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 EGEUBLAD, 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 ΔPEPI and ΔLVEDD 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 ΔPEPI and ΔLVEDD 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. 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, 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 Lægevidenskabens Fremme”.

Received for publication 11 June 1980
Correlation between changes in systolic time intervals

During 10 consecutive beats, total electromechanical systole (QS11), left ventricular ejection time (LVET), and pre-ejection period (PEP) were measured and corrected for heart rate (QS11, LVET, PEP). PEP/LVET was calculated from the uncorrected data.

Echocardiography was performed using either an Aloka SSD 11OS-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 QS11, 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 interobserver 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.

| Table 1 Weight, diuresis, pulse rate, and blood pressure ± 1 SEM before and after frusemide |
|-----------------|-----|-----|-----|
| Control         | 15 min | 30 min |
| Weight (kg)     | 66±8 ±3±0 | 65±8 ±3±0 |
| Diuresis (ml)   | 456±79 | 947±67 |
| Pulse rate (beats/min) | 71 ±5 | 66 ±4 |
| Systolic blood pressure (mmHg) | 138±8 | 137±7 |
| Diastolic blood pressure (mmHg) | 81±7 | 83±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 ± SEM) was 456 ± 79 ml and 947 ± 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, QS11, 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 (ΔLVEDD) versus changes in systolic time index and diuresis are seen in Table 3. No correlation was found between ΔLVEDD and the absolute diuretic volume or the diuretic volume as a percentage of the initial body weight. A correlation was shown between ΔLVEDD and changes in systolic time intervals, both when a linear and a non-linear
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. 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, but are mainly caused by a decrease in preload. According to the Starling principle, a decrease in preload will lead to a decrease in cardiac performance if the left ventricle is not overloaded.

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. This offers an explanation of the lack of correlation between ALVEDD and diuresis in the present study.

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

<table>
<thead>
<tr>
<th></th>
<th>$r_s$</th>
<th>$p$</th>
<th>$r$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALVEDD versus APEPI</td>
<td>0.467</td>
<td>NS</td>
<td>0.249</td>
<td>NS</td>
</tr>
<tr>
<td>ALVEDD versus LVETI</td>
<td>0.579</td>
<td>&lt;0.05</td>
<td>0.509</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ALVEDD versus ALVEDD</td>
<td>-0.708</td>
<td>&lt;0.01</td>
<td>-0.660</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ALVEDD versus APEPI/LVET</td>
<td>-0.711</td>
<td>&lt;0.01</td>
<td>-0.666</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ALVEDD versus diuresis</td>
<td>-0.158</td>
<td>NS</td>
<td>-0.144</td>
<td>NS</td>
</tr>
</tbody>
</table>

$r_s$ = Spearman’s rank correlation coefficient.

$r$ = linear correlation coefficient.

The systolic time intervals with the closest correlation to invasive measurements of myocardial contractility are pre-ejection period index and PEP/LVET. 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 and left ventricular end-diastolic diameter 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

---

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

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>15 min</th>
<th>30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>48.6 ± 2.3</td>
<td>46.9 ± 2.3</td>
<td>46.1 ± 2.3</td>
</tr>
<tr>
<td>QSII (ms)</td>
<td>529 ± 6</td>
<td>529 ± 6</td>
<td>524 ± 7</td>
</tr>
<tr>
<td>LVETI (ms)</td>
<td>419 ± 4</td>
<td>410 ± 4</td>
<td>397 ± 4</td>
</tr>
<tr>
<td>PEPI (ms)</td>
<td>110 ± 6</td>
<td>119 ± 5</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>PEP/LVET</td>
<td>0.270 ± 0.023</td>
<td>0.304 ± 0.012</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

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

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


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