Evaluation of Left-Ventricular Function in Normal Persons and Patients With Heart Disease

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After equilibration of Tc-99m albumin in the vascular compartment, left-ventricular time-activity curves were obtained by synchronization of the scintillation camera with the electrocardiogram from normal persons and patients with heart disease. These curves were divided into various intervals, and the following indices were obtained: pre-ejection period (PEP), PEP/R-R; left-ventricular ejection time (LVET), LVET/R-R; left-ventricular rapid-filling time ($LVFT_1$), $LVFT_1$/R-R; left-ventricular diastasis including atrial systole ($LVFT_2$), $LVFT_2$/R-R, PEP/LVET; ejection fraction (EF) and EF/LVET. The relative systolic time intervals derived from time-activity curves were compared with those obtained in 30 patients by carotid pulse tracing, phonocardiography and ECG. Significant correlations ($p < 0.001$) were found ($r = 0.89$ for LVET/R-R, $r = 0.77$ for PEP/LVET). In addition, the time-activity curve indices obtained from 27 patients with either essential hypertension, myocardial infarction, idiopathic cardiomyopathy or congestive heart failure were compared with indices obtained from eight normal volunteers. Patients with congestive heart failure and cardiomyopathy showed prolongation of PEP/R-R and an increased PEP/LVET. In hypertensive patients, prolongation of $LVFT_1$/R-R and shortening of $LVFT_2$/R-R were found. Ejection fraction remained normal in hypertensive patients, was slightly decreased in myocardial infarction patients, and markedly reduced in patients with congestive heart failure and cardiomyopathy. These initial results suggest that display and analysis of synchronized left-ventricular time-activity curves may be of value in the study of patients with certain types of heart disease.

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Assessment of left-ventricular function is usually based on contrast ventriculography. Ultrasonography and gamma-imaging techniques are simpler and have been proposed as possible means of "noninvasive" evaluation of ventricular function (*1–7*). We have derived systolic and diastolic time intervals, ejection fractions, and the rates of left-ventricular ejection from left-ventricular time-activity curves acquired after equilibration of intravenously injected Tc-99m albumin, by synchronizing the scintillation camera with the electrocardiogram. The resulting time-activity curves describe the changes of radioactivity within the left ventricle in relation to the electrocardiographic R-R cycle. Systolic time intervals were also obtained from 30 patients by combined carotid

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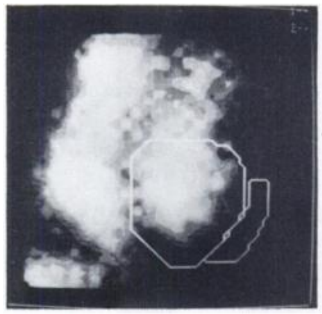

FIG. 1. Heart image in 40° LAO view with left ventricular area of interest and background area marked. Original images were in color, with area above left ventricle clearly visible as left atrium because of its green color. Based on count levels, end-systolic image is shown routinely in green, end-diastolic image in red, and these are superimposed in a final composite image.

pulse tracing (C), phonocardiography (P), and electrocardiography (E), and were compared with those derived from time-activity curves. The combined study is referred to as CPE. The indices obtained from the patients with various heart disease were then compared with the indices of eight normal volunteers to determine whether certain heart diseases were associated with characteristic changes.

METHODS

All patients received a 25 mCi i.v. injection of Tc-99m albumin while lying supine beneath a scintillation camera fitted with a high-resolution, low-energy, parallel-hole collimator. An electrocardiographic gate was used to monitor the R waves of each patient's ECG. Camera images synchronized with the ECG were obtained for 64 intervals during a cardiac cycle, with the patient lying in a 40–50° LAO position. Eight million counts were obtained in approximately 15 min.

Selection of regions of interest. The left-ventricular area of interest was selected from a color-coded image where systole was shown in green and diastole in red. Care was taken to avoid the right ventricle, left atrium, and pulmonary vasculature (Fig. 1). In an independent study we found that interobserver variability in selection of this area was approximately 5% (coefficient of variation).

