Effect of low doses of scopolamine on RR interval variability, baroreflex sensitivity, and exercise performance in patients with chronic heart failure

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Abstract

Objective—To study the effect of transdermal scopolamine on heart rate variability, baroreflex sensitivity, and exercise performance in patients with heart failure and age matched healthy volunteers.

Design—Double blind, randomised, placebo controlled, crossover study.

Patients—16 patients with chronic, stable heart failure due to ischaemic cardiomyopathy (mean (SEM) age 58 (2) years; mean (SEM) radionuclide left ventricular ejection fraction 28 (2)%; New York Heart Association class II-III) and eight age matched healthy controls.

Intervention—Transdermal scopolamine (500 µg delivered over 72 h) or a placebo patch was administered for 48 h.

Main outcome measures—Indices of tonic and reflex cardiac vagal activity and exercise performance.

Results—In both groups scopolamine produced a reduction in the 24 h average heart rate and an increase in the time domain measures of heart rate variability. Both the incidence and severity of ventricular arrhythmias remained unchanged. Baroreflex sensitivity, evaluated by the phenylephrine technique, increased significantly ($P < 0.001$) with scopolamine in patients with heart failure (6.22 (2.81) ms/mm Hg) and in healthy volunteers (5.97 (2.20) ms/mm Hg) as did the amplitude of respiratory sinus arrhythmia, computed by autoregressive spectral analysis of 10 min electrocardiographic recordings (319.9 (123.5) and 657.3 (126.6) ms² respectively, $P < 0.001$). While exercise performance did not change, heart rate at submaximal exercise was significantly reduced by scopolamine in each group.

Conclusions—In patients with mild to moderate heart failure low doses of scopolamine increased tonic and reflex cardiac vagal activity. This was achieved without affecting exercise tolerance or the incidence and severity of ventricular arrhythmias.

(Heart 1996;75:274-280)

Keywords: scopolamine; chronic heart failure; RR interval variability; exercise performance

Neurohumoral activation¹ and reduced cardiac vagal control^{2,3} are independent predic-

tors of a poor prognosis in patients with ischaemic heart disease or chronic heart failure (CHF). Although in humans there is no direct proof of a causal relation between autonomic imbalance and mortality, interventions which can antagonise neurohumoral activation have been successful in improving the survival of patients with CHF or ischaemic heart disease, or both.⁴ Increasing parasympathetic activity could provide an alternative means of correcting the autonomic imbalance in CHF. Studies in humans have shown that this can be achieved by the administration of very low doses of muscarinic blocking agents, such as atropine or scopolamine in patients after myocardial infarction.⁵⁻⁸ Although these alkaloids are normally used for their anticholinergic properties, at very low doses they can induce a paradoxical increase in cardiac vagal activity. This, in turn, could increase the electrical stability of the ventricular myocardium and protect against ischaemia induced ventricular fibrillation.⁹⁻¹¹

Several problems, however, might arise from the clinical use of small doses of muscarinic blocking agents. Firstly, it is not clear whether increasing vagal efferent activity would be effective in improving the autonomic balance to the heart in patients with CHF. Experimental studies have indicated that a reduction in the number and affinity of muscarinic receptors¹² and an impairment in their intracellular transduction mechanisms¹³ (rather than a decrease in central vagal traffic) might be chiefly responsible for the reduced cardiac vagal tone in CHF. Secondly, vagal stimulation exerts a negative inotropic effect on the ventricular myocardium.¹⁴ Finally, it has been suggested that the vagally mediated reflex bradycardia which can accompany acute ischaemia could promote arrhythmias by unmasking ventricular automaticity.¹⁵

The aims of the present study were to answer the following questions: (1) Would low doses of scopolamine increase cardiac vagal activity in patients with CHF to the same extent as in age matched healthy volunteers? (2) Would the increase in cardiac vagal activity affect exercise performance or the incidence of ventricular arrhythmias?

