EFFECTS OF ATROPINE ON CARDIAC RHYTHM IN CONSCIOUS AND ANESTHETIZED MAN

R. E. JONES, M.D., S. DEUTSCH, M.D., PH.D., H. TURNDORF, M.D.

It is well known that atropine has a peripheral parasympatholytic effect which results in an increase in cardiac rate, preceded in a certain number of instances by transient cardiac slowing.

Less familiar are the electrocardiographic alterations which frequently follow the administration of atropine to normal man. A-V dissociation was first reported by Wilson in 1915 and more recently has been described in detail as the electrocardiographic alteration most frequently noted following the intravenous administration of atropine to normal man. Other types of arrhythmias also occur, including nodal and ventricular extrasystoles. Atropine can, depending on dose, either stimulate or block vagal activity, and the arrhythmias noted after its administration may be attributable to these actions.

General anesthetic agents affect both sympathetic and parasympathetic activity, suggesting that responses to atropine might differ in conscious and anesthetized persons. That this is true has been demonstrated in this study. The findings of greatest interest were the high incidence of ventricular arrhythmias (over 50 per cent) in patients anesthetized with cyclopropane, contrasted with their complete absence in unanesthetized subjects, and in subjects anesthetized with ether or oxygen or with thiopental, nitrous oxide and oxygen. On the other hand, supraventricular arrhythmias were frequent in conscious subjects but much less so during all four types of general anesthesia.

Since atropine is administered frequently to patients who will be or are receiving general anesthetics, we believe that this study contributes information of practical importance to anesthetists. Beyond this, modifications of the electrocardiographic responses to atropine afford evidence regarding the autonomic actions of various anesthetics.

METHODS

Studies were conducted on 7 healthy young subjects who were not anesthetized and 46 healthy patients anesthetized as follows: 13 with cyclopropane and oxygen, 12 with halothane and oxygen, 11 with ether and oxygen, and 10 with thiopental, nitrous oxide and oxygen. The patients ranged in age from 18 to 73 years. Twenty-nine were young women scheduled for minor gynecological procedures. The remaining 17, eleven of whom were male, were scheduled for minor surgical procedures. With three exceptions, all studies were completed before operation was begun.

Atropine sulfate was administered intravenously, and 0.4 mg. was used in all instances except in 8 of those patients anesthetized with cyclopropane who received various amounts as indicated in the text under results.

Continuous electrocardiographic recordings (lead 2) were made before, during and for a minimum of five minutes after each administration of atropine. Arterial pressure was measured simultaneously. In 8 of the 13 who were anesthetized with cyclopropane and in 4 of the unanesthetized subjects, arterial pressure was measured directly through a needle placed in a brachial artery. In the remainder, the Riva-Rocci auscultatory method was used. Measurements were made for periods longer than five minutes if electrocardiographic alterations persisted. In the 8 individuals anesthetized with cyclopropane in whom direct arterial pressure measurements were made, carbon dioxide tension in the expired gases was measured with an infrared analyzer utilizing the microcatheter technique of Collier, Affeldt and Farr. These were corrected for the effect of cyclopropane on the infrared analyzer, and for the tension of water...
TABLE 1
ARRHYTHMIAS AND CHANGES IN CARDIAC RATE AND BLOOD PRESSURE DURING ANESTHESIA AFTER PREMEDICATION WITH ATROPINE

<table>
<thead>
<tr>
<th>Anesthetic Agent</th>
<th>Unanesthetized</th>
<th>Thiopental-N₂O</th>
<th>Ether</th>
<th>Halothane</th>
<th>Cyclopropane</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Per Cent</td>
<td>No.</td>
<td>Per Cent</td>
<td>No.</td>
<td>Per Cent</td>
</tr>
<tr>
<td>Arhythmia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>85.7</td>
<td>0</td>
<td>9.1</td>
<td>41.7</td>
<td>70.9</td>
</tr>
<tr>
<td>Ventricular</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16.7</td>
</tr>
<tr>
<td>Supra-Ventricular (including nodal)</td>
<td>85.7</td>
<td>0</td>
<td>9.1</td>
<td>25.0</td>
<td>23.0</td>
</tr>
<tr>
<td>Mean cardiac rate before atropine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change produced by atropine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>-9.6 ± 6.1</td>
<td>22 ± 11.9</td>
<td>54 ± 21</td>
<td>37 ± 9.1</td>
<td>67 ± 21.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>4.0 ± 5.7</td>
<td>6.9 ± 8.4</td>
<td>15 ± 15</td>
<td>16 ± 9.6</td>
<td>16 ± 28.9</td>
</tr>
<tr>
<td>4 minutes after injection</td>
<td>6.0 ± 4.1</td>
<td>9.0 ± 9.8</td>
<td>12 ± 11.5</td>
<td>13 ± 6.6</td>
<td>10.5 ± 7.2</td>
</tr>
</tbody>
</table>

Results

A summary of all observations is presented in table 1. The changes in cardiac rate and arterial pressure are those measured four minutes after administration of atropine.