In order to obtain the background (extraventricular) activity an area of interest was selected immediately lateral to the left ventricle, but not overlapping the pulmonary artery or the left ventricle. Overlapping the pulmonary artery resulted in a rise of the background activity during systole. If a part of the left ventricle was included in the background area, background activity was observed to decrease during ventricular systole. Both these conditions created errors in true background estimation, and were avoided. Curves of net count rate over the left ventricule and the background area were generated by computer. The average background activity was then subtracted from the left ventricular curve (Fig. 2).

Indices of ventricular function. The following indices were obtained from the net left-ventricular time-activity curves (Fig. 3):

1. Ejection fraction (EF):

$$\frac{\text{End-diastolic counts} - \text{End-systolic counts}}{\text{End-diastolic counts}} \times 100.$$

2. Pre-ejection period (PEP): period of electromechanical delay and isovolumic contraction.
3. Left-ventricular ejection time (LVET): period of ventricular emptying.
4. Left-ventricular rapid inflow time ($LVFT_1$): phase of rapid ventricular filling after closure of the aortic valve.
5. Left-ventricular diastasis including atrial systole ($LVFT_2$): slow phase of ventricular filling before the next systole.
6. PEP/LVET ratio.
7. EF/LVET ratio: rate of left-ventricular emptying.

When the slope of the initial plateau (PEP)

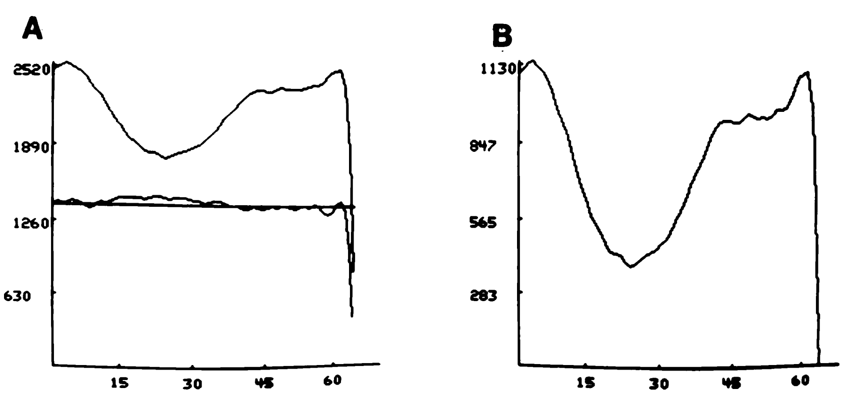

FIG. 2. Left ventricular time-activity curve with background is shown (A). (B) is the same ventricular curve with background subtracted and vertical scale expanded.

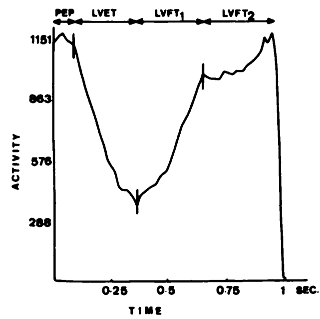

FIG. 3. Time-activity curve with systolic and diastolic intervals marked.

changed and the count rate began to fall, a cursor position was recorded and that point was designated as the beginning of LVET. Similarly when the slope went through zero at the nadir of the curve, that point was chosen as the end of LVET. This LVET period does not include protodiastole, the period when the aortic valve is still open but the ventricle has ceased ejection (*8*).

A preliminary experiment was done to evaluate the method of selecting the end of LVET. Three different lengths of LVET were chosen by selecting the end of LVET as: point A, where the down-slope suddenly changed to a horizontal position (Fig. 3); point C, where the activity started rising again; and point B, the mid-point between points A and C. These three values of LVET were correlated with the LVET obtained by carotid pulse tracing, phonocardiography, and electrocardiogram in eight normal volunteers and eight patients with various heart diseases. The correlation coefficient was found to be 0.78 for point A, 0.70 for point B, and 0.54 for point C. Point A was therefore selected as the end of LVET in this study. $LVFT_1$ was defined as starting at this point and ending at the transition point where the rapid rise suddenly slowed. From this point to the end of a cardiac cycle was defined as the $LVFT_2$ period (Fig. 3).

Reproducibility of the selection of these time intervals was determined by a study in which six observers independently derived systolic and diastolic time intervals in 20 randomly selected left-ventricular time-activity curves. The data are described under results. The heart rate was used to calculate the ventricular function indices as a fraction of the R-R interval (e.g., PEP/R-R), and it is these relative indices which are described in this paper.

