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The Cardiac Pre-ejection Period:

A Correlate of Peak Ascending Aortic Blood-flow Acceleration

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The relationship between peak ascending aortic blood-flow acceleration and the cardiac pre-ejection period (PEP) was studied in five chronically prepared dogs. Acceleration was measured as the first derivative of the signal from a flow probe placed around the aortic root. PEP was derived indirectly by subtracting left ventricular ejection time (obtained from a central arterial pressure signal) from the total active electromechanical time (the Q-S_2 interval measured from the ECG and heart sounds). Resulting values of PEP were inverted and squared so that they shared a common time unit with acceleration-time^{-2}. Comparison of $1/PEP^2$ and peak acceleration produced correlation coefficients from 0.74 to 0.96. A linear relationship between these two measurements was maintained over a sixfold change in the inotropic state of the heart. The quotient $1/PEP^2$ appears to be an easily obtainable, potentially noninvasive expression of the myocardial contractile state. (Key words: Patient monitoring; Inotropy; Pre-ejection period; Blood flow acceleration.)

IN RECENT YEARS several promising indices for evaluating myocardial function have been proposed. Among these are the initial ventricular impuse,[1] the maximum positive slope of the left ventricular pressure curve and its combination with isometric pressures,[2] the isometric time–tension index,[3] and blood-flow acceleration.[4] All of these measurements involve invasive techniques potentially hazardous to patients. The purpose of this study was to investigate the relationship between peak ascending aortic blood-flow acceleration and the cardiac pre-ejection period, an interval that can be obtained indirectly by noninvasive means.[5]

Methods

Five mongrel dogs with chronically implanted, pulsed, ultrasonic ascending aortic-flow probes were studied. Indwelling polyvinyl catheters in the aortic arch and a central vein were used for pressure measurements and sampling. All wires and catheters were brought out through the dorsum of the neck. Experiments were conducted at least ten days after the final surgical procedures, when the dogs appeared fully recovered from the implantation operation and had returned to normal activity. No clinically observable infections occurred. Anesthesia was induced with methohexital, 12.5 mg/kg. Pulmonary ventilation was controlled at approximately 1½ times the normal minute volume through an endotracheal tube with a mixture of nitrous oxide, 70 per cent, and oxygen, 30 per cent, with supplemental graded doses of halothane ranging from 0.3 to 3.0 per cent. In every instance, a steady state of anesthesia was demonstrated by equilibrium between end-tidal and inspired gas concentrations. A constant infusion of succinylcholine abolished electromyographic interference. The electrocardiogram was a standard lead 1. Pressures were measured by Statham P-23 Db transducers. Heart sounds were recorded from a Biocom 1010B microphone placed on the chest wall or with an AEL model 204 esophageal microphone. Signals from the electrocardiogram

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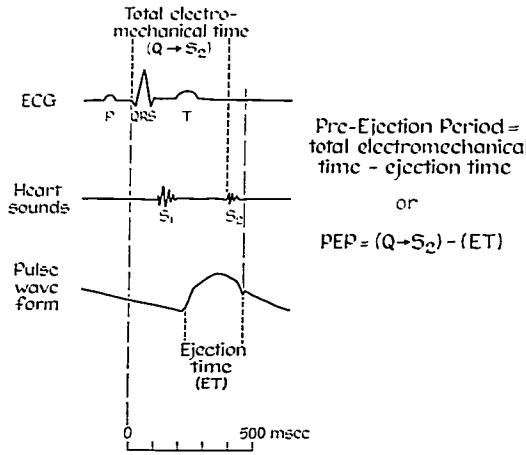

FIG. 1. The method of indirect calculation of the cardiac pre-ejection period is illustrated. The pulse waveform may be recorded transcutaneously from various peripheral arterial sites.

and phonocardiogram, aortic pressure (pulse waveform), and flow-probe signals were recorded with a Beckman model R Dynograph and transferred simultaneously to an Ampex FR-1300 magnetic FM recorder. Data used in analysis were played from tape onto a Clevite-Brush Mark 200 Rectilinear Recorder at 100 mm/sec.