Unanesthetized Subjects. Electrocardiographic alterations occurred in 6 of the 7 subjects. In three A-V dissociation with interference developed, the P waves remaining upright but moving in and out of the QRS complexes. This abnormality persisted two to four minutes followed by reversion to sinus rhythm.

In two others of the 6 who developed alterations, there was A-V dissociation with retrograde excitation of the atria as evidenced by P-wave inversion and P-R intervals less than 0.10 second. Both had nodal extrasystoles which caused the sensation of palpitation. In one of these, the dissociation persisted for four, and in the other for fifty-three minutes, although the nodal extrasystoles disappeared within four minutes.

The sixth subject with electrocardiographic alterations developed a nodal rhythm characterized by an apparent absence of P waves. This abnormality has been called A-V dissociation with synchronization and is said to occur when the sinus and atrioventricular nodes are

vapor at 24 degrees centigrade. The remaining subjects were thought by the anesthetist and the investigators to have adequate pulmonary ventilation.

In patients receiving cyclopropane, analyses of end-expired gas samples for cyclopropane content were made by absorption in 31N sulfuric acid. These concentrations ranged between 9 and 28 volumes per cent. When halothane was used, inspired concentrations ranging from 0.75 to 2.6 volumes per cent were delivered by adjustment of a "Fluotee" previously calibrated by thermal conductivity and shown to deliver within 0.3 volumes per cent of the selected concentration. Thiopental and diethyl ether concentrations in blood ranged from 2–3 and 80–120 mg. per cent respectively. Cardiac rate was determined from the electrocardiographic record by counting all ventricular complexes occurring within one minute.

Of the 46 patients given anesthesia, 8 anesthetized with cyclopropane, one with ether and one with halothane, received no preanesthetic medication. The remaining 30 received, intramuscularly, 0.4 or 0.6 mg. of atropine or scopolamine and in most instances 100 mg. of secobarbital sodium.
activated simultaneously. The result is that the
P waves are obscured within the QRS com-
plexes. More commonly, however, this electro-
cardiographic pattern is designated simply as a
nodal rhythm, the explanation for the absence
of the P waves being that the pacemaker in the
A-V node produces retrograde conduction
within the atrium, the inverted P waves being
unrecognizable in the QRS complexes.

In all subjects but one there was a reduction
in cardiac rate which persisted an average of
five minutes following the administration of
atropine. The subject whose cardiac rate was
not reduced developed A-V dissociation.

Arterial pressure tended to increase slightly.

*Thiopental and Nitrous Oxide.* None of the
10 patients developed electrocardiographic
abnormalities. Cardiac rate increased, from
10 to 45 per minute, in all but one in whom
there was no change.

Arterial pressure was unaltered in 2 and
elevated in 8.

*Ether.* One of 11 patients developed a
cardiac arrhythmia. This was A-V dissociation
with interference which persisted for 30 sec-
onds, then reverted to sinus rhythm. All
patients developed increase in cardiac rate,
the mean increase being more than twice that
observed in those anesthetized with thioental,
nitrous oxide and oxygen.

Arterial pressure was elevated in 8, un-
changed in two and depressed in one patient.

