Epinephrine Infusion in Man

Standardization, Normal Response, and Abnormal Response
in Idiopathic Hypertrophic Subaortic Stenosis


SUMMARY
A standard test was designed for measurement of the effect of epinephrine infusion on systolic time intervals in 14 normal subjects as a dose-response phenomenon. In order that we might examine the sensitivity of the test, it was applied in nine patients with idiopathic hypertrophic subaortic stenosis.

Normal subjects had a characteristic response—a progressive shortening of the duration of electromechanical systole, left ventricular ejection time, and pre-ejection period. Their left ventricular ejection time, corrected for heart rate, did not change. Patients with idiopathic hypertrophic subaortic stenosis responded to epinephrine infusion with paradoxical lengthening of their left ventricular ejection time, corrected for heart rate. After beta blockade (with propranolol), reinfusion of epinephrine shortened the left ventricular ejection time, corrected for heart rate, to normal levels.

Additional Indexing Words:
Dose response  Systolic time intervals  Beta blockade

Studies dealing with the interaction of the sympathetic nervous system and the heart are hampered by: (a) the technical difficulty of the measurement of plasma catecholamines and (b) the unknown physiological significance of these measurements. Estimation of end-organ (myocardial) sensitivity might prove to be a useful tool for the study of these interactions. The systolic time intervals standardized by Weissler are atraumatic and easily reproducible. They offered a parameter for measurement of this response.

We have measured the systolic time intervals of normal individuals during graded epinephrine infusions, thereby establishing the effects of sympathetic stimulation upon cardiovascular dynamics as a dose-response curve. In order to examine the sensitivity of the test, we studied nine patients with idiopathic hypertrophic subaortic stenosis (IHSS). The results show that the epinephrine infusion test is capable of identifying an abnormal response in this clinical entity, and, in addition, it can detect the normalization of response that occurs with reinfusion of epinephrine after beta blockade.

Materials and Methods

The study population consisted of 14 normal males (mean age 25; range 17–41 years) and nine patients with IHSS (six males, three females; mean age 38; range 18–54 years).

The normal subjects were evaluated by detailed cardiovascular history, physical examination, chest X-ray, and resting electrocardiogram. In all nine patients, the diagnosis of IHSS was
Table 1

Catheterization Data in Patients with IHSS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Peak systolic gradient (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.C.</td>
<td>53</td>
<td>M</td>
<td>10  125*</td>
</tr>
<tr>
<td>J.G.</td>
<td>22</td>
<td>F</td>
<td>38  100*</td>
</tr>
<tr>
<td>E.R.</td>
<td>54</td>
<td>M</td>
<td>90  -</td>
</tr>
<tr>
<td>L.M.</td>
<td>23</td>
<td>F</td>
<td>100 -</td>
</tr>
<tr>
<td>N.S.</td>
<td>48</td>
<td>M</td>
<td>0   65f</td>
</tr>
<tr>
<td>E.A.</td>
<td>32</td>
<td>F</td>
<td>0   100*</td>
</tr>
<tr>
<td>T.H.</td>
<td>18</td>
<td>M</td>
<td>17  -</td>
</tr>
<tr>
<td>R.H.</td>
<td>40</td>
<td>M</td>
<td>20  50*</td>
</tr>
<tr>
<td>R.H.</td>
<td>33</td>
<td>M</td>
<td>0   76*</td>
</tr>
</tbody>
</table>

*Valsalva.
†Epinephrine infusion.

confirmed at cardiac catheterization (table 1). In each patient a gradient across the left ventricular outflow tract was demonstrated either at rest with premature beats by Valsalva’s maneuver, or with epinephrine infusion. The infundibular chamber was also demonstrated in most cases (seven of nine) by characteristic left ventricular angiographic features in the LAO projection. The presence of a subvalvular gradient, together with apposition of ventricular septum and anterior leaflet of the mitral valve and prolonged left ventricular ejection time, was believed sufficient for exclusion of the possibilities that catheter entrapment or valvular aortic stenosis might have produced the gradient. Two patients (E.R. and L.M.) have had resection of their infundibular chambers, resulting in complete relief of their left ventricular outflow obstruction.

Epinephrine Infusion Test

One ampule of standard clinical epinephrine (1000 µg) was diluted into 250 ml of 5% dextrose and water. Epinephrine was administered in stepwise increments at each of six infusion rates selected for delivery of 0.01, 0.02, 0.03, 0.06, 0.10, and 0.18 µg/kg body weight/min (µg/kg/min). A calibrated constant infusion pump was used for delivery of the drug for 6 min at each rate. The electrocardiogram, phonocardiogram, external carotid pulse, and blood pressure were recorded during the last (sixth) minute of each infusion.

