Provocation of Ventricular Ectopy by Cheyne-Stokes Respiration in Patients with Heart Failure

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INTRODUCTION

CHEYNE-STOKES RESPIRATION WITH CENTRAL SLEEP APNEA (CSR-CSA) IS A FORM OF PERIODIC BREATHING IN WHICH CENTRAL APNEAS AND HYPOPNEAS ALTERNATE WITH VENTILATORY PERIODS HAVING A CRESCENDO-DECRESCEDNO PATTERN OF TIDAL VOLUME. CSR-CSA is common among patients with heart failure (HF), where it is present in 30% to 40% of patients in the largest reported series.1,2 Growing evidence indicates that CSR-CSA is part of a vicious pathophysiologic cycle involving the cardiovascular, pulmonary, and autonomic nervous systems that ultimately contributes to increased mortality among patients with HF.3-5 Ventricular premature beats (VPB) are a risk factor for both arrhythmic and nonarrhythmic death in patients with ischemic heart disease.6 Therefore, one possible explanation for higher mortality in patients with CSR-CSA is increased ventricular irritability due to apnea-related hypoxia, arousals from sleep, sympathetic nervous system activation, and associated elevations in blood pressure and heart rate.3,5,7,8 A number of previous reports have established an association between CSR-CSA and ventricular ectopy,9,10 but a cause-effect relationship has yet to be definitively established. Notably, Javaheri11 observed, in a posthoc analysis, that those patients whose CSR-CSA was alleviated by application of continuous positive airway pressure (CPAP) also experienced a reduction in the frequency of ventricular ectopy. However, in none of these previous studies was it demonstrated that CSR-CSA actually provokes ventricular ectopy.

If CSR-CSA indeed precipitates ventricular ectopy, we hypothesized that VPB would occur more frequently during episodes of CSR-CSA than during periods of regular breathing in the same patients. We further hypothesized that the frequency of VPB during CSR-CSA would be greater during the hyperpneic phase when chemostimulation, blood pressure, and heart rate reach their peak than during the apneic phase when these variables are at their nadir. To test these hypotheses, in patients with HF, we compared the frequency of VPB between CSR-CSA and regular breathing, and between the ventilatory and apneic phases of CSR-CSA.

METHODS

Subjects

Subjects were 23 consecutive patients (Table 1) with HF referred to the Toronto Rehabilitation Institute Sleep Research Laboratory who met the following entry criteria: (1) left ventricular systolic dysfunction (left ventricular ejection fraction < 45% by nuclear angiography or echocardiography), and (2) CSR-CSA based on the presence of central apneas and hypopneas with a frequency more than 10 per hour, with intervening hypopneas having a crescedo-decrescendo pattern of tidal volume. Patients

Study Objectives: Previous reports have suggested an association between Cheyne-Stokes respiration with central sleep apnea (CSR-CSA) and ventricular ectopy, but there has been relatively little evidence of a cause-effect relationship. The objective of this study was to determine whether CSR-CSA directly provokes ventricular ectopy and, if so, whether it is associated with any particular phase of the CSR-CSA breathing cycle.

Design: We compared the frequency of ventricular premature beats (1) between the apneic and hyperpneic phases of CSR-CSA, (2) between periods of CSR-CSA and periods of regular breathing during sleep, and (3) in response to the elimination of CSR-CSA by administration of a low concentration of inhaled CO2.

Setting: Hospital-based cardiopulmonary sleep laboratory.

Patients: Twenty-three patients with heart failure and CSR-CSA.

Measurements and Results: Ventricular premature beats were found to occur 40% more frequently during the hyperpneic phase than the apneic phase of CSR-CSA (mean ± SD, 7.0 ± 7.4 versus 4.9 ± 5.7 ventricular premature beats per minute, \( P = .003 \)). Ventricular premature beat frequency was also found to be higher during periods of CSR-CSA than during periods of regular breathing occurring either spontaneously (median [25th, 75th percentile], 2.2 [1.2, 6.5] versus 1.1 [0.8, 2.0] ventricular premature beats per minute, \( P = .027 \)), or induced through inhalation of CO2 (from 4.7 ± 3.8 to 3.3 ± 4.0 ventricular premature beats per minute, \( P = .048 \)).

