Correlation between changes in systolic time intervals and left ventricular end-diastolic diameter after preload reduction

*Non-invasive monitoring of pharmacological intervention**

J BUCH, H EGEBLAD, P B HANSEN, H KJAERGÅRD,
S WALDORFF, E STEINESS

From the Cardiovascular Laboratory, Medical Department B, Rigshospitalet, and Department of Pharmacology, University of Copenhagen, Copenhagen, Denmark

SUMMARY In order to measure the effect of a decrease in preload on systolic time intervals and left ventricular end-diastolic diameter (LVEDD) measured by echocardiography, eight healthy young subjects were given 40 mg frusemide intravenously. The pre-ejection period index (PEPI) increased and the left ventricular end-diastolic diameter decreased. A correlation between Δ PEPI and Δ LVEDD was shown. Using changes in systolic time intervals in the evaluation of changes in contractility it is important to correct for changes in preload. For normal subjects it is suggested that the relation between Δ PEPI and Δ LVEDD as a percentage of the mean values should be used for this correction. A method is suggested for estimating the changes in pre-ejection period index induced by changes in left ventricular end-diastolic diameter.

Systolic time intervals are influenced by preload, afterload, and myocardial contractility.¹⁻³ Thus, given a constant pre- and afterload or provided that the relative influence of pre- and afterload can be accounted for, changes in systolic time intervals can be used as an indicator of changes in myocardial contractility.

No feasible method exists for measuring preload non-invasively. Alterations in left ventricular end-diastolic diameter, however, can be used as an indicator of changes in preload,⁴ especially in acute studies where changes in myocardial compliance, not caused by volume changes, may be considered minimal.

The present study was undertaken in order to examine whether a preload reduction induced by frusemide, 40 mg intravenously, would cause a decrease in left ventricular end-diastolic diameter detectable by quantitative echocardiography.

Simultaneous measurements of systolic time

intervals were performed in order to investigate whether an expected decrease in cardiac performance, as recorded by systolic time intervals, could be correlated with left ventricular end-diastolic diameter.

Subjects and methods

Eight healthy subjects, five male and three female, aged 21 to 28 years, volunteered for the study by written informed consent. After voiding urine, they were weighed and control recordings of systolic time intervals, left ventricular end-diastolic diameters, and blood pressures were made.

Frusemide, 40 mg, was given intravenously. After 15 and 30 minutes repeated measurements of systolic time intervals, left ventricular end-diastolic diameter, blood pressure, weight, and diuresis were performed.

Systolic time intervals were recorded at a paper speed of 100 mm/s on a Siemens Mingograph 62 using two Siemens 860 transducers, for phonocardiography and carotid pulse wave tracings.

*Supported in part by the Danish Heart Foundation and "Fonden til Laegevidenskabens Fremme".

Received for publication 11 June 1980

During 10 consecutive beats, total electromechanical systole (QS_{II}), left ventricular ejection time (LVET), and pre-ejection period (PEP) were measured and corrected for heart rate (QS_{II}I, LVETI, PEPI).⁵ PEP/LVET was calculated from the uncorrected data.

Echocardiography was performed using either an Aloka SSD 110S-E instrument interfaced to a Honeywell 1856A Visicorder or a Mediscan 30 ultrasonic apparatus in combination with a Cambridge multichannel recorder. The echocardiogram was recorded in the left lateral position during normal, quiet respiration. Left ventricular end-diastolic diameter was measured in five consecutive beats immediately inferior to the mitral leaflets at the peak of the electrocardiographic R wave.

The reliability of the measured values was tested as follows. The systolic time intervals were analysed blindly by two observers. The mean interobserver differences were: 0.4 per cent for QS_{II}I, 0.5 per cent for left ventricular ejection time index, 1.1 per cent for pre-ejection period index, and 2.3 per cent for PEP/LVET. In order to avoid inter-observer variations, the echocardiograms were analysed blindly by a single observer. Repeated examinations of left ventricular end-diastolic diameter in eight persons with a 10 week interval have previously shown a mean difference of 2.3 per cent (H Egeblad, unpublished data).

