Scopolamine Improves Autonomic Balance in Advanced Congestive Heart Failure

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Background  Sympathetic hyperactivity and parasympathetic withdrawal in patients with congestive heart failure correlate closely with disease severity and overall survival. The modulating effects of drugs on the autonomic dysfunction may contribute to improve survival. Low-dose scopolamine has a vagomimetic effect in normal subjects and patients after acute myocardial infarction. We assessed whether transdermal scopolamine would increase vagal activity in patients with congestive heart failure.

Methods and Results  Heart rate variability was assessed at baseline, 24 hours after one patch of transdermal scopolamine, and 48 hours after scopolamine withdrawal in 21 patients with moderate to severe heart failure. Scopolamine increased both time- and frequency-domain parameters of heart rate variability. Specifically, the mean RR interval and its SD increased by 5.5% (P<.001) and 45% (P<.001), respectively. The change remained significant when corrected for mean heart rate with a 39% (P<.01) increase of the coefficient of variation. The absolute power of the high-frequency component was also significantly augmented. All the parameters returned to baseline after scopolamine withdrawal. Individual analysis showed that in the 7 patients in whom scopolamine did not increase mean RR interval, heart rate variability did not change.

Conclusions  Transdermal scopolamine increases vagal activity as assessed by heart rate variability in patients with congestive heart failure. This autonomic modulation does not occur in all patients and can be predicted by RR interval changes. Whether such restoration of the autonomic balance might have beneficial effects in the long-term management of patients with congestive heart failure remains to be determined. (Circulation. 1994;90:838-843.)

Key Words  • scopolamine • heart rate • nervous system • heart failure

In recent years, significant advances have been made in the understanding of the pathophysiology of heart failure.1 The “neurohormonal theory” emphasizes the central role of neurohormonal activation in the further impairment of myocardial function and in the determination of prognosis.2 Compelling evidence has been provided that blockade of neurohormonal activation rather than direct stimulation of the failing myocardium improves survival.3

In heart failure patients, profound abnormalities have been shown both in the sympathetic4-6 and the parasympathetic control of the cardiovascular system.7,8 Heart rate variability (HRV) is increasingly used as a noninvasive means to assess cardiac autonomic activity and is very suitable for serial determinations, since measures of HRV have been found to be remarkably stable both in normal subjects9 and in cardiac patients.10,11 The marked reduction in spectral and nonspectral parameters of HRV, which is found in patients with heart failure,12,13 has been regarded as an index of neurohumoral maladaptation.14

The antimuscarinic agent hyoscyamine (scopolamine) at low doses (0.1 to 0.2 mg) may decrease heart rate by a paradoxical vagomimetic effect. Delivery by transdermal patch substantially increases both baseline and reflexly augmented levels of cardiac parasympathetic activity over 24 hours in normal subjects15,16 and post-myocardial infarction patients.17-20 Given the growing mass of data pointing to the adverse prognostic implication of reduced levels of vagal cardiac activity in susceptibility to life-threatening arrhythmias,21-23 it has been proposed that an intervention that increases vagal cardiac activity may improve prognosis in high-risk postinfarction patients.24

The present study was undertaken to test the hypothesis that in patients with congestive heart failure, the administration of low-dose scopolamine could alter cardiac parasympathetic activity and hence HRV. The clinical implication would be that an increase in parasympathetic activity might be useful to counterbalance, at least in part, the sympathoexcitation that accompanies congestive heart failure. Preliminary data have been presented.25

Methods

Study Group

Twenty-four patients with congestive heart failure referred for evaluation for cardiac transplantation constituted the study group. Twenty-two were men; their age (mean±SEM) was 54±2 years (range, 42 to 67 years). The cause of congestive heart failure was idiopathic dilated cardiomyopathy in 11 patients and ischemic cardiomyopathy in 13. All patients were being treated with diuretics and converting enzyme inhibitors. After tailored therapy and clinical stabilization, 8 patients were in New York Heart Association functional class II, and 16 were in class III. All were in a stable condition with no changes in signs and symptoms in the 2 weeks before the study. During the previous 3 months, none had experienced a myocardial infarction or undergone revascularization procedures.

