Physical Signs, Apexcardiography, Phonocardiography, and Systolic Time Intervals in Angina Pectoris

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SUMMARY

Coronary artery disease and angina pectoris are frequently associated with disordered myocardial function which may cause abnormalities in precordial motion, heart sounds, and/or systolic time intervals. The pathophysiologic basis for these abnormalities has been studied by correlating them with more direct measurements of myocardial function. Large a waves on the apexcardiogram and atrial gallops are related to accentuated left ventricular a waves which reflect diminished left ventricular compliance. Uncoordinated left ventricular contraction (asynergy) may cause abnormal systolic motion which can sometimes be recorded on the apexcardiogram. Ventricular (early diastolic) gallops in coronary artery disease are usually associated with extensive obstructive lesions, left ventricular asynergy, and a low cardiac output. Transient paradoxic splitting of the second sound in angina pectoris has been reported though rarely documented by phonocardiography. Mitral insufficiency due to papillary muscle dysfunction implies significant damage to the papillary muscles and the surrounding ventricular wall, usually by severe coronary artery disease. Systolic time intervals are a sensitive technic which may reflect diminished contractility (prolonged preejection period) or low stroke volume (shortened left ventricular ejection time) in patients with coronary artery disease. However, systolic time intervals are also sensitive to many other pharmacologic and hemodynamic influences, including changes in left ventricular preload and afterload which may result in misleading values. Therefore, as a technic for evaluating individual patients with coronary artery disease and angina pectoris, the role of systolic time intervals remains limited.

The continuing search for sensitive and reliable noninvasive diagnostic technics has led to a recent revival of interest in cardiac auscultation, phonocardiography, apexcardiography, and systolic time intervals. This increased popularity of noninvasive technics is also attributable to their direct correlation with results of high-fidelity hemodynamic measurements, cineangiography, and coronary visualization. The potential usefulness of noninvasive technics in the study of angina pectoris is enhanced by the fact that variable degrees of abnormal myocardial function are present in many patients with angina pectoris even in the absence of clinically evident cardiac enlargement or failure.1-5

When the auscultatory findings, apexcardiogram, phonocardiogram, and systolic time intervals are abnormal due to coronary artery disease, they are not believed to reflect the extent of the obstructive lesions per se, but rather the resultant disordered myocardial function. It follows that not all patients with angina pectoris should have abnormal physical signs or abnormal graphic studies. Additionally, none of the physical signs or graphic

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abnormalities is specific for angina pectoris. Such abnormalities may nevertheless, when properly sought and interpreted, give confirmatory clues for the diagnosis of angina pectoris and may provide information about associated abnormalities of myocardial function.

**Precordial Motion and Apexcardiography**

Precordial motion may be externally recorded by a number of methods including kinetocardiography, vibrocardiography, impulse cardiography, and fiberoptics. Subsequent discussion refers to records obtained by apexcardiography. Several authors have discussed the requirements of recording equipment as well as the proper technic for the performance of apexcardiography. It is important to avoid using a microphone-transducer system with a too-short time constant. Although utilized frequently for apexcardiography, such equipment may produce artifactual tracings. The sharpened peaks and valleys thus obtained may in fact be distortions of the true complex which may also lead to errors in the timing of events by apexcardiography. The apexcardiogram is usually performed with the patient lying on his left side. The microphone is held directly on the apical impulse either manually or with a band, and recordings are made during quiet or held respiration. Technically satisfactory tracings may not be obtainable in patients with pulmonary emphysema, severe right ventricular hypertrophy, exogenous obesity, pleural effusion, or mediastinal disease. A normal apexcardiogram and a simultaneous left ventricular high-fidelity pressure recording obtained with a catheter-tip micromanometer is shown in figure 1. The a wave corresponds

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**Figure 1**

(Left) Normal apexcardiogram (ACG). The a wave is small, and there are no abnormal systolic bulges. Following the 0 point there is a normal rapid filling wave (RFW). (Right) U point of a technically satisfactory ACG corresponds exactly with the onset of rapid left ventricular pressure rise which was measured with a catheter-tip micromanometer.

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to the left ventricular presystolic filling wave caused by atrial contraction and follows the rise of left atrial pressure by 10–20 msec. The u point coincides with the onset of left ventricular isovolumic contraction which is indicated by the sharp upstroke of the left ventricular pressure curve. The e (ejection) point is not always clearly demarcated and often varies significantly from the true onset of left ventricular ejection. The o point follows left ventricular-left atrial pressure crossover during early diastole by an interval of up to 50 msec. This is followed by the rapid filling wave, the peak of which correlates with the physiologic third sound or its pathologic counterpart, the ventricular diastolic gallop (fig. 2). The slow filling wave is an inconstant feature.