*Halothane.* Five of the 12 patients de-
veloped electrocardiographic irregularities. In
three the abnormality was A-V dissociation
with interference. This persisted for 21 sec-

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**TABLE 2**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>End-Exp. Cycle (Vol. 28)</th>
<th>End-Exp. Press. (mm. Hg)</th>
<th>Total Dose Atropine (mg.)</th>
<th>Initial Dose Atropine (mg.)</th>
<th>Interval between First and Last Inf. of Atropine (min.)</th>
<th>Electrocardiographic Alteration</th>
<th>Type</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td></td>
<td>0.4</td>
<td>0.4</td>
<td>*</td>
<td>45 sec. A-V Dissociation with Interference</td>
<td>Type</td>
<td>Duration</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td></td>
<td>0.4</td>
<td>0.4</td>
<td>*</td>
<td>104 sec. Occasional Vent. Extrasystoles</td>
<td>2 Min.</td>
<td>1 Min.</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td></td>
<td>0.4</td>
<td>0.4</td>
<td>*</td>
<td>35 sec. 1st Heart Block</td>
<td>3 Min.</td>
<td>1 Min.</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td></td>
<td>0.4</td>
<td>0.4</td>
<td>*</td>
<td>30 sec. Bigeminy</td>
<td>7 Min.</td>
<td>1 Min.</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>37</td>
<td>0.4</td>
<td>0.4</td>
<td>*</td>
<td>51 sec. Bigeminy-Vent. Alternating with sinus</td>
<td>11 Min.</td>
<td>5 Min.</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>38</td>
<td>0.2</td>
<td>0.2</td>
<td>*</td>
<td>45 sec. Multifocal Vent. Tachycardia</td>
<td>3 Min.</td>
<td>1 Min.</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>37</td>
<td>0.6</td>
<td>0.6</td>
<td>*</td>
<td>10 sec. Nodal Extrasystoles</td>
<td>32 Min.</td>
<td>5 Min.</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>41</td>
<td>0.8</td>
<td>0.1</td>
<td>23</td>
<td>57 sec. Bigeminy-Vent. Alternating with sinus</td>
<td>9 Min.</td>
<td>7 Min.</td>
</tr>
<tr>
<td>9</td>
<td>16</td>
<td>33</td>
<td>0.8</td>
<td>0.2</td>
<td>18</td>
<td>30 sec. A-V Dissociation/Interfer.</td>
<td>18 Min.</td>
<td>3 Min.</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>45</td>
<td>0.8</td>
<td>0.2</td>
<td>13</td>
<td>30 sec. 1st Block</td>
<td>1 Min.</td>
<td>4 Min.</td>
</tr>
<tr>
<td>11</td>
<td>19</td>
<td>42</td>
<td>0.8</td>
<td>0.1</td>
<td>17</td>
<td>A-V Dissociation with Synchronization</td>
<td>Increased sinus rate</td>
<td>2 Min.</td>
</tr>
<tr>
<td>12</td>
<td>14</td>
<td>48</td>
<td>0.8</td>
<td>0.2</td>
<td>8</td>
<td>Increased sinus rate</td>
<td>8 Min.</td>
<td>2 Min.</td>
</tr>
<tr>
<td>13</td>
<td>14</td>
<td>38</td>
<td>0.8</td>
<td>0.2</td>
<td>10</td>
<td>Increased sinus rate</td>
<td>10 Min.</td>
<td>2 Min.</td>
</tr>
</tbody>
</table>

* Rapid single injection.
atropine (0.6 mg.), was also one of the two most deeply anesthetized. The arterial and electrocardiographic recordings made during the period of ventricular tachycardia are reproduced in figure 1. This patient was a healthy 34 year old white female scheduled for an elective dilatation and curettage of the cervix and uterus. At the time of administration of the atropine sulfate she had been anesthetized 42 minutes, with an endotracheal tube in place for 35 minutes. Respirations were controlled by hyperventilation.

Six patients at moderate depths of anesthesia (expired cyclopropane concentrations of 14 to 19 volumes per cent) were given 0.9 mg. of atropine in increments of 0.1 or 0.2 mg. The interval between each increment was 2 minutes or longer. Three did not develop an arrhythmia, A-V dissociation occurred in two, and a ventricular arrhythmia in one.

Considering all thirteen patients, the average cyclopropane concentration at which ventricular arrhythmias occurred was 22.2 ± 4.2 (S.D.) volumes per cent as compared to 13.3 ± 3.2 volumes per cent in patients who developed only supraventricular arrhythmias. This difference was statistically significant (P < 0.05).

Atropine produced an increase in cardiac rate in every patient anesthetized with cyclopropane. The mean increase during ventricular arrhythmias (71.9 ± 24.8) was significantly greater than that during supraventricular arrhythmias (42.6 ± 9.7) (P < 0.05). The mean increase in those who developed only sinus tachycardia was 63.3 ± 9.1.

