Brief Communication

Low Doses of Scopolamine Increase Cardiac Vagal Tone in the Acute Phase of Myocardial Infarction

Barbara Casadei, MD; Athanase Pipilis, MD; Fabrizio Sessa, MD; James Conway, MD, FRCP; Peter Sleight, MD, FRCP

Background. Reduced cardiac vagal tone in patients with myocardial infarction (MI) is associated with a high risk of sudden death. Muscarinic blocking agents in small doses induce a paradoxical increase in cardiac vagal activity in normal subjects. We tested whether low doses of scopolamine delivered transdermally enhance tonic and reflex cardiac vagal activity in patients in the acute phase of MI.

Methods and Results. Patients were randomized to a scopolamine (n=17) or a placebo patch (n=19) in a double-blind fashion.4.20±0.18 days after acute MI. Cardiac vagal activity was assessed by testing the arterial baroreflex sensitivity (BRS) using the phenylephrine method and by power spectral analysis of the RR interval variability. Twenty-four hours after scopolamine, we found a significant increase in BRS (from 7.85±1.21 to 13.99±2.33 ms/mm Hg, P<.05) and in RR variability, expressed as the mean standard deviation of 512 normal consecutive RR intervals (from 18.09±2.64 to 31.16±4.16 milliseconds, P<.05). The amplitude of respiratory sinus arrhythmia, measured by the absolute power of the high-frequency spectral component, was also enhanced (from 62.55±21.49 to 305.33±95.68 milliseconds squared, P<.05), whereas the power in the low-frequency spectral component of the RR variability, which results from the interaction between cardiac sympathetic and vagal activity, did not change significantly (from 73.12±24.44 to 126.46±44.29 milliseconds squared, P=.93).

Conclusions. In patients in the acute phase of MI, low doses of scopolamine cause a sustained increase in cardiac vagal tone and improve the autonomic indices associated with mortality. (Circulation 1993;88:353-357)

Key Words • baroreflex sensitivity • spectral analysis • myocardial infarction • scopolamine • vagal nerve • Brief Communication

After myocardial infarction (MI), indices of poor cardiac vagal tone (eg, reduced respiratory sinus arrhythmia, low RR interval variability, and low baroreflex sensitivity) are strongly associated with a high mortality rate, in particular sudden death.1-4 Stimulation of the vagus has a powerful antiarrhythmic effect in animal models of acute ischemia5,6 and can terminate ventricular tachycardia in humans.7 Atropine is known to cause tachycardia by blocking peripheral muscarinic receptors. At low doses, however, a transient "paradoxical" bradycardia can be seen, probably as a result of a stimulation of cardiac vagal motoneurons in the ventrolateral medulla.8-10 In humans, low doses of a lipophilic muscarinic blocking agent such as scopolamine, while having a negligible peripheral blocking effect, markedly enhance cardiac vagal efferent activity to cause a persistent bradycardia.11,12

The aim of this study was to investigate whether low doses of scopolamine delivered transdermally (a preparation normally used for travel sickness) could induce a sustained increase in tonic and reflex cardiac vagal outflow in patients in the acute phase of MI.

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Methods

Subjects

Forty-three patients admitted to the coronary care unit of the John Radcliffe Hospital with a documented acute first MI were randomized to Scopoderm TTS (a patch releasing an average of 500 μg of scopolamine in 72 hours) (n=20) or placebo (n=23) in a double-blind fashion. All studies were performed 4 to 6 days (mean±SEM, 4.20±0.18 days) after the onset of chest pain and at least 3 days after starting any new drug. Patients with diabetes mellitus, prostatism, a family history of glaucoma, atrial fibrillation, frequent (>1%) ectopic beats, cardiac conduction abnormalities, or liver and/or kidney diseases were excluded. Data from seven patients (four were on placebo and three on scopolamine) who developed chest pain and/or fever during the study were also excluded.

Baseline characteristics of the patients in the two treatment groups are shown in Table 1. The patients were informed about the possible side effects of scopolamine (eg, dryness of mouth, blurred vision, sleepiness, or dizziness) and asked to report them at the end of the study. The study protocol was approved by the Central Oxford Research Ethics Committee.