In patients with coronary artery disease the a-wave percentage amplitude (aWPA) (a-wave amplitude/e to o-point amplitude) may be increased (fig. 3). In normal persons this ratio averages less than 15–20%, while in patients with coronary artery disease it averages approximately 25%. Benchimol and Dimond found an increased aWPA on the apexcardiogram of nearly all patients with ischemic heart disease. Exercise may be used to bring out or accentuate an abnormal aWPA in patients with coronary artery disease (fig. 4). In normal persons, during Master’s two-step exercise, aWPA remained below 15–20%. In contrast, patients with coronary artery disease responded with a significant increase in aWPA. Those patients who also developed

![Phonocardiogram and apexcardiogram from a patient with coronary artery disease and severe angina pectoris, showing a holosystolic murmur and a late systolic bulge on the apexcardiogram. This combination along with sinus rhythm, a prominent apical a wave, and an atrial gallop (S4) suggests acute mitral insufficiency in this case due to papillary muscle dysfunction. The late systolic bulge on the apexcardiogram suggests asynergy of left ventricular contraction which was demonstrated by a left ventricular cineangiogram. There is also a faint ventricular diastolic gallop (S3).](image)

**Figure 2**

![Abnormal apexcardiogram in a patient with severe angina pectoris due to coronary artery disease. The a wave is prominent and the a-wave percentage amplitude (aWPA) is increased. This is accompanied by a prominent atrial gallop (S4) on the phonocardiogram (PCG). There is, in addition, a late systolic bulge (SB) suggesting asynergy of left ventricular contraction. Recorded with Sanborn model 374 microphone. (Figure courtesy of Dr. Eugene P. Haddock.)](image)

**Figure 3**
angina pectoris during the exercise showed the greatest response.19-21

Hemodynamically an increased aWPA is related to an elevated left ventricular end-diastolic pressure which is frequently present in patients with coronary heart disease and which often increases further during an attack of spontaneous or exercise-induced angina pectoris or during experimentally induced myocardial ischemia.1-5 Voigt and associates18 and Cohn and associates22 directly correlated the apexcardiogram with hemodynamic measurements in patients with coronary artery disease and showed an aWPA of greater than 15% to be consistently associated with an elevated left ventricular end-diastolic pressure. If left ventricular end-diastolic pressure was elevated due to early diastolic filling abnormalities, however, aWPA was often normal. On the other hand, a good correlation was found between the height of the left ventricular a wave (atrial filling wave) and aWPA.18 A positive correlation between the a wave of the apexcardiogram and left ventricular end-diastolic pressure has also been found in patients with hypertensive heart disease, primary myocardial disease, and aortic valve disease.23, 24 Occasionally, abnormal a waves have been noted in patients who are asymptomatic or who have normal coronary arteriograms. Some of these persons also developed abnormal electrocardiographic S-T depression during maximal exercise,21 and others were later found at catheterization to have an elevated left ventricular end-diastolic pressure presumably due to a cardiomyopathy.22

The second type of apexcardiographic abnormality due to coronary heart disease, an abnormal systolic bulge, is illustrated in figures 2 and 3. Harrison noted in 1958 that abnormal precordial systolic bulges could usually be recorded by the kinetocardiogram during an attack of angina pectoris.25 When the angina was relieved, the abnormal bulge disappeared. Lane and co-workers26 reported various types of abnormal systolic bulges in 41 patients with coronary artery disease whose left ventricular angiograms also showed uncoordinated or paradoxical ventricular contraction (asynergy). Harrison postulated that the paradoxical impulse observed transiently during angina pectoris was caused by a functional ventricular aneurysm which disappeared along with cessation of the angina pectoris.25

It may therefore be concluded that a large apical a wave on a technically good apexcardiogram provides confirmatory evidence of diminished left ventricular compliance with an accompanying strong left atrial contraction, while an abnormal systolic bulge suggests asynergy of ventricular contraction. It is clear, however, that a normal apexcardiogram does not exclude coronary artery disease. Thus, in the series of Cohn and co-workers22 51 of 93 patients with coronary artery disease (greater than 75% obstruction of at least one major coronary artery) were found to have a normal aWPA on the apexcardiogram. Likewise, the

Figure 4

Comparison of a-wave percentage amplitude (aWPA) before and after exercise in a patient with angina pectoris. Although the a wave and aWPA were normal (14%) at rest, aWPA increased to 33% during exercise which produced angina pectoris. An atrial gallop (S4) is also present on the phonocardiogram. Recorded with Sanborn model 374 pickup. (Figure courtesy of Dr. Eugene P. Haddock.)