Two-dimensional echocardiography, baseline right hemodynamics, 24-hour Holter recording, and evaluation of barore...
ceptor reflexes by the phenylephrine test were obtained within 1 week of entry into the study protocol. Left ventricular ejection fraction ranged from 12% to 32% (mean ± SEM, 23 ± 1.3%). Left ventricular filling pressure was elevated (18 ± 2 mm Hg; range, 5 to 35 mm Hg), and cardiac index was depressed (2.2 ± 0.1 L·min⁻¹·m⁻²; range, 1.45 to 3.34 L·min⁻¹·m⁻²) in the vast majority of patients. All patients were in sinus rhythm without frequent ectopic ventricular or supraventricular beats. Baroreflex sensitivity was 3.3 ± 0.6 ms/mm Hg. These values are well below those observed not only in healthy individuals (16.0 ± 1.8 ms/mm Hg) but also in postinfarction patients (7.8 ± 0.6 ms/mm Hg).

Informed consent was obtained from all subjects, and the investigation was approved by the local Human Ethics Committee.

**Study Protocol**

All studies were carried out in the morning. A standard ECG and respiratory signal (via an endonasal thermistor) were recorded and analyzed off-line. After 30 minutes of supine rest, at least 30 minutes of recording was obtained during spontaneous breathing. Three measurements were performed on each subject: at baseline, after 24 hours of transdermal scopolamine, and at 48 hours after scopolamine withdrawal. Therapy was administered via a patch (Transcyp, Ceporadi) applied behind one ear, which delivered 0.5 mg of scopolamine every 24 hours.

**Signal Acquisition and Processing**

The principles of the software for data acquisition and processing have been described. Briefly, all recordings were split into epochs of 512 beats; segments containing artifacts and fast transients were excluded. Signals were digitized off-line by an analog-to-digital converter (model Das-8, Metabyte, 12-bit resolution, ±5 V) at a sampling rate of 250 Hz. The measurements of the RR intervals were taken from the zero-crossing point of the interpolated first derivative of the signal, thus raising the time resolution up to 1 millisecond. For each RR interval, a sample of the respiratory signal was taken corresponding to the R wave to obtain the reference value of the respiratory frequency. Premature ectopic beats were identified and corrected by linear interpolation with the previous and following beats.

For each epoch, the SD of consecutive RR intervals and the root mean square of successive difference (rMSSD) were considered time-domain indexes of HRV. The coefficient of variation (CV), which normalizes SD by the mean RR interval, was also computed.

The power spectral density was calculated with an autoregressive model after a least-squares minimization of the prediction error. The optimum order of autoregressive model identification was chosen through minimization of the Akaike information criteria figure of merit, starting from a minimum of 8. Records of data that did not satisfy the Anderson test (whiteness test) on the prediction error were excluded from the analysis. For each sequence, the main spectral components were identified automatically, with their power and central frequency computed according to Zeitzer. The following parameters were analyzed: (1) power in the low-frequency (LF, 0.03 to 0.15 Hz) band, which reflects modulation of both sympathetic and parasympathetic cardiac efferent activity, and (2) power in the high-frequency (HF, 0.15 to 0.45 Hz) band, which reflects modulation of parasympathetic activity synchronous with respiration. Very-low-frequency power (0 to 0.03 Hz) was not considered for analysis in this study; such a power, although potentially containing clinical information in patients with congestive heart failure, is rather erratic when calculated over short time series and has not yet received a well-defined pathophysiological explanation.

**Statistical Analysis**

Statistical analysis was performed for each parameter on the mean of three good-quality records. The results are presented as mean ± SEM. Normality of the distribution of the data was assessed with a goodness-of-fit test. Nonparametric statistical methods were used when the variables did not show a normal distribution. Differences among mean values in the three experimental conditions (baseline, scopolamine, washout) were assessed by one-way ANOVA for repeated measures or by Kruskal-Wallis test for nonparametric distributions (HF and LF power spectral densities). Differences between pairs of means were subsequently analyzed with a t test for paired samples or with the Wilcoxon signed rank test. Spearman rank correlation coefficients and the corresponding test of significance were used to assess relations between variables. Statistical significance was defined at the P < .05 level. Adjustment for multiple comparisons was made according to the Bonferroni correction when appropriate.

**Results**

Two patients were excluded because of excessive premature beats in one of the three trials, and one other patient was excluded because of worsening of the clinical status requiring inotropes. The final analysis was thus related to 21 sets of recordings.

The scopolamine patch was well tolerated by all patients: adverse side effects, such as dry mouth or drowsiness, were minor and were not spontaneously reported by any patient.

The effects of scopolamine on the time- and frequency-domain measures of heart rate variability are displayed in Table 1. Scopolamine substantially increased average RR interval and measures of parasympathetic cardiac activity, and scopolamine withdrawal induced a similar decrease. The average RR interval increased by 5.5% (P < .001) after scopolamine, and the SD and the rMSSD increased by 45% (P < .001) and by 54% (P < .001), respectively. The CV increased by 39% (P < .001), indicating that the increased variability was not related simply to the increase in mean RR interval. Similar effects were seen on heart rate power spectra: LF power increased by 43% (NS) and HF power by 65% (P < .02). All parameters returned to baseline value 48 hours after scopolamine withdrawal, thus indicating that the observed changes were dependent on treatment rather than on spontaneous fluctuations.

There was no association between changes in mean RR interval after scopolamine and the mean RR interval baseline values (r = −.21, P = .36). Significant correlations were found between changes in RR interval and changes in SD (r = .70, P < .001), rMSSD (r = .84, P < .0001) (Fig 1), HF power (r = .66, P < .001), and LF power (r = .47, P < .03), showing a relation between the magnitude of changes in RR interval and the magnitude of changes in HRV. When the individual changes are analyzed (Fig 1), it appears that in a number of patients the RR interval did not change or even decreased. Patients were then grouped according to the presence or the lack of an increase in mean RR interval. The 14 patients in whom there was an increase were defined as responders, and the remaining 7 were defined as nonresponders. On this basis, the data will henceforth be analyzed according to the response in heart rate.

Demographic and baseline HRV data of responders and nonresponders are depicted in Table 2. Slight differences were found between the two groups; nonresponders showed a trend toward a more advanced hemodynamic decompensation and a more depressed HRV. These differences are not significant, probably because of the small sample size. After scopolamine,
there was a marked change in both time- and frequency-domain indices of HRV in responders, whereas no change was shown in nonresponders (Figs 2 and 3). Specifically, SD increased by 65% (P<.001), rMSSD by 82% (P<.001), CV by 46% (P<.001), the LF power by 53% (NS), and the HF power by 102% (P<.005). HF power showed a greater increase than LF power not only in absolute value (102% versus 53%) but also as reflected by the ratio of the HF and LF power to power in the band 0.03 to 0.45 Hz (HF power from 38% to 46%, LF power from 54% to 49%).

Discussion

The present investigation demonstrates that administration of transdermal scopolamine increases resting HRV in patients with moderate to severe congestive heart failure. The data suggest that it is possible to increase a marker of vagal activity, thus effectively reducing the autonomic imbalance that accompanies hemodynamic decompensation.

Scopolamine in Healthy and Postinfarction Subjects

Low-dose scopolamine has a vagomimetic effect in healthy subjects and in patients after myocardial infarction. This is largely due to a complex mechanism depending on a direct effect on the vagal centers in the medulla, although one cannot exclude peripheral effects involving either cholinesterase inhibition leading to increased receptor responsiveness to acetylcholine or blockade of the muscarinic receptor at the presynaptic level. In the two studies in normal subjects, the average RR interval increased by 13% and 19%, respectively, whereas in postinfarction patients, increases ranging from 7% to 14% have been reported. In all studies, time-domain HRV changed to a greater extent than mean RR interval, showing that the improvement in autonomic balance is not solely dependent on the reduction in mean heart rate.