Corresponding data for each individual were compared using Student's *t* test for paired data. Correlations were calculated using Spearman's rank correlation and least square linear correlation. When expressing percentage changes, regression towards the mean was avoided by conventional statistical methods.⁶

Table 1 Weight, diuresis, pulse rate, and blood pressure $\pm$ 1 SEM before and after frusemide

	Control	15 min	30 min
Weight (kg)	66.8 $\pm$ 3.0		65.8 $\pm$ 3.0
Diuresis (ml)		456 $\pm$ 79	947 $\pm$ 67
Pulse rate (beats/min)	71 $\pm$ 5	68 $\pm$ 4	66 $\pm$ 4
Systolic blood pressure (mmHg)	138 $\pm$ 8	140 $\pm$ 7	137 $\pm$ 7
Diastolic blood pressure (mmHg)	81 $\pm$ 7	84 $\pm$ 6	83 $\pm$ 6

Results

The changes in body weight, pulse rate, and blood pressure are seen in Table 1. The variation in pulse rate and blood pressure were not statistically significant. The diuresis (mean $\pm$ SEM) was 456 $\pm$ 79 ml and 947 $\pm$ 67 ml after 15 and 30 minutes, respectively. Alterations in systolic time intervals and left ventricular end-diastolic diameter were observed after 15 minutes. For left ventricular end-diastolic diameter, QS_{II}I, and left ventricular ejection time index the changes were not significant until after 30 minutes (Table 2).

The relation between left ventricular end-diastolic diameter and pre-ejection period index is visualised in Fig. 1. The relation between left ventricular end-diastolic diameter and PEP/LVET was similar.

The correlation coefficients between changes in left ventricular end-diastolic diameter (Δ LVEDD) versus changes in systolic time index and diuresis are seen in Table 3. No correlation was found between Δ LVEDD and the absolute diuretic volume or the diuretic volume as a percentage of the initial body weight. A correlation was shown between Δ LVEDD and changes in systolic time intervals, both when a linear and a non-linear

Fig. 1 Simultaneous measurements of left ventricular end-diastolic diameter (LVEDD) and pre-ejection period index (PEPI) before (●) and 30 minutes after (×) frusemide, 40 mg intravenously.

Table 2 Left ventricular end-diastolic diameter and systolic time intervals before and after frusemide (mean $\pm$ 1 SEM)

	Control	15 min		30 min	
LVEDD (mm)	48.6 $\pm$ 2.3	46.9 $\pm$ 2.3	NS	46.1 $\pm$ 2.3	p < 0.01
QS _{TI} (ms)	529 $\pm$ 6	529 $\pm$ 8	NS	524 $\pm$ 7	p < 0.05
LVETI (ms)	419 $\pm$ 4	410 $\pm$ 4	NS	397 $\pm$ 4	p < 0.001
PEPI (ms)	110 $\pm$ 6	119 $\pm$ 5	p < 0.05	127 $\pm$ 6	p < 0.005
PEP/LVET	0.270 $\pm$ 0.023	0.304 $\pm$ 0.012	p < 0.05	0.348 $\pm$ 0.019	p < 0.005

method was used (Table 3). The relation between Δ LVEDD as a percentage of the mean value and Δ PEPI as a percentage of the mean value is depicted in Fig. 2.

Discussion

Left ventricular end-diastolic volume and left ventricular end-diastolic diameter are very sensitive to changes in filling pressure, if the ventricle is not overloaded.^{4,7,8} In this situation it is therefore possible to use changes in left ventricular end-diastolic diameter as an indicator of changes in preload.

The haemodynamic effects of frusemide are not the result of changes in contractility,⁹ but are mainly caused by a decrease in preload.^{10,11} Ac-

cording to the Starling principle, a decrease in preload will lead to a decrease in cardiac performance if the left ventricle is not overloaded.^{7,12}

The first 30 minutes after frusemide administration the effect on preload is mainly the result of an increase in venous capacitance and only later of a decrease in plasma volume.¹⁰ This offers an explanation of the lack of correlation between Δ LVEDD and diuresis in the present study.

Table 3 Nonlinear and linear correlation between Δ LVEDD and changes in systolic time intervals and diuresis after both 15 and 30 minutes

	r_s	p	r	p
Δ LVEDD versus Δ QS _{TI}	0.467	NS	0.249	NS
Δ LVEDD versus Δ LVETI	0.579	< 0.05	0.569	< 0.05
Δ LVEDD versus Δ PEPI	-0.708	< 0.01	-0.660	< 0.01
Δ LVEDD versus Δ PEP/LVET	-0.711	< 0.01	-0.666	< 0.01
Δ LVEDD versus diuresis	-0.158	NS	-0.144	NS

r_s = Spearman's rank correlation coefficient.
 r = linear correlation coefficient.

Fig. 2 The calculated correlation between percentage change in pre-ejection period index (Δ PEPI%) and percentage changes in left ventricular end-diastolic diameter (Δ LVEDD%). The dotted lines represent 95 per cent confidence limits.