Comparison with independently measured systolic time intervals. Immediately after the radionuclide studies of 30 patients, the durations of the systolic time intervals (PEP, LVET) were measured by simultaneous carotid pulse tracing, phonocardiography and electrocardiography (CPE) (*9*) employing a multichannel photographic system*. A microphone was placed over the upper part of the precordium in a position optimum for the recording of the initial high-frequency vibrations of the second heart sound. The pulsations within the carotid artery were recorded with a small plastic funnel attached by polyethylene tubing to a strain gauge. The recordings were obtained at a paper speed of 100 mm/sec. The total electromechanical systole (QS2) was measured from the onset of the QRS complex to the first high-frequency vibrations of the aortic component of the second heart sound, and the left-ventricular ejection time (LVET) was measured from the beginning of upstroke to the trough of the incisura of the carotid arterial pulse tracing. LVET was then subtracted from the total systole (QS2) to obtain the pre-ejection period (PEP). All intervals were calculated from the mean of measurements made on six to ten consecutive beats, each read to the nearest 5 msec. The heart rate was again used to express these results as relative time intervals (e.g., PEP/R-R), and these relative time intervals were compared with those obtained from ventricular time-activity curves.

Clinical comparison. Left-ventricular time-activity curves were obtained in 104 patients and eight normal volunteers. The volunteers were young males aged 22–34 (mean 26) who had normal electrocardiograms and no signs, symptoms, or history of cardiovascular disease. The patients were classified as follows:

1. Essential hypertension ($n = 10$): Patients with a longstanding (range 5–12 yr) history of hypertension, but no history of myocardial infarction or congestive heart failure. All were taking antihypertensive medication (e.g., diuretics, hydralazine, α-methyldopa). The blood pressures (mean $\pm$ SD) of these patients at the time of the current study were: Systolic $= 175 \pm 37$; diastolic $= 104 \pm 13$.
2. Recent myocardial infarction ($n = 4$): Patients without hypertension or congestive heart failure who had a documented (clinical, ECG, enzymes) myocardial infarction, not more than 4 wk before the blood-pool study.
3. Congestive heart failure ($n = 10$): Patients whose primary illness was hypertension, or myocardial infarction (not within 4 wk) or both together with clinical and radiographic evidence of congestive heart failure. These patients were being treated with digitalis and diuretics.
4. Idiopathic cardiomyopathy ($n = 3$): Patients diagnosed as having primary cardiomyopathy, with no evidence of hypertension or myocardial

infarction. These patients showed biventricular dilatation, had no perfusion defects on Tl-201 studies and had diffuse myocardial hypokinesis. They were also being treated with digitalis and diuretics.

5. Others (n = 77): Patients with combinations of the problems cited above.

The clinical comparisons in this paper will be concerned with patients in groups 1–4 only (age range 38–84, mean age 58, 60% males) and the normal volunteers (total N = 35). The data from patients with multiple cardiac problems will not be reported because the complexity of their disease prevented clear-cut analysis. The relative indices obtained from the curves of these patients were compared to the indices derived from the curves of normal volunteers. The mean heart rate of the normal volunteers (59 ± 12/min) was similar to that of the patients with hypertension (68 ± 14) and recent myocardial infarction (72 ± 11), and was slightly slower than that of the patients with congestive failure (79 ± 14) and cardiomyopathy (87 ± 13). Statistical analyses were performed using the t-test.

RESULTS

Reproducibility among six observers in selecting systolic and diastolic time intervals was good, with a coefficient of variation of 10.7% for PEP, 6.3% for LVET, 20.0% for $LVFT_1$ and 5.6% for $LVFT_2$. The mean indices (±1 s.d.) derived from the curves of eight normal volunteers were: PEP/R-R 0.10 ± 0.02, LVET/R-R 0.26 ± 0.04, $LVFT_1$/R-R 0.25 ± 0.03, $LVFT_2$/R-R 0.39 ± 0.07, PEP/LVET 0.38 ± 0.08, EF 0.56 ± 0.08, EF/LVET 2.11 ± 0.40. A close relationship was found in 30 patients between systolic time intervals obtained by CPE and those derived from the time-activity curves. The correlation coefficient was 0.78 for PEP/R-R, 0.89 for LVET/R-R, and 0.77 for PEP/LVET. The regression lines for the LVET/R-R and the PEP/LVET ratios are shown in Fig. 4. The correlation was also good between PEP/LVET and ejection fraction in 27 patients with various heart diseases and eight normal volunteers (Fig. 5). The PEP/LVET ratio increases as the ejection fraction falls ($r = 0.77$, $p < 0.001$).

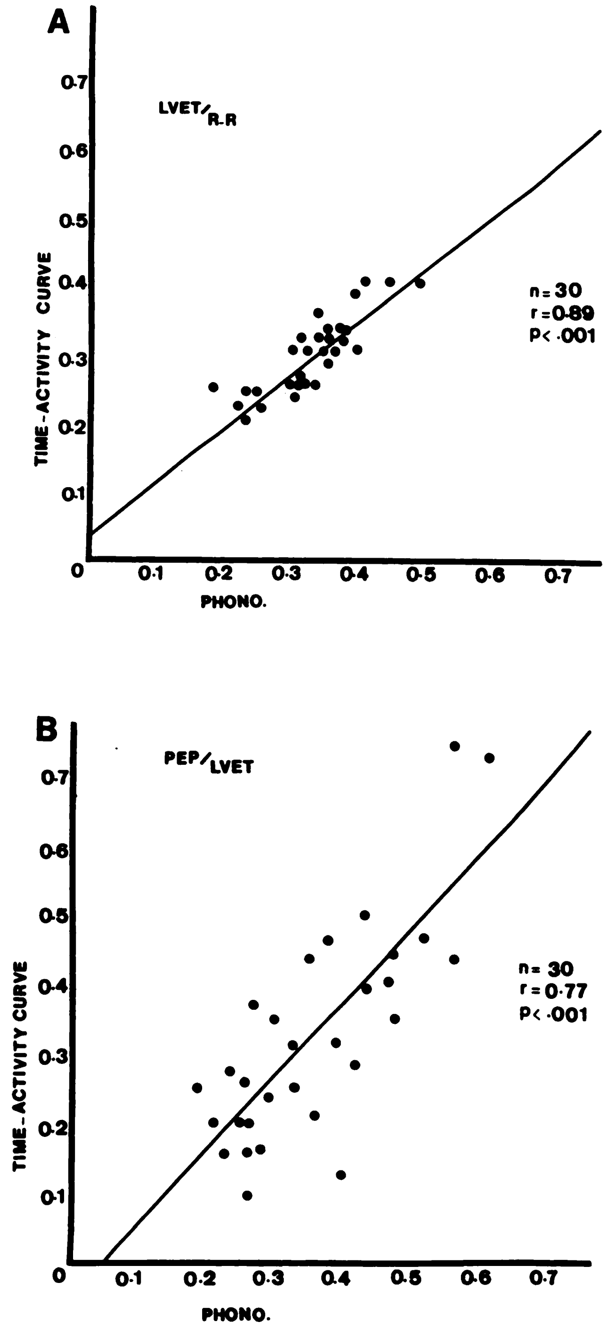

FIG. 4. Correlation between LVET/R-R as derived from time-activity curves and CPE is shown (A). (B) shows correlation between PEP/LVET derived by same procedures.

The indices of left ventricular function obtained in patients are compared with those of the normal volunteers in Fig. 6. In patients with hypertension there was prolongation of $LVFT_1$/R-R and shortening of $LVFT_2$/R-R, whereas PEP/R-R and PEP/LVET remained normal (Fig. 6a). Patients with congestive heart failure showed prolongation of PEP/R-R and an increase in the PEP/LVET ratio (Fig. 6b). Patients with myocardial infarction showed prolongation of $LVFT_1$/R-R (Fig. 6c). Primary cardiomyopathy produced prolongation of PEP/R-R, shortening of $LVFT_2$/R-R and an increased PEP/LVET (Fig. 6d).

