The Short Cardiac Pre-Ejection Period
An Index to Thyrotoxicosis

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SUMMARY
Systolic time intervals (STI) were determined from simultaneous records of the electrocardiogram, carotid pulse and phonocardiogram in 17 consecutive patients with thyrotoxicosis and sinus rhythm. None of the patients had clinical evidence of congestive heart failure. Intervals measured included electromechanical systole (Q-S₂), heart sound interval (S₁-S₂) and left ventricular ejection time (LVET). From these, the pre-ejection period (PEP), isovolumetric contraction time (ICT) and Q-S₁ intervals were derived. Deviations (ΔSTI) of observed values from expected values (Weissler equations) for the same heart rate were obtained by subtraction. The mean deviation of the thyrotoxic patients ± SEM from the normal population were ΔQ-S₂* = -37.8 ± 4.2; ΔLVET = -4.0 ± 4.1; ΔPEP* = -33.8 ± 1.8. The shortening of PEP was due largely to a shortened ICT (ΔICT* = -27.2 ± 1.1). In eight patients studied serially during treatment the short PEP returned to the normal range concurrently with serum T₄ measurements. This study indicates that the PEP is a unique noninvasive measurement of biological end organ responsiveness with thyroid dysfunction; a short PEP is characteristic of uncomplicated thyrotoxicosis and serial changes in PEP may be a useful index of therapeutic response.

*P < .001.

Additional Indexing Words: Systolic time intervals Isovolumetric contraction time

Hyperthyroidism is associated with a number of hemodynamic alterations which have been the subject of previous reports. Characteristically there is an increase in oxygen consumption, heart rate, cardiac output, left ventricular systolic ejection rate, and the rate of rise of left ventricular pressure (LV dp/dt).¹ ¹ With the exception of heart rate, accurate measurement of the remaining parameters requires complex instrumentation or invasive methods which are hardly applicable as routine clinical tests. Noninvasive techniques to assess the influence of thyroid function on the circulatory system have not routinely been used in spite of their widespread application to assess cardiovascular problems. The indirect determination of systolic time intervals from simultaneous recording of the carotid pulse, ECG and phonocardiogram, reflects both cardiac output and left ventricular dp/dt.⁷ ¹⁰ Hence this approach can provide a rapid means to study repetitively and without risk the influence of hyperthyroidism on the cardiovascular system.

This study completes in detail our recent preliminary report¹¹ which indicated that a short pre-ejection period (PEP), determined by indirect measurement of systolic time intervals, is typical of hyperthyroidism uncomplicated by other cardiovascular abnormalities. Furthermore, in serial determinations made during treatment, the PEP returns toward normal in parallel with chemical parameters.

Methods

Patient Selection

The patients were chosen consecutively from adults who presented to the Medical Service at Wilford Hall USAF Medical Center or the Baltimore Veterans Administration Hospital with signs or symptoms suggesting thyrotoxicosis. All participants agreed to have determination of systolic time intervals. Criteria for inclusion were: (1) laboratory confirmation of thyrotoxicosis by a) an increased T₄ (Murphy-Pattee: normal = 5.0 – 13.7 μg%) and an increased uptake of radioiodine at 6 and 24 hours, or b) increased T₃ by radioimmunoassay* (normal = 120-312 ng/100 ml) with failure of suppression of radioiodine uptake

*After Gharib H, Mayberry WE, Ryan RJ: J Lab Clin Med 76: 869, 1970 with antibody kindly supplied by Dr. H. Gharib.
Figure 1

Simultaneous carotid pulse, phonocardiogram and electrocardiogram. Paper speed — 150 mm/sec; time lines — 20 msec. The points determining Q-S1, S1-S2 and LVET are illustrated. The derivation of PEP, and its subintervals ICT and Q-S1, are shown at bottom left.

after 10 days of 100 μg triiodothyronine/day; (2) presence of sinus rhythm and of an electrocardiographic QRS interval of less than 10 sec; and (3) no clinical evidence of congestive heart failure (cardiomegaly, basal rales). Two of the Wilford Hall Medical Center patients and all of the Baltimore VA patients returned for determination of systolic time intervals after definitive treatment of their thyrotoxicosis with propylthiouracil and/or radioiodine.

Determination of Systolic Time Intervals

Systolic time intervals were determined in the supine state at least three hours post-prandially after a 15 min period of rest. Multichannel recordings of a simultaneous carotid pulse, electrocardiogram and phonocardiogram were performed on an Electronics for Medicine DR-12 photographic recorder. Paper speeds were 150 mm/sec with time lines demarcated every 20 msec.