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systolic configuration of the apexcardiogram may appear to be normal despite significant asynergy of left ventricular contraction. For example, in one series of 30 patients with a previous myocardial infarction and fluoroscopic evidence of ventricular aneurysm, a paradoxic apical pulsation or late systolic bulge was recorded in only five.27

Although a detailed critique of the methods for measuring precordial movement is beyond the scope of this review, some of the unresolved problems which have discouraged the routine clinical use of apexcardiography deserve mention. First, it has been difficult to compare the recordings of precordial motion between different laboratories because of variations in instrumentation and technique. Kinetocardiography, impulse cardiography, vibrocardiography, and fiberoptics record absolute precordial displacement in relation to a fixed external point. Apexcardiography, on the other hand, records displacement relative to the surrounding rib cage and chest wall. Second, equipment for apexcardiography requires further standardization. The popular crystal microphone most frequently used in the past to obtain apexcardiograms often has a short time constant, i.e., 0.3 sec, which as noted earlier may give rise to artifacts.28, 29 Figures 3 and 4 were obtained with this crystal microphone, while the recording apparatus used to obtain figures 1, 2, and 8 has a longer time constant (1.6–2.0 sec). Hopefully, further standardization of equipment will facilitate comparison of apexcardiograms between institutions, eventually increasing the cardiologist's ability to delineate abnormalities.

Heart Sounds in Angina Pectoris

Although usually normal in patients with angina pectoris, the first heart sound may be accentuated in some patients with papillary muscle dysfunction due to coronary artery disease.30 The explanation advanced for this finding, reported to occur occasionally even in the presence of a prolonged P-R interval, is that the malfunctioning papillary muscle fails to take up chordal slack during early systole. When the rapidly rising left ventricular pressure then forces the mitral valve toward the left atrium a sudden chordal tautening and resultant sudden checking action on the valve is postulated to cause an accentuated first sound. This accentuated sound was found to occur later in the isovolumic contraction period than the normal first sound.30 Paradoxic splitting of the second heart sound (with expiratory splitting and a single sound during inspiration) may occur in patients with coronary artery disease as shown on phonocardiograms by Agnew and co-workers31 in 13 patients. Although rarely documented by phonocardiograms, it is stated to occur transiently either during a spontaneous attack of angina pectoris32-34 or during exercise stress testing in patients with coronary artery disease.35, 36 Normal and paradoxic splitting are shown in fig. 5. During inspiration the pulmonic component normally follows the aortic closure sound by 20–40 msec, and during expiration the sounds merge. About two thirds of the inspiratory widening is ascribed to an increase in the Q-P2 interval and about one third to shortening of the Q-A2 interval.37-39 Paradoxic splitting is usually caused by prolongation of the Q-A2 interval rather than by shortening of Q-P2. Normal directional respiratory movements of Q-A2 and Q-P2 are preserved in paradoxic splitting, but because Q-A2 is prolonged inspiration results in fusion rather than splitting of the two components. The underlying cause of paradoxic splitting in angina pectoris is not clear. A significant increase in systemic arterial pressure, an increase in preejection period, or a left bundle-branch block, any of which may occur in patients with angina pectoris, might prolong the Q-A2 interval.4, 40-42 On the other hand, a shortened left ventricular ejection time which is often present in patients with chronic heart failure would tend to shorten the Q-A2 interval.41

The true incidence of paradoxic splitting in coronary artery disease is not known. Auscultatory impressions of paradoxic splitting not
Normal (top) and paradoxic (bottom) splitting of the second heart sound. Normally during expiration the Q-A2 and the Q-P2 intervals are nearly equal. Normal inspiratory splitting occurs from lengthening of Q-P2 (2/3) and shortening of Q-A2 (1/3). In paradoxical splitting Q-A2 is prolonged. Inspiratory shortening of Q-A2 and lengthening of Q-P2 then results in fusion of the two components. Splitting occurs during expiration when Q-A2 again becomes longer and Q-P2 shortens.

documented by a phonocardiogram can be deceptive since fading of the second sound during inspiration may be interpreted as a single sound. The report of Caulfield and co-workers is instructive in this regard. Of 20 patients with acute myocardial infarction, 25% were diagnosed by auscultation as having either paradoxic splitting or a single second sound during inspiration. However, in each instance, careful interpretation of the phono-

cardiograms revealed normal splitting. In addition, paradoxic splitting or a single second sound is sometimes present in asymptomatic elderly persons where it may or may not be due to coronary artery disease.