The systolic time intervals with the closest correlation to invasive measurements of myocardial contractility are pre-ejection period index and PEP/LVET.^{3,13} This study shows the feasibility of measuring a change in cardiac performance by systolic time intervals and a decrease in left ventricular end-diastolic diameter caused by a decrease in preload after an intravenous dose of 40 mg frusemide.

Similar changes in systolic time intervals^{14,15} and left ventricular end-diastolic diameter¹⁶ have been obtained when the decrease in preload was induced by tilting, dialysis, or administration of glyceryl trinitrate. The importance of correlating changes in these indices has not previously been stressed. Using the pre-ejection period index and PEP/LVET for the evaluation of cardiac effects of drugs, it is therefore important to bear in mind that haemodynamic changes, measured by systolic time intervals, may not only be the result of changes in contractility.

In a group of subjects, as in this study, Fig. 2 can be used to estimate whether the haemodynamic effect of a drug or a physiological manoeuvre can be explained by changes in preload or contractility or both. For example, if a drug induces a decrease in

left ventricular end-diastolic diameter of 5 per cent, this may cause an increase in pre-ejection period index of 1 to 13 per cent. Thus, only if an increase in pre-ejection period index greater than 13 per cent is encountered, is an additional mechanism such as decreased myocardial contractility necessary to explain the results. This figure will not necessarily be valid for a group of patients with heart disease, with abnormal left ventricular compliance and size.

The present study has shown a statistically significant correlation between a decrease in left ventricular end-diastolic diameter as an indicator of preload and changes in pre-ejection period index and PEP/LVET in normal subjects. We feel confident that combined measurements of systolic time intervals and echocardiographic determinations of left ventricular end-diastolic diameter will improve the ability to evaluate the haemodynamic effects of drugs.

References

- 1 Harris WS, Schoenfeld CD, Weissler AM. Effects of adrenergic receptor activation and blockade on the systolic preejection period, heart rate, and arterial pressure in man. *J Clin Invest* 1967; **46**: 1704-14.
- 2 Harley A, Starmer CF, Greenfield JC Jr. Pressure-flow studies in man: an evaluation of the duration of the phases of systole. *J Clin Invest* 1969; **48**: 895-905.
- 3 Garrard CL Jr, Weissler AM, Dodge HT. The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease. *Circulation* 1970; **42**: 455-62.
- 4 Rankin LS, Moos S, Grossman W. Alterations in preload and ejection phase indices of left ventricular performance. *Circulation* 1974; **51**: 910-15.
- 5 Weissler AM, Harris WS, Schoenfeld CD. Systolic time intervals in heart failure in man. *Circulation* 1968; **37**: 149-59.
- 6 Oldham PD. A note on the analysis of repeated measurements of the same subjects. *J Chronic Dis* 1962; **15**: 969-77.
- 7 Patterson SW, Piper H, Starling EH. The regulation of the heart beat. *J Physiol* 1914; **48**: 465-513.
- 8 Burggraf GW, Parker JO. Effects of dextran infusion on left ventricular volume and pressure in man. *Cathet Cardiovasc Diagn* 1978; **4**: 383-90.
- 9 Poole-Wilson PA, Cobbe SM, Fry CH. Acute effects of diuretics on potassium exchange, mechanical function and the action potential in rabbit myocardium. *Clin Sci Mol Med* 1978; **55**: 555-9.
- 10 Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJC. Renal and external hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. *N Engl J Med* 1973; **288**: 1087-90.
- 11 Mond H, Hunt D, Sloman G. Haemodynamic effects of frusemide in patients suspected of having acute myocardial infarction. *Br Heart J* 1974; **36**: 44-53.
- 12 Crexells C, Chatterjee K, Forrester JS, Dikshit K, Swan HJC. Optimal level of filling pressure in the left side of the heart in acute myocardial infarction. *N Engl J Med* 1973; **289**: 1263-6.
- 13 Ahmed SS, Levinson GE, Schwartz CJ, Ettinger PO. Systolic time intervals as measures of the contractile state of the left ventricular myocardium in man. *Circulation* 1972; **46**: 559-71.
- 14 Stafford RW, Harris WS, Weissler AM. Left ventricular systolic time intervals as indices of postural circulatory stress in man. *Circulation* 1970; **41**: 485-92.
- 15 Bornstein A, Zambrano SS, Morrison RS, Spodick DH. Cardiac effects of hemodialysis: noninvasive monitoring by systolic time intervals. *Am J Med Sci* 1975; **269**: 189-92.
- 16 Redwood DR, Henry WL, Epstein SE. Evaluation of the ability of echocardiography to measure acute alterations in left ventricular volume. *Circulation* 1974; **50**: 901-4.

Requests for reprints to Dr J Buch, Medical Department B, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark.