Evaluation of Left Ventricular Residual Function Using Postextrasystolic Potentiation

Relation between Systolic Time Intervals and Angiographic Study

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SUMMARY

The effects of postextrasystolic potentiation (PESP) on systolic time intervals and left ventricular wall motion were studied during diagnostic cardiac catheterization in 20 patients (4 normal individuals, 11 patients with coronary artery disease and 5 patients with idiopathic dilated cardiomyopathy). Postextrasystolic changes in the aortic pressure and systolic time intervals were measured from the electrocardiogram and aortic pressure tracing. After a micromanometer-tipped catheter was positioned in the ascending aorta just above the aortic valve, a single ventricular premature beat was introduced using an R-wave coupled stimulator. PESP was then studied during left ventriculography which was undertaken simultaneously in the right anterior oblique 30° and left anterior oblique 60° positions. Following two or three normal sinus beats, a right ventricular extrastimulus was delivered again under the same stimulating condition. PESP in all patients caused a decrease in the ratio of the preejection period to the left ventricular ejection time (PEP/ET). The average percent decrease was 21% (from 0.429±0.162 to 0.339±0.102, p<0.001). The left ventricular ejection fraction (EF) increased in all patients with PESP from 0.52±0.20 to 0.61±0.17 (p<0.001). The postextrasystolic changes in the PEP/ET ratio and EF were greater in patients with low cardiac performance. There was a good correlation (r = -0.85, p<0.001) between the changes in the EF and those in PEP/ET in PESP. Thus, it is possible to determine left ventricular...
residual function (the postextrasystolic change in the global EF) using the postextrasystolic change in PEP/ET in patients with coronary artery disease and dilated cardiomyopathy.

**Additional Indexing Words:**
Pre-ejection period  Left ventricular ejection time  Left ventricular ejection fraction  Ventricular premature beat  R-wave coupled stimulator  Myocardial viability  Coronary artery disease  Dilated cardiomyopathy

**POSTEXTRASYSTOLIC** potentiation (PESP), the phenomenon of augmented myocardial contractility immediately following a premature contraction, has been shown to be an excellent predictor of myocardial viability and residual function in ischemic heart disease, mitral stenosis and idiopathic dilated cardiomyopathy.

Systolic time intervals, which can be obtained noninvasively through the use of phonocardiography with pulses, have been studied extensively, and measurement of these intervals allows detection of beat-to-beat changes of left ventricular performance. The pre-ejection period/left ventricular ejection time (PEP/ET) ratio represents the most widely studied of these measurements and is considered to be the most clinically useful index. Ranganathan and associates described the effects of PESP on systolic time intervals. Stack and associates reported a good correlation of PEP/ET with the angiographic left ventricular ejection fraction (EF). However, the relation between postextrasystolic changes in systolic time intervals and angiographic changes of the EF in PESP remains to be clarified. Thus, we studied this relationship during diagnostic cardiac catheterization.

**MATERIALS AND METHODS**

**Study group:**

Twenty patients undergoing diagnostic cardiac catheterization were studied. Seventeen of the patients were men and 3 were women. The average age was 51 years (27 to 66 years). The study group consisted of 4 patients who were referred for diagnosis of chest pain or discomfort and were found to have normal coronary arterial and left ventriculographic studies at cardiac catheterization, 4 patients with significant coronary artery disease but no evidence of previous myocardial infarction, 7 with old myocardial infarction, and 5 with idiopathic dilated cardiomyopathy. All had normal sinus rhythm, and none had angiographic evidence of mitral regurgitation.

Cardiac catheterization was carried out in the fasting state and con-
sisted of right and left heart catheterization, left ventricular angiograms and selective coronary arteriograms. Right heart catheterization was performed using a 7F Swan-Ganz thermodilution catheter, and cardiac output was measured by the thermodilution method (model 9520 cardiac computer, Edwards). Following this, a micromanometer-tipped catheter (PC361 or 471, Millar Inst.) was positioned in the ascending aorta just above the aortic valve using the retrograde femoral arterial approach. The micromanometer was calibrated electronically before insertion. The Swan-Ganz catheter was then removed and a bipolar pacing catheter was positioned in the apex of the right ventricle for ventricular stimulation.