Arterial pressure increased in 8, decreased in two and was unchanged by atropine in three of the 13 patients anesthetized with cyclopropane. Both of those in whom arterial pressure decreased developed only sinus tachycardia. The mean changes in systolic and diastolic pressure of the group were comparable to those seen in the patients anesthetized with halothane and ether (table 1).

**Discussion**

In normal man the intravenous administration of 0.4 mg. of atropine does not produce an apparent block of the cardiac vagus nerves. Morton and Thomas reported that this amount led to cardiac slowing, and that 0.6 mg. or
more was necessary to produce an increase in cardiac rate. They found that the increase in cardiac rate caused by amounts of atropine over 0.6 mg. was proportional to the dose. It has been our experience that amounts ranging from 1.2 to 2.0 mg. of atropine administered intravenously are necessary before complete vagal blockade is accomplished, as evidenced by the absence of further increases in cardiac rate in response to additional atropine. Filcher and Sollman found that similar amounts (0.02 and 0.04 mg./kg.) were required in unanesthetized dogs.

Cardiac slowing seen with comparatively small amounts of atropine has been hypothesized as due to direct stimulation of the vagal nuclei. Regardless of site of action, the electrocardiographic alterations produced by 0.4 mg. of atropine administered intravenously are similar to those seen following vagal stimulation or administration of acetylcholine. The latter has been shown in dogs and cats not only to slow the atrial rate but to produce as well a negative inotropic effect on the auricle. The effect on the ventricle is negligible, presumably because only the uppermost portion of this chamber receives vagal fibers. Acetylcholine has no effect on the heart of a chick embryo before the vagal fibers have grown into it but affects ventricles and auricles alike in the frog heart in which vagal fibers are supplied equally to both.

It seems reasonable that a given amount of atropine might be expected to produce different cardiac effects depending on the amount of existing vagal activity. We shall attempt to explain the results noted in this study in terms of the effects of the anesthetics used on autonomic balance.

**Effects of Anesthetics on Vagal Activity.** In the presence of normal vagal activity it has been noted that the initial response to 0.4 mg. of atropine administered intravenously is one of vagal stimulation. This was observed in the form of bradycardia and A-V dissociation in our unanesthetized subjects. Similar effects were seen to precede tachycardia in all patients anesthetized with cyclopropane or halothane. It is thought that both these drugs enhance vagal tone. In the case of halothane, the bradycardia, hypotension and elevation in central venous pressure, usually corrected by the administration of atropine, are cited as evidence of vagal stimulation. Atrial pressure is also increased during cyclopropane anesthesia and in the case of both drugs may be a reflection of the negative inotropic effect of vagal activity upon the auricle. The existence of significant vagal stimulation during cyclopropane anesthesia can also be inferred from the fact that despite considerable sympathetic stimulation evoked by that agent, cardiac rate is not increased.

In contrast to those anesthetized with cyclopropane and halothane, patients anesthetized with ether or thiopental and nitrous oxide developed neither bradycardia nor A-V dissociation but only an increase in cardiac rate after receiving 0.4 mg. atropine. Ether produces vagal blockade rather than stimulation, and in patients anesthetized with this drug, the mean cardiac rate of 95 was significantly higher than in those anesthetized with cyclopropane or halothane.

The mean heart rate of 85, observed in those anesthetized with thiopental and nitrous oxide would suggest, if not vagal block, at least that there was not vagal stimulation during anesthesia produced with this combination. That vagal stimulation follows the intravenous administration of 0.4 mg. atropine only in the presence of a significant amount of vagal tone is suggested by the fact that patients anesthetized with thiopental and nitrous oxide or ether did not, while those anesthetized with cyclopropane or halothane did, manifest evidence of such stimulation.

**Effects of Anesthetics on Sympathetic Activity.** It has been said that because adrenergic impulses become dominant and unopposed, the end result of the administration of bellaromia alkaloids simulates over-activity of the sympathetic nervous system resembling the response to an injection of epinephrine. If one assumes that the magnitude of the tachycardia which follows the administration of a standard amount of atropine reflects the quantity of sympathetic activity which is unmasked, the unanesthetized subjects in this study would seem to have displayed the least such activity.