Patients and methods

STUDY DESIGN

This was a randomised, double blind, crossover trial comparing short-term treatment (48 h) with a transdermal preparation of scopolamine with placebo in 16 patients (two women; mean (SEM) age 58 (2) years) with

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Accepted for publication 21 August 1995

stable mild to moderate CHF and eight age matched (mean (SEM) age 54 (4) years) healthy volunteers. The latter, who were recruited by advertisement, had a normal physical examination and were not taking any medication.

Participants with prostatism and/or a family history of glaucoma, diabetes mellitus, atrial fibrillation, cardiac conduction abnormalities, ischaemia limiting exercise, and liver and/or kidney diseases were excluded.

The active patch (Scopoderm TTS; Ciba-Geigy) contains 1.5 mg of scopolamine and delivers 500 μ g at an approximately constant rate over 72 h.¹⁶ Participants were familiarised with the procedures and performed at least three incremental exercise tests (see later) before entering the study. Measurements of baroreflex sensitivity, exercise performance, and short-term RR interval variability were taken on three occasions: at baseline (no treatment) and 24 h after the two treatments—that is, after a scopolamine or a placebo patch. Twenty four h Holter monitoring was started 24 h after the application of either patch. In order to avoid carry over effects, the two treatments were separated by at least 1 week.¹⁶ All participants were informed of the common side effects of scopolamine¹⁶ and were asked to report them at any time during the study. The protocol was approved by the Central Oxford Research Ethics Committee.

POWER SPECTRAL ANALYSIS OF RR INTERVAL VARIABILITY

Lead II of the electrocardiogram (ECG) and a non-calibrated signal of respiratory induced changes in chest impedance (Minimon 7136; Kontron Instruments, UK) were recorded in all participants for 15 min at rest supine and for 10 min standing, in a quiet room at a controlled temperature of 22°C. The signals were digitised on line (AT-Codas; Dataq Instruments, USA) at a sampling rate of 400 Hz. Premature beats were corrected by linear interpolation with the previous and following beats. The ECG recordings of one patient who had more than 1% of extrasystoles were excluded from spectral analysis.¹⁷ The power spectral density of time series of 256 RR intervals was evaluated by an autoregressive technique.¹⁸ The model order was chosen by the Akaike information criterion¹⁹ starting from a minimum order of six. A spectral decomposition method²⁰ was then applied to evaluate the power and the central frequency of each spectral component. Spectral analysis of the chest impedance signal was performed on the signal sampled once every cardiac cycle. These spectra were used as a reference to identify the frequency of RR interval oscillations due to respiratory sinus arrhythmia.

The spectral power was computed for the high (HF) and low (LF) frequencies. The HF component, centred on about 0.25 Hz, reflects the respiratory sinus arrhythmia and is mediated by the vagus.²¹ The LF component, (from 0.03 to 0.14 Hz) reflects modulation of vagal and sympathetic efferent activities,²² possibly by the baroreflex.²³ Given the short dura-

tion of the ECG recordings performed in the laboratory, very slow RR interval oscillations could not be adequately assessed. Thus, the spectral power at frequencies below 0.03 Hz was not included in the results.

The spectral power of the LF and HF components was expressed in absolute terms (ms^2) and normalised units calculated as: $[\text{Power of the component, ms}^2]/[\text{Total power, ms}^2 - \text{very low frequency power (< 0.03 Hz), ms}^2]$.

BAROREFLEX SENSITIVITY

Baroreflex sensitivity was assessed by the phenylephrine method.²⁴ Beat to beat blood pressure recordings were obtained from the finger (2300 Finapres BP Monitor; Ohmeda, Englewood, Colorado, USA). Four to six rapid intravenous injections of phenylephrine hydrochloride were given at about 3 min intervals. The initial dose (0.09 mg in healthy volunteers and 0.15 mg in patients with CHF) was adjusted to obtain an increase between 15 and 25 mm Hg in systolic blood pressure. The test was then repeated until at least three recordings were made with the optimum dose of phenylephrine. The sensitivity of the baroreflex, expressed in ms/mm Hg , was obtained from the average slope of at least three regression lines relating the RR interval to the preceding systolic blood pressure.

EXERCISE TESTING

Incremental upright cycle ergometry (Tunturi, Finland) was performed at the end of each visit. The starting work rate of 25 W was increased by 25 W every 5 min until exhaustion. Inspired air volume (Harvard Apparatus, Kent, UK), expired oxygen and carbon dioxide concentrations (Servomex 570A and Servomex PA404, Sussex), and a three lead ECG were recorded throughout the test. The gas analysers were calibrated before each test and all volumes were corrected to standard temperature and pressure (dry). Peak oxygen consumption (VO_2) was taken from the mean over the last completed minute of exercise. Heart rate was calculated over the last minute of each work rate.

TWENTY FOUR H HOLTER MONITORING

Twenty four h ECG monitoring (modified V1 and V5 leads) was performed using a two channel ECG recorder (Oxford MR14; Oxford Medical Instruments). The recordings were digitised at 128 samples/s and submitted to standard algorithms for QRS labelling and editing (Biomedical Systems, St Louis, Missouri, USA). They were then analysed for the frequency of premature ventricular complexes (h^{-1}) and the presence of ventricular repetitive arrhythmias (couplets and salvos of three or more ventricular extrasystoles). The standard deviation of all normal RR intervals (SDNN, ms) and of the mean RR intervals for all 5 min segments (SDANN index, ms) of a 24 h ECG recording, and the percentage of differences between adjacent normal RR intervals greater than 50 ms (pNN50, %) were automatically calculated. Each time domain measure was also computed for daytime and

night time separately. Data from one patient were excluded because of the poor quality of the 24 h ECG recording.

All participants completed a questionnaire about their daytime activities, time to bed and wake up time. The conditions under which the two 24 h ECG recordings were performed, were, as far as possible, standardised for each participant.

STATISTICAL ANALYSIS

Data were examined for balanced allocation and absence of carry over effects according to the recommendation of Hills and Armitage²⁵ for crossover trials. The frequency distribution of each variable was plotted and assessed for skewness using the value of the standardised third moment around the mean. If the skewness coefficient was > 1 , the data were log transformed and re-examined. This procedure led to a normal distribution in all cases. Repeated measures analysis of variance (SPSS for Windows, Release 6; SPSS, Chicago, Illinois, USA) was used to test for differences within the trial stages and between participant groups—that is, patients with CHF versus healthy volunteers. Interaction between participant groups and the effect of scopolamine were also assessed. Values are presented as mean (SEM). Significance was accepted at $P < 0.05$.

Short-term intraparticipant reproducibility of measures of spectral power, baroreflex sensitivity, and exercise performance was evaluated by computing the mean and standard deviation of the differences between measurements (taken during placebo and at baseline).²⁵ The interclass correlation coefficient of the two measurements was also obtained.

Results

REPRODUCIBILITY OF THE TESTS AND STATISTICAL POWER OF THE STUDY

Table 1 shows the mean differences between the data collected in the placebo period and at baseline, their standard deviation and the correlation coefficient of the two measurements. There was no statistical difference between the placebo and baseline data. Precision was calculated according to the formula of Hills and Armitage²⁵ and indicates the change with active treatment that this trial could detect with a statistical power of 0.9.

Measurements of baroreflex sensitivity and

peak VO_2 showed satisfactory stability (table 1). Spectral analysis data, however, were less reproducible with the exception of the absolute power of the HF component (a measurement of the amplitude of respiratory sinus arrhythmia).

BASELINE CHARACTERISTICS OF PATIENTS WITH CHRONIC HEART FAILURE

There were no significant differences between the baseline measurements in patients allocated to placebo or transdermal scopolamine. All patients had a documented myocardial infarction and had been in stable heart failure for at least 3 months. They were all taking diuretics and 13 of 16 had been receiving angiotensin converting enzyme inhibitors for a mean (SEM) of 14 (1) months. None of the patients was receiving digitalis or any antiarrhythmic drug. The radionuclide left ventricular ejection fraction ranged from 18 to 40% (mean (SEM) 28 (2)%, normal range from 50 to 80%).

BAROREFLEX SENSITIVITY

The sensitivity of the baroreflex in patients with CHF given placebo did not show any significant correlation with short-term or long-term measures of RR interval variability, left ventricular ejection fraction, and peak VO_2 . Baroreflex sensitivity in patients with CHF was significantly lower than in healthy volunteers ($P < 0.05$). Transdermal scopolamine caused a similar increase in baroreflex sensitivity in patients with CHF (from 9.16 (1.60) to 15.37 (2.50) ms/mm Hg, $P < 0.001$) and in healthy volunteers (from 15.84 (1.91) to 21.81 (2.63) ms/mm Hg, $P < 0.001$). The changes in baroreflex sensitivity with scopolamine varied from participant to participant (fig 1), ranging from -4.41 to 28.6 ms/mm Hg. The slope of the regression line between measurements of baroreflex sensitivity during placebo and scopolamine was not different

Figure 1 Individual and mean (SEM) baroreflex sensitivity in 16 patients with heart failure (solid lines, closed symbols) and in eight age matched healthy volunteers (dotted lines, open symbols) 24 h after placebo or transdermal scopolamine. * $P < 0.001$ for comparison between scopolamine and placebo in both groups. † $P < 0.05$ for comparison between patients with heart failure and healthy volunteers.

Table 1 Reproducibility of laboratory investigations in patients with chronic heart failure

	D	SDD	ICC	Precision*
Ln BRS (ms/mm Hg)	0.04	0.17	0.96	0.15
Ln RRV (ms^2)	-0.12	0.70	0.86	0.65
Ln HFa (ms^2)	-0.35	1.01	0.77	0.27
HFb (n.u.)	-1.93	18.43	0.65	16.6
Ln LFa (ms^2)	-0.08	1.03	0.69	0.89
LFb (n.u.)	-0.57	19.15	0.65	17.2
Peak VO_2 ($\text{l}\cdot\text{min}^{-1}$)	0.02	0.13	0.93	0.11
Exercise time (min)	0.31	2.02	0.89	1.64

*Change with active treatment detected by this trial with a statistical power of 0.9.

D, absolute difference between placebo and baseline ($P = \text{NS}$); ICC, interclass correlation coefficient; Ln, natural logarithm; SDD, standard deviation of the differences; BRS, baroreflex sensitivity by the phenylephrine bolus method; HFa and HFb, absolute and normalised power of the high frequency spectral component; LFa and LFb, absolute and normalised power of the low frequency spectral component; peak VO_2 , oxygen uptake; RRV, RR interval variance.

Figure 2 Tachogram (upper panel) and spectral analysis of RR interval variability (lower panel) 24 h after placebo and transdermal scopolamine in one patient. Note that most of the increase in RR interval variability is due to an increase in the spectral component centred on around 0.32 Hz—that is, the high frequency component. The power of this component reflects the amplitude of respiratory sinus arrhythmia.

from 1 ($y = 5.8 + 1.01x$, $r = 0.70$, $P < 0.001$), indicating that scopolamine caused a proportional increase over the entire range of initial baroreflex sensitivity.

POWER SPECTRAL ANALYSIS OF RR INTERVAL VARIABILITY

Results of the spectral analysis were expressed in absolute and normalised units—that is, as a percentage of the spectral power calculated from 0.03 to 0.8 Hz. This allowed us to investigate the effects of scopolamine on the spectral power and its distribution across the frequency axis.

Supine

Scopolamine increased the mean RR interval, its variance, and the absolute power of the HF component (fig 2) (table 2) in 12 of 15 patients with CHF and in seven of eight healthy volunteers. Scopolamine caused either no change or a modest reduction in RR interval and its variability in the remaining participants. Scopolamine also caused an increase in absolute power of the LF component in 10 of 15 patients and in seven of eight healthy volunteers (table 2).

The normalised power of the HF compo-

nent increased significantly with scopolamine (from 31.06 (4.35) to 48.79 (5.20) n.u. in patients with CHF and from 46.75 (6.70) to 63.65 (3.50) n.u. in healthy volunteers, $P < 0.001$). This was accompanied by a significant reduction in the LF power ($P < 0.005$). The individual responses to the active treatment, however, were variable and only 17 of 23 participants (10 of 15 patients with CHF) showed an increase in normalised HF power with scopolamine. While changes in the absolute power of spectral components were related to those in RR interval and its variance, no such relation was seen for the changes in normalised power. The spontaneous frequency of breathing (HFc) and the central frequency of the LF component (LFC) did not change throughout the trial (table 2).