Gallop Rhythm

Atrial (late diastolic) gallops occur commonly in patients with coronary heart disease, particularly in acute myocardial infarction.
where they are nearly always at least transiently present. Cohn and co-workers recorded an atrial gallop or prominent a wave on the apexcardiogram in 34 of 93 patients who were found by coronary angiography to have greater than 75% obstruction of one or more coronary arteries. An atrial gallop was recorded in three of 37 patients in that series with normal coronary angiograms. When auscultation is carried out during an attack of angina pectoris, an atrial gallop may be heard evanescently.

The stress of exercise may bring out an atrial gallop in patients with coronary heart disease, particularly if angina pectoris develops during the test. Proudfoot reported the appearance of an atrial gallop in 16 of 24 patients in whom angina was precipitated by exercise. The effectiveness of a Master's two-step test in bringing out gallops was reported by Aronow and co-workers who recorded atrial gallops at rest in 43 of 100 patients with angina pectoris, and in 94 immediately following Master's two-step exercise. Forty-nine patients developed angina pectoris during exercise, all of whom also developed an atrial gallop. These authors also reported an atrial gallop at rest in 14 of 100 age-matched persons (mean age 51 years) with no clinically evident heart disease, and in 29% following exercise. A low-frequency recording cutoff of 25 Hz may have contributed to the high incidence of atrial gallops recorded by these authors. Isometric exercise such as maximal sustained handgrip may result in an atrial gallop in patients with coronary heart disease (fig. 6). An advantage of isometric stress is that phonocardiographic recording and auscultation can be performed during the exercise.

The hemodynamic abnormality associated with an atrial gallop in coronary heart disease, as with an accentuated apical a wave on the apexcardiogram, is a prominent left ventricular a wave resulting in an elevated left ventricular end-diastolic pressure. In those patients with an atrial gallop but not a ventricular (early diastolic) gallop, heart size and cardiac output are usually normal. There is an increase in the ratio of left ventricular end-diastolic pressure to volume indicative of decreased left ventricular compliance.

Ventricular gallops, although less common than atrial gallops in patients with angina pectoris, have more serious clinical implications. Harvey observed a ventricular gallop to be one of the earliest and perhaps most frequently overlooked findings in heart failure, an observation now verified by hemodynamic studies. In contrast to patients with only an atrial gallop, those patients with a ventricular gallop usually had an elevated left ventricular end-diastolic pressure, a decreased cardiac index, and some degree of left ventricular asynergy as well. A ventricular gallop in coronary heart disease is nearly always accompanied by an atrial gallop. Like the atrial gallop, a ventricular gallop may sometimes be "brought out" by the stress of exercise.

Despite previous extensive studies of gallop rhythm, persistent problems remain in their interpretation. Depending in part on the method used for their detection, the reported

Figure 6

Phonocardiogram illustrating the value of exercise in "bringing out" an atrial diastolic gallop in patients with angina pectoris. In this patient, an atrial gallop which was not recorded at rest appeared during the performance of sustained handgrip.
incidence of gallop rhythm varies considerably.\textsuperscript{48, 52, 53} Gallops occur predominantly at the low-frequency end of the sound spectrum where hearing acuity is poor.\textsuperscript{52, 54} Therefore atrial gallops may sometimes be felt, or recorded as an a wave on the apexcardiogram, better than heard. Considerable confusion has resulted from the fact that very low-frequency vibrations (\(10-40\) Hz), which may be inaudible with the stethoscope, and perhaps of no pathologic significance, may frequently be recorded if the phonocardiogram is adjusted to pick up these vibrations. (fig. 7). On the other hand, unless specifically sought on auscultation, pathologic gallops are easily missed, or in the case of an atrial gallop may be confused with the first sound-ejection sound sequence.

