Relationships of Left Ventricular Systolic Time Intervals with Hemodynamic Variables in Intact and Failing Hearts

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SUMMARY

Deviation of systolic time intervals (STI) from the regression lines obtained from 122 normal subjects was studied in 22 healthy adults (Group I), 18 N.Y. functional class I cardiac patients (Group II) with ischemic (IHD) or primary myocardial disease (PMD), and 15 similar patients (pts) but N.Y. functional class II with prior heart failure (Group III).

STI_c (corrected for heart rate) were normal in Groups I and II. Supine exercise caused shortening of pre-ejection period PEP_c and prolongation of left ventricular ejection time ET_c in both groups. Group III pts had a significantly longer PEP_c and shorter ET_c at rest. Supine exercise caused further prolongation of PEP_c and a slight prolongation of ET_c in this group.

In 8 mongrel dogs, the effect of controlled changes of hemodynamic variables on STI was studied with intact hearts and repeated after myocardial impairment has been induced by pentobarbital. Doubling of venous return while the heart was intact produced changes in STI similar to the effects of supine exercise in Groups I and II human subjects. With myocardial impairment, comparable increase in venous return had an effect on STI similar to the effect of supine exercise in Group III patients. Controlled increase in each of heart rate or blood pressure, with other hemodynamic variables kept constant, produced changes in STI different from the effect of supine exercise on human subjects.

The study suggests that the value of supine exercise induced changes in STI in reflecting left ventricular performance is attributable primarily to increased volume load. In this respect supine exercise is probably superior to other forms of exercise in disclosing impaired left ventricular performance.

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THERE is recent growing interest in systolic time intervals (STI) as a simple, non-invasive means of assessment of left ventricular performance in man.¹⁾⁻⁷⁾ Alterations in STI at rest have been shown to correlate with changes in stroke volume, cardiac output,¹⁸⁾ left ventricular ejection fraction,⁹⁾ as well as with direct parameters of left ventricular contractility.¹⁰⁾ More recently changes in STI in response to quantitated exercise have been examined in cardiac patients¹¹⁾⁻¹⁵⁾ and compared with the normal response. However, these studies have yielded controversial results. Therefore more work is needed to define the place of exercise induced changes in STI in disclosing impaired left ventricular performance and the type of exercise that is most useful in this respect.

The present study was undertaken with the following objectives: 1) clinically, to compare the changes of STI induced by supine exercise in patients with and those without congestive heart failure; 2) experimentally, to investigate the effect of different hemodynamic variables and of myocardial impairment on STI; and 3) to attempt to interpret changes in STI at rest and after supine exercise in patients with congestive heart failure in the light of clinical and experimental observations.

MATERIALS AND METHODS

I. Clinical Study:

The human subjects comprised 21 healthy adults (Group I) and 33 patients with heart disease. Cardiac patients consisted of 29 men and 4 women with an age range 16-65 years. Eighteen of these patients (Group II) had normal effort tolerance (N.Y. functional class I) and no prior history of heart failure; these included 13 patients with ischemic heart disease (IHD) with an old uncomplicated myocardial infarction or angina pectoris on severe exertion and 5 patients with primary myocardial disease (PMD) diagnosed by cardiomegaly with or without gallop rhythm but associated with ECG abnormalities exclusive of left bundle branch block. The remaining 15 patients (Group III) had a history of congestive heart failure (CHF) that was controlled satisfactorily by medical treatment so that their effort tolerance was ultimately only slightly decreased from normal (N.Y. functional class II). Twelve of these patients were suffering from ischemic heart disease and 3 had primary myocardial disease.

Patients included in the study were exercised by a Collins pedal mode bicycle ergometer* in the supine position for 4 min at a work load of 1 watt/Kg of body

* Warren E. Collins, Inc.

weight. Systolic time intervals, blood pressure, as well as cardiac output, were measured before and after exercise.

Systolic time intervals were obtained from simultaneous external recordings of carotid pulse, phonocardiogram and electrocardiographic Lead II by a Fukuda MRR-150 recorder at a paper speed of 100 mm/sec with 10 msec time lines. Carotid pulse was recorded using a Fukuda TY302 transducer. The phonocardiogram was obtained using a Fukuda TY301 microphone positioned in the left third intercostal space just outside the sternal border.