Standing

As in the supine position, during standing scopolamine caused an increase in the mean RR interval (from 776.3 (30.4) to 821.3 (32.5) ms, $P < 0.005$ in patients with CHF and from 832.7 (21.5) to 930.4 (43.1) ms, $P < 0.05$ in healthy volunteers) and its variability (from 770.6 (149.4) to 1399.8 (241.5) ms,² $P < 0.005$ in patients and from 1048.5 (75.6) to 2932.6 (654.6) ms,² $P < 0.05$ in healthy volunteers). The absolute power of the HF component was also increased (from 147.7 (42.3) to 205.6 (68.4) ms,² $P < 0.05$ in patients with CHF and from 102.3 (22.1) to 310.7 (80.5) ms,² $P = 0.06$ in healthy volunteers).

Standing caused a significant increase in the normalised power of the LF in healthy volunteers but not in patients with CHF (fig 3). This is consistent with impairment in the sensitivity of the baroreflex and abnormal cardiac sympathovagal balance in patients with CHF.²⁶ Interestingly, in these patients scopolamine tended to restore the physiological rise in the normalised power of LF ($P = 0.11$) on standing (fig 3).

TWENTY FOUR H HOLTER MONITORING

Table 3 summarises the data from 24 h ECG recordings obtained after placebo and trans-

Figure 3 Low frequency power (mean (SEM)) in normalised units (n.u.) in the supine position and during standing after placebo and transdermal scopolamine in patients with chronic heart failure (CHF) and age matched healthy volunteers (N). * $P < 0.05$ for comparison between low frequency power in the supine position and during standing in healthy volunteers.

Table 2 Effects of transdermal scopolamine on the spectral analysis of RR interval variability

	Patients with CHF (n = 15)		Healthy volunteers (n = 8)	
	Placebo	Scopolamine	Placebo	Scopolamine
RR (ms)	859.1 (32.5)	949.8 (43.8)	959.1 (23.4)§	1177.5 (26.6)†‡
RRV (ms ²)	1243.8 (393.6)	2109.1 (568.6)	1399.2 (88.22)	3382.67 (451.2)†‡
LFa (ms ²)	216.69 (67.95)	409.93 (183.53)	211.71 (39.91)	526.11 (113.63)*
HFa (ms ²)	177.12 (82.02)	497.00 (192.48)	245.14 (51.94)	902.42 (123.62)†‡
LFc (Hz)	0.10 (0.01)	0.10 (0.01)	0.09 (0.01)	0.09 (0.01)
HFc (Hz)	0.28 (0.01)	0.29 (0.01)	0.27 (0.02)	0.26 (0.01)

Values are mean (SEM).

CHF, chronic heart failure; HFc and LFc, central frequencies of the high and low frequency components; RRV, RR interval. Other abbreviations as in table 1.

* $P < 0.05$; † $P < 0.001$ for comparison between placebo and scopolamine in each of the groups; ‡ $P < 0.05$ versus patients with CHF given scopolamine (the effect was significantly greater in healthy volunteers than in patients with CHF); § $P < 0.01$ versus patients with CHF given placebo or baseline.

Table 3 24 h ambulatory electrocardiogram (ECG) recording

	Patients with CHF (n = 15)		Healthy volunteers (n = 8)	
	Placebo	Scopolamine	Placebo	Scopolamine
Mean HR (bpm)	77.1 (2.8)	73.5 (3.0)	65.9 (1.9)*	57.8 (1.0)†‡
SDNN (ms)	138.30 (11.96)	155.43 (14.04)	175.89 (10.20)*	210.79 (8.80)†
SDANN (ms)	126.86 (11.32)	140.23 (13.91)	169.54 (14.44)*	194.56 (11.05)†
pNN 50 (%)	6.51 (1.65)	11.55 (2.67)	10.07 (1.77)	19.56 (12.19)†

Values are mean (SEM).