Ejection fraction was normal in hypertensive patients, slightly diminished in patients with myocardial infarction, and markedly decreased in patients with cardiomyopathy or congestive heart failure. The

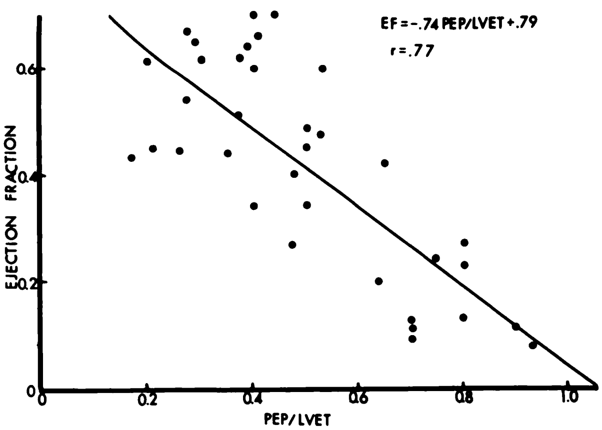

FIG. 5. Correlation between PEP/LVET and ejection fraction obtained from left ventricular time-activity curves in 27 patients and 8 normal volunteers.

rate of ejection of blood from the left ventricle (EF/LVET) was diminished in all patients except those with hypertension. In the normal volunteers and patients with heart disease the total duration of electromechanical systole per R-R interval (0.39 ± 0.07) remained relatively constant even when the PEP/LVET ratio changed significantly.

Figure 7 illustrates a normal time-activity curve (Fig. 7a) and curves in patients with various heart diseases. The time-activity curve from a hypertensive patient (Fig. 7b) shows relative prolongation of the fast-filling time ($LVFT_1$) and shortening of the diastasis plus atrial systole ($LVFT_2$). The curves of patients with congestive heart failure (Fig. 7c) and cardiomyopathy (Fig. 7d) showed relative prolongation of PEP and an increased PEP/LVET ratio. An application of these curves is demonstrated by pre- and postoperative studies from a patient with aortic stenosis (Fig. 8). The LVET/R-R ratio was elevated preoperatively (0.40), but decreased after surgery (0.27). Ejection fraction increased from 39% to 69% and the rate of left-ventricular ejection more than doubled postoperatively (3.29 against 1.24 preoperatively).

DISCUSSION

Synchronized blood-pool imaging of the heart with Tc-99m albumin provides information about