Gallops are labile events which occur when there is an abnormal relationship between the rate of early (ventricular gallop) or late (atrial gallop) diastolic ventricular filling and the ventricular capacity to accommodate its increasing volume.\textsuperscript{55} Therefore, factors other than changes in the intrinsic state of the myocardium can alter the timing or intensity of gallops or cause their appearance or disappearance. A sudden decrease in venous return caused by inflation of peripheral tourniquets, for example, may decrease the intensity of an atrial gallop and cause it to merge with the first heart sound.\textsuperscript{56} The intensity of gallops may be decreased by a simple maneuver such as upright tilt\textsuperscript{57} or it may be increased by leg raising, by the cold pressor test,\textsuperscript{58} or by saline infusion.\textsuperscript{51} It is recognized that both atrial and ventricular gallops may occur in the absence of intrinsic heart disease, e.g., in hyperkinetic states such as thyrotoxicosis\textsuperscript{59} or pregnancy.\textsuperscript{60} A physiologic third sound corresponding to a ventricular gallop is normally present during youth. Audibility of atrial gallops is enhanced by a prolonged P-R interval.\textsuperscript{56} However, an atrial gallop which is due to coronary heart disease is most likely caused by increased resistance to late ventricular diastolic filling due to decreased ventricular compliance and an augmented left atrial contraction.\textsuperscript{61} A ventricular diastolic gallop suggests the additional abnormality of poor ventricular contraction usually associated with a low cardiac output and an increased early ventricular diastolic filling pressure.\textsuperscript{22, 61}

A nonejection systolic click originating from the mitral valve apparatus, and occasionally introducing a murmur of mitral insufficiency, has been described recently in 15 patients with coronary heart disease.\textsuperscript{62} The authors suggest that the damaged papillary muscles fail to take up chordal slack properly during systole and may therefore be responsible for the click. The combination of a nonejection click and mitral insufficiency may be a further extension of the syndrome of papillary dysfunction due to coronary artery disease.\textsuperscript{63}

\begin{figure}[h]
\centering
\includegraphics[width=\linewidth]{figure7.png}
\caption{Comparison of apical heart sounds recorded at different frequency settings. An atrial gallop (\(S_4\)) was not heard and was not recorded on the phonocardiogram (top) at the frequency settings of 120-500 Hz, which are usually used in this laboratory. However, an \(S_4\) was recorded (bottom) at a low-frequency cut-off of 20-40 Hz.}
\end{figure}
Murmurs in Angina Pectoris

Systolic murmurs due to coronary artery disease present a variable hemodynamic and clinical picture. At one end of the spectrum is the dramatic onset of heart failure with rapid clinical deterioration caused by rupture of a papillary muscle or the interventricular septum, while at the opposite end are those patients with a murmur of mitral insufficiency and angina pectoris who may have little or no cardiomegaly.

Burch, in 1963, described the syndrome of characteristic electrocardiographic abnormalities and a systolic murmur due to left ventricular papillary muscle dysfunction. Subsequently, it was shown that a wide spectrum of electrocardiographic abnormalities associated with papillary muscle dysfunction exists and that the associated murmur may be holosystolic (fig. 2), or late systolic, or may have ejection characteristics. Its timing, duration, and intensity may change under observation and, unlike the murmur of rheumatic mitral insufficiency, it may diminish in intensity with postextrasystolic beats. It may appear transiently during an attack of angina pectoris, or, if permanent, its intensity and/or duration may increase.

Patients with a murmur of papillary muscle dysfunction are reported to have a high incidence of severe angina pectoris. The murmur is often first noted during an acute myocardial infarction. In patients with angina pectoris, a murmur of papillary muscle dysfunction suggests extensive coronary artery disease. Coronary arteriograms have usually shown major obstruction (greater than 75% narrowing) in at least two major vessels, and poor left ventricular contraction is frequently seen on the left ventricular angiogram. Experimental studies in dogs have shown that neither transient ischemia nor isolated infarction of a papillary muscle leads to mitral incompetence. It was produced, however, by infarction of a papillary muscle in addition to the surrounding ventricular muscle. Papillary muscle infarction was found at autopsy in 54% of 133 patients with acute or healed myocardial infarction, but, in retrospective analysis, the prevalence of murmurs in this group was not significantly higher than in those patients without papillary muscle infarction. The relationship between mitral insufficiency and papillary muscle infarction in patients, therefore, appears to be similar to that observed in the experimental model. A murmur of papillary muscle infarction, even though it appears transiently during angina pectoris, is not likely to be due simply to papillary muscle ischemia, but implies additional preexisting damage to a papillary muscle and/or the surrounding myocardium.

Flow murmurs may result from stenotic coronary artery lesions. Since coronary blood flow is maximal during diastole, this murmur is also louder during diastole and may be confused with the rumble of mitral stenosis. It is higher pitched, however, and, unlike the rumble of mitral stenosis, may decrease in intensity during inhalation of amyl nitrite.