CHF, chronic heart failure; HR, heart rate; bpm, beats/min; SDNN, standard deviation of all normal RR intervals; SDANN, standard deviation of the mean RR intervals for all 5 min segments of a 24 h ECG recording; pNN 50, percentage of differences between adjacent normal RR intervals greater than 50 ms.

*P < 0.01 versus patients with CHF given placebo; †P < 0.001 for comparison between placebo and scopolamine in each of the two groups; ‡P < 0.05 versus patients with CHF given scopolamine (the effect was greater in healthy volunteers than in patients with CHF).

dermal scopolamine during placebo. Time domain indices of 24 h RR interval variability in healthy volunteers were significantly greater than in patients with CHF. Scopolamine produced a significant decrease in the mean 24 h heart rate due to a reduction in daytime and night time heart rate. Although time domain indices of RR interval variability were significantly augmented by scopolamine in both groups, this effect was of greater magnitude in healthy volunteers than in patients with CHF (table 3). There was no difference in the frequency and severity of ventricular extrasystoles with scopolamine.

EXERCISE PERFORMANCE

Peak VO_2 was not significantly affected by scopolamine (1.24 (0.09) *v* 1.28 (0.07) $\text{l}\cdot\text{min}^{-1}$ in patients with CHF and 1.97 (0.18) *v* 1.86 (0.17) $\text{l}\cdot\text{min}^{-1}$ in healthy volunteers). Heart rate during submaximal exercise was reduced by scopolamine, however, while peak heart rate was unchanged (fig 4).

SIDE EFFECTS

Five patients with CHF and seven healthy volunteers complained of dry mouth with scopo-

Figure 4 Mean (SEM) heart rate (bpm, beats/min) during incremental cycle ergometry in patients with chronic heart failure (circles) and in age matched healthy volunteers (triangles) after placebo (open symbols) and transdermal scopolamine (closed symbols). *P < 0.05; **P < 0.005 for comparison of scopolamine *v* placebo in age matched healthy volunteers. †P < 0.05 for comparison of scopolamine *v* placebo in patients with heart failure.

lamine. One patient receiving placebo felt light headed, while two volunteers receiving scopolamine complained of blurred vision.

Discussion

This study shows that transdermal scopolamine can reduce heart rate and increase 24 h RR interval variability, baroreflex sensitivity, and respiratory sinus arrhythmia in patients with mild to moderate CHF secondary to ischaemic heart disease. This was achieved without affecting exercise performance or the frequency and severity of ventricular arrhythmias.

MECHANISMS OF ACTION

The mechanism underlying the paradoxical vagomimetic effect of low doses of antimuscarinic drugs has not been fully explained. High doses of atropine have been shown to increase the firing of cardiac vagal efferent nerves through central stimulation of the vagal motoneurons.²⁷ It is not clear, however, whether the same mechanism is responsible for the vagomimetic effect seen with plasma concentrations of scopolamine low enough to have a negligible peripheral antimuscarinic effect.

A preferential peripheral blockade of presynaptic muscarinic autoreceptors (M_1) has been suggested as an alternative mechanism for the vagomimetic effects of low doses of antimuscarinic drugs.²⁸ The recent finding that the selective M_1 -muscarinic blocking agent, pirenzepine (which does not readily pass the blood-brain barrier) has a vagomimetic effect similar to that of transdermal scopolamine²⁹ supports this hypothesis.

AUTONOMIC BALANCE IN ISCHAEMIC HEART DISEASE

The findings of the important prognostic value of RR interval variability,³⁰ respiratory sinus arrhythmia,² and baroreflex sensitivity³ in patients after myocardial infarction have been instrumental in attracting attention towards the possible beneficial effects of parasympathetic activity. It is now known that muscarinic stimulation⁹⁻¹¹ is at least as effective as β blockade in preventing ischaemia induced fatal arrhythmias in animal models of sudden cardiac death. In humans it has been shown that reflex vagal activation during acute myocardial infarction is associated with a reduced incidence of malignant ventricular arrhythmias and a better prognosis.³¹ Thus, the increase in cardiac vagal activity induced by transdermal scopolamine might be of therapeutic value in post-myocardial infarction patients, especially in those with mild to moderate heart failure who have a relatively higher incidence of ischaemia induced malignant ventricular arrhythmias.³² It could be argued, however, that the degree of parasympathetic activation seen with transdermal scopolamine is so much smaller than elicited by electrical or pharmacological vagal stimulation⁹⁻¹¹ that it may not confer a significant protective effect against arrhythmias.³³ A further reason of concern is