Dye-dilution cardiac output determinations were made using indocyanine green during various stable states of myocardial excitation or depression, and the actual cardiac output values were computed by the forward triangulation method. Two to seven dye-dilution curves were obtained during each animal experiment. Calibration of the flow probes was accomplished *in vivo* by simultaneous comparison of the beat-to-beat stroke volume (the integrated ascending aortic-flow signal) with the calculated dye-dilution cardiac output values. The first derivative of the flow signal (acceleration) was obtained electronically on a Beckman EASE 2000 series analog computer. The differentiator was calibrated daily with known voltages from a triangular waveform generator.

The cardiac pre-ejection period was derived indirectly in the following manner: the interval from the Q-wave of the ECG through the first high-frequency component of the second heart sound constituted the total active electromechanical time of the ventricle. Left ventricular ejection time was measured from the onset of the upstroke through the dicrotic notch on a pulse waveform—in these experiments, the aortic pressure tracing. The pre-ejection period (PEP) was calculated by subtracting the left ventricular ejection time from the total active electromechanical time. This indirect approach to the measurement of the pre-ejection period was unaffected by pulse-wave transmission delay, and is illustrated in figure 1. All measurements of PEP were done manually on rectilinear paper tracings at a speed of 100 mm/sec.

In order to compare the pre-ejection period with ascending aortic blood-flow acceleration, the pre-ejection period was inverted and squared so that its units coincided with those of acceleration. During each drug response, a representative $1/PEP^2$ was derived from ten consecutive heart beats. These values were compared with the mean peak acceleration value over the same ten cardiac cycles. Measurements were obtained during apnea and under stable circulatory conditions. Figure 2 is a representative sample of the data output necessary for comparison of indirect $1/PEP^2$

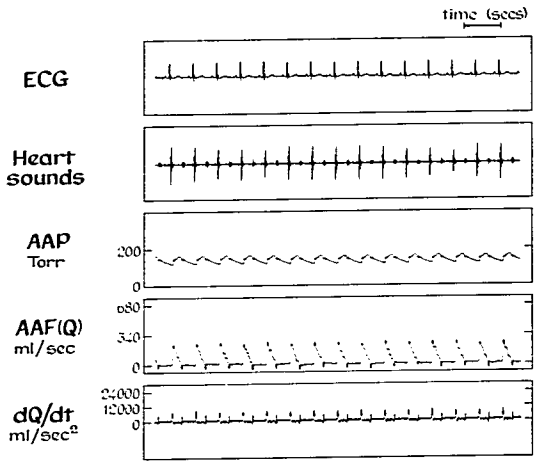

FIG. 2. These tracings show the data output necessary during an animal experiment. AAP = ascending aortic pressure (the pulse waveform), AAF = ascending aortic flow, dQ/dt = blood flow acceleration. The recording was taken from a dog during halothane-induced myocardial depression.

with peak ascending aortic blood-flow acceleration. In the bottom tracing peak acceleration is the maximum amplitude of the first positive deflection during each cardiac cycle.

Final correlations, *t* tests and probability values were calculated on an IBM 360 computer using a standard statistical program. In addition, computer plot programs were uti-

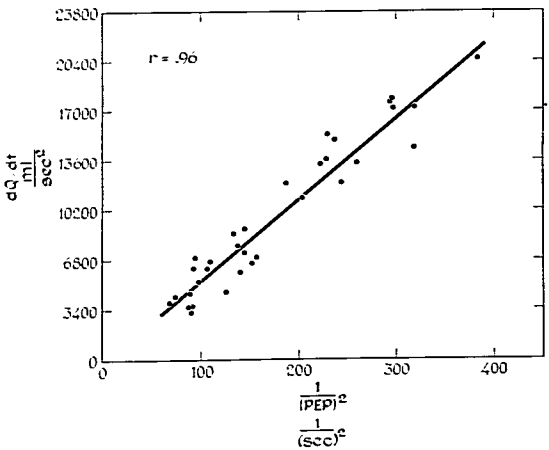

FIG. 3. This scattergram plots peak blood flow acceleration on the ordinate against indirectly derived $1/PEP^2$ on the abcissa. A comparison of 33 separate inotropic states is represented in this graph of data from experiment 6 in table 1. In each experiment, computer plot programs were utilized to produce similar scattergrams.

lized to produce scattergrams similar to figure 3 for each experiment.

The inotropic state of the heart was changed with graded doses of isoproterenol, propranolol, calcium gluconate, sodium citrate, epinephrine, and halothane. In addition, heart rate was augmented with atropine, afterload was altered with phenylephrine and amyl nitrate introduced by inhalation, and a rapid saline infusion was used to increase preload. Generally, the changes in inotropy produced in any one animal were sixfold.

Results

Correlation coefficients between peak blood-flow acceleration and $1/PEP^2$ ranged from 0.74 to 0.96 (table 1). P values were less than 0.001 in five of seven of the experimental runs. Experiments with less significant results were done early in the series when fewer individual alterations in inotropic state were obtained.

A scattergram which plots peak blood-flow acceleration against $1/PEP^2$ in one dog is shown in figure 3. The best-fit line was drawn from an equation calculated by computer program. The correlation coefficient in this case was 0.96. Thirty-three pairs of data points were compared, representing 330 heart beats analyzed, since each point was the mean of ten cardiac cycles.

Discussion

In this study a reproducible, linear relationship between $1/PEP^2$ and peak ascending aortic blood-flow acceleration was demonstrated.

Noble *et al.*[4] found that the maximum acceleration of blood ejected from the left ventricle is a remarkably sensitive indicator of myocardial ischemia. It reflects the depression of coronary blood flow in conscious dogs earlier, and to a greater degree, than peak ascending aortic flow, stroke volume (cardiac output), or left atrial pressure. Unfortunately, measurement of blood-flow acceleration entails major invasive surgery and does not lend itself to patient monitoring.

Systolic time intervals may be obtained noninvasively by measuring the arterial pulse waveform superficially from a convenient source, such as the carotid or brachial artery.[5] Metzger *et al.*[6] and Bush *et al.*[7] have shown excellent correlations between the externally derived (noninvasive) intervals and direct measurements using end-catheter micromanometers. In our study the pulse waveform was obtained from a central aortic catheter so that blood pressure and arterial blood gases could be measured directly. The use of such a technique in this work should not reflect on the potentially noninvasive character of $1/PEP^2$.

Table 1. Comparison and Statistical Evaluation of the Relationship between Peak Blood-flow Acceleration and $1/PEP^2$ *

Experiment	N	Correlation Coefficient	t	P
1	5	0.95	5.3	<0.02
2	14	0.83	5.1	<0.001
3	9	0.74	2.9	<0.05
4	16	0.87	6.5	<0.001
5	31	0.94	14.3	<0.001
6	33	0.96	18.4	<0.001
7	20	0.82	6.1	<0.001

* Correlation coefficients, t-test values, and P values were calculated on a digital computer using standard statistical programs. N represents the number of steady-state conditions analyzed during each experimental run.

Clinical uses of the cardiac pre-ejection period have been studied by several authors. Weissler *et al.*[8] found that the pre-ejection period was prolonged in patients with overt heart failure, and this prolongation correlated well with reduced cardiac output. Diamant and Killip[9] observed a significant lengthening of the pre-ejection period in serial studies of patients undergoing acute myocardial infarction. In volunteer subjects, Harris *et al.*[10] showed that beta-adrenergic stimulation by isoproterenol, epinephrine, and moderate doses of nonepinephrine shortened the pre-ejection period, while beta-adrenergic blockade by propranolol lengthened it.

However, certain investigations have shown the pre-ejection period to be influenced by changes in preload or afterload; that is, lengthening by increased afterload and shortening by increased preload.[10-12] Conversely, Noble[13] observed that changes in ventricular preload and output impedance caused little variation in peak blood-flow acceleration.

