Systolic Time Intervals in Febrile States

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Summary

Systolic time intervals (STI) were measured non-invasively in 12 controls and 10 cases each with fever due to acute malaria, acute viral infection, typhoid fever, and fever induced by T.A.B. vaccine. Apart from tachycardia, no clinical feature of impaired cardiovascular function was present in any of the febrile cases. Abnormalities of STI were found in all febrile groups. Of the total 40 cases, only 18 showed normal STI, 2 cases showed decreased PEP/LVET indicative of hyperdynamic circulatory state, and 20 cases showed increased PEF/LVET suggesting the presence of subclinical impairment of myocardial function.

Additional Indexing Words:
Left ventricular performance  Cardiovascular function  Acute malaria  Acute viral infections  Typhoid fever  T.A.B. vaccine

Many febrile illnesses including viral infections, typhoid fever, and malaria have been reported to show pathological evidences of myocardial damage.1) The frequency of cardiac involvement in these illnesses is not known because they are usually treatable or self-limiting and rarely reach the autopsy table. Tachycardia is commonly observed in fever but other clinical features of impaired cardiovascular function e.g. hypotension, gallop rhythm, and congestive heart failure are infrequent. Hemodynamic studies by invasive methods have been rarely performed on such cases, therefore it is not known how often subclinical impairment of cardiovascular function occurs in these conditions. Non-invasive measurement of systolic time intervals (STI) is a simple procedure which has been found useful in detection of impairment of cardiovascular function in many cardiac and non-

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It was therefore decided to assess cardiovascular function in a variety of febrile states by STI measurements.

**Materials and Methods**

Twelve healthy afebrile subjects and 10 cases each with fever due to acute malaria, acute viral infections, enteric fever, and fever induced by T.A.B. vaccine were studied (Table I). Diagnosis of acute malaria was established by the presence of malarial parasite in peripheral blood smear, of enteric fever by positive blood culture or positive Widal test, of acute viral hepatitis by typical prodromal features followed by appearance of hepatocellular jaundice and of acute viral upper respiratory infection on the basis of clinical features. In 10 afebrile volunteers fever was induced by intramuscular injection of 1 ml of T.A.B. vaccine 12-16 hours before the measurement of STI. Patients having clinical or electrocardiographic evidence of any underlying cardiovascular disease were not included in the study. Also those having severe anemia (hemoglobin below 7 Gm%), thyroid disease, or chronic lung disease were excluded because they are known to cause alterations in STI.

All drugs including antipyretics were withheld 24 hours before the STI measurement, and oral temperature, pulse rate and blood pressure were recorded at the time of STI measurement in every case. All STI measurements were done between 8 and 10 A.M. with the subject supine and resting, about 2 hours post-prandially.

STI measurements were done from simultaneous recordings of phonocardiogram, electrocardiogram, and carotid pulse tracings as described earlier from this laboratory. Total electromechanical systole (QS2) was measured from the onset of q wave to the onset of first high frequency vibrations of second heart sound, left ventricular ejection time (LVET) was measured from the onset of rapid upstroke to the trough of the dicrotic notch of carotid pulse tracing, and pre-ejection period (PEP) was calculated by subtracting LVET from QS2. These measurements were corrected for heart rate and were designated as QS2c, LVETc, and PEPc respectively. PEP/LVET ratio was calculated from uncorrected measurements.

Statistical comparison of results between groups was done by Student's 't' test for non-paired data. Correlation coefficient (r) analysis was carried out by the least square method. The level of significance was set at p<0.05.