Pressure and systolic time interval measurements:

After baseline recordings were obtained, a single ventricular premature contraction was introduced using a window-type R-wave coupled stimulator, which we developed,8) and a right ventricular bipolar electrode catheter. The stimulus length was twice threshold, and the coupling ratio (interval between the premature contraction and the preceding sinus beat, divided by the control RR interval) was about 0.5 in every case. Aortic pressure and systolic time intervals were measured from the electrocardiogram and aortic pressure tracing. These tracings were done with the use of a multichannel direct-writing recorder (Mingograf 82, Siemens-Elema Inst.) at a paper speed of 100 mm/sec. The preejection period (PEP) was measured as the interval from the start of the Q wave to the beginning of the upstroke of the aortic pulse. The left ventricular ejection time (LVET) was measured as the interval from the beginning of the upstroke of the aortic pulse to the dicrotic notch. For each interval and aortic pressure, we took the mean of the measurements of three extrasystolic sequences. The systolic aortic pressure and the PEP/ET ratio, measured in the control beat, were subtracted from respective measurements in the postextrasystolic beat to provide the respective changes in the systolic aortic pressure (Δsystolic AoP) and the PEP/ET ratio (Δ[PEP/ET]). The micromanometer-tipped catheter was then introduced into the left ventricle. The response of the left ventricular pressure and the left ventricular dp/dt (the rate of rise of intraventricular pressure), which was derived electronically by means of a differentiator, were measured during the same extrastimulation sequence.

Angiographic study:

After recordings of high-fidelity pressures, a 7F pigtail catheter was positioned in the left ventricle. Left ventricular cineangiograms were obtained simultaneously in the right anterior oblique 30° and left anterior oblique 60° positions by injecting 30 to 35 ml of 76% amidotrizoate sodium meglumine at a rate of 10 to 12 ml/sec using a power injector (Mark 4, Medrad). Cine-
angiograms were taken with a 35-mm camera at 50 frames/sec, utilizing a 10-inch image intensifier system (Angioskop C, Siemens). Following two or three normal sinus beats, a single right ventricular extrastimulus was delivered through the pacing catheter using an R-wave coupled stimulator under the same conditions as above.

End-diastolic and end-systolic left ventricular silhouettes were digitized from a 35-mm Vanguard projector using a sonic pen interfaced with a mini-computer system (PDP 11/34, DEC). End-diastolic and end-systolic volumes (EDV, ESV) were obtained using a grid-calibration technique and the modified Simpson’s integration method.\(^9\) The stroke volume (SV) was calculated as EDV minus ESV and LVEF as SV/EDV. Data comparison was done between the sinus beat preceding the ventricular premature contraction (the control beat) and the PESP beat. After left ventriculography, selective coronary cinearteriography was performed in several projections by the Judkins technique with manual injection of 76% amidotrizoate sodium meglumine using a 7-inch image intensifier system.

All values are given as the mean±standard deviation. Statistical analysis was performed using Student’s t-test for paired values, and the least square method for linear regression analysis was used to correlate \(\Delta(PEP/ET)\) with \(\Delta EF\) (the change in the EF in PESP).

**RESULTS**

The heart rate was within the physiological range in all patients (73±

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<th>Table I. The Effects of Postextrasystolic Potentiation on the Aortic Pressure, LV dp/dt, Systolic Time Intervals and LV Volume</th>
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AoP=aortic pressure; LV=left ventricular; PEP=preejection period; LVET=left ventricular ejection time; LVEDV=left ventricular end-diastolic volume; LVESV=left ventricular end-systolic volume; SV=stroke volume; EF=ejection fraction; p=level of statistical significance; NS=not significant.
Fig. 1. The effects of postextrasystolic potentiation on aortic pressure. In Case 1, the aortic pressure following the premature beat had a lower peak systolic pressure as compared to the control beat. Case 2 is a patient with idiopathic dilated cardiomyopathy. The peak systolic aortic pressure increased with PESP as compared to the control. PESP = postextrasystolic potentiation.

12 beats/min), the cardiac index was $3.3 \pm 0.7 \text{l/min/m}^2$, the systolic aortic pressure $140 \pm 20 \text{mmHg}$ and the diastolic aortic pressure $83 \pm 12 \text{mmHg}$. The findings concerning the effects of PESP on the aortic pressure, left ventricular (LV) positive dp/dt, systolic time intervals, LV volume and LVEF are summarized in Table I.