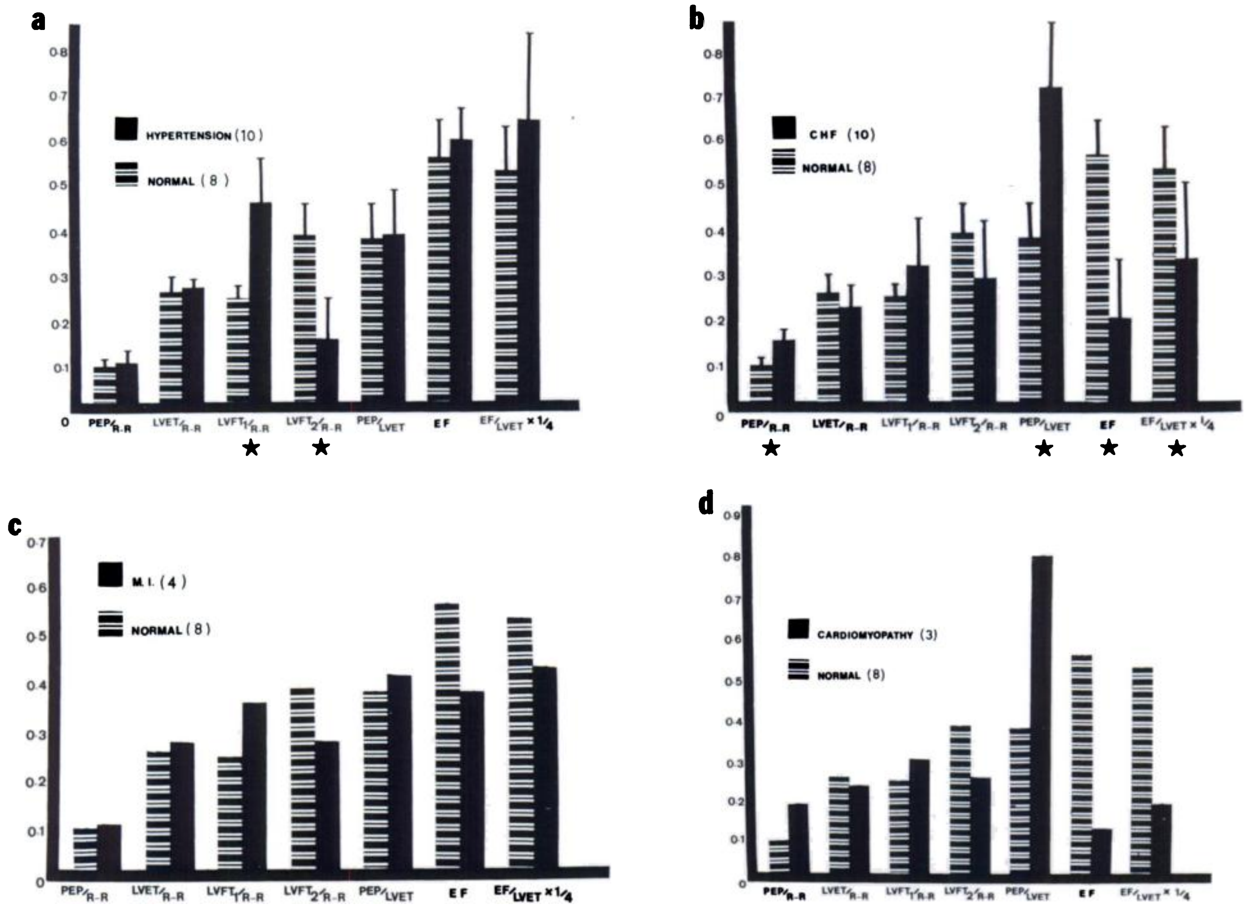

FIG. 6. Comparison of ventricular function indices in normal volunteers and in patients with various heart diseases. Star appears beneath data columns where function indices of normals and patients were significantly different ($p < 0.05$). Statistical analysis is not shown in (C) and (D) due to small sample size. MI = myocardial infarction; CHF = congestive heart failure.

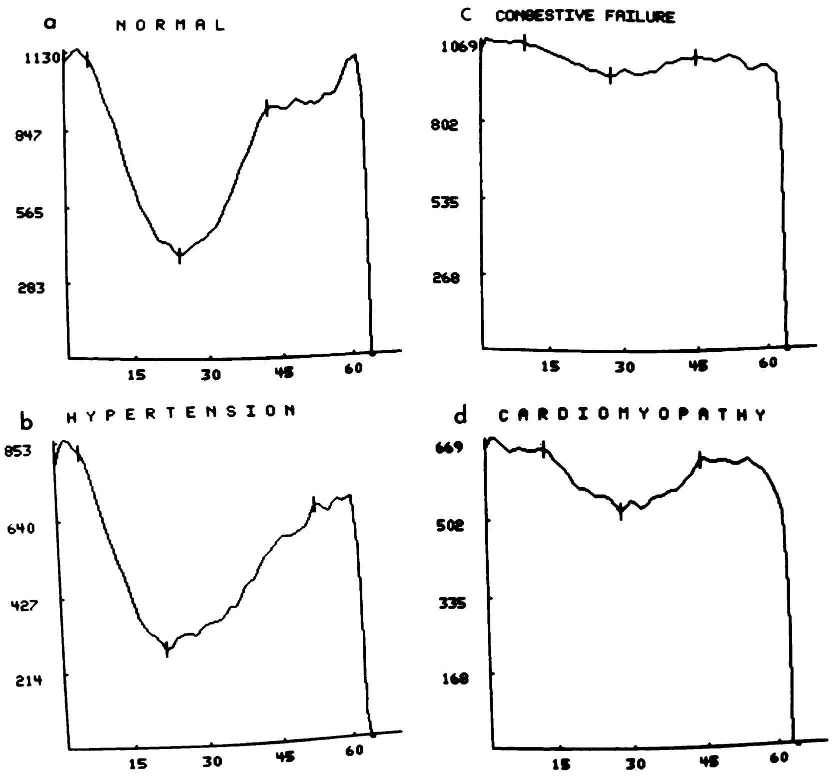

FIG. 7. Representative ventricular time-activity curves are shown for a normal control (a), and patients with hypertension (b), congestive heart failure (c) and cardiomyopathy (d).