**Table I. Case Materials**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Cases</th>
<th>Sex</th>
<th>Age, Years Mean ± S.D.</th>
<th>Hemoglobin, Gm% Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12</td>
<td>M</td>
<td>24 2.6</td>
<td>13.2 1.6</td>
</tr>
<tr>
<td>Acute Malaria</td>
<td>10</td>
<td>F</td>
<td>23 7.5</td>
<td>10.8 1.8</td>
</tr>
<tr>
<td>Acute Viral Infections</td>
<td>10</td>
<td>M</td>
<td>22 4.5</td>
<td>11.0 1.7</td>
</tr>
<tr>
<td>Ac. upper resp. inf.</td>
<td>7</td>
<td>F</td>
<td>21 4.2</td>
<td>10.7 1.8</td>
</tr>
<tr>
<td>Ac. viral hepatitis</td>
<td>3</td>
<td>M</td>
<td>24 5.3</td>
<td>11.6 1.4</td>
</tr>
<tr>
<td>Enteric Fever</td>
<td>10</td>
<td>M</td>
<td>19 4.1</td>
<td>10.5 2.4</td>
</tr>
<tr>
<td>Induced Fever</td>
<td>10</td>
<td>F</td>
<td>25 13.9</td>
<td>10.6 1.2</td>
</tr>
</tbody>
</table>

S.D. = 1 standard deviation.
Table II. Temperature, Heart Rate, and Systolic Time Intervals in the Various Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Temperature °C</th>
<th>Heart Rate per min</th>
<th>QS_{C}</th>
<th>PEP_{C}</th>
<th>LVET_{C}</th>
<th>PEP/LVET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±S.D. P</td>
<td>Mean±S.D. P</td>
<td>Mean±S.D. P</td>
<td>Mean±S.D. P</td>
<td>Mean±S.D. P</td>
<td>Mean±S.D. P</td>
</tr>
<tr>
<td>Control</td>
<td>36.7 0.1</td>
<td>75 9</td>
<td>523 14</td>
<td>119 6</td>
<td>404 14</td>
<td>.329 .025</td>
</tr>
<tr>
<td>Acute Malaria</td>
<td>39.0 &lt;.001</td>
<td>96 17 &lt; .01</td>
<td>519 16 NS</td>
<td>119 15 NS</td>
<td>400 14 NS</td>
<td>.336 .017 NS</td>
</tr>
<tr>
<td>Acute Viral Infections</td>
<td>38.5 &lt;.001</td>
<td>92 15 &lt; .01</td>
<td>514 30 NS</td>
<td>123 17 NS</td>
<td>391 18 NS</td>
<td>.366 .058 &lt; .05</td>
</tr>
<tr>
<td>Enteric fever</td>
<td>38.5 &lt;.001</td>
<td>90 9 &lt; .01</td>
<td>512 15 NS</td>
<td>123 12 NS</td>
<td>392 16 NS</td>
<td>.372 .064 &lt; .05</td>
</tr>
<tr>
<td>Induced Fever</td>
<td>38.3 &lt;.001</td>
<td>99 11 &lt; .001</td>
<td>523 25 NS</td>
<td>129 10 &lt; .01</td>
<td>395 19 NS</td>
<td>.404 .045 &lt; .001</td>
</tr>
</tbody>
</table>

QS_{C}=total electromechanical systole, corrected for heart rate, millisecond; PEP_{C}=pre-ejection period, corrected for heart rate, millisecond; LVET_{C}=left ventricular ejection time, corrected for heart rate, millisecond; PEP/LVET=ratio of PEP to LVET; S.D.=1 standard deviation; NS=not significant.
RESULTS

The results are summarized in Table II. While none of the control cases had temperature above 37°C, it was above 38°C in all the febrile cases. Heart rate was significantly higher in all febrile groups compared to controls. Apart from tachycardia, no other clinical feature of impaired cardiovascular function (e.g. hypotension, gallop rhythm, or congestive heart failure) was present in any of the febrile cases. Although mean QS2c was not significantly different from control in any of the febrile groups, mean PEPc was increased in all febrile groups, but the increase was statistically significant in only induced febrile group, and mean LVETc was slightly decreased in all febrile groups but the difference from control was not significant in any of them. Mean PEP/LVET ratio was increased in all febrile groups and the difference from control was significant in all excepting acute malaria.