The procedure was modified for the study of the patients with IHSS. Because of the onset of chest pain at the epinephrine infusion rate of 0.06 µg/kg/min in eight patients and at 0.03 µg/kg/min in the ninth, the initial dose-response curve was terminated at that level. Propranolol was given intravenously (0.1 mg/kg) at a rate of 1 mg/min. Twenty minutes after propranolol administration was completed, the epinephrine infusion was repeated. Two normal subjects had infusion of epinephrine after beta blockade (by propranolol, 0.1 mg/kg, i.v.).

In order to define experimentally the effect of a change in heart rate, alone, on the systolic time intervals, we measured the systolic time intervals in the cardiac catheterization laboratory during right atrial pacing at various heart rates in four normal subjects.

Measurements

The Q₂ interval was measured from the onset of the QRS complex of the electrocardiogram to the first high frequency component of the second heart sound. Left ventricular ejection time (LVET) was measured from the carotid pulse to the interval from the onset of the upstroke to the trough of the incisura. The pre-ejection period (PEP) was calculated by subtraction of the LVET from the Q₂ interval. The PEP/LVET ratio was calculated and expressed as a per cent.

To minimize beat-to-beat variation, we measured systolic time intervals at end-expiration. The ejection time intervals of one cardiac cycle was determined to be an accurate sample (coefficient of variability less than 1%) of all the cardiac cycles, hence only one cycle was measured.

Results were expressed both in absolute terms (msec) and corrected for heart rate as the per cent of the expected value for the observed heart rate. The latter was calculated by:

\[
\text{Systolic time interval (per cent of expected) =} \left( \frac{\text{Observed}}{\text{Predicted}} \right) \times \text{Systolic Time interval (msec) \times 100.}
\]

The predicted systolic time interval was calculated by the regression equations of Weisler:²

Calculations:

Males

\[
Q₂ \quad (M) = -2.1 \text{ hr} + 546
\]

PEP (M) = -0.4 hr + 131

LVET (M) = -1.7 hr + 413

Females

\[
Q₂ \quad (F) = -2.0 \text{ hr} + 549
\]

PEP (F) = -0.4 hr + 133

LVET (F) = -1.6 hr + 418

Mean, standard deviation, and standard error of the mean were calculated by standard statistical methods.²

Differences in the same subject before and after a change in state were tested for significance by the t-test for paired samples. Differences between normal subjects and patients with IHSS were tested for significance by the t-test for unpaired samples.
EPINEPHRINE INFUSION IN MAN

The effect of graded epinephrine infusion on the systolic time intervals of normal subjects. ● represents the mean ± SEM for heart rate and systolic time interval. The epinephrine infusion rate is noted to the right of each marker.

Results

Normal Subjects

Epinephrine Infusion Test

See figure 1 and table 2. Epinephrine administration in the normal subjects produced a progressive rise in mean heart rate from 64.1 ± 2.5 to 90.1 ± 4.1 beats/min, (P < 0.001) and a progressive increase in mean systolic blood pressure from 123.8 ± 4.6 to 160.8 ± 11.5 mm Hg, (P < 0.01). Diastolic blood pressure fell from 75.1 ± 2.3 to 61.7 ± 4.8 mm Hg, (P < 0.01).

Coexistent with these changes in heart rate and blood pressure, there was progressive shortening of the: PEP from 91.9 ± 3.8 to 42.5 ± 3.9 msec (P < 0.001); LVET from 298.2 ± 5.9 to 251.4 ± 5.1 msec (P < 0.001); Q2 from 390.1 ± 6.8 to 294.0 ± 7.4 msec (P < 0.001); and PEP/LVET ratio from 31.0 ± 1.4 to 17.0 ± 1.4% (P < 0.001). When corrected for heart rate by the regression data of Weissler, the PEP shortened, but the LVET did not (fig. 2). The PEP decreased from 87.4 ± 3.6 to 44.8 ± 3.8% of the expected value (P < 0.001), whereas the LVET did not change significantly.

Coexistent with these changes in hemodynamics (fig. 3), the first heart sound in each normal subject became progressively louder. A third or fourth heart sound appeared, or if it were present in the control tracings, became louder. A systolic murmur developed in all subjects. Premature beats occurred infrequently. Various emotional states including anxiety, fear, and elation were experienced by normal subjects. Most were aware that their heart beat faster, but none complained of chest pain. None experienced uncontrollable emotional lability as has been reported by Frohlich.3