Systolic Time Intervals

Systolic time intervals, which have been utilized in an attempt to gain insight into left ventricular performance in various cardiac disorders, may be measured by several methods (fig. 8). From high-speed recordings of the electrocardiogram, phonocardiogram, and external carotid pulse, the following may be obtained: (1) total prejection period (PEP) measured as the interval from the Q wave of the electrocardiogram to aortic closure (Q-A$_2$) minus left ventricular ejection time (LVET), which is measured from the carotid pulse tracing as the interval between onset of ejection to dicrotic notch (PEP = Q-A$_2$ - LVET); (2) preejection period may be further subdivided into the Q-S$_1$ interval and external isovolumic contraction time (EICT), which is measured as S$_1$-A$_2$ minus LVET (fig. 8); and (3) the onset of true isovolumic contraction time (ICT) may also be determined from a simultaneously obtained apexcardiogram (fig. 8).

Since the sharp systolic upstroke of a technically adequate apexcardiogram (u point) corresponds to the onset of left

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VENTRICULAR PRESSURE RISE, measured from a catheter-tip micromanometer \(^{16,17}\) (fig. 1, right), the isovolumic contraction time measured from the apexcardiogram may be referred to as “true” ICT. Isovolumic contraction time, measured as the interval \(S_1-A_2\) minus LVET, is shorter than “true” ICT since \(S_1\) occurs after the \(u\) point of the apexcardiogram and left ventricular pressure rise (fig. 8). Of the foregoing methods, measurement of total PEP offers several technical advantages. The measurement points are sharp and well defined in contrast to the onset of the first heart sound which is sometimes poorly defined, but which must be identified in the measurement of external ICT. A sharp \(u\) point on the apexcardiogram is not always obtainable. Furthermore, there is evidence that alteration of total PEP by acute interventions changes only the interval left ventricular pressure rise to aortic opening (“true” ICT) and that the interval \(Q\) to left ventricular pressure rise (“electromechanical coupling interval”) does not change significantly.\(^{80}\) Acute interventions have been shown in dogs\(^{81}\) and in man\(^{80}\) to cause equal changes in PEP and “true” ICT. Therefore, PEP showed a close linear correlation with “true” ICT over a wide range of observed values, when the latter was measured with catheter-tip micromanometers as the interval from the rapid

**Figure 8**

*(Left) Total PEP may be divided as follows: (1) measurement of \(QS_1\) interval and the interval from \(S_1\) to aortic pressure rise (EXT ICT); and (2) measurement of the interval from the \(Q\) wave of the ECG to \(u\) of the ACG (\(Qu\)) and the interval from the \(u\) point to aortic pressure rise. Since the \(u\) point of the ACG corresponds to the onset of rapid left ventricular pressure rise (see fig. 1), ICT measured from the ACG is referred to as “TRUE” ICT. Note that “TRUE” ICT is longer than EXT ICT since the \(u\) point of the ACG occurs before \(S_1\). (Right) Three standard techniques for indirect measurement of systolic time intervals are shown. PEP = \(QA_u - LVET\); “TRUE” ICT = \(uA_2 - LVET\); and EXT ICT = \(S_1A_2 - LVET\).*
onset of left ventricular pressure rise to the onset of aortic ejection.80

The validity of externally measured systolic time intervals has been tested by directly correlating them with indices of myocardial function. A prolonged PEP or an increase in the ratio PEP/LVET has been correlated with left ventricular asynergy as determined by left ventricular cineangiograms.82 During acute interventions, maximal rate of left ventricular pressure rise (dP/dt) changes inversely with changes in preejection period.80, 83 In patients with myocardial dysfunction, a reasonably good correlation has been noted between a low ejection fraction and prolongation of PEP or an increase in the ratio PEP/LVET.84–86 This correlation was not present, however, in experimentally produced acute myocardial infarction.87

A knowledge of their hemodynamic determinants provides a necessary basis for correct clinical usage of systolic time intervals. Changes in PEP or ICT are related to three hemodynamic variables: (1) contractility, (2) left ventricular preload, and (3) systemic arterial pressure. The relationship between these variables may be expressed in part as a right triangle in which the base represents ICT; the height represents the difference between left ventricular end-diastolic pressure and aortic opening pressure, and the slope of the hypotenuse represents the mean left ventricular dP/dt81, 88 (fig. 9). Although not apparent from figure 9, changes in preload also change the rate of isovolumic left ventricular pressure rise. Preload is therefore a very important determinant of PEP.83 If left ventricular preload and afterload are kept constant, ICT (or PEP) varies inversely with maximal left ventricular dP/dt (i.e., with contractility).83 Digitalis administration,86 thyrotoxicosis,89 and beta-adrenergic stimulation with isoproterenol91 shorten preejection period predominantly by increasing the rate of left ventricular pressure rise. Myxedema has an opposite effect.90 Preejection period changes directly, but to a lesser extent, with acute changes in systemic arterial pressure when other hemodynamic variables are constant.92, 93