Postextrasystolic pressure response:

The diastolic aortic pressure was decreased significantly with PESP, from $83 \pm 12$ to $68 \pm 11 \text{mmHg}$ ($p<0.001$), in all patients. The systolic aortic pressure also declined from $140 \pm 20$ to $133 \pm 19 \text{mmHg}$ as a whole. However, the postextrasystolic response of the systolic aortic pressure was variable. There was an increase in the systolic aortic pressure of the PESP beat in 5 patients and a decrease in 15. Fig. 1 shows 2 examples of the effects of PESP on the aortic pressure. Case 1 (upper panel) is a 58-year-old man who was admitted to our hospital for evaluation of chest pain and found to have normal coronary arteriograms and normal LV wall motion. The aortic pressure
following the premature beat had a lower peak systolic pressure as compared to the control beat; then, the pressure gradually returned to the control level. Case 2 (lower panel) is a 27-year-old woman with idiopathic dilated cardiomyopathy. Cardiac catheterization revealed an increased end-diastolic LV volume index of 143 ml/m², a depressed LVEF of 0.18 and normal coronary arteriograms. The diastolic aortic pressure following the extrasystolic beat was lower than the control level. However, the peak postextrasystolic aortic pressure increased as compared to the control beat, and subsequent beats showed pressure alternation. The LV dp/dt, an index of LV contractility, was increased with PESP in all cases, and the postextrasystolic change was from 1560±366 to 1934±359 mmHg/sec (p<0.001).
Fig. 4 (left). The effects of postextrasystolic potentiation on PEP/ET. The PEP/ET ratio decreased with PESP in all patients, and the change was greater in patients with an abnormally increased PEP/ET ratio. PEP/ET = pre-ejection period/left ventricular ejection time.

Fig. 5 (right). The effects of postextrasystolic potentiation on the LVEF. The LVEF increased in all patients. LVEF = left ventricular ejection fraction; LVG = left ventriculogram.

Postextrasystolic changes in systolic time intervals:
The change in the PEP in the postextrasystolic beat is shown in Table I and Fig. 2. In all patients, there was a shortening of the PEP of the first postextrasystolic beat, and this shortening was greater in patients with a prolonged PEP (Fig. 2). The average percent shortening of PEP was 18% (0.117 ± 0.028 to 0.096 ± 0.021 sec, p < 0.001).

Following an extrasystole, the LVET was unchanged from 0.286 ± 0.038 to 0.290 ± 0.028 sec. However, the prolongation of the LVET was observed in patients with a shortened LVET (Fig. 3).

The PEP/ET ratio decreased significantly with PESP in all patients.
The average percent change was 21% (0.429±0.162 to 0.339±0.102, p<0.001). The postextrasystolic change in the PEP/ET ratio was greater in patients with an abnormally increased PEP/ET ratio (Fig. 4).

*Change in LV volumes and ejection fraction:*

Postextrasystolic changes in the EDV, ESV, SV and EF are shown in Table I. There was an increase in the EDV (150±62 to 159±70 ml, p<0.05) and a decrease in the ESV (88±65 to 76±59 ml, p<0.01), resulting in an increase in the SV (63±17 to 83±26 ml, p<0.005) and EF (0.52±0.20 to 0.61±0.17, p<0.001, Fig. 5) of the postextrasystolic beat.

*PEP/ET versus change in the systolic aortic pressure:*

The correlation of PEP/ET and the postextrasystolic change in the peak systolic aortic pressure (Δsystolic AoP) is shown in Fig. 6. The correlation coefficient was 0.85 (p<0.001), demonstrating a good correlation between the PEP/ET ratio, which provides a useful index of LV performance, and the change in the systolic aortic pressure in response to the postextrasystolic potentiation. In other words, the peak systolic aortic pressure was increased.
Fig. 7. The relation between the change in the PEP/ET ratio and the change in the EF. The solid line is the regression line between the PEP/ET ratio and EF in our laboratory.

\[ \Delta \left( \frac{\text{PEP}}{\text{ET}} \right) \text{ vs. } \Delta \text{EF} \]

Fig. 8. The relation between a decrease in the PEP/ET ratio and an increase in the angiographic LVEF in PESP. The solid line is the regression line. \( \Delta (\text{PEP/ET}) \) = the change in pre-ejection period/left ventricular ejection time with PESP; \( \Delta \text{EF} \) = the change in the LVEF in PESP.
with PESP in patients with low cardiac performance.

