DIASTOLIC TIME AFTER ATROPINE/Conrad

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SUMMARY Atropine was given intravenously to 10 normal volunteers in increments of 0.01 mg/kg to a total dose of 0.04 mg/kg. This produced an increase in heart rate from \(65 \pm 11\) to \(112 \pm 14\) beats/min, a decrease in diastolic time from \(534 \pm 131\) to \(180 \pm 65\) msec, and a decrease in percent diastole from \(55.6 \pm 5.3\%\) to \(32.4 \pm 7.2\%\) \((p < 0.001)\). Administration of isoproterenol in doses that increased heart rate from \(69 \pm 9\) to \(99 \pm 12\) beats/min produced a decrease in diastolic time from \(485 \pm 98\) to \(312 \pm 47\) msec and only a slight decrease in percent diastole, from \(54.2 \pm 4.3\%\) to \(50.6 \pm 3.9\%\). Atropine, in doses commonly used clinically, may significantly reduce diastolic time and the percent diastole. Because diastolic time is an important determinant of coronary perfusion, administration of atropine to patients with coronary artery disease may increase myocardial ischemia.

DIASTOLIC TIME is an important determinant of subendocardial perfusion and, therefore, of myocardial oxygenation. The effects of various pharmacologic agents on diastolic time and percent diastole have been described recently. A significant increase in percent diastole occurs after administration of propranolol, dobutamine and cedilanid; isoproterenol significantly reduces percent diastole. Atropine is frequently used in patients who have acute myocardial infarction. This study was conducted because the effects of this drug upon diastolic time have not been assessed. The effects of propranolol and isoproterenol on diastole were also studied to confirm the work of other investigators and to compare the effects of these drugs, particularly isoproterenol, with those of atropine.

Methods

Twenty-one normal subjects, 16 males and five females, ages 22–33 years, were selected for participation in the study. Serial systolic time intervals (STIs) were measured before and after the administration of atropine, propranolol or isoproterenol as outlined below.

Group 1 consisted of five male and five female volunteers who received i.v. atropine in increments of 0.01 mg/kg to a total dose of 0.04 mg/kg. STIs were measured 5 minutes after administration of each dose of atropine.

Group 2 consisted of 11 male volunteers who were given a standard isoproterenol test, consisting of administration of increments of isoproterenol as follows: 0.5, 1, 2, 5, 10, 20, 50, 100 and 200 \(\mu\)g until the heart rate increased by at least 25 beats/min. STIs were measured after each dose of isoproterenol. The volunteers returned for another study no earlier than 2 weeks after the isoproterenol test. At that time, resting STIs were measured and propranolol, 40 mg by mouth four times a day, was given. The next day, the STIs were measured one more time.
The STIs were measured, with the subject in the supine position, between 8 a.m. and 10 a.m. Left ventricular ejection time (LVET) was measured by ear densitometry. ECG and phonocardiogram were recorded in the usual fashion. The QS₂ was measured from the onset of ventricular depolarization to the first high-frequency vibration of the aortic sound. The preejection period (PEP) was calculated by subtracting LVET from QS₂. Blood pressure was measured in the arm not used for drug infusion. The standard Korotkoff technique was used, taking phase V (disappearance of sounds) as the diastolic pressure.

Diastolic time was calculated as the cycle length (RR) minus electromechanical systole (QS₂). The percent of diastole was calculated as the ratio of diastolic time to the RR times 100. The percent diastole was compared with that predicted by the polynomial equation(s) described earlier:

\[
\text{Diastole (males)} = 100 - \frac{546}{600} \times \text{HR} + \frac{2.1}{600} \times (\text{HR})^2 \quad (1)
\]

\[
\text{Diastole (females)} = 100 - \frac{549}{600} \times \text{HR} + \frac{2.0}{600} \times (\text{HR})^2 \quad (2)
\]

where HR = heart rate.

Statistical Methods

Changes in heart rate, blood pressure, diastolic time and percent diastole were evaluated by use of repeated measures analysis of variance test. Where differences were identified, the level of significance was calculated by use of the Newman-Keuls test. The changes in QS₂, PEP and LVET with increasing heart rate after atropine and isoproterenol were analyzed by linear regression. The significance of differences between the slopes of QS₂, PEP and LVET plotted as a function of heart rate (i.e., slope after atropine vs slope after isoproterenol) was determined using a modification of the t test.

Results

Group 1

Administration of atropine produced a decrease in QS₂ that was less than that which would be expected to occur as a result of the spontaneous variation in heart rate described by Weissler et al. (fig. 1A). There was no significant difference between males and females in the QS₂ response to atropine. The relationship between QS₂ and heart rate after atropine may thus be described as

\[
\text{QS}_2 = -1.202 \times (\text{HR}) + 494 \quad (3)
\]

The correlation coefficient \(r\) for equation 3 is -0.86 \((p < 0.001)\).

Similarly, the decrease in LVET that occurred with atropine was less than that predicted by Weissler (fig. 1B). Again, there was no significant difference between males and females in LVET response to atropine. The relationship between LVET and heart rate was

\[
\text{LVET} = -1.04 \times (\text{HR}) + 378 \quad (4)
\]

The correlation coefficient \(r\) for equation 4 is 0.87 \((p < 0.001)\). The PEP did not change after atropine (fig. 1C).

The systolic blood pressure increased from 111 ± 12 to 128 ± 8 mm Hg after 0.04 mg/kg atropine \((p <\)
Diastolic time after atropine/Conrad 0.005). Diastolic blood pressure increased from 69 ± 10 to 94 ± 6 mm Hg (p < 0.01).

The duration of diastole was shortened by atropine to a similar degree in males and females (table 1). Therefore, these results will also be discussed in terms of the group as a whole. Administration of 0.01 mg/kg atropine produced an increase in heart rate of only 12 beats/min, but shortened diastolic time from 534 ± 131 to 394 ± 87 msec (p < 0.001). The percent diastole was reduced from 55.6 ± 5.3% to 49.2 ± 4.6% (p < 0.001) (fig. 2). There was a progressive shortening of diastolic time and percent diastole after administration of each additional increment of atropine. The percent diastole as a function of heart rate is shown in figure 3. After the heart rate exceeded 70–75 beats/min, the percent diastole dropped below the predicted value. At the highest dose of atropine, the diastolic time was only 180 ± 65 msec and percent diastole was 32.4 ± 7.2%; the heart rate at this dose of atropine averaged 112 beats/min.

Combining the regression equation for QS after atropine (equation 3) with that used to calculate per-

![Figure 1](https://example.com/figure1.png)

**Figure 1.** (A) The change in QS after atropine and isoproterenol. The solid lines represent the best fit of data obtained after the drugs. The dashed line represents the slope predicted by Weissler. Circles represent males; triangles represent females. (B) The change in left ventricular ejection time (LVET) after atropine and isoproterenol. (C) The change in preejection period (PEP) after atropine and isoproterenol.
Table 1. Effects of Atropine on Diastolic Time

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>HR (beats/min)</th>
<th>DT (msec)</th>
<th>%D</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>66</td>
<td>506</td>
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</tr>
<tr>
<td>2</td>
<td>M</td>
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<td>M</td>
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<tr>
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<td>M</td>
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<td>M</td>
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<td>6</td>
<td>F</td>
<td>54</td>
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<td>F</td>
<td>66</td>
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<td>8</td>
<td>F</td>
<td>73</td>
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<td>9</td>
<td>F</td>
<td>68</td>
<td>478</td>
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</tr>
<tr>
<td>10</td>
<td>F</td>
<td>54</td>
<td>677</td>
<td>60.9</td>
</tr>
</tbody>
</table>

The level of significance of the difference between the value given and that at the preceding dose of atropine:

* p < 0.025,
† p < 0.01,
‡ p < 0.001.
§ p = NS.

Abbreviations: HR = heart rate; DT = diastolic time; %D = percent diastole.

cent diastole (%D = [RR - QS₂] / RR × 100), the percent diastole after atropine shortens as follows:

\[ \text{Diastole} = 100 - \frac{494}{600} \cdot \text{HR} + \frac{1.2}{600} \cdot \text{HR}^2 \]  \hspace{1cm} (5)

![Graph showing percent diastole and heart rate after atropine.](image)

**Group 2**

Isoproterenol produced an increase in heart rate, from 69 ± 9 to 99 ± 12 beats/min. However, the changes in systolic time intervals after isoproterenol were significantly different from those after atropine.

The QS₂ (fig. 1A) shortened more after isoproterenol than would be expected by spontaneous variation in heart rate:\[ QS₂ = -2.626 \cdot \text{HR} + 576 \]  \hspace{1cm} (6)

The correlation coefficient for equation 6 is \(-0.90\) (\(p < 0.001\)). This regression equation is different from that after atropine (equation 3) at the \(p < 0.001\) level.

The LVET (fig. 1B) shortened to the extent predicted by Weissler:\[ \text{LVET} = -1.358 \cdot \text{HR} + 393 \]  \hspace{1cm} (7)

The correlation coefficient for equation 7 is \(-0.78\) (\(p < 0.001\)). This equation is also different from that due to atropine (equation 4) at the \(p < 0.001\) level.

The PEP (fig. 1C) shortened significantly with isoproterenol:

\[ \text{PEP} = -1.27 \cdot \text{HR} + 185 \]  \hspace{1cm} (8)

The correlation coefficient for equation 8 is 0.80 (\(p < 0.001\)). This change is much more dramatic than the slight change in PEP described by Weissler and contrasts with the lack of effect of atropine upon PEP.

The systolic blood pressure was 118 ± 6 mm Hg before isoproterenol and 134 ± 1 mm Hg at the maximal dose of isoproterenol (\(p < 0.001\)). However, diastolic blood pressure after isoproterenol was 50 ± 10 mm Hg, compared with 70 ± 6 mm Hg in the con-
control state ($p < 0.001$). Mean arterial pressure actually decreased from $86 \pm 4$ to $78 \pm 6$ mm Hg ($p < 0.001$) with isoproterenol.

Diastolic time declined from $485 \pm 98$ to $312 \pm 47$ msec at the maximal dose of isoproterenol. The percent diastole decreased also, but only from $54.2 \pm 4.3\%$ to $50.6 \pm 3.9\%$. This change is not as marked as would be predicted at the heart rate achieved (fig. 4). In no case did diastolic time or the percent diastole decrease as dramatically with isoproterenol as they did with atropine.

Oral administration of propranolol caused a reduction in heart rate and an increase in percent diastole that was exactly as predicted by equation 1 (fig. 5).

**Discussion**

This study demonstrated a significant difference in the effects of atropine and isoproterenol upon electromechanical systole and, as a consequence, on diastolic time.

Atropine produces changes in supine STIs that are similar to those produced by atrial pacing. The QS$_2$ shortens with both atrial pacing and with atropine, but this shortening is less than the shortening of QS$_3$ with spontaneous variation in heart rate or that produced by isoproterenol. This is because the shortening of LVET with pacing and atropine is less than expected and because the PEP does not shorten after these interventions. Although increases in blood pressure may produce an increase in LVET, it is not likely that this plays an important role in the changes produced by atropine, because the changes in LVET reported here are similar to those seen with pacing (where blood pressure changes are usually minimal) and because systolic pressure increased only 17 mm Hg after the highest dose of atropine.

**Figure 3.** Percent diastole before and after administration of atropine. The open symbols are values obtained before atropine administration; the closed symbols are values after atropine. Circles represent males; triangles represent females. The solid line represents the percent diastole predicted at the heart rate achieved.3
As a result of these changes in QS, diastolic time decreases more rapidly after atropine than expected. Significant shortening of diastole after atropine may be noted even as the heart rate exceeds 75 beats/min. Although the effect of atropine is maximal at a dose of 0.04 mg/kg, a significant reduction in percent diastole occurs after only 0.01 mg/kg.

During infusion of isoproterenol, the percent diastole is preserved as tachycardia develops as a consequence of the expected catecholamine-induced shortening of both components of QS — PEP and LVET. In fact, because QS shortens more after isoproterenol than predicted, the percent diastole is actually slightly higher than expected.

Myocardial perfusion occurs primarily in diastole. Patients with obstruction to coronary flow may lose coronary flow during systole because the perfusion pressure distal to the obstruction is less than systolic ventricular wall pressure. Myocardial blood flow in these patients, as well as in those with left ventricular hypertrophy, may depend upon diastolic perfusion time as well as perfusion pressure.

Several case reports of atropine-induced ventricular fibrillation have appeared in the literature. Development of ventricular fibrillation may relate to the fact that in patients with coronary artery disease, myocardial blood flow does not increase after atropine administration. In fact, increased myocardial ischemia has been demonstrated in patients with myocardial infarction after atropine.

Atropine seems to be unique among pharmacologic agents in its potent reduction of diastolic time. This reduction may play an important role in the development of myocardial ischemia after atropine. Administration of this drug to patients with coronary artery disease and bradycardia should be considered only if bradycardia is producing symptoms and if no other methods of treatment, such as elevation of the legs, are effective in improving cardiovascular performance.

References
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