The systolic intervals determined are shown in figure 1. These included Q-S2, the total duration of electromechanical systole, the heart sound interval (S1-S2) and left ventricular ejection time (LVET). From these, the pre-ejection period (PEP), isovolumetric contraction time (ICT) and the Q-S1 intervals were derived by subtraction. The distinctive onset of the loud first heart sound in thyrotoxicosis permitted subdivision of the pre-ejection period into its components with considerable precision. The procedure for averaging systolic intervals obtained in a clinical recording and the significance of these intervals have been described in multiple recent publications.10-14

Systolic time intervals were corrected for heart rate variation using the regression equations of Weissler et al. The deviation from the predicted systolic interval (STI) at the patient’s measured heart rate was expressed as ΔSTI where ΔSTI equals STI observed minus STI predicted by the Weissler equation.18 Statistical analyses were performed according to standard formulae using a Hewlett-Packard 9810 programmable calculator.

Results

Patients Studied

The study population consisted of 8 men and 9 women whose ages averaged 39 years (range 23 to 56). Eight of these individuals returned for serial studies over the course of six or more months. Table 1 lists the direct measurements and T4 values for all these patients when they initially presented and for the eight returnees after their thyrotoxicosis was successfully treated. When seen initially four patients (RC, AH, MN and LW) had T3 toxicosis. At no time during the course of serial studies did any patients develop symptoms or signs compatible with congestive heart failure or receive digitalis therapy. No patient had fever or an anemia when any recordings were made.

Table 1

<table>
<thead>
<tr>
<th>Pt.</th>
<th>HR (beats/min)</th>
<th>Q-S1 (msec)</th>
<th>S1-S2 (msec)</th>
<th>LVET (msec)</th>
<th>T4 (μg %)</th>
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<tr>
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<td>254</td>
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<td>260</td>
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<td>72</td>
<td>375</td>
<td>325</td>
<td>300</td>
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<tr>
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<tr>
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<td>308</td>
<td>256</td>
<td>248</td>
<td>10.1*</td>
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</table>

*TS>400 nanograms/100 ml, no suppression of radioiodine uptake after 100 μg triiodothyronine/day for 10 days.

Figure 2

Relation of Q-S2 to heart rate in study population. Values for each patient are represented by the closed circle. The continuous regression line in the center of the shaded area represents the Q-S2 interval predicted by the Weissler equation. The shaded area represents ± 2 SD.
The resting heart rate (mean ± SD) for the thyrotoxic patients was 97 ± 14 beats/min and their blood pressure (mean ± SD) was 142 ± 20/72 ± 11 mm Hg.

Resting Systolic Intervals in Thyrotoxicosis

Figures 2-6 show the relationship of systolic time intervals determined at rest to heart rate in the study population. Table 2 shows the mean deviations of the systolic intervals from the normal population as predicted by the regression equations of Weissler. The mean values for all of the STI were short, but certain intervals were particularly affected. Overall electromechanical systole in the thyrotoxic population averaged 37.8 msec less than normal. The mean ΔLVET was shortened by only 4.0 msec, which was not significantly different from Weissler's normal population. Therefore the shortening of Q-S₂ was predominantly due to a short PEP, as the mean ΔPEP was 33.8 msec less than predicted. Further analysis of the subintervals of PEP (figs. 5 and 6) showed that this was mainly due to an abbreviated period of isovolumetric contraction (mean ΔICT = −27.2 msec).

Serial Studies

The eight individuals who returned for serial studies were followed until they were verified to be euthyroid by clinical criteria and serum T4 measurements on at least two successive visits. Figure 7 shows the mean ΔPEP ± SEM increased from −37.0 ± 1.8 msec to −13.5 ± 2.5 msec after resolution of thyrotoxicosis (P < .001).

The PEP became longer concomitantly with chemical evidence of return to euthyroidism. Figures 8 and 9 show the relationship of T4 and ΔPEP in two thyrotoxic individuals over the course of 8 months. While patient RV (fig. 8) became euthyroid and remained so on treatment with propylthiouracil, patient NO (fig. 9) relapsed with clinical and chemical evidence of hyperthyroidism, when his propylthiouracil was discontinued in preparation for radiiodine treatment. This relapse was associated with concurrent shortening of the pre-ejection period.

The reverse situation was seen on serial studies of a patient with myxedema (fig. 10). Here a long PEP accompanied chemical evidence of hypothyroidism, and both returned toward normal with thyroid hormone therapy.

Discussion

In this study of seventeen consecutive patients with uncomplicated thyrotoxicosis there was marked shortening of the pre-ejection period which was largely due to an abbreviated period of isovolumetric systole. The mean Q-S₁ interval and LVET were also short. However the change in Q-S₁ was a minor part of the over-all effect on the pre-ejection period, while the change in LVET was not significantly different from normal. In all patients, the pre-ejection period fell more than 2 SD below the mean predicted by the Weissler equations (fig. 4), while LVET distributed evenly around the predicted response (fig. 3).