Scopolamine in Patients With Congestive Heart Failure

The present data in patients with moderate to severe congestive heart failure are in agreement with the observations in normal subjects and patients after myocardial infarction, with a significant (46%) increase in

### Table 2. Demographic and Heart Rate Variability Data of Responders and Nonresponders to Scopolamine Administration

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=14)</th>
<th>Nonresponders (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52±2</td>
<td>57±3</td>
</tr>
<tr>
<td>EF, %</td>
<td>24±2</td>
<td>20±2</td>
</tr>
<tr>
<td>CI, L · min⁻¹ · m⁻²</td>
<td>2.27±0.14</td>
<td>2.19±0.16</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>22.3±2.9</td>
<td>28.4±5.9</td>
</tr>
<tr>
<td>PCP, mm Hg</td>
<td>16.7±2.9</td>
<td>19.7±3.5</td>
</tr>
<tr>
<td>RR, ms</td>
<td>835±31</td>
<td>875±71</td>
</tr>
<tr>
<td>SD, ms</td>
<td>20±3</td>
<td>19±4</td>
</tr>
<tr>
<td>rMSSD, ms</td>
<td>11.4±2</td>
<td>9.7±2.5</td>
</tr>
<tr>
<td>CV, %</td>
<td>2.4±1.2</td>
<td>2.2±1.0</td>
</tr>
<tr>
<td>LFP, ms²</td>
<td>97±37</td>
<td>39±18</td>
</tr>
<tr>
<td>HFP, ms²</td>
<td>68±23</td>
<td>47±25</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; CI, cardiac index; PAP, mean pulmonary artery pressure; PCP, mean pulmonary capillary pressure; RR, mean RR interval; rMSSD, root mean of successive square difference; CV, coefficient of variation (SD/RR · 100); LFP, low-frequency power; and HFP, high-frequency power.
the CV, which normalizes SD by mean RR interval. Compared with normal subjects and with patients after myocardial infarction, the magnitude of changes in mean RR interval (5.5%) was somewhat lower in our population of patients with congestive heart failure. This could be explained by differences in pump function and sympathetic-parasympathetic activity among the three groups of subjects. In fact, our patients with congestive heart failure had markedly depressed left ventricular function and signs of a major autonomic derangement, as expressed by the very depressed baroreflex sensitivity (3.3±0.6 ms/mm Hg) and HRV indexes. This could have reduced the possibility of a decrease in mean heart rate compared with postinfarction patients, who had a less compromised left ventricular function, and healthy subjects.

Fig 2. Bar graphs showing changes in mean RR interval and time-domain parameters of heart rate variability among responders (patients with a scopolamine-induced increase in mean RR interval) and nonresponders at baseline, after a patch of transdermal scopolamine for 24 hours, and after 48 hours of scopolamine withdrawal. Significant changes in heart rate variability were seen only in responders. *One-way ANOVA for repeated measures for mean RR (P=.004), SD (P=.002), root mean of successive square difference (rMSSD) (P=.001), and coefficient of variation (P=.0009).

Fig 3. Bar graphs showing changes in frequency-domain parameters (LFP indicates low-frequency power; HFP, high-frequency power) of heart rate variability among responders (patients with a scopolamine-induced increase in mean RR interval) and nonresponders at baseline, after a patch of transdermal scopolamine for 24 hours, and after 48 hours of scopolamine withdrawal. Changes were seen only in responders. *Kruskal-Wallis test for LFP (P=.010) and HFP (P=.008). Comparisons between means by Wilcoxon signed rank test showed a significant difference in LFP from scopolamine to washout but not from baseline to scopolamine and in HFP from both baseline vs scopolamine and scopolamine vs washout.
Similarly, a reduced magnitude of changes was observed for spectral parameters as well. In normal subjects, Vybiral et al. observed a major increase (251\%) in HF power after scopolamine; in post-myocardial infarction patients, Casadei et al. reported a fivefold increase in the absolute power of the HF component. In chronic congestive heart failure patients, we observed only a 65\% increase in the HF power. A quantitatively similar change in the HF power was described by Casadei et al. in a preliminary report on postinfarction patients with a markedly depressed left ventricular function. Our patients also showed an increase (although not significant) in the LF component, which is not surprising when we consider that the LF component reflects both parasympathetic and sympathetic nervous modulation.31

Different degrees of correlation were found between the magnitude of RR interval changes and HRV changes. The highest correlation was found between RR interval and rMSSD, which is strictly related to vagal activity,37 and the lowest for LF power. Similar data have been reported in normal subjects. In the study by Dibner-Dunlap et al., there was a moderate \((r = .58)\) but significant \((P = .03)\) association between changes in RR interval and changes in SD, whereas Vybiral et al. found highly significant correlations among changes in mean RR and all other parameters.