Conclusions: CSR-CSA provokes ventricular ectopy that is most pronounced during the hyperpneic phase. Such an increase in ventricular premature beats might contribute to the higher mortality rates reported in heart failure patients with CSR-CSA.

Key Words: periodic breathing, arrhythmia, respiration, heart failure

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with atrial fibrillation were excluded. All patients were referred to the sleep laboratory by cardiologists for 2 principal reasons: either symptoms suggestive of a sleep apnea syndrome, such as excessive daytime sleepiness, snoring, nocturnal dyspnea, or restless sleep, or persistent dyspnea and exercise limitation despite optimal medical management of HF, or both.

Sleep Studies

Overnight sleep studies were performed in all subjects with the use of standard techniques for scoring of sleep stages and arousals.12 Respiratory efforts and tidal volume were recorded with a calibrated respiratory inductance plethysmograph (Respitrace, Ambulatory Monitoring, Inc., Ardsley, NY). Oxyhemoglobin saturation (SaO₂) was measured with an oximeter (Nellcor N200; Nellcor Puritan Bennett Inc, Pleasanton, Calif). Heart rate was monitored continuously via a lead I electrocardiogram (ECG). Transcutaneous PCO₂ was measured continuously with a transcutaneous capnograph (Kontron Medical; Hoffman-La Roche, Basel, Switzerland), with the electrode placed on the anterior chest wall. The instrument was calibrated before and after each study as previously described.13

Central apneas were defined by the absence of tidal volume excursions for at least 10 seconds in the absence of ribcage and abdominal movement. Central hypopneas were defined as a 50% or greater reduction in tidal volume from the baseline value, persisting for at least 10 seconds in the absence of paradoxical motion or phase shift of the ribcage and abdominal signals.13,14 Obstructive apneas and hypopneas were similarly defined except that they had to be accompanied by paradoxical or phase-shifted movements of the rib cage and abdomen. The frequency of apneas and hypopneas per hour of sleep was expressed as the apnea-hypopnea index (AHI). Scoring of apneas and hypopneas was performed by a polysomnographic technician who was blinded to the ECG findings.

VPB: Hyperpnea versus Apnea

Ten-minute segments of stable CSR-CSA during stage 2 sleep were identified, and apneas and hypopneas were scored prior to scoring of the ECG by personnel blinded to the ECG signal. After the representative segments were chosen, ECG analysis was performed with scoring of each beat as being sinus, paced, or ventricular in origin. VPB were identified manually on the basis of a wide QRS complex, the lack of a P wave, and a short preceding RR interval.15 The frequency of VPB during apneas and hypopneas was compared with that during hyperpneas. Because there is a tendency for mean HR to increase during hyperpnea, this comparison was also performed with VPB frequency expressed per 100 heart beats in order to correct for differences in HR.

VPB: Regular Breathing versus CSR-CSA

In subjects who had sufficient periods of both CSR-CSA and regular breathing, the frequency of VPB during 10-minute segments of CSR-CSA was compared with the frequency of VPB during matched 10-minute segments of spontaneously occurring regular breathing during stage 2 sleep within the same subjects. However, in those subjects who had continuous CSR-CSA with no spontaneously occurring periods of regular breathing during sleep, we could not carry out such an analysis. Therefore, in a subset of 4 of these subjects, we induced regular breathing during stage 2 sleep by administering a CO₂-enriched gas, which we have previously shown abolishes CSR-CSA.16 We then compared the frequency of VPB during periods of CSR-CSA to that during periods of regular breathing induced by CO₂. Since elimination of CSR-CSA by CO₂ inhalation also eliminates apnea-related O₂ desaturation, in these subjects we also administered an O₂-enriched gas sufficient to raise SaO₂ to the same level as during CO₂ inhalation in order to separate the effects of eliminating CSR-CSA from those of eliminating apnea-related O₂ desaturation. The details of these interventions have been reported previously16 and will only be summarized here.

Patients breathed through a tight-fitting facemask, with built-in low-resistance inspiratory and expiratory valves. Two different Douglas bags with 60-L capacity were connected to a 3-way stopcock, which was in turn connected to the inspiratory port of the facemask. One bag delivered a CO₂-enriched gas (4% CO₂, 21% O₂, 75% N) mixed with compressed air such that a constant inspired fraction of 21% O₂ was maintained. The fraction of inspired CO₂ was adjusted by manually controlling the flow rates of the 2 gas streams into the Douglas bag that was maintained partially full. The second bag delivered compressed air and O₂. Through this bag, the subjects breathed either compressed air or an O₂-enriched gas mixture. Patients expired through a separate low-resistance valve that minimized dead space and prevented pressure buildup inside the mask. The circuit allowed the subjects to breathe either the air or CO₂ or O₂ mixtures with the switching and concentrations of the inspired gases controlled by the experimenter in a separate room from the subject to minimize sleep disruption.

**Table 1—Characteristics of the Subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>No.</td>
<td>23</td>
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<tr>
<td>Age, y</td>
<td>66.0 ± 10.9</td>
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<tr>
<td>BMI, kg/m²</td>
<td>27.8 ± 4.5</td>
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<td>Cardiac rhythm, no.</td>
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<tr>
<td>Sinus</td>
<td>22</td>
</tr>
<tr>
<td>Paced</td>
<td>1</td>
</tr>
<tr>
<td>Central AHI, events/h sleep</td>
<td>38.3 ± 14.4</td>
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<tr>
<td>Obstructive AHI, events/h sleep</td>
<td>4.03 ± 8.2</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>25.9 ± 10.4</td>
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<tr>
<td>Etiology of cardiac disease, no. (%)</td>
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<tr>
<td>Ischemic</td>
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<tr>
<td>Idiopathic</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Valvular</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Medications, no. (%)</td>
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<tr>
<td>ACEI / ARB</td>
<td>20 (87.0)</td>
</tr>
<tr>
<td>β-adrenergic receptor-blocking agent</td>
<td>13 (56.5)</td>
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<tr>
<td>Digoxin</td>
<td>11 (47.8)</td>
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<tr>
<td>Amiodarone</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>22 (95.7)</td>
</tr>
<tr>
<td>Calcium channel blocking agent</td>
<td>5 (21.7)</td>
</tr>
<tr>
<td>Nitrate</td>
<td>10 (43.5)</td>
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</tbody>
</table>

Values are mean ± SD except as otherwise indicated. BMI refers to body mass index; AHI, apnea-hypopnea index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor-blocking agent.
Subjects were studied in a quiet room in the supine position where they went to sleep wearing a facemask, initially breathing room air. All interventions were performed on a single night during stage 2 non-rapid eye movement sleep in order to control for the potential influence of different sleep stages. Once stage 2 sleep with CSR-CSA became firmly established for at least 15 minutes, the gas mixture was switched to CO₂. The concentration of inspired CO₂ was slowly increased until CSR-CSA was eliminated. CO₂ inhalation was continued for 15 to 30 minutes at this concentration, after which the patient was switched back to air inhalation. If the subject awoke or went into a deeper stage of sleep, he was switched back to air. After the trial of CO₂, the O₂-enriched gas mixture was administered, at a concentration sufficient to increase the SaO₂ to the same level as during CO₂ inhalation. The protocol was approved by the Human Subjects Review Committee of the University of Toronto, and all patients gave written informed consent before participation.

DATA ANALYSIS

Data are reported as mean ± SD when normally distributed and median [25th percentile, 75th percentile] when nonnormally distributed. Comparisons of VPB frequencies between the apneic and hyperpneic phases of CSR-CSA, and between CSR-CSA and spontaneously occurring regular breathing were made by 2-tailed paired t tests or Wilcoxon signed rank tests for normally and nonnormally distributed data, respectively. The frequencies of VPB were also compared between periods of CSR-CSA and periods of regular breathing induced by CO₂, as well as during O₂ inhalation by 1-way repeated measures analysis of variance (ANOVA) followed by Tukey tests. The statistical software package used was Sigmastat 2.03 (SPSS Inc., Chicago, Ill). A value of P < .05 was considered statistically significant.

RESULTS

Characteristics of the subjects

Clinical and polysomnographic characteristics of the 23 subjects are summarized in Table 1. Subjects were all middle-aged to elderly men, who were slightly overweight. All except 1 patient, who was paced, were in sinus rhythm. They had a moderate to severe degree of CSR-CSA as indicated by their AHI. Left ventricular ejection fraction was moderately to severely depressed. Heart failure was mainly due to ischemic cardiomyopathy. All subjects were on appropriate pharmacologic therapy for HF.

VPB: Hyperpnea versus Apnea

Data for all 23 subjects are shown in Figure 1. First, we found that the frequency of VPB was significantly greater during the hyperpneic phase of CSR-CSA than during the apneic phase (P = .003). This difference persisted even after correcting for differences in heart rate (5.7 [2.5, 13.9] versus 3.6 [1.1, 11.9] VPB per 100 beats, P < .001) (Figure 2). Mean and mean nadir SaO₂ (mean of the lowest SaO₂ during each periodic breathing cycle) differed between the hyperpneic and apneic phases, but the differences were very small (92.7% ± 3.1% versus 95.4% ± 1.9%, P < .001 and 90.8% [88.05, 94.5%] versus 93.5% [91.7%, 96.3%], P < .001 respectively). These data demonstrate that VPB occur preferentially during the hyperpneic phase of CSR-CSA even in the absence of hypoxia.

VPB: Regular Breathing versus CSR-CSA

The frequency of VPB during 10-minute segments of CSR-CSA were compared with those observed during 10-minute segments of spontaneous regular breathing during stage 2 sleep. Of the 23 subjects, 9 had periods of stable regular breathing of sufficient duration for this analysis. Individual data are shown in Figure 3. Compared to regular breathing, there was a 2-fold increase in the frequency of VPB (P = .027) despite similar mean SaO₂ between the 2 periods (94.3% ± 2.9% versus 93.9% ± 2.4% respectively, P = NS).

Data from 1 of the subset of 4 subjects who had no spontaneous regular breathing, and who received inhaled CO₂ and O₂,
are shown in Figure 4. Inhaled CO$_2$ (mean fraction of inspired CO$_2$ of 1.9% ± 0.6%) raised PtcCO$_2$ (from 32.0 ± 3.5 to 34.9 ± 2.9 mm Hg, $P = .003$) above the apneic threshold and eliminated CSR-CSA (the AHI fell from 41.6 ± 8.4 per hour during room air breathing to 1.5 ± 3.0 per hour, $P < .001$). This led to a significant reduction in the frequency of VPB ($P = .048$, Figure 5). In contrast, administration of O$_2$ sufficient to maintain the SaO$_2$ above 92% at levels similar to those during CO$_2$ breathing (96.1 ± 2.2% during CO$_2$ versus 97.4% ± 1.4% during O$_2$, $P = NS$) had no significant effect on the AHI (from 41.6 ± 8.4 per hour during room air breathing to 36.6 ± 10.8 per hour on O$_2$, $P = NS$) and had no significant effect on the frequency of VPB (Figure 5). However, compared to during CO$_2$ inhalation, the frequency of VPB during O$_2$ inhalation was significantly higher ($P = .008$). Taken together, these data indicate that VPB are less frequent during periods of regular breathing, whether occurring spontaneously or in response to CO$_2$ inhalation, than during periods of CSR-CSA, whether breathing room air or supplemental O$_2$.

**DISCUSSION**

Findley et al$^{17}$ first reported VPB occurring more frequently during the hyperpneic phase than the apneic phase of CSR-CSA in 1984. However, this was only a single case report in which an intervention was not tested. Javaheri et al$^{9}$ found that patients with HF and hypocapnia ($PaCO_2 < 35$ mmHg) had both a higher prevalence of CSR-CSA and a higher rate of ventricular ectopic beats than did eucapnic patients. Similarly, Lanfranchi et al$^{10}$ described a higher frequency of ventricular arrhythmias among patients with HF and severe CSR-CSA than in those without CSR-CSA. Further evidence for an association between ventricular ectopy and CSR-CSA was provided by the observation, in a posthoc analysis of a nonrandomized trial, that among HF patients with CSR-CSA, those who experienced alleviation of CSR-CSA by CPAP also experienced a reduction in the frequency of VPB.$^{11}$ However, by increasing intrathoracic pressure, CPAP exerts a number of direct effects on the heart, which are unrelated to normalization of breathing. Direct effects of CPAP which might reduce ventricular irritability include reductions in both heart size and cardiac sympathetic nerve traffic.$^{18-21}$