These results confirm the findings of Amidi et al. In an invasive study of left ventricular ejection in thyrotoxic patients they simultaneously measured a high cardiac output with a normal rate-corrected left ventricular ejection time. Thus the left ventricular ejection rate (cardiac output/LVET) is characteristically high in uncomplicated thyrotoxicosis.
Unfortunately ejection rates are not a readily available clinical measurement.

The pre-ejection period is the summation of electrical and mechanical events between the onset of electrical depolarization of the left ventricle and the opening of the aortic valve. It can be subdivided by the first heart sound into the Q-S1 interval and isovolumetric systole. Since the Q-S1 interval was minimally shortened (fig. 5 and table 2) in this group of patients, the short PEP largely reflects a short ICT. ICT represents the time required by the ventricle, starting at end-diastole to generate sufficient pressure to open the aortic valve. Hence its determinants are the left ventricular end-diastolic pressure, the aortic diastolic pressure and the mean rate of left ventricular pressure development. In the animal with normal left ventricular and aortic pressures the peak rate of left ventricular pressure development (LV dp/dt) is reflected by the duration of PEP and ICT. The population studied had normal aortic diastolic pressures. Moreover in the absence of clinical signs of congestive heart failure they were unlikely to have markedly elevated left ventricular end-diastolic pressures. Hence the short ICT and PEP strongly suggest a high peak LV dp/dt. LV dp/dt is used as an index of myocardial contractility, and is high in thyrotoxicosis when measured by conventional catheter recordings. The short PEP therefore indicates a state of enhanced myocardial contractility in thyrotoxicosis. This is in agreement with in vitro studies on cardiac muscle and in vivo studies on laboratory animals. While the biochemical mechanism responsible for enhanced contractility may be thyroxine activation of myocardial adenyl cyclase this hypothesis has been the subject of recent debate.

A short PEP is not specific for thyrotoxicosis. A short PEP, usually accompanied by a long LVET, is typical of severe uncomplicated aortic stenosis and insufficiency. Interestingly, a short PEP, with a normal LVET, can be produced by graded epinephrine infusion. However acute β-adrenergic blockade in thyrotoxicosis has not been shown to influence the PEP. Our observations made consecutively in this group of patients indicate that a short PEP is characteristic of uncomplicated thyrotoxicosis.

Serial determinations of PEP during treatment were particularly informative. The patients documented to be euthyroid all showed a significant lengthening of rate-corrected PEP. Moreover, the serial lengthening of PEP accompanied simultaneous improvement in serum measurements of thyroid function. These results indicate that determination of PEP is useful in following the course of thyrotoxicosis. Moreover this measurement has certain inherent advantages; the method is completely noninvasive and the results are available immediately.

## Table 2

Mean Deviations ± SEM of Systolic Intervals in Study Population Compared to Normal Population*

<table>
<thead>
<tr>
<th>ΔSTI</th>
<th>msec</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔQ-S2</td>
<td>−37.8± 4.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ΔLVET</td>
<td>−4.0± 4.1</td>
<td>NS</td>
</tr>
<tr>
<td>ΔPEP</td>
<td>−33.8± 1.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ΔQ-S1</td>
<td>−7.7± 2.1</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ΔICT</td>
<td>−27.2± 1.1</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Predicted from Weissler regression equations.

[Figure 7](#)

Mean deviation of PEP from predicted normal in 8 patients, initially when they were hyperthyroid and later when they were euthyroid. The vertical line represents the mean ± SEM (P < .001).

[Figure 8](#)

Serial determinations of T4 and ΔPEP in subject RV. The shaded area represents the normal range ± 2 SD for both T4 and PEP. The subject became euthyroid on propylthiouracil (PTU) and remained so when the medication was stopped for treatment with radiiodine (RAI).

[Figure 9](#)

Serial determinations of T4 and ΔPEP in subject NO. Format as figure 8. The patient became euthyroid with initial administration of PTU but escaped when the medication was stopped for RAI treatment. Note that ΔPEP decreased concomitantly with chemical evidence of the transient recurrence of thyrotoxicosis.

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The set of serial observations made in our patient with myxedema also suggest that the method may be applied analogously in evaluating hypothyroidism. Since radioiodine commonly induces hypothyroidism, serial observations of systolic time intervals after therapy may have application in early detection of this complication.

Finally, in contrast to the usual parameters of thyroid gland activity, PEP directly reflects responsiveness of a sensitive end organ to thyroid dysfunction. Hence its determination will allow the opportunity for further physiologic observations which may not be derived solely from serum measurements or radioiodine tracer studies. As the data in four of our patients suggest, the PEP appears to be useful in detecting unusual forms of hyperthyroidism such as T3 toxicosis. It may also provide a clue to thyroid dysfunction when abnormal iodine loads, serum protein changes or drug administration render routine laboratory methods useless. Since this study defines the typical cardiac response to hyperthyroidism, departures from this may also indicate potentially significant cardiovascular complications.

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