We used changes in mean RR interval to identify patients likely to modify their HRV. By separating patients who did not increase their mean RR interval, we identified patients who did not show significant changes in HRV. Thus, among patients with congestive heart failure, there is not a uniform response to scopolamine administration, which is probably related to the more advanced cardiac decompensation. Patients who did not respond to scopolamine administration had a more depressed baseline HRV and a worse clinical condition as indicated by the lower ejection fraction and by the higher pulmonary capillary pressure compared with subjects who increased HRV. On this basis, it could be speculated that among patients with congestive heart failure, there is a subgroup with a more advanced sympathoexcitation in whom modulation of heart rate is so depressed that 24-hour administration of scopolamine is not effective in altering both RR interval and HRV. This hypothesis is supported by a recent paper in which six congestive heart failure patients, with SDs as low as those observed in heart transplant patients, did not show any significant change in average RR interval after low-dose atropine administration. This might also be partly because, among the antimuscarinic agents, atropine has a reduced central effect in comparison to scopolamine.39

Both spectral and nonspectral parameters of HRV returned to baseline value 48 hours after scopolamine withdrawal, thus indicating that the observed increase in cardiac vagal activity was actually dependent on scopolamine administration. Other factors, such as changes in clinical status or changes in the prescribed therapy, which could have induced changes of HRV parameters unrelated to the drug, remained constant for the whole study period.

Pharmacological agents could also have influenced the response to scopolamine. However, there was no difference in the medical regimen between responders and nonresponders.

Plasma scopolamine levels were not determined in the present study, and the issue of the effect of scopolamine administered on a long-term basis has not been addressed. We cannot rule out the possibility that a chronic administration of scopolamine might have converted the nonresponders into responders.

**Clinical Implications**

In congestive heart failure, the derangement of the neuroendocrine axis and the abnormalities of autonomic control of cardiovascular function do contribute to the hemodynamic decompensation and to the progression of the disease. According to Packer, among the possible pharmacological interventions in congestive heart failure, sympathomimetic drugs increase cardiovascular morbidity and mortality, and the most important predictor of response to therapy appears to be the effect of these drugs on the neurohormonal system. The favorable effects shown by angiotensin-converting enzyme inhibitors and digitalis glycosides have been related to restoration of neurohormonal mechanisms governing cardiovascular function. Both the inhibition of sympathetic and the increase of parasympathetic outflows from the central nervous system could contribute to the restoration of neural mechanisms.

HRV is a noninvasive clinical tool for the investigation of the autonomic control of the heart that can be used in the evaluation of response to therapeutic intervention. Flapan et al. and Binkley et al. recently demonstrated that in chronic cardiac failure, the clinical benefit after long-term angiotensin-converting enzyme inhibitor therapy was paralleled by increased cardiac parasympathetic activity, as assessed by HRV. Our data demonstrate that scopolamine administration is effective in increasing HRV in a meaningful proportion (60\%) of congestive heart failure patients. In patients after myocardial infarction, a shift in the autonomic balance toward a more pronounced parasympathetic activity has been suggested to be useful in the prevention of sudden death. In patients with congestive heart failure, given the central role of the sympathetic nervous system in the progression of the disease, an increase in parasympathetic activity could, at least in part, counterbalance sympathetic overstimulation.

In conclusion, this study demonstrates that in patients with severe congestive heart failure, cardiac parasympathetic activity can be enhanced by short-term administration of low-dose scopolamine and returns to baseline after drug withdrawal. The increase in HRV may be predicted by the change in RR interval. Twenty-four hours of scopolamine appears not to be effective in the more advanced stage of the disease. Whether the extent of changes in vagal activity produced by scopolamine might be sufficient to contribute to a better management of these patients is not known at present. Vagal activation may indeed break the vicious circle that relates sympathetic hyperactivity to the further progression of cardiac failure. Scopolamine provides the possibility of a selective manipulation of the autonomic balance aimed at limiting sympathetic hyperactivity and deserves consideration as a new and interesting adjunct to the therapeutic regimen for congestive heart failure.

**References**

La Rovere et al  Scopolamine in Congestive Heart Failure 843


Scopolamine improves autonomic balance in advanced congestive heart failure.
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