Power Spectral Analysis of RR Interval Variability

ECG recordings and baroreflex testing were performed at the bedside with the patient in the semire-
TABLE 1. Baseline Characteristics of Patients in the Two Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=19)</th>
<th>Scopolamine (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>61.3±1.6</td>
<td>59.4±1.9</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>17/2</td>
<td>15/2</td>
</tr>
<tr>
<td>Mean days to randomization</td>
<td>4.2±0.3</td>
<td>4.2±0.2</td>
</tr>
<tr>
<td>Infarct location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterolateral</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Inferoposterior</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Peak AST (U/L)</td>
<td>683.3±109.1</td>
<td>800.3±85.5</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptokinase</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Aspirin</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Nitrates</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Captopril</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Diuretics</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

AST indicates aspartate transaminase.

Vagal activity, and a low-frequency (LF) peak centered at about 0.1 Hz, which can be mediated by both sympathetic and vagal outflow to the heart.17-20

Baroreflex Sensitivity

After the ECG recording for spectral analysis, baroreflex sensitivity (BRS) was assessed by the phenylephrine ramp method.21 Beat-to-beat blood pressure (BP) recordings were obtained noninvasively from the finger by an infrared photoplethysmograph (2300 Finapres BP Monitor, Ohmeda, Englewood, Colo). The accuracy of this instrument in measuring BP changes induced by injections of vasoactive drugs has been validated previously.22 All patients received four to six rapid intravenous injections of phenylephrine HCl at 3-minute intervals. The initial dose of 0.1 mg was adjusted to obtain an increase between 20 and 30 mm Hg in systolic blood pressure (SBP). The test was then repeated until at least three recordings were made with the optimum phenylephrine dose. The sensitivity of the baroreflex, expressed in milliseconds per millimeter of mercury, was obtained from the average slope of at least three regression lines relating beat-to-beat change in RR interval to the change in the preceding SBP, as described by Smyth et al.23 Only regression lines that had a correlation coefficient >0.80 were used. All measurements were made before and 24 hours after application of a patch (of scopolamine or placebo) behind the ear. Differences between treatments were assessed by two-factor (time and treatment) ANOVA. Significance was established at probability values <.05. Data are given mean±SEM.

Results

There were no statistical differences in the characteristics of the patients in the two treatment groups (Table 1). Only data from patients who were uncomplicated and on a stable drug regimen (ie, last new treatment started at least 3 days before the beginning of the study) were included in the results (see “Methods”). Scopolamine was well tolerated: Only two patients complained of dry mouth, and no other side effects were seen.

The mean value of BRS was almost doubled by low doses of scopolamine (from 7.05±1.21 to 13.99±2.33 ms/mm Hg, $P<.05$) (Table 2). As shown in Fig 1, BRS increased in all except one of the patients. In that patient, scopolamine also decreased RR interval, suggesting that the peripheral muscarinic receptor blockade predominated over the paradoxical vagomimetic effect.

The results of the spectral analysis of the RR variability for the two treatments are summarized in Table 2. The standard deviation of the RR (ie, the square root of the total spectral power) was significantly higher after scopolamine ($P<.05$). The absolute power of the HF component increased with scopolamine ($P<.05$), whereas the LF power did not change significantly ($P=.93$). This indicates that the increase in the amplitude of the respiratory sinus arrhythmia, and hence, in cardiac vagal tone, was mainly responsible for the rise in RR variability. Low doses of scopolamine also increased the average RR interval, but this was not statistically significant ($P=.24$).
TABLE 2. Effect of Placebo and Low Doses of Scopolamine on RR Interval Variability and Baroreflex Sensitivity

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=19)</th>
<th>Scopolamine (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR interval (ms)</td>
<td>Baseline</td>
<td>After 24 h</td>
</tr>
<tr>
<td></td>
<td>792.2±33.6</td>
<td>791.2±35.1</td>
</tr>
<tr>
<td>RR SD (ms)</td>
<td>22.10±3.13</td>
<td>19.92±2.77</td>
</tr>
<tr>
<td>BRS (ms/mm Hg)</td>
<td>7.14±1.38</td>
<td>7.16±1.51</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>91.12±28.81</td>
<td>115.73±36.95</td>
</tr>
<tr>
<td>HFc (Hz)</td>
<td>0.31±0.02</td>
<td>0.31±0.01</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>113.72±43.29</td>
<td>176.77±88.84</td>
</tr>
</tbody>
</table>

**RR SD** indicates standard deviation of 512 normal consecutive RR intervals; **BRS**, baroreflex sensitivity; **HF** and **LF**, high-frequency and low-frequency spectral components of the RR interval variability; **HFc**, center frequency of the HF component, ie, the average breathing frequency.