Epinephrine reinfusion after beta blockade in two normal subjects resulted in a slowing of
Table 2
Cardiovascular Responses to Epinephrine Infusion in 14 Normal Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control 0.01</th>
<th>Epinephrine infusion rate (μg/kg body weight/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64.1 ± 2.5</td>
<td>76.6 ± 3.2</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>123.8 ± 4.6</td>
<td>125.9 ± 5.9</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>75.1 ± 2.3</td>
<td>73.1 ± 3.7</td>
</tr>
<tr>
<td>Qs (msec)</td>
<td>390.1 ± 6.8</td>
<td>363.9 ± 7.1</td>
</tr>
<tr>
<td>LVET (msec)</td>
<td>298.2 ± 5.9</td>
<td>284.9 ± 7.6</td>
</tr>
<tr>
<td>PEP (msec)</td>
<td>91.9 ± 3.8</td>
<td>79.0 ± 4.2</td>
</tr>
<tr>
<td>LVET (% expected)</td>
<td>98.6 ± 0.9</td>
<td>101.6 ± 2.1</td>
</tr>
<tr>
<td>PEP (% expected)</td>
<td>87.4 ± 3.6</td>
<td>78.7 ± 4.2</td>
</tr>
<tr>
<td>PEP/LVET (×100)</td>
<td>31.0 ± 1.4</td>
<td>28.1 ± 1.9</td>
</tr>
</tbody>
</table>

The effect of graded epinephrine infusion on the CV time intervals corrected for heart rate in normal subjects not followed by a large change in PEP. The PEP and LVET initially lengthened and Qs shortened at low epinephrine infusion rates then shortened when corrected for changes in heart rate, with no significant change in either the systolic or diastolic blood pressure. There was no significant change in heart rate, systolic or diastolic blood pressure, Qs or LVET. There was a progressive rise in heart rate (fig. 9) and LVET (fig. 3). The PEP did not change with even large changes in heart rate (fig. 9).
The effect of epinephrine infusion (0.10 μg/kg/min) on the phonocardiogram. The rate is more rapid; S3 increases in intensity; S4 and S5 appear, and an early systolic murmur develops.

The phonocardiographic correlates were the same in the patients with IHSS as in the normal subjects except that most of the patients with IHSS had a systolic murmur during the control record, which increased in intensity with increasing epinephrine infusion rates (fig. 5).

Eight of the nine patients experienced chest pain at an epinephrine infusion rate of 0.06 μg/kg/min. One patient (E.R.) experienced chest pain and dyspnea at an epinephrine infusion rate of 0.03 μg/kg/min. In all patients the chest pain and/or dyspnea were relieved within minutes after epinephrine infusion was discontinued and propranolol (0.1 mg/kg) was administered.

Epinephrine Infusion Test after Administration of Propranolol

After beta blockade (with propranolol) the baseline systolic time intervals corrected for heart rate were not significantly different from the control measurements before blockade (table 3 and fig. 6). Reinfusion of epinephrine resulted in a decrease in heart rate and LVET corrected for heart rate, and both the systolic and diastolic blood pressures increased.

Differences in the results of epinephrine infusion in patients with IHSS before and after beta blockade were most marked at an epinephrine infusion rate of 0.06 μg/kg/min. After administration of propranolol, the heart rate was slower, 62.4 ± 3.5 compared to 95.1 ± 4.7 beats/min, (P < 0.01); the systolic blood pressure was higher, 148.1 ± 11.0 compared to 128.8 ± 9.2 mm Hg (P < 0.01); the diastolic blood pressure was higher, 86.9 ± 4.7 compared to 69.4 ± 3.9 mm Hg (P < 0.01). The PEP was longer, 98.8 ± 5.6 compared to 62.8 ± 7.3 msec (P < 0.01). When corrected for heart rate, the LVET was shorter, 104.1 ± 2.5 compared to 121.4 ± 4.1% of the expected value (P < 0.01), and the PEP was longer, 93.4 ± 6.1 compared to 68.1 ± 8.6% of the expected value (P < 0.01).

In each patient epinephrine reinfusion after beta blockade resulted in a progressive decrease in the intensity of the ejection murmur.

Comparison of Normal Subjects with Patients with IHSS

Patients with IHSS had resting heart rates that were more rapid than those of normal subjects, 76.1 ± 3.5 compared to 64.1 ± 2.5 beats/min, (P < 0.02). When corrected for heart rate, all the resting mean systolic time intervals were longer in patients with IHSS: LVET, 113.0 ± 3.8 compared to 98.6 ± 0.9% of the expected value (P < 0.01); PEP, 92.7 ± 6.9 compared to 87.4 ± 3.6% of the expected value; and Q2, 106.5 ± 3.5 compared

Figure 3

The effect of epinephrine infusion (0.10 μg/kg/min) on the phonocardiogram. The rate is more rapid; S3 increases in intensity; S4 and S5 appear, and an early systolic murmur develops.

Figure 4

The effect of right atrial pacing in four normal subjects. There is no change in PEP over a wide range of atrial pacing rates.
**Table 3**

*Cardiovascular Responses to Epinephrine Infusion in 9 Patients with IHSS before and after Beta Blockade*

<table>
<thead>
<tr>
<th>Epinephrine infusion rate (µg/kg body weight/min)</th>
<th>Before propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76.1 ± 3.5</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>130.6 ± 7.7</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>76.1 ± 4.1</td>
</tr>
<tr>
<td>Q2 (msec)</td>
<td>410.2 ± 10.9</td>
</tr>
<tr>
<td>LVET (msec)</td>
<td>317.2 ± 9.6</td>
</tr>
<tr>
<td>PEP (msec)</td>
<td>93.0 ± 6.2</td>
</tr>
<tr>
<td>Q2 (% expected)</td>
<td>106.5 ± 3.5</td>
</tr>
<tr>
<td>LVET (% expected)</td>
<td>113.0 ± 3.8</td>
</tr>
<tr>
<td>PEP (% expected)</td>
<td>92.7 ± 6.9</td>
</tr>
</tbody>
</table>

**Figure 5**

An unusual example of a patient with idiopathic hypertrophic subaortic stenosis who had no murmur and a normal carotid pulse during the control record. With epinephrine infusion (0.06 µg/kg/min), a harsh systolic murmur and characteristic carotid pulse tracing appeared. The control tracing after administration of propranolol resembled the record before propranolol was given. After administration of propranolol, reinfusion of epinephrine resulted in a slower heart rate, softer S1, and normal phonocardiogram and carotid pulse tracing.

The key feature in the epinephrine infusion test which helped identify the patient with

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IHSS was the paradoxical lengthening of the LVET corrected for heart rate at low epinephrine infusion rates (0.02 μg/kg/min) when compared to normal subjects whose LVET corrected for heart rate did not change.

Discussion

As evidenced by the dose-response curves, measurement of the systolic time intervals is a reproducible technique for measurement of the changes in left ventricular function that occur during epinephrine infusion. Normal subjects had a characteristic response—a progressive shortening of their Q2, LVET, and PEP intervals. Their heart rate and systolic blood pressure increased and their diastolic blood pressure decreased.

These results are in agreement with the results of a single epinephrine infusion rate of 5 μg/min reported by Harris. Calculations from his data show that this represents an average infusion rate of 0.07 μg/kg/min. The heart rate, Q2, LVET and PEP were: 80 beats/min, 344 msec, 280 msec, and 63 msec, respectively, in Harris' subjects. This compares favorably with 82 beats/min, 334 msec, 273 msec, and 62 msec, respectively, from our data at an infusion rate of 0.06 μg/kg/min.

Also in agreement with the data of Harris were the results of reinfusion of epinephrine after beta blockade in normal subjects. This was characterized by progressive bradycardia with increasing epinephrine infusion rates. However, there was no change in the LVET corrected for heart rate. The mechanism for this response was probably peripheral arterial constriction (an unopposed alpha-adrenergic effect) producing reflex bradycardia.

Right atrial pacing, alone, produced no shortening of the PEP over a wide range of heart rates in any normal subject studied. This agrees with data reported in patients with organic heart disease. These data imply that the shortening of PEP produced by epinephrine is a function of increased performance of the myocardium unrelated to the increase in heart rate, i.e., it reflects the inotropic rather than the chronotropic influence of the drug.

The patients with IHSS had an abnormally long resting mean LVET, presumably reflect-
The response of these patients to epinephrine infusion differed qualitatively from that of normal subjects. Although the heart rate increased, the LVET lengthened (normal subjects had shorter LVET with tachycardia). This was most marked at low epinephrine infusion rates (0.02 μg/kg/min). Three of the patients with IHSS had normal systolic time intervals at rest. Provocation by epinephrine infusion was needed for demonstration of the abnormality.

Propranolol reversed the paradoxical response to epinephrine. After beta blockade, increasing epinephrine infusion rates resulted in progressive shortening of the LVET, probably indicating diminished obstruction of left ventricular outflow.

This study emphasizes the practicality of these relatively simple methods in evaluation of left ventricular function. We have standardized an epinephrine infusion test in normal subjects and have applied it in patients with IHSS. The test is capable of demonstrating the epinephrine-induced exacerbation of this syndrome and the prevention of this effect after beta blockade.

This relatively simple test, a bioassay of the results of epinephrine administration on the left ventricular function, may offer a tool for study of the interaction of the sympathetic nervous system and the heart.

References
Epinephrine Infusion in Man: Standardization, Normal Response, and Abnormal Response in Idiopathic Hypertrophic Subaortic Stenosis
STEPHEN H. SALZMAN, MAJOR, STEVEN WOLFSON, MAJOR, BRUCE JACKSON, CAPT and ELIOT SCHECHTER, LT. COLONEL

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