that, in the presence of endothelial damage, the stimulation of muscarinic receptors induces coronary vasoconstriction.³⁴ A recent report, however, has indicated that the paradoxical vagomimetic effect of a muscarinic blocking agent improves exercise tolerance in patients with ischaemia on effort.³⁵ This might be the result of the reduction in heart rate at submaximal exercise seen with low doses of muscarinic blocking agents (fig 4).

Although vagal activity has a negative inotropic effect on the ventricular myocardium,¹⁴ the vagomimetic effect of transdermal scopolamine was not accompanied by a deterioration in exercise performance in patients with CHF or healthy volunteers. Interestingly, in papillary muscles and isolated myocytes the reduction in contractility induced by acetylcholine has been shown to last only for a few minutes.³⁶ Thus, although the negative inotropic action of vagal activity could have a role in the context of short lasting reflex responses,³⁷ it may not be sustained.

LIMITATIONS OF THE STUDY

The relation between RR interval variability and mortality in patients with heart failure has not been as extensively investigated as in post-myocardial infarction patients. Binder *et al*³⁸ have shown that standard deviation of the 5 min mean RR interval in the 24 h ECG recording—that is, the SDANN index, was superior to left ventricular ejection fraction, pulmonary artery wedge pressure, cardiac index, and serum sodium levels in predicting the risk of death in patients with heart failure. The size of the trial was, however, rather small (n = 61) and the aetiology of heart failure was mainly dilated cardiomyopathy.

Our study was necessarily restricted to patients with mild to moderate CHF. Four patients with severe CHF, who were originally recruited, had to be excluded as a high incidence of arrhythmias (ventricular and supraventricular) prevented the assessment of baroreflex sensitivity and RR interval variability. Nevertheless, an increase in 24 h RR interval variability with transdermal scopolamine has been demonstrated in patients with advanced congestive heart failure awaiting cardiac transplantation.³⁹ The number of patients who did not show a reduction in heart rate after transdermal scopolamine (seven of 21 patients) in this study was higher than in ours (3 of 15 patients), suggesting that the severity of the disease may affect the response to the drug. Although variability in the response to transdermal scopolamine has also been shown in healthy individuals,^{40 41} we found that the average increase in RR interval and its variability in patients with CHF was significantly smaller than in age matched healthy volunteers. This may be owing to a reduction in the number and affinity of muscarinic receptors in heart failure^{12 13} or possibly to the concomitant treatment with angiotensin converting enzyme inhibitors as these agents have also been shown to increase cardiac vagal tone in patients with CHF.⁴² Interestingly, low doses of atropine have failed to elicit an increase in

vagal tone in patients⁴³ and animal models of CHF⁴⁴ treated with digitalis, suggesting that cardiac glycosides and low doses of muscarinic blocking agents might exert a vagomimetic effect through similar mechanisms; thus the result of their simultaneous administration on cardiac vagal tone is not additive. A similar interaction between scopolamine and angiotensin converting enzyme inhibitors might have been responsible for the reduced vagomimetic effect of the former in patients with CHF.

Finally, we have no information regarding the safety and efficacy of long-term transdermal scopolamine. Severe adverse events have not been reported when the drug was administered for a longer period.⁴⁵ This evidence, however, is based on trials of small size in healthy individuals. Whether the vagomimetic effect of transdermal scopolamine would be maintained on chronic treatment is still to be assessed.

We thank Dr TE Meyer and Dr C Barlow for their help in identifying the patients for this study and Mr M Eagle of the Department of Statistics, University of Oxford, for his assistance with the analysis of the results. The study was supported by the British Heart Foundation and the Norman Collison Foundation. BC is the Joan and Richard Doll Research Fellow at Green College, Oxford.

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