Fig. 1 shows PEP/LVET ratio in individual cases in the various groups. It shows a wide scatter of this value in all febrile groups, suggesting that the variation in PEP/LVET is not related to the etiology of fever. In an attempt to identify the cause(s) of variation in PEP/LVET, febrile cases of all etiologies were pooled together and the relationship of PEP/LVET to several other variables (patient's age, hemoglobin concentration, heart rate, systolic pressure, diastolic pressure, mean pressure, pulse pressure, body temperature, and

![Fig. 1. PEP/LVET values in individual cases in the control and the 4 groups of febrile cases with their mean and S.D. The solid horizontal line is at mean PEP/LVET value in the control group and the dashed lines above and below it are at ±2 S.D. of the mean in the control group. Statistical significance of the difference between the means in the control and the various febrile groups are also indicated. NS=not significant.](image-url)
duration since onset of fever) were statistically evaluated by determining the correlation coefficient \((r)\) between PEP/LVET and each of the above variables in the control and febrile cases, the significance of \(r\), and the significance of difference of \(r\) between the control and febrile cases ('z' test). No significant correlation was found with any of these parameters.

**DISCUSSION**

PEP/LVET ratio is considered to be the best among the various STI measurements for use as an index of left ventricular performance, increased PEP/LVET being related to decreased cardiac output and other parameters of impaired left ventricular function, and decreased PEP/LVET to increased cardiac output.\(^2\) If mean PEP/LVET + 2 S.D. in our control group is considered normal for our cases, it was found to be normal in 18 febrile cases (acute malaria 7, acute viral infection 4, enteric fever 6, and induced fever 1), decreased in 2 (acute malaria 1, acute viral infection 1), and increased in 20 cases with fever (acute malaria 2, acute viral infection 5, enteric fever 4, and induced fever 9) (Fig. 1).

The mean PEP/LVET in our control group \((0.329 \pm 0.022)\) was lower than that reported by Weissler et al \((0.345 \pm 0.036)\),\(^2\) although the values in 11 of our control cases were within 1 S.D. and in the twelfth it was within 2 S.D. of the mean reported by them. The reason for the low mean value in our controls may be the small number of cases in this group. Even if the mean \(\pm 2\) S.D. of Weissler et al\(^2\) are taken as normal for our cases, only 27 of our 40 febrile cases had normal PEP/LVET (acute malaria 7, acute viral infection 7, enteric fever 7, and induced fever 6); 2 cases had decreased PEP/LVET (acute malaria 1, acute viral infection 1), and 11 cases had increased PEP/LVET (acute malaria 2, acute viral infection 2, enteric fever 3, and induced fever 4).

Malaria, typhoid, and viral infections are all known to cause morphological damage to the myocardium.\(^1\) Our results suggest that functional impairment of the myocardium, as indicated by increased PEP/LVET, is also frequently present in these cases. It is not known whether T.A.B. vaccine causes morphological damage to the myocardium or not, but impaired myocardial function as indicated by raised PEP/LVET was surprisingly frequent in our group of induced fever with T.A.B. vaccine.

Increased cardiac output has been reported to be frequently associated with increased body temperature, whether due to raised environmental temperature\(^9\) or heat stroke.\(^10\) But increased cardiac output, as indicated by decreased PEP/LVET, was found in only 2 of our 40 febrile cases. There
is no other report of PEP/LVET or any other systolic time intervals in any febrile state in the literature. However, in shock, cardiac output has been reported to be increased, normal, or decreased. Physical findings in hyperdynamic circulatory states are characterized by tachycardia, increased pulse pressure due to increased systolic pressure and decreased diastolic pressure, functional murmurs, third heart sound, and venous hum. Functional murmurs, third heart sound or venous hum were not recorded in our cases, but increased heart rate, elevated systolic pressure, decreased diastolic pressure, and increased pulse pressure in various combinations were present in 38 of the 40 febrile cases. It is, therefore, possible that many of these cases had increased cardiac output but PEP/LVET was found to be either normal or increased in most cases, probably because there was impairment of left ventricular function which did not allow PEP/LVET to decrease.

In conclusion, STI in the febrile states studied seem to suggest a high incidence of subclinical impairment of myocardial function in them. However, study on larger number of cases is required to determine the frequency of impairment of myocardial function in each of these conditions, and confirmation by other methods of assessment of myocardial function should be done to determine the reliability of STI as indicators of cardiac performance in these conditions. Because of the effect of possible myocardial damage by the disease which caused fever, it is not possible to determine from the results of this study the effect of raised body temperature itself on the STI measurements.

Acknowledgments

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