Left ventricular ejection time (ET) was measured from the onset of rapid carotid upstroke to the trough of the incisura in carotid pulse tracing. Q-2 interval was measured as the interval from the beginning of QRS complex to the first high frequency vibration of the aortic component of the second heart sound. Pre-ejection period (PEP) was calculated by subtracting ET from Q-2 interval. Measurement of these intervals was made to the nearest 5 msec on the beat whose preceding R-R was closest to the average R-R interval of 10 consecutive beats. Deviations from the normal for ET and PEP (ΔET and ΔPEP) in milliseconds were calculated as the difference between the observed intervals and those predicted for normal individuals at the given heart rate according to the regression equations:

$$\begin{aligned} \text{PEP (msec)} &= -0.31 \times \text{heart rate} + 122 \\ \text{ET (msec)} &= -1.4 \times \text{heart rate} + 384 \end{aligned}$$

These equations were derived from a previous study on 122 normal subjects.¹⁶⁾

Cardiac outputs were measured by the dye dilution method using an carpicce photocell (Waters Co, Model RR-52).

II. *Experimental Study:*

The experimental study was performed on 8 mongrel dogs weighing 10 to 13 Kg. Animals were anesthetized with intravenous injection of sodium pentobarbital in a dose of 30–35 mg/Kg body weight and an additional dose was supplemented when necessary. Under artificial ventilation, the chest was opened at the left fourth intercostal space. The descending aorta was sectioned to introduce a blood circuit (Fig. 1) which consists of Starling's resistance, a blood reservoir, an adjustable pump, and an electromagnetic flowmeter probe.¹⁷⁾ By this extracorporeal circuit, diastolic aortic blood pressure and cardiac output could be controlled independently at desired levels. For pressure measurement, a catheter was inserted into the ascending aorta via the right carotid artery and another was introduced directly into the left atrium via the left atrial appendage. Branches arising from the aortic arch were then ligated. Heart rate was controlled by electrical pacing with a bipolar electrode sutured on the right atrium. Flow rate through the distal descending aorta and the left common carotid artery (Fig. 1) was assumed to approximate the venous return to the left heart and was termed cardiac output.

Left atrial mean pressure, aortic pressure, electrocardiogram, and aortic mean flow rate were recorded at a paper speed of 200 mm/sec. Left ventricular ejection time (ET) was measured from the aortic pressure tracings as the interval from beginning of the fast upstroke to the dicrotic notch and pre-ejection period (PEP) was measured as the interval between the Q wave of electrocardiogram and the onset of aortic pressure upstroke. Heart rate was calculated from R-R intervals.

Measurements of ET and PEP were carried out while changing heart rate,

Fig. 1. Schematic representation of the perfusion system in the experimental study. SR=pneumatically controlled resistance of the Starling type; EMF=electromagnetic flow transducer; LAP=left atrial pressure; AF=aortic flow through the perfusion pump.

Fig. 2. Left panel shows left ventricular ejection time (ET) and pre-ejection period (PEP) in Group II cardiac patients with ischemic (IHD) and primary myocardial disease (PMD), and Group III patients with congestive heart failure (CHF). The regression lines represent normal values obtained from 122 healthy subjects. Right panel shows percentage change of PEP and ET with change in heart rate in animals with intact hearts while cardiac output (CO) and aortic diastolic pressure (DP) were kept constant.

aortic diastolic pressure and cardiac output one at a time while the other variables were kept constant. Subsequently, myocardial depression was induced by adding 500–1,000 mg of sodium pentobarbital to the blood reservoir perfusing the heart until elevation of mean left atrial pressure was observed. The experiment was then repeated after left atrial pressure had stabilized over 5 min at the new higher level.

RESULTS

I. Effect of Changes in Hemodynamic Variables on STI

A. *Clinical Study*: Heart rate and STI in cardiac patients were compared to the regression lines in normal controls obtained from a previous study.¹⁶⁾ As seen in Fig. 2, most patients with congestive heart failure in this study had longer PEP and shorter ET at rest. Prolongation of PEP and shortening of ET in these patients tended to be more pronounced in patients with lower resting cardiac index but was generally independent of diastolic arterial blood pressure (Fig. 3). Group II cardiac patients (IHD, PMD) had normal STI, with few exceptions, even when they had a relatively low cardiac index. PEP/ET ratio was 0.343 ± 0.043 in Group I (normal subjects), 0.336 ± 0.079 in Group II (IHD), 0.403 ± 0.078 in Group II (PMD), and $0.489 \pm$

Fig. 3. Relationship between Δ PEP and Δ ET and cardiac index (left panel) and aortic diastolic pressure (right) in the different groups of patients. Δ PEP and Δ ET are the deviations of those values from the mean values obtained from 122 normal subjects (0 lines).

Fig. 4. The distribution and mean values (transverse lines) of PEP/ET in the different groups of patients. Patients with congestive heart failure (CHF) had significantly higher PEP/ET than normal ($p < 0.01$). Group II patients (IHD, PMD) had values that are not significantly (ns) different from normal.

0.078 in Group III (CHF pts.), thus indicating a significantly higher value in this latter group ($p < 0.01$) (Fig. 4).