In comparing the pre-ejection period and blood-flow acceleration, no specific analysis of

the effects of heart loading was made in our study, yet the high correlation coefficients between the two measurements would seem to preclude any great variation caused by preload or afterload. An augmentation of left ventricular dp/dt with increasing left ventricular afterload in dogs has been described by Wallace *et al.*[14] Our measurements were made during steady-state conditions in dogs with intact sympathetic nervous systems; during this time the rate of rise of ventricular pressure in the isovolumic phase may have increased sufficiently in response to an increased afterload (via phenylephrine) so that any prolongation of the pre-ejection period was minimized. Shortening of the interval by increasing preload may have been too subtle for detection with our statistical techniques.

A few technical difficulties arise in the use of the pre-ejection period as a monitor of myocardial function. Systolic heart murmurs may diffuse the second heart sound so that the $Q\text{-}S_2$ interval becomes indistinct. During operations the use of electrocautery obliterates the ECG. Finally, the external transducing of the arterial pulse is susceptible to muscle artifacts and gross displacement of sensors by vigorous movements of the patient.

In spite of these problems, the cardiac pre-ejection period, particularly its inverse square ($1/PEP^2$), appears to be a good indicator of ventricular functions, and it is applicable as a noninvasive, beat-to-beat monitor in the operating room or intensive care unit, and in clinical studies.

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References

1. Rushmer RF: Initial ventricular impulse. A potential key to cardiac evaluation. Circulation 29:268–283, 1964
2. Mason DT: Usefulness and limitations on the rate of rise of intraventricular pressure (dp/dt) in the evaluation of myocardial contractility in man. Amer J Cardiol 23: 516–527, 1969
3. Siegel JH, Sonnenblick EH: Isometric time–tension relationship as an index of myocardial contractility. Circ Res 12:597–610, 1963
4. Noble MIM, Trenchard D, Guz A: Left ventricular ejection in conscious dogs: I. Measurement and significance of the maximum acceleration of blood from the left ventricle. Circ Res 19:139–147, 1966
5. Weissler AM, Harris WS, Schoenfeld CU: Bedside techniques for the evaluation of ventricular function in man. Amer J Cardiol 23:577–583, 1969
6. Metzger CC, Chough CB, Kroetz FW, *et al.*: True isovolumic contraction time. Amer J Cardiol 25:434–442, 1970
7. Bush CA, Lewis RP, Leighton RF, *et al.*: Verification of systolic time intervals and true isovolumic contraction time from the apexcardiogram by micromanometer catheterization of the left ventricle and aorta. Circulation 42 suppl 3:121, 1970
8. Weissler AM, Harris WS, Schoenfeld CD: Systolic time intervals in heart failure in man. Circulation 37:149–159, 1968
9. Diamant B, Killip T: Indirect assessment of left ventricular performance in acute myocardial infarction. Circulation 42:579–592, 1970
10. Harris WS, Schoenfeld CD, Weissler AM: Effects of adrenergic receptor activation and blockade on the systolic pre-ejection period, heart rate, and arterial pressure in man. J Clin Invest 46:1704–1714, 1967
11. Wallace AG, Mitchell JH, Skinner NS, *et al.*: Duration of the phases of left ventricular systole. Circ Res 12:611–619, 1963
12. Talley RC, Meyer JF, McNay JL: Evaluation of the pre-ejection period as an estimate of myocardial contractility in dogs. Amer J Cardiol 27:384–391, 1971
13. Noble MIM: The maximum acceleration of blood in the ascending aorta: Its measurement and significance in relation to cardiac performance. Ph.D. Thesis, 1965, Department of Medicine, Charing Cross Hospital Medical School, Fulham Hospital, London, England
14. Wallace AG, Skinner NS Jr, Mitchell JH: Hemodynamic determinants of the maximal rate of rise of left ventricular pressure. Amer J Physiol 205:30–37, 1963