*P<.05 for the effect of scopolamine evaluated by two-way ANOVA.

The rate of breathing, indicated by the center frequency of the HF component (HFc), has also been shown to affect the amplitude of respiratory sinus arrhythmia (ie, the HF power).23 This variable, however, did not impinge on our results since, as shown in Table 2, HFc did not change (P=.64) in either group of patients after scopolamine or placebo.

There is no evidence to suggest that the paradoxical increase in BRS and RR variability observed with low doses of antimuscarinics results from a direct inhibition of cardiac sympathetic activity.24 However, it is known that the two limbs of the autonomic nervous system interact at the presynaptic level by modulating the release of the respective neurotransmitters.25 It is therefore possible that increased concentrations of acetylcholine in the synaptic cleft induced by scopolamine could inhibit the release of norepinephrine from the sympathetic nerve terminals.26 To test for a possible role of the sympathetic nervous system in the paradoxical effect of low doses of scopolamine, we have separately analyzed the subgroup of patients on β-blockers (βB+). As expected, measurements at baseline in the βB+ patients differed from those in the control group (βB−) (Table 3), but the effect of scopolamine, evaluated by percent changes from the baseline values, was not different in the two subgroups. Although this analysis is limited by the small sample size and the differences between the patients in the two subgroups, the results further suggest that the effect of low doses of scopolamine is mediated by the vagus.

**Discussion**

Our results have confirmed that low doses of scopolamine, delivered transdermally, can induce a sustained increase in BRS and RR variability. We have also demonstrated that the rise in RR variability was mainly due to an increase in the amplitude of the respiratory sinus arrhythmia. This supports the hypothesis that a rise in cardiac vagal outflow is the mechanism underlying the paradoxical effect of low doses of scopolamine. Furthermore, the present study has shown that a sustained pharmacological stimulation of cardiac vagal tone is attainable in patients in the acute phase of MI. These findings may have important therapeutic implications for two reasons. First, in patients after MI, there is a strong relation between autonomic balance and mortality. High sympathetic activity and low vagal outflow, indicated by low BRS,4 reduced respiratory sinus arrhythmia,1 and RR variability,23 characterize the post-MI patients with a high mortality risk and in

![Graph](image_url)

FIG 1. Plots show individual and mean±SEM baroreflex sensitivity (BRS) at baseline and 24 hours after placebo or low doses of scopolamine. *P<.05.
particular the risk of sudden death. Although in humans it is difficult to demonstrate the presence of a causal relation between sympathetic-vagal imbalance and mortality, studies in experimental models have strongly indicated that this is the case.27 Augmenting vagal tone, either by electrical stimulation of the vagus or by infusion of carbachol,28 has been shown to protect against fatal arrhythmias in the presence of ischemia and high sympathetic activation even when the heart rate was held constant by pacing. Even smaller rises in vagal outflow, such as those obtained with infusion of low doses of atropine, have been shown to reduce the vulnerability to ventricular fibrillation in the presence of ischemia in the dog.29 We may therefore expect that restoring the autonomic balance in patients after MI could improve their prognosis, probably by protecting them against life-threatening arrhythmias.

The second important point to be considered is whether or not pharmacological vagal stimulation is safe. At present, the main problem in using drugs designed to prevent arrhythmias and sudden death after MI is their intrinsic proarrhythmic actions and their negative effect on the residual ventricular function. Experimental evidence indicates that vagal stimulation can produce direct vasodilatation in the coronary vascular bed30 and increase the electrical stability of the myocardium during ischemia,5 while having a very modest negative inotropic effect on the ventricle.31

