Antagonistic Effects on the Sinus Node of Acetylstrophanthidin and Adrenergic Stimulation

By Reginald A. Nadeau, M.D., and Thomas N. James, M.D.

In a previous study with direct perfusion of the canine sinus node it was shown that high concentrations of rapid acting cardiac glycosides slowed the heart rate and caused sinus arrest. This negative chronotropic effect was not modified by vagotomy or atropine. It was further observed that epinephrine injected into the sinus node artery transiently restored sinus rhythm when arrest followed perfusion of either acetylstrophanthidin or digoxin.

In the present work the accelerator response of the sinus node to epinephrine and to right stellate ganglion stimulation was determined before and at regular intervals after direct perfusion with acetylstrophanthidin.

**Methods**

Twelve dogs weighing 10 to 15 kg were anesthetized with intraperitoneal pentobarbital sodium (30 mg/kg). After tracheal intubation for mechanical ventilation, the heart was exposed through a midsternal incision. A small polyethylene catheter was inserted into the ligated distal portion of the right coronary artery and wedged into the branch supplying the sinus node. The details of the preparation have been described elsewhere. Acetylstrophanthidin for sinus node perfusion was prepared at concentrations of 0.5 and 1 µg/ml in Ringer's solution. Epinephrine hydrochloride was diluted in Ringer's to a concentration of 0.1 µg/ml for injection into the sinus node artery.

The right stellate ganglion was exposed in the thorax and stimulated with an electronic square wave stimulator, at a frequency of 30 impulses/sec, with an impulse duration of 1 msec at supramaximal intensity, for periods of 6, 10, or 20 seconds.

The basal heart rate and the maximum acceleration obtained from epinephrine injection into the sinus node artery and from right stellate stimulation were determined from an electrocardiogram. The increment in heart rate obtained was expressed as a percentage of the basal rate preceding adrenergic stimulation, a method employed by Rosenbluth and Simone and by Méndez et al.

**Results**

**The Effect of Acetylstrophanthidin Perfusion of the Sinus Node on the Positive Chronotropic Effect of Epinephrine Injected into the Sinus Node Artery**

As described elsewhere, epinephrine 0.1 µg/ml injected directly into the sinus node artery during a 30-second period produces a characteristic immediate acceleration of the heart rate. In five experiments the response to epinephrine was compared before and after a two-minute perfusion of the sinus node with acetylstrophanthidin 2.5 µg in a 5-ml volume.

In four of the five experiments the maximum acceleration obtained from epinephrine was reduced after acetylstrophanthidin, as recorded in table 1. The greatest reduction in accelerator response occurred between 4 and 11 minutes after the acetylstrophanthidin perfusion. The actual increment in heart rate in all five experiments averaged 24 beats/min less than control during this period. The mean control acceleration from epinephrine equaled 41.7% of the basal heart rate, while after acetylstrophanthidin the mean acceleration obtained was 23.5%. A return to a control response, determined as a per cent increase in rate, was recorded within 10 to 45 minutes in these five experiments.

Figure 1 illustrates one of the experiments. In part A the increase in heart rate with each epinephrine injection is recorded by a verti-
ANTAGONISM OF ACETYLSTROPHANTHIDIN AND EPINEPHRINE

FIGURE 1

A. Action of acetylstrophanthidin on the response of the sinus node to epinephrine. Ordinate: heart rate per minute. Abscissa: time in minutes before and after acetylstrophanthidin. Arrow: injection of acetylstrophanthidin into the sinus node artery (2.5 µg in 5 ml in two minutes). Bars: change in heart rate from epinephrine injection into the sinus node artery (0.1 µg in 1 ml in 30 seconds).

B. Ordinate: increase in heart rate expressed as a percentage of the basal rate. Abscissa: time in minutes before and after acetylstrophanthidin (at arrow).

The effect of acetylstrophanthidin perfusion of the sinus node on the cardoaccelerator effect of right stellate stimulation.