B. *Experimental Study:* The effects of change in each of heart rate, aortic diastolic pressure and minute cardiac output on STI were studied experimentally in dogs. As heart rate was increased at a constant stroke volume and aortic diastolic pressure, there was shortening of PEP accompanied by more pronounced shortening of ET (Fig. 5A). Increase in heart rate with a constant minute cardiac output, i.e., at a lower stroke volume, caused less marked shortening of PEP and more marked shortening of ET than when stroke volume was kept constant (Fig. 2). Increase of stroke volume at a constant heart rate and arterial diastolic pressure resulted in prolongation of ET and simultaneous shortening of PEP (Fig. 5B). Elevation of aortic diastolic pressure at a constant heart rate and stroke volume resulted in prolongation of PEP and shortening of ET. This change was observed until a pressure of about 100 mmHg, beyond which further increase of aortic diastolic pressure

Fig. 5 A, B, C and D. Experimental study: Effect of change of each of heart rate (HR), stroke volume (SV), arterial diastolic blood pressure (DP), and induced impairment of myocardial function on PEP and ET while other hemodynamic variables are kept constant ($\sim$). % Δ PEP and % Δ ET = percentage change in these intervals from control values. Δ lap = increase in left atrial pressure above control values with induced impairment of myocardial function.

resulted in abbreviation of PEP and prolongation of ET (Fig. 5C). When myocardial depression was induced by a large dose of sodium pentobarbital, while the other hemodynamic variables were kept the same as with the intact heart, there was prolongation of both ET and PEP (Fig. 5D) with increase in PEP/ET.

II. STI Changes Induced by Exercise or Increased Stroke Volume

A. *Clinical Study*: Table I shows hemodynamic changes induced by supine exercise in the different groups studied. Normal individuals (Group I) showed increase in heart rate and cardiac index, but insignificant change in stroke volume and arterial diastolic blood pressure (Table I). Fig. 6 shows exercise-induced changes in STI in the studied groups. There was prolongation of ET and shortening of PEP in Groups I and II while there was prolongation of both PEP and ET in Group III. Postexercise PEP/ET showed a further significant increase in Group III ($p < 0.01$) while the ratio decreased in Groups I and II (Fig. 7).

B. *Experimental Study*: In dogs, changes in STI were studied in re-

Table I. Hemodynamic Changes Induced by Supine Exercise in the Different Groups Studied

	At rest	After exercise
Cardiac index (L/min/M ²)		
Group I	3.0±0.9	4.6±1.6
Group II-IHD	3.0±0.7	4.7±1.8
-PMD	3.2±0.7	5.5±1.8
Group III	2.6±0.9	3.1±0.7
Stroke volume index (ml/beat/M ²)		
Group I	43±10	57±20
Group II-IHD	47±15	62±30
-PMD	47±12	60±11
Group III	36±10	33±7
Heart rate (beats/min)		
Group I	70±10	85±11
Group II-IHD	68±13	81±16
-PMD	69±9	92±15
Group III	71±12	93±16
Diastolic blood pressure (mmHg)		
Group I	75±8	76±10
Group II-IHD	84±11	94±10
-PMD	73±6	69±13
Group III	80±13	74±28

The values are mean±1 standard deviation. Group I=normal individuals; Group II-IHD=ischemic heart disease; Group II-PMD=primary myocardial disease; Group III=patients with prior congestive heart failure.

Fig. 6. Changes in PEP and ET from base line values in response to supine exercise (ΔPEP_e and ΔET_e) in Group I normal subjects, Group III congestive heart failure patients and Group II cardiac patients (IHD and PMD).

sponse to doubling of stroke volume while heart rate and arterial diastolic pressure were kept constant. As shown in Fig. 8, increase in stroke volume resulted in shortening of PEP and prolongation of ET while the heart was intact, but when myocardial depression was induced by pentobarbital, similar

Fig. 7. Changes in PEP/ET from base line control values (0 line) in response to supine exercise (PEP/ET_e) in the different groups of patients. Note the significantly higher values ($p < 0.01$) in CHF patients.

Fig. 8. Experimental study: Percentage change in PEP and ET from control values (0 line) in response to doubling of stroke volume while heart rate and diastolic blood pressure were kept constant. Left panel shows values with intact heart and right panel shows values after induction of myocardial impairment.

increase in stroke volume resulted in prolongation of both PEP and ET with increase in PEP/ET. The response of STI to increased preload in animals with intact heart is therefore similar to STI response to supine exercise in human subjects with healthy hearts or non-limiting heart disease. Also, STI response to increased volume load after induction of myocardial impairment

in animals is similar to STI changes in response to supine exercise in patients with prior congestive heart failure.