The mechanism underlying the paradoxical vagomimetic effect of low doses of antimuscarinic drugs has not been fully explained. Central stimulation of the vagal centers resulting in a rise in cardiac vagal efferent activity has been suggested.8-10 However, plasma concentrations of scopolamine as low as those seen with the transdermal preparation (approximately 140 pg/mL)11 have not been tested. Katona et al9 showed a 50% increase in cardiac vagal efferent activity with 0.15 mg IV atropine in spontaneously breathing dogs. This dose, which should result in plasma concentrations of approximately 60 000 pg/mL, was substantially higher than the average dose (0.06 mg), which caused a 50% blockade of peripheral muscarinic receptors. Hence, it is not clear whether concentrations of antimuscarinic drugs low enough to have a negligible peripheral blocking effect would be able to stimulate the cardiac vagal motoneurons centrally. Furthermore, quaternary compounds, such as atropine methylbromide, which do not readily pass the blood-brain barrier, have also been shown to induce bradycardia in dogs.32

The vagomimetic effect of atropine may result from its preferential blockade of cardiac presynaptic muscarinic receptors (M1-subtype). Wellstein and Pitschner24 recently have suggested that synaptic acetylcholine could inhibit its own release through the activation of the M3 presynaptic receptors. Since atropine has a relatively higher affinity for the M1-subtype receptors, in low concentrations it would preferentially bind to them, leaving the postsynaptic M2-subtype receptors relatively unaffected. This would result in a greater release of acetylcholine for any given level of neural activation and hence in a higher postsynaptic vagal outflow. Importantly, these investigators also ruled out a possible role of the ß-adrenergic system in mediating the atropine-induced bradycardia. Although our study could not completely exclude a possible interaction between scopolamine and ßB+, the results suggest that the paradoxical effects of scopolamine are mediated by the vagus (Table 3).

Unfortunately, the design of the present study did not allow us to investigate the effect of low doses of scopolamine on 24-hour RR variability, which is undoubtedly the best-validated prognostic indicator in this group of patients. However, our preliminary data from a controlled cross-over study in patients with chronic heart failure of ischemic etiology show a substantial increase in both 24-hour RR interval and its variability with transdermal scopolamine.33

In summary, we have shown that low doses of scopolamine cause a sustained increase in cardiac vagal tone and improve the autonomic indices associated with a high mortality in patients in the acute phase of MI. This suggests that pharmacological vagal stimulation may have important therapeutic potential in preventing sudden death in patients after MI. However, previous studies have shown that reversing the prognostic indicators of sudden death does not necessarily result in a decrease in fatal arrhythmias.34 Although experimental evidence from animal models of sudden death strongly suggests that vagal stimulation is effective and safe,6,28,29 large trials are needed to assess the validity of this treatment in humans. Likewise, we have no information concerning the tolerability and efficacy of transdermal scopolamine on long-term treatment. There is no clear evidence of a greater incidence of side effects when transdermal scopolamine is administered for a week35; however, whether the paradoxical vagomimetic effect of scopolamine would be maintained on chronic administration remains to be assessed.

**TABLE 3. Effect of ß-Blockers on the Vagomimetic Effect of Low Doses of Scopolamine**

<table>
<thead>
<tr>
<th></th>
<th>ßB− (n=11)</th>
<th>ßB+ (n=6)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR interval (ms)</td>
<td>688.9±25.9</td>
<td>986.3±85.9</td>
<td>+12.4±4.0 .85</td>
</tr>
<tr>
<td>RR SD (ms)</td>
<td>13.3±1.6</td>
<td>26.8±5.4</td>
<td>+82.2±20.1 .83</td>
</tr>
<tr>
<td>BRS (ms/mm Hg)</td>
<td>5.1±1.1</td>
<td>11.1±2.0</td>
<td>+125.4±14.7 .87</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>30.5±12.3</td>
<td>121.2±50.7</td>
<td>+329.8±82.4 .89</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>34.0±12.7</td>
<td>144.85±56.9</td>
<td>+179.9±84.4 .54</td>
</tr>
</tbody>
</table>

* ßB− indicates baseline measurements in patients with no ß-blockade; ßB+, baseline measurements in patients on ß-blockers; %Δ, percent difference from the baseline measurements observed with low doses of scopolamine; P for differences in the effect of scopolamine (ie, %Δ) in the two groups evaluated by unpaired Student's t test. RR SD, standard deviation of 512 normal consecutive RR intervals; BRS, baroreflex sensitivity; HF and LF, high-frequency and low-frequency spectral components of the RR interval variability.

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References

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