Using this criterion we would list, in order of increasing sympathetic activity, (1) conscious subjects and patients anesthetized with (2) thiopental and nitrous oxide, (3) halo-
thane, (4) ether, and (5) cyclopropane. Justification for this sequence can be found in studies of the effects of these drugs on the sympathetic nervous system. The administration of cyclopropane results in a considerable stimulation of the sympathetic nervous system, manifest in most patients by an elevation in arterial pressure, cardiac output and plasma catecholamine concentration.18-21 These effects can be reversed by sympathetic blockade. That increased sympathetic stimulation results from deeper cyclopropane anesthesia is suggested by the correlation between plasma catecholamines and cyclopropane concentrations.22 This may explain the significantly higher incidence of ventricular arrhythmias in patients more deeply anesthetized. As previously noted, every patient anesthetized with cyclopropane developed bradycardia, A-V dissociation or both after administration of atropine. Every ventricular arrhythmia was immediately preceded by one or both of these phenomena, suggesting that, with suppression of the normal pacemaker, impulses "escaped" from foci in the ventricular myocardium sensitized to catecholamines by cyclopropane and stimulated by an excess of sympathetic activity.

Ether also produces significant sympathetic stimulation as measured by plasma catecholamine concentration.21,22 Unlike that to cyclopropane this response to ether is less predictable and bears no consistent relation to the concentration of anesthetic in the blood.21

The exaggeration of cardiovascular depression which results from sympathetic inactivation in patients anesthetized with halothane, suggests that an intact sympathetic nervous system responds to halothane with mild protective activity.18 This response is relatively weak when compared with that produced by ether and cyclopropane as indicated by the absence of a consistently measurable increase in plasma catecholamine concentration during halothane anesthesia.21

Little is known of the effect of the combination of thiopental and nitrous oxide on the sympathetic nervous system other than, like halothane, it stimulates no measurable increase in plasma catecholamine concentrations.21 The comparatively minor response to atropine in terms of tachycardia which was observed in the patients anesthetized with thiopental and nitrous oxide seems to indicate the presence of little or no sympathetic activity. Clinical Implications. The administration of atropine intravenously prior to the injection of prostigmine or in order to block untoward reflexes occurring during the course of anesthesia is a not uncommon clinical practice. Seldom is thought given to the possibility of harm. This lack of concern is unjustified when the anesthetic agent is cyclopropane. Ventricular arrhythmias, some of which were alarming, occurred with significant incidence in the group of healthy patients involved in this study. It is unlikely that many of these would have been noted, much less properly diagnosed, without the aid of an electrocardiographic record.

Had our patients had cardiovascular disease the results might have been serious. Prior to this study, one of the authors had anesthetized a young woman with cyclopropane for mitral commissurotomy and had administered 0.4 mg. of atropine intravenously to treat bradycardia and hypotension which developed immediately after finger fracture of the valve. Ventricular fibrillation ensued in less than a minute and resuscitative efforts failed. In retrospect, it seems that fibrillation might have been caused by the sudden release of an overwhelming amount of sympathetic activity upon a myocardium already ischemic and sensitized to catecholamines. The result could not have been more final had epinephrine been administered.

Our data suggest that when the intravenous injection of atropine is indicated during cyclopropane anesthesia, it should be administered slowly and in small doses (0.2 mg.). Of the 6 patients to whom atropine was given in fractional doses, only one developed a ventricular arrhythmia despite the fact that the total dose approximated 1 mg. This is in sharp contrast to the 6 of 7 who developed such arrhythmias following the rapid administration of atropine. The hazard is also considerably less when low concentrations of cyclopropane are used.

Summary

In 11 individuals anesthetized with ether, which stimulates sympathetic and depresses vagal activity, the result of the administration
of 0.4 mg. of atropine intravenously was a marked sinus tachycardia.

When cyclopropane, which produces both vagal and sympathetic stimulation, was used as the anesthetic in 13 patients the result was dependent on the anesthetic concentration. When this was low, the immediate usual response was that of vagal stimulation which was followed by tachycardia. With higher concentrations of cyclopropane, which invoke a greater sympathetic response, signs of vagal stimulation were often followed by or associated with ventricular arrhythmias and a pronounced tachycardia which reflected the increase in sympathetic activity.

During halothane anesthesia in 12 patients which increases vagal, but little affects sympathetic function, the initial response was one of vagal stimulation following which there was only a modest increase in heart rate, an expression of the relatively slight sympathetic stimulation.

Atropine, in the amount used, produced the least effect on 10 patients who were anesthetized with thiopental, nitrous oxide and oxygen. There was no evidence of vagal stimulation and a comparatively minor increase in cardiac rate, suggesting little vagal or sympathetic tone.

The mechanisms and clinical significance of these responses are discussed.

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REFERENCES