Relation of the change in PEP/ET to the change in the LVEF:

Fig. 7 shows the relationship between the change in the PEP/ET ratio and the change in the angiographic EF. In our previous study, there was a significant linear negative correlation between measurements of the EF and the PEP/ET ratio in patients with ischemic heart disease. The long solid line in Fig. 7 is the regression line for our laboratory. The change in PEP/ET and the EF from a sinus beat (open circles) to a postpremature beat (closed circles) was located along this regression line in almost all patients. This postextrasystolic change was greater in patients with low cardiac performance. Fig. 8 shows the relation between the decrease in the PEP/ET ratio and the increase in the angiographic EF in PESP. There was a highly significant linear correlation \( r = -0.85, p < 0.001 \) between \( \Delta(\text{PEP/ET}) \) and \( \Delta\text{EF} \), and the regression line was \( Y = -0.91X + 0.01 \).

DISCUSSION

The augmentation of myocardial contractility during the beat immediately following a premature contraction (postextrasystolic potentiation) has become a well recognized phenomenon since it was first described by Langendorff. In 1964, Cranefield reported the treatment of acute cardiac failure by maintained PESP. However, paired electrical stimulation gave rise to high myocardial oxygen consumption, and the interest in PESP declined from a clinical point of view. In 1974, Dyke and associates demonstrated that, in patients with coronary artery disease, PESP could be a safe, effective method of detecting residual contractile function in the myocardium. Since that report, PESP has been shown to be a useful predictor of viability in the ischemic heart muscle, residual myocardial function in mitral stenosis and idiopathic dilated cardiomyopathy, and morbidity and mortality after coronary bypass surgery. In 1981, Azancot and associates stated that PESP might be useful in acute transmural infarction to discriminate potentially reversible ischemic from definitely jeopardized areas.

The precise fundamental mechanism of PESP is still unknown. It is suggested that the augmented contractility of PESP may be primarily due to the increased availability of intracellular calcium at the contractile sites. Other hemodynamic factors associated with PESP which may contribute to enhanced myocardial contractility include increased preload (increased LV filling) and decreased afterload (decreased systemic resistance). These two extrinsic factors are considered as having a contributory rather than a major role in PESP. More recently, Geschwind and associates suggested
the role of sympathetic nervous system activation in the enhancement of contractility during PESP.

Effects of PESP on LV dp/dt and aortic pressure:

In all our patients, there was an increase in LV positive dp/dt, reflecting the increased contractility accompanying PESP. This finding was similar to those of other investigators. Beck and associates demonstrated that the postextrasystolic pressure response in the normal left ventricle was a decline or no change in peak systolic pressure, whereas in the failed left ventricle, the severely volume-overloaded left ventricle and the obstructed left ventricle, the pressure response was usually a rise. Hamby and associates reported on a postextrasystolic aortic pressure pulse response in coronary artery disease and demonstrated that, in patients who had an increased systolic pressure in PESP, the cardiac output, SV and EF were significantly less and the LVEDV was significantly higher, as compared to patients who had a lower or equal systolic pressure in PESP. In our study, the peak systolic aortic pressure was also increased with PESP in patients with low cardiac performance. Also, there was a good correlation (r=0.85, p<0.001) between the PEP/ET ratio and the change in the systolic aortic pressure (Δsystolic AoP). This observation demonstrated that a higher peak systolic aortic pressure response following a premature beat should be considered as the state of an abnormal LV performance.

Effects of PESP on systolic time intervals:

Following a premature beat, there was significant shortening of the PEP in all patients. The PEP is the period from the beginning of the QRS complex to the aortic pulse upstroke and is a composite of the isovolumetric contraction period plus the electromechanical interval. Increased LV preload and increased myocardial contractility are important determinants of the shortened PEP. There was a slight increase in LVEDV and a significant increase in peak positive LV dp/dt, so the shortening of the PEP is considered to reflect the increased contractility accompanying potentiation.

There was no change in the LVET in the postextrasystolic beat. Following a postectopic beat, an increase in the velocity of ejection will tend to shorten the ejection time, whereas an increase in the SV will tend to lengthen it. The net effect on the LVET will depend on which factor dominates. The LVET was prolonged with PESP in our patients with low cardiac LV performance (Fig. 3). In these patients, the increase in the stroke volume may overcome the effect of the increased rate of ejection. This result is in agreement with the previously noted observation that the prolongation in LVET occurred with PESP in patients with LV failure.

