysfunction, while interventions that improve blood flow through a critically obstructed artery or through new or preexisting collateral channels have the opposite effect.

2) If a single complete or near-complete (> 95%) occlusion is allowed to persist, infarction of the sustained myocardium will occur with death of the most vulnerable or susceptible myocardial cells approximately 20 minutes after the initiation of the obstruction. Additional elements of myocardium are progressively involved for a further 3–6 hours when the final extent of infarction usually is established.

3) Release of a complete occlusion at normothermia in occlusions of less than 8–10 minutes in duration will usually result in a prompt restoration of function over a time span of 1–2 minutes. If the occlusion is maintained for 10–20 minutes, there is slower restoration of function, but without infarction. For occlusions lasting greater than 20 minutes but less than approximately 3 hours, the resulting myocardial infarct appears to be of smaller magnitude than would otherwise develop. Release of occlusions at time intervals of 3–6 hours or beyond does not appear to be associated with a reduction in the magnitude in extent of final injury compared with animals in which the ligation is permanent.

4) A deficiency in the contractile state of one region of the heart rendered ischemic appears to be balanced by an increase in the contractility of the healthy perfused areas in experimental animals. Hence, significant alterations in regional contractile state can exist without corresponding alterations in parameters of global pump function. At times, however, remote infarction may occur in myocardium not primarily supplied by the occluded vessel.

5) If the territory involved is large or if the remaining areas of myocardium are supplied by coronary vessels with restrictive narrowings, then compensatory mechanisms are inadequate and changes in global performance are identified. These include a reduction in the magnitude of negative and subsequently in positive dp/dt, in peak ventricular systolic pressure and by a rise in ventricular diastolic pressure. The function of at least 25% of the myocardium of the left ventricle must be seriously impaired before a rise in diastolic pressures can be detected. Reduction of negative peak dp/dt is caused by failure of normal diastolic lengthening of the in-parallel ischemic segment that undergoes diastolic shortening according to the passive length-tension relationship for cardiac tissue. Maximal dp/dt is reduced when the number of noncontracting muscle units is large and significant passive systolic lengthening characterizes the segment of ischemic tissue. A later change is the rise in end-diastolic pressure and fall in peak systolic ventricular pressure.

6) The regional mechanical effect of critical cor-
monary narrowing is a dynamic relation between normal function under circumstances of adequate perfusion, depressed or absent function in viable and hypoperfused myocardium, and absent function in areas of infarction and, by definition, is nonreversible. This dynamic relationship is determined in part by adequacy of blood supply relative to metabolic demand. Increase in heart rate, preload, afterload, contractile state, diastolic stiffness and volume elevate metabolic requirements; the effects of asynchronous contraction have not been investigated in detail. In normal myocardium perfused by vessels without, or even with minimal atherosclerosis, increases in metabolic demand are balanced by an equivalent increase in blood flow. Although metabolically induced local intramyocardial vasodilation is primary in autoregulation of myocardial blood flow and its distribution, the system remains highly dependent on diastolic aortic pressure. In addition, a gradient in intramyocardial tension exists across the ventricular wall with the greatest diastolic intramyocardial tension in the subendocardial layers. Recent evidence suggests that diastolic subendocardial intramyocardial pressure can even exceed left ventricular diastolic pressure. With proximal high-grade obstruction of the coronary arteries, myocardial blood flow and its distribution are determined by the relation between the epicardial intracoronary arterial pressures — reduced by upstream restriction — and the regional intramyocardial pressure. The relation of subendocardium myocardial pressure to elevated levels of intraventricular diastolic pressures has not yet been described in detail. Vasodilation in the metabolically active regions of myocardium causes further falls in epicardial perfusion pressures with marked changes in blood distribution, in general favoring the outer layers of the myocardium at the expense of the subendocardial layer. In conditions of extreme demand with associated increases in diastolic intraventricular pressures, little or no blood flow may reach areas of particular vulnerability, while flow to epicardial areas may actually increase — so-called coronary steal. This may explain the common clinical syndrome of subendocardial ischemia that, if prolonged, may result in subendocardial infarction.

Although much can be learned about human ischemic heart disease from the experimental animal, every model has important deficiencies. These deficiencies include variability in the coronary circulation and its preexisting collateral pathways (particularly in the dog); responses to anesthesia and surgical techniques; and most important, the relatively simplistic nature of the experimental models, in contrast to the complex pathology that usually characterizes coronary artery disease in the asymptomatic or symptomatic human subject. Careful studies on the highly instrumented, conscious, free-roaming animal have been carried out in a few centers. However, these studies are difficult and costly, and the experiments still suffer from the basic limitation in the translation of results from such preparations to concepts of mechanisms or appropriate therapeutic interventions in human ischemic heart disease.

**Human Application**

The rapid development of regional abnormalities of myocardial contraction after experimental coronary occlusion and their dynamic relation to interventions that alter the supply-demand ratio strongly suggest that studies of regional function in man in a dynamic setting would allow the prediction of important coronary artery disease. Angina pectoris, although usually a symptom of the ischemic process, may not be experienced at all despite alterations in the mechanical and electrical functions of the heart. Further, the demonstration of dynamic changes under stress can be relevant in determining the physiologic significance of an angiographically recognized stenosis in the subcritical (60–80%) range. Cardiac contraction and left ventricular end-diastolic pressure may be within the normal range or only minimally elevated, even in the presence of significant atherosclerosis of several coronary arteries. In most patients with previous myocardial infarction or in those who have significant angina pectoris, diastolic ventricular pressure is usually at the upper limit of normal and increases dramatically during stress, i.e., after contrast angiography, exercise or cardiac pacing. This elevation can usually be reversed by nitroglycerin. Experimental data suggest that the extent of regional mechanical dysfunction should affect 25% of the left ventricular myocardium to cause a significant elevation of diastolic pressure. More extreme rises in diastolic pressure, i.e., greater than 30 mm Hg, suggests the presence of more extensive impairment of regional function due to either permanent scar, repairing infarct or reversible ischemia.

**Contrast Angiography**

Demonstrations of alterations of regional wall motion have been derived from left ventricular angiography. Radiographic contrast has an inherent depressant effect on myocardial contractility and, by its osmotic effects, causes an expansion of the intravascular volume. Ventriculograms reveal alterations in the location, extent and magnitude of regional systolic contraction and diastolic relaxation as well as changes in the overall ejection fraction. Substantive information is provided by these studies and may permit the differentiation between ischemic, but reversible, myocardial paralysis in contrast to wall motion abnormalities due to permanent scar. However, the angiographic technique has serious practical limitations. It is invasive and associated with a small but important morbidity and mortality, usually accompanied by natural anxiety and a relative degree of unavoidable discomfort in the patient. Multiple ventriculograms can be ethically justified in only a minority of subjects. In spite of these limitations, dynamic changes may be defined in a quantitative manner. Reduction in the global ejection fraction correlates well with the number of myocardial segments that reveal abnormal wall motion. Many sophisticated techniques used to estimate the nature and extent of disordered mechanics have been defined. For example, a recent report based on angiography in
man indicated that the average values for the peak rate of systolic wall thickening and diastolic wall thinning was significantly less in patients with coronary atherosclerosis than in normal subjects. In the nonexercising state, the reduction in peak rate of diastolic thinning identified patients with the most severe degree of stenosis in the vessels subserving the affected regions.

Noninvasive Techniques

The practical requirements of evaluation of human coronary artery disease and myocardial ischemia and scar mandate noninvasive procedures. Exercise electrocardiography as a crude screen for the presence and severity of coronary stenosis is a testimony to this need, in spite of the poor predictive accuracy associated with electrocardiographic changes alone. Noninvasive procedures to detect and quantify abnormalities of regional wall motion — if cost-effective — may provide stronger end points than previously have been available. If such noninvasive procedures could suggest the presence of significant coronary artery disease in the asymptomatic patient at likelihood levels of 90% or greater, angiography might be justified to define not only the presence of coronary artery disease, but also its location and severity.

Scintigraphy

Multiple-gated technetium-99m labeled red blood cell scintigraphy appears to be the most highly developed noninvasive method in use. Also, first-pass measurement of the change in radioactivity can be obtained during the high-concentration phase of its circulation. More often, a 2-6-minute sample of electrocardiographically gated activity is collected over several hundred successive cardiac cycles after equilibrium. From these data, a signal-averaged complete cardiac cycle is generated that permits the estimation of ejection fraction with a remarkably small intrinsic variability and a satisfactory correlation with contrast angiography in man. More important from the standpoint of regional mechanics, changes in the perimeter of the nuclear image during the cardiac cycle allow assessment of the magnitude and rate of systolic reduction and diastolic expansion of the endocardial-blood pool interface. While the latter estimates require further comparative evaluations and are currently regarded as qualitative, they are readily quantifiable by data reduction techniques. If required, the circulatory state can then be altered by exercise, cardiac pacing, position or vasoactive drugs, and after steady-state conditions have been reached, a second scintigraphic ventriculogram can be recorded. Regional wall motion changes during stress compared with a previous state or states allows the definition of dynamic alterations implicating reversible ischemia and by inference, subcritical coronary artery disease.

Although technetium-99m scintigraphy is noninvasive and uses a relatively inexpensive isotope, the technique has specific limitations other than inherent methodologic constraints. A 2-6-minute observation period is required; arrhythmias cause edge blurring; beat-to-beat alterations cannot be compared, and wall thickness and its cyclical change cannot be measured. Also, equipment is bulky, expensive and not likely to be readily available in the physician's office. Nevertheless, scintigraphy clearly offers a powerful and generally satisfactory tool to investigate the thesis that dynamic changes in regional wall motion are sensitive and clinical markers of myocardial ischemia and infarction. The cost, size and complexity of current gamma cameras virtually preclude their use in the usual clinical facilities except for very large hospitals and even then, frequently in research applications. The nuclear "stethoscope" may give a satisfactory estimate of ejection fraction but cannot provide evidence of abnormality of dynamic alteration in regional wall motion.

Ultrasonography

M-mode echocardiography is a well-established technique for noninvasive evaluation of endocardial motion and, under certain circumstances, wall thickness and its changes. Current technical developments in wide-angle, sector-scanning devices enhance such applications. Although the technique appears to allow reasonably valid estimations of ejection fraction in the symmetrically contracting ventricle, the asynery associated with ischemic heart disease apparently increases the variability levels, which precludes useful application in these syndromes. Quantification of wall motion changes and their interpretation remain in the early stage of clinical evaluation. The procedure is more readily applicable in a clinical setting than technetium-99m scintigraphy, although satisfactory recordings cannot be obtained in approximately 25% of subjects. The technique is also highly dependent on operator skills, and the projections are not precisely standardized. Sector-scanning techniques have not resolved discontinuities in the endocardial echoes. Certain important regions of the heart — for example, the apex of the left ventricle — can be defined only with difficulty. Therefore, ultrasonic evaluation of regional wall motion is qualitative, is not yet quantifiable, and not applicable to all regions of interest. Selected M-mode recordings of cyclical wall thickness monitored as to position within an ultrasonic sectoscand may provide valuable evidence of dynamic changes in regions readily accessible to the ultrasonic beam.

External Mechanical Recordings

Several technical approaches, including ballistocardiography, apexcardiography and impedance cardiography, have been applied with such a modest degree of success that they have not been generally accepted. Two newer examples of such techniques are worthy of brief note because, although limited in application, they offer a simple, low-cost device that could generally be applicable in physicians' offices.
The cardiokymogram is a small device that may be placed on the anterior chest wall slightly lateral to the left edge of the sternum. It generates a magnetic field that apparently responds to the position of the anterior myocardium. The signal obtained from such a device resembles the changes in wall motion identified both in man (angiographically) and in the experimental animal (ultrasonic crystal, length gauge). Alteration in wall motion from a normal pattern to an outward systolic movement during exercise has been demonstrated in a series of patients subsequently proved to have ischemic heart disease. Nevertheless, satisfactory signals are not obtained in all subjects, the output of the device is complex and nonlinear in relationship to distance and mass of myocardium and the nature of intervening tissue, and the application is probably limited to disease in the anterior descending or left main coronary artery.

The photokymogram is a device which may be applied to a videofluorographic recording of the movement of the epicardium and the anterior and lateral walls of the left ventricle. Successive applications of the photokymogram to successive segments of the moving image and its correlation with the electrical phases of the cardiac cycle also permit the generation of a signal that resembles the phasic movement of regional ventricular myocardium. However, such a signal is heavily influenced by the phase and depth of respiration, cardiac rotation and other alterations. However, the development of simplified techniques that use low-cost, small, noninvasive devices is essential if these concepts, once proved valid, are to achieve general application throughout the community.

Pathophysiologic Studies

Using the above techniques, preliminary studies in man with myocardial ischemia or infarction have already permitted validation and extension of previous concepts of the pathophysiologic mechanisms of ischemic heart disease:

1) Abnormality of regional wall motion characterizes ischemic heart disease and correlates with changes in ejection fraction. The magnitude of such changes show a high degree of variability between patients. Mortality is inversely related to ejection fraction.

2) In acute myocardial infarction, the reduction in ejection fraction (and corresponding changes in regional wall motion) are surprisingly large, appear to be immediate relative to the onset of the illness in most instances, and remain relatively unchanged for at least 2–3 weeks.

3) Anterior infarctions are associated with a more profound depression of regional wall function than inferior infarction. Inferior infarction causes a greater depression of right ventricular function.

4) The location of the infarct by electrocardiography is identified by akinesis or dyskinesis in the corresponding ventricular wall, but remote areas may also show changes. Thus, in about 50% of patients, first-event myocardial infarction in the inferior wall may be associated with a depression in anterior wall motions, suggesting concomitant disease in the anterior system.

5) Hypercontractility of remote areas has been demonstrated in a few patients.

6) Exercise scintigraphy shows an increase in ejection fraction and in regional wall motion indices in normal subjects. In patients with subsequently proven significant coronary atherosclerosis, ejection fraction is reduced and wall motion studies show regional ischemia.

Significance in the Diagnosis of Coronary Artery Disease

Identification, localization and quantification of abnormalities of regional myocardial mechanical performance and its reversibility or nonreversibility appear to offer a new approach to the identification of coronary artery disease in the community. At present, the limitation of current screening techniques in enhancing diagnostic probabilities are being recognized and improved. To be effective, however, any such test must strongly increase probability criteria in low-prevalence populations or effectively lower probability for disease in a high-prevalence cohort. Hence, a positive electrocardiographic stress test in a patient population with a high prevalence of coronary artery disease as determined by age, sex, history of chest pain, smoking and hypertension adds little to an already high probability. Similarly, the occasional positive or borderline electrocardiographic test in a member of a low-probability cohort is more frequently a source of considerable confusion to physician and patient alike.

If the experimental data on regional wall motion and the preliminary impressions from clinical application are validated, accurate identification of regional wall motion changes during test conditions that alter the relation between myocardial blood flow and myocardial oxygen supply should prove to be sensitive and powerful markers of ischemia. By secondary inference, such findings should enhance diagnostic effectiveness regarding the presence or absence of significant coronary artery disease.

It is vital to eliminate dependence on the symptom of chest pain to alert the physician and health care personnel and patients of the possibility of ischemic heart disease. It is equally important to discard testing techniques that have little or no effect on diagnostic efficiency and replace them with new approaches. These in themselves are worthy goals of future research in cardiology. However, identification of patients with a high probability for the presence of coronary artery disease in an otherwise low-prevalence (asymptomatic) population, and of those with known disease (i.e., old myocardial infarction) who are at the highest risk for complications (i.e., sudden death), is essential to evaluate the effect of behavioral and therapeutic interventions on cardiovascular morbidity and mortality.
References


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