DISCUSSION

The present study conforms with previous reports showing that with intact hearts, while other hemodynamic variables are kept constant, increase in heart rate leads to shortening of PEP and marked shortening of ET while increase in venous return leads to shortening of PEP and prolongation of ET.¹⁸⁾⁻²¹⁾

Our data indicate that STI response to controlled elevation of diastolic blood pressure depends on the degree of such elevation; less severe elevation of blood pressure leads to prolongation of PEP and shortening of ET while further blood pressure elevation leads to reversal of these findings. Wallace et al²¹⁾ reported prolongation of PEP and shortening of ET in response to sudden increase of mean aortic pressure in animal experiments. Although there is no mention by these authors of a second phase in which STI values were reversed, close examination of their data suggests that with mean aortic pressures in excess of 120 mmHg there was no further change of ET while total systole shortened in duration indicating PEP shortening. Furthermore, Mitchell et al²²⁾ have shown, in a similar experiment, that increase of mean aortic pressure from 58 ± 2 to 120 ± 4 mmHg did not alter myocardial contractility but further increase of pressure from 114 ± 8 to 139 ± 8 mmHg was accompanied by increased velocity of left ventricular fiber shortening and prolongation of ET. On the other hand, human experiments did not show an initial phase of PEP prolongation and ET shortening in response to methoxamine induced increase in mean aortic pressure;²³⁾ the discrepancy may be due to the more gradual increase in aortic pressure in the latter experiments and/or an earlier enhancement of left ventricular contractility in human hearts.

In patients with heart disease deviation of STI from normal is probably primarily influenced by the degree of impairment of left ventricular performance. Our group of patients with ischemic heart disease or primary myocardial disease but no history of congestive failure not only had normal STI at rest but also behaved in response to supine exercise similarly to healthy individuals. By contrast, patients with the same type of underlying heart disease and limited effort tolerance had significantly different findings in STI at rest and in response to supine exercise.

The effect of exercise on cardiac performance probably consists of 2 major components; augmented sympathetic activity and increased venous

return.²⁴⁾ In the normal heart, increased sympathetic activity should lead to decrease in all components of mechanical systole²⁵⁾ while increased venous return is expected to lead to shortening of PEP and prologation of ET. This latter pattern was encountered in healthy individuals and cardiac patients with normal effort tolerance whom we studied with supine exercise. The primary role of increased venous return in causing these changes is further suggested from our experimental study in which controlled increase in stroke volume had similar effects on STI in animals with intact hearts. On the other hand, patients with prior congestive cardiac failure showed more prolongation of PEP and slight prolongation of ET and therefore appreciable increase in PEP/ET in response to supine exercise which is similar to our findings in animals with induced myocardial impairment when they were subjected to a larger volume load (Fig. 8).

Several investigators have studied exercise-induced changes in STI in symptomatic cardiac patients or those with subclinical or non-limiting heart disease. McConahay et al¹⁵⁾ reported that patients with angina pectoris had significantly increased PEP and decreased ET and a greater PEP/ET at rest and after exercise than a control group of normal individuals. They also noted that cardiac patients showed an STI response to exercise similar to normal subjects. They therefore concluded that exercise did not improve the predictability of STI in differentiating patients with coronary artery disease from clinically healthy individuals. That study, however, did not include cardiac patients with prior congestive heart failure. Aronow et al¹³⁾ showed that among patients with coronary heart disease, those with a left ventricular ejection fraction of less than 50 % had a lesser decrease of isovolumic contraction time/ET in response to upright exercise than normal individuals or patients with an ejection fraction of 50 % or more. These findings conform with those of Kondo¹¹⁾ who noted that exercise caused less than usual abbreviation of PEP in the majority of patients with heart disease. By contrast, Pouget et al¹²⁾ observed that 2 step exercise test for 4 min resulted in more prolongation of ET and more shortening of PEP than usual in patients with angina pectoris as well as in patients with heart failure due to primary myocardial disease.

The discrepancy in these results is not readily explainable, but the type of exercise employed might have influenced the results in certain studies. It has been shown that a normal individual in the supine position has a shorter PEP and a longer ET than values obtained in the upright position, while a patient with congestive heart failure will demonstrate no significant change in STI with posture.²⁶⁾ Also stroke volume and cardiac output have been shown to be significantly lower during upright than supine exercise in normal subjects, whereas no significant difference in cardiac output or stroke volume was found

in patients with heart disease with the 2 forms of exercise.²⁷⁾ If one considers that venous return increases appreciably in the supine position, one may expect that exaggerated cardiac distension in that position should make supine exercise more useful than upright exercise in revealing an underlying state of impaired myocardial performance.

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