In six experiments the right stellate was stimulated before and after perfusing the sinus node with acetylstrophanthidin (2.5 µg/5 ml) for two minutes. A typical experiment is illustrated in figure 2. In all six experiments the maximum acceleration obtained from right stellate ganglion stimulation was less after acetylstrophanthidin than before. The reduction in accelerator response was most marked within 6 to 15 minutes, and aver-

TABLE 1

Comparative Acceleration of the Sinus Node from Intranodal Epinephrine (0.1 µg in 1 ml for 30 Seconds) Before and After Perfusion with Acetylstrophanthidin (2.5 µg in 5 ml for 2 Minutes)

<table>
<thead>
<tr>
<th>Basal heart rate</th>
<th>Maximum heart rate</th>
<th>Δ heart rate</th>
<th>Δ per cent heart rate</th>
<th>Basal heart rate</th>
<th>Maximum heart rate</th>
<th>Δ heart rate</th>
<th>Δ per cent heart rate</th>
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</thead>
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<td>220</td>
<td>70</td>
<td>46.6</td>
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<td>45</td>
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<td>20</td>
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<td>190</td>
<td>40</td>
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<tr>
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<td>70.7</td>
<td>47.1</td>
<td>Mean</td>
<td>150</td>
<td>44.6</td>
<td>29.0</td>
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</table>

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aged 38.8 beats/min. The mean acceleration equaled 57.5% of the basal heart rate before acetylthrophalinidin and 29.5% after. These results are recorded in table 2. A return to control response of the sinus node to right stellate ganglion stimulation, expressed as a percentage of the basal rate, was noted within 30 minutes in two experiments. In one a decreased response was still present 40 minutes after acetylthrophalinidin. In the three remaining experiments stellate stimulation was not continued for more than 10 minutes.

**REVERSAL OF TOXIC ACETYLTHROPHALINIDIN EFFECT WITH RIGHT STELLATE STIMULATION**

In four dogs the sinus node was perfused with 10 µg of acetylthrophalinidin in a 10-ml volume for a period of five minutes. In three experiments this perfusion led to sinus arrest and A-V nodal escape rhythm. In two of these, stellate stimulation evoked sinus rhythm briefly (fig. 3). When sinus rhythm later reappeared spontaneously, stellate stimulation did not accelerate the heart rate more than 10 to 15 beats/min.

**Discussion**

These experiments demonstrate that the sinus node does develop a relative insensitivity to adrenergic stimulation after perfusion with acetylthrophalinidin. Our results thus confirm the findings of Méndez et al. with intravenous digitoxin. An important aspect of the present work is the observation that such adrenergic inhibition occurs rapidly and is totally reversible. In time it parallels the effect of acetylthrophalinidin on myocardial potassium arteriovenous difference reported by Regan et al., and is comparable to the duration of chronotropic effects reported in our previous study with this experimental model.1

**TABLE 2**

Comparative Acceleration of the Sinus Node from Right Stellate Ganglion Stimulation Before and After Perfusion with Acetylthrophalinidin (2.5 µg in 5 ml for 2 Minutes)

<table>
<thead>
<tr>
<th>Before acetylthrophalinidin</th>
<th>Six experiments</th>
<th>After acetylthrophalinidin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal heart rate</td>
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<td>Δ heart rate</td>
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<td>90</td>
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<td>80</td>
</tr>
<tr>
<td>145</td>
<td>220</td>
<td>75</td>
</tr>
</tbody>
</table>

Mean 57.5

Mean 29.5

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In addition, sympathetic stimulation was shown to restore transient sinus rhythm when arrest followed perfusion with high concentrations of acetylstrophanthidin, confirming a similar previously described effect from intranodal epinephrine. This must be interpreted as further evidence for the antagonistic relationship of catecholamines and cardiac glycosides on sinus node function. The opposing pharmacological actions of these substances, notably on transmembrane ionic fluxes in atrial tissue and on the diastolic and threshold potentials of pacemaking cells, have been well documented. Cardiac glycosides may also directly inhibit amine uptake, an effect Dengler et al. have demonstrated with ouabain on heart tissue incubated with labeled noradrenaline.

The relationship between adrenergic inhibition and the bradycardia from digitalis is not clear. In our experiments, the antiaecelerator effect most often preceded the onset of sinus bradycardia and was most marked during the initial tachycardia from acetylstrophanthidin perfusion itself. Moreover, the return to a control accelerator response (expressed as the percentage of the basal rate) from both epinephrine injections and stellate stimulation was obtained in most instances while the basal heart rate was still slower than control. Further studies will be necessary to determine whether the decreased response to adrenergic stimulation is simply coincidental or an important determinant of the negative chronotropic effect of acetylstrophanthidin.

**Summary**

Acetylstrophanthidin perfused directly into the sinus node artery of the dog decreases the response of the sinus node to adrenergic stimulation. When sinus arrest followed perfusion of high concentrations of glycosides, either sympathetic stimulation or intranodal epinephrine transiently restored sinus rhythm.

**References**

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