Left ventricular ejection time measured from the external carotid pulse is identical to that measured from the central aorta.80, 94 Its duration is dependent on the complex interrelationships between the contractile state of the myocardium heart rate, left ventricular end-diastolic volume, and conditions of afterload.92, 93, 95 For example, an appropriately

Figure 9
Diagram of the right-triangle relationship between the hemodynamic determinants of isovolumic contraction time. If left ventricular end-diastolic pressure (LVEDP) and aortic diastolic pressure remain constant, a change in ICT reflects a change in the rate of rise of left ventricular pressure which in turn reflects an alteration in the contractile state of the myocardium. If LVEDP increases, however, an increase in the rate of left ventricular pressure rise may result from the Frank-Starling mechanism. Changes in the rate of left ventricular pressure rise are represented by changes in the slope b/a. PEP and ICT may be used interchangeably since interventions which change PEP appear to have little effect on the interval Q-LV pressure rise.
placed atrial contraction may increase left ventricular ejection time by augmenting left ventricular end-diastolic volume, thereby increasing stroke volume.\textsuperscript{80, 93} Shaver and co-workers\textsuperscript{40} showed that changes in afterload produced by an acute elevation of the mean systolic arterial pressure during methoxamine infusion significantly increased the duration of left ventricular ejection. In this study, both stroke volume and heart rate were kept constant, and a decreased left ventricular ejection rate was thought to be responsible for prolongation of left ventricular ejection. Interventions such as isoproterenol or digitalis, on the other hand, shorten ejection time primarily by increasing the contractile state of the myocardium.\textsuperscript{88, 97} With this background information and a knowledge of the specific hemodynamic changes caused by an intervention, it should be possible to predict the effect of that intervention on the systolic time intervals. Table 1 lists some observed responses of systolic time intervals to various physiologic and pharmacologic interventions.\textsuperscript{98-104}

When used clinically, systolic time intervals are corrected for heart rate and compared to normal values such as those developed by Weissler\textsuperscript{105} or Spodick and Kumar.\textsuperscript{106} Left ventricular ejection time and the Q-A\textsubscript{2} interval which vary inversely with heart rate are corrected with regression equations shown in table 2, and the result is compared to a "normal" index. The normal indices shown in table 2 are actually normal systolic time intervals extrapolated to a heart rate of zero. Expressed in another way, an abnormal left ventricular ejection-time index (LVET) or Q-A\textsubscript{2}I interval means that the observed interval deviates significantly from the normal mean regression line for heart rate.\textsuperscript{102} Preejection period is not usually corrected for heart rate since, in most clinical situations, rate has a minimal effect on its duration.

Attention has been focused primarily on two abnormalities of systolic time intervals which may result from cardiac dysfunction: (1) prolongation of PEP and (2) abbreviation of LVET. Both of these abnormalities have been found in patients with hypertensive heart disease, cardiomyopathy, and arteriosclerotic heart disease.\textsuperscript{31, 97} In some instances, it has been possible, using systolic time intervals, to distinguish between various degrees of myocardial dysfunction. For example, mean PEP and LVET were normal in patients with hypertensive heart disease when cardiac function was compensated, but PEP prolonged and LVET shortened during heart

### Table 1

**Effects of some Physiologic and Pharmacologic Interventions on Systolic Time Intervals**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>PEP</th>
<th>LVET</th>
<th>Q-S</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased heart rate</td>
<td>←−</td>
<td>↓</td>
<td>↓</td>
<td>41, 97-99</td>
</tr>
<tr>
<td>Increased stroke volume</td>
<td>↓</td>
<td>↑</td>
<td>←−</td>
<td>80, 92, 93, 95</td>
</tr>
<tr>
<td>(↑ venous return) (↑ LVEDP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upright posture</td>
<td>↑</td>
<td>↓</td>
<td>←−</td>
<td>100</td>
</tr>
<tr>
<td>(↓ venous return)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhythmic exercise (walking)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>42</td>
</tr>
<tr>
<td>Sustained handgrip (30% of max voluntary contraction)</td>
<td>←−</td>
<td>←−*</td>
<td>←−</td>
<td>101</td>
</tr>
<tr>
<td>Increased systemic arterial pressure (a-adrenergic stimulation)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>40, 91</td>
</tr>
<tr>
<td>Decreased systemic arterial pressure (a-adrenergic stimulation)</td>
<td>↓</td>
<td>↓</td>
<td>*</td>
<td>80, 102</td>
</tr>
<tr>
<td>Digitalis</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>89, 95</td>
</tr>
<tr>
<td>(\beta)-Adrenergic stimulation (isoproterenol)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>91</td>
</tr>
<tr>
<td>(\beta)-Adrenergic blockade (propranolol)</td>
<td>←−</td>
<td>←−</td>
<td>↑</td>
<td>91, 101, 103, 104</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>↓</td>
<td>↓</td>
<td>←−</td>
<td>90</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>↑</td>
<td>↓</td>
<td>←−</td>
<td>41</td>
</tr>
</tbody>
</table>

*Shows increase if corrected for heart rate.

*Circulation, Volume XLVI, December 1972*
In patients with angina pectoris, Pouget and co-workers\(^42\) reported a longer mean preejection period and shorter left ventricular ejection time than in a control group. Perry and co-workers\(^42\) found normal preejection periods and PEP/LVET in patients with coronary artery disease who had normal left ventricular cineangiograms. However, in those patients with coronary artery disease and abnormal left ventricular cineangiograms, PEP and the ratio PEP/LVET were abnormal. However, individual false-negative results (normal systolic time intervals in the presence of heart disease) occurred frequently, while other investigators found no significant difference between the mean systolic time intervals of patients with angina pectoris or myocardial infarction and normal persons.\(^{107, 108}\)

Systolic time intervals have been studied in patients with angina pectoris during both static (sustained handgrip) and rhythmic (walking or bicycle) exercise. The normal response to sustained handgrip held for 3 min at 35% of maximal voluntary contraction includes lengthening of LVETI and Q-A\(_2\), while preejection period does not change.\(^{101}\) Normal responses are also found in patients with coronary artery disease and angina pectoris.\(^{106, 110}\) Moderate bicycle exercise or walking, such as a Master's two-step test, normally causes shortening of preejection period, left ventricular ejection time, and Q-2, but no change in LVET corrected for heart rate (LVETI).\(^{42, 107}\) In patients with angina pectoris, however, such exercise was reported by Pouget and co-workers\(^42\) to cause significant increases in LVETI. Prolongation of LVETI was also noted in patients with primary myocardial disease and heart failure, but not in patients with nonanginal chest pain. Preejection period during isotonic exercise is comparable in normal persons and in patients with angina pectoris.\(^{42, 107}\)

Although systolic time intervals provide a valid and reproducible index of cardiac function in many situations, their low degree of specificity and, ironically, a high degree of sensitivity, have impaired their general usefulness. The complex hemodynamic changes which may occur during angina pectoris, myocardial infarction, exercise, or drug therapy often complicate attempts to relate changes in systolic time intervals directly to intrinsic alterations in myocardial contractility. For example, decreased myocardial contractility in a patient with angina pectoris or myocardial infarction would directly prolong PEP. However, in such a patient, left ventricular end-diastolic fiber length (preload) and intrinsic catecholamine levels may also rise, causing PEP to shorten.

Recently, in a group of critically ill cardiac patients, the ratio of arterial diastolic pressure minus pulmonary wedge pressure/PEP was found to be highly predictive of left ventricular dP/dt, systolic ejection fraction, and mortality.\(^{111}\) Therefore, the specificity and usefulness of PEP as a measure of myocardial performance might be increased if preload could be measured noninvasively.

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![Table 2](http://circ.ahajournals.org/)

<table>
<thead>
<tr>
<th>Measured interval (msec)</th>
<th>Index</th>
<th>sd of index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-S(_2) (F) + 2.0 HR</td>
<td>549</td>
<td>14</td>
</tr>
<tr>
<td>Q-S(_2) (M) + 2.1 HR</td>
<td>546</td>
<td>14</td>
</tr>
<tr>
<td>PEP (F) + 0.4 HR</td>
<td>133</td>
<td>11</td>
</tr>
<tr>
<td>PEP (M) + 0.4 HR</td>
<td>131</td>
<td>13</td>
</tr>
<tr>
<td>LVET (F) + 1.6 HR</td>
<td>418</td>
<td>10</td>
</tr>
<tr>
<td>LVET (M) + 1.7 HR</td>
<td>413</td>
<td>10</td>
</tr>
</tbody>
</table>

Abbreviations: Q-S\(_2\) = total electromechanical systole; PEP = preejection phase; LVET = left ventricular ejection time; HR = heart rate; M = male; F = female; sd = standard deviation of the systolic time-interval index.
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