The PEP/ET ratio is considered to be an adequate measure of LV
performance in patients with diffuse cardiomyopathy and coronary artery disease. In all our patients, the PEP/ET ratio decreased significantly with PESP (Fig. 4). This change in PEP/ET was mainly due to the shortening in the PEP, because the LVET remained unchanged with PESP.

Effects of PESP on LV volumes:
The changes in LV volumes and EF with PESP are shown in Table I. The immediate effects of contrast medium injection on the LV volume, SV and EF were evaluated by Vine and associates. They demonstrated that the injection of moderate amounts of contrast medium (0.6-0.8 ml/kg) at rates of 20-25 ml/sec did not cause significant changes in the LV volume or EF through the sixth postinjection beat. We obtained left ventriculograms by injecting 30-35 ml of contrast medium at rates of 10-12 ml/sec, so it is reasonable to analyze LV cineangiograms during PESP. There was a slight increase in the EDV with PESP in our patients. Several investigators have demonstrated that the EDV was augmented after extrasystolic beats, and this increased preload contributes to the enhanced performance (Starling's law). Hamby and associates studied the response of the left ventricle to PESP in 62 patients with coronary artery disease and demonstrated that 51 of them had an increase in the EDV of the first postextrasystolic beat, but there was no such change in the remaining 11. Sung and associates studied the relationship between PESP and the EDV in 26 normal subjects and concluded that the former was independent of the latter and that the Frank-Starling mechanism played no major role in normal human hearts. The reason for these differences is unknown, but may be explained by a difference in responsiveness to PESP by the diseased left ventricle. The amount of decrease in PEP/ET and increase in the EF with PESP was greater in our patients with severe ventricular dysfunction, and this finding is in agreement with previously noted observations. The postextrasystolic changes in the ESV, SV and EF were significant, and this result is consistent with those of other investigators.

The PEP/ET ratio versus the EF:
The PEP/ET ratio is considered to be a clinically useful index for prediction of cardiac function, and there is a good correlation of PEP/ET with the cardiac output, SV and EF in patients with coronary artery disease and diffuse cardiomyopathy. However, other investigators have pointed out that the correlation may be poorer in ischemic heart disease than in diffuse myocardial disease because of regional wall motion abnormalities. Although some disagreement exists, most investigators believe that the PEP/ET ratio is reliably associated with internal events. It is considered that the change in the PEP/ET ratio has clinical value in the evaluation of the
doxorubicin cardiotoxicity in neoplastic diseases\textsuperscript{28, 29} and vasodilator or diuretic therapy in congestive heart failure.\textsuperscript{30, 31} In this study, the correlation coefficient for $\Delta$(PEP/ET) vs $\Delta$EF was $-0.85$ ($p<0.001$). Therefore, $\Delta$(PEP/ET) provides a useful means of evaluating $\Delta$EF during PESP. Thus, the postextrasystolic change in PEP/ET is considered to be a clue in estimating LV residual function in patients with ischemic heart disease and dilated cardiomyopathy.

\textit{Clinical application:}

Evaluation of the change in the global EF induced by PESP ($\Delta$EF) in patients with a depressed EF is helpful in identifying those patients with the greatest contractile reserve and better prognosis with either medical or surgical therapy.\textsuperscript{14} In our study, there was a good correlation between $\Delta$EF and $\Delta$(PEP/ET) in PESP, so it is possible to determine the LV residual function ($\Delta$EF) using the systolic time interval ($\Delta$(PEP/ET)). In patients with spontaneous premature beats, the use of systolic time intervals makes it possible to detect the LV residual function. In addition to an invasive method, an external mechanical stimulating method,\textsuperscript{23} esophageal pacing\textsuperscript{22} and an external electrical stimulating method\textsuperscript{34} can be used noninvasively to produce premature beats. Furthermore, noninvasive evaluation of PESP may be made using radionuclide ventriculography\textsuperscript{35} and two-dimensional echocardiography.\textsuperscript{36, 37} The measurement of systolic time intervals is a safe, reliable and easily applicable method in almost all patients, and the postextrasystolic change in PEP/ET is a useful index for evaluating the postextrasystolic change in the global EF. Thus, it may be possible to assess LV residual function noninvasively by a combination of the noninvasive stimulating method and an echophonocardiographic study at the bedside.

\textbf{References}