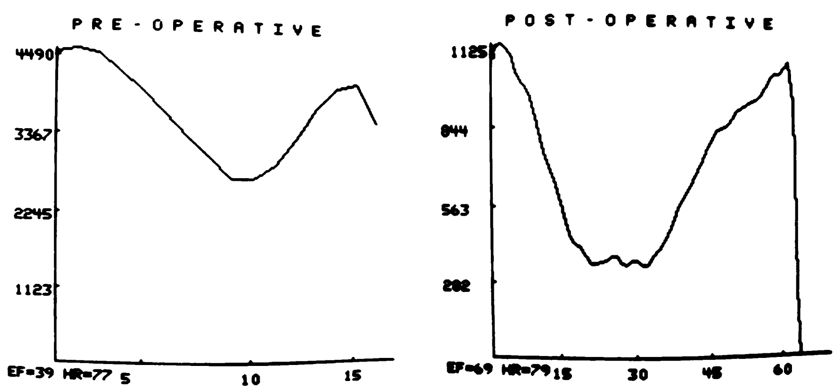

FIG. 8. Pre- and postoperative curves from patient with aortic stenosis.

both regional and overall ventricular function. The current study demonstrates that systolic and diastolic time intervals, ejection fraction, and the rate of ejection of blood from left ventricle can be obtained from left-ventricular time-activity curves. A characteristic shape for this curve was found in eight normal volunteers and shapes of the curves were altered (as were the derived ventricular indices) in patients with various types of heart disease. There was no single parameter that determined characteristics of the curve for a specific disease, but multiple parameters considered in combination suggested certain diseases—e.g., hypertensive heart disease. Drugs alone (particularly those with inotropic effects) may alter these ventricular function indices. Several patients reported in this study were being treated with digitalis. However, these patients were in congestive heart failure at the time of their study and the alterations in their function curves are felt to represent primarily those of ventricular failure. In this preliminary review of patients, left-ventricular failure, regardless of its cause, resulted in an elevation of the PEP/LVET ratio, a decreased rate of ejection, and a diminished ejection fraction.

The relative ventricular time intervals obtained from time-activity curves correlate closely with those obtained by CPE, but they are not identical. The LVET derived from time-activity curves in this study specifically denotes the period of left-ventricular ejection, without including the short, isovolumic phase (protodiastole) that precedes closure of the aortic valve. The PEP is also slightly shorter than that determined by CPE, since it is measured from the upstroke of the R wave, not the downstroke of the Q wave. Since both the PEP and LVET obtained from time-activity curves are shortened (compared with CPE measurements), the PEP-LVET ratio is relatively unchanged. An advantage of the time-activity curve method over CPE is its ability to provide diastolic indices of left-ventricular function, ejection fraction, and the rate of ventricular ejection, in addition to systolic time intervals.

Several technical factors require emphasis. The background area must be selected with care. A background area overlying portions of the left ventricle or large pulmonary arteries gives erroneous values. Extra-systoles and other types of arrhythmia produce variable R-R intervals and cause distortion of the time-activity curves, particularly the diastolic component. The ejection fraction in such patients tends to be spuriously low.

The correlation between ejection fraction and PEP/LVET derived from time-activity curves ($r = 0.77$) is in close agreement with that obtained by Weissler and others (*10*) who compared CPE with contrast ventriculography. However, the PEP-LVET ratio and ejection fraction cannot be used as synonymous terms, since we have observed appreciable abnormalities in PEP/LVET in some patients without alterations in ejection fraction. For example, patients with hypothyroidism may have a prolonged PEP and elevated PEP/LVET ratio without a diminished ejection fraction. In addition, patients with arterial hypertension (without congestive heart failure) had normal ejection fractions, whereas their filling time was significantly prolonged and diastasis shortened compared with the normal. It seems possible that in certain types of heart disease, indices other than ejection fraction may be more sensitive in early detection of ventricular dysfunction. Further studies are needed to determine more precisely the relative utility of radionuclide determination of ejection fraction and other ventricular function indices in assessment of cardiac dysfunction.

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FOOTNOTE

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