The present study complements the findings of those previous reports by providing additional evidence that CSR-CSA pro-
vokes, and that its abolition alleviates, ventricular ectopy. First, we showed in 23 patients that VPB do not occur randomly during the CSR-CSA breathing cycle but, instead, are concentrated during the hyperpneic phase. Second, we found in a subset of 9 patients who had episodes of both regular breathing and of CSR-CSA that VPB were more frequent during CSR-CSA than during spontaneous regular breathing in the same night and sleep stage in the same individual. Such temporal relationships indicate that VPB are not only associated with, but are directly provoked by, CSR-CSA. These observations also exclude the possibility that the differences in the frequency of VPB were due to changes in medications, heart function, or state of consciousness between the 2 periods. The types of medications that patients were on had no influence on this effect. Third, in a subset of subjects, we showed that the frequency of VPB was reduced by inhalation of a low concentration of CO2, an intervention that eliminates CSR-CSA but, unlike CPAP, does not have direct effects on intrathoracic pressure or cardiac size. Finally, we demonstrated that elimination of apnea-related dips in SaO2 by O2 inhalation had no effect on either CSR-CSA or the frequency of VPB. Taken together, these findings provide compelling evidence that CSR-CSA provokes ventricular ectopy that can be alleviated by reversal of the CSR-CSA. While the possible role of hypoxia in causing VPB cannot be completely excluded, our findings suggest that hypoxia may not be a key mechanism for triggering VPB in such patients.

Mechanisms by which CSR-CSA might trigger ventricular ectopy are unclear, but our observation that VPB occur preferentially during the hyperpneic phase suggests several possibilities. The large tidal volumes generated during the hyperpneic phase of CSR-CSA are indicative of intense respiratory drive. Since activation of brainstem respiratory neurons can coactivate adjacent central sympathetic neurons in animal preparations, surges in respiratory drive during the hyperpneic phase of CSR-CSA in humans could stimulate phase-linked bursts of central sympathetic outflow. The advantage, under normal circumstances, of such coactivation of respiratory and cardiovascular systems would be to match lung perfusion, through alterations in HR and cardiac output, with ventilation to optimize gas exchange during changing metabolic demands. However, this interaction of the 2 systems might also lead to deleterious effects during CSA-CSA, such as excessive sympathetic activation and increased ventricular irritability in the setting of a diseased or ischemic myocardium. Indeed, CSR-CSA in patients with HF is associated with increased sympathetic activity, which is in turn related to ventricular arrhythmias.

HR increases during the hyperpneic phase of CSR-CSA, and it has been observed that the frequency of VPB increases in association with increases in HR. It remains unclear, however, to what extent these HR effects on ectopy are manifestations of changes in autonomic tone, or to HR itself. It is conceivable that faster HR might lead to increasing conduction delay, which would predispose to reentrant ventricular ectopic beats. Alternatively, increases in HR might also lead to increases in myocardial O2 demand, and trigger VPB by provoking ischemia.

Finally, the hyperpneic phase of CSR-CSA is obviously associated with large tidal volumes and exaggerated negative intrathoracic pressure, which might lead to passive mechanical stretch of the ventricle. Transient passive dilatation of myocardial tissue has been shown to trigger VPB through mechano-electrical feedback.

Since inhaled CO2 increased mean transcutaneous PCO2 and, therefore, the mean level of chemostimulation, it is quite remarkable that it also reduced the frequency of VPB. This observation suggests that even though mean chemostimulation is increased during CO2 inhalation, the effect on ventricular irritability is less pronounced than during the intermittent intense chemostimulation that accompanies CSR-CSA. This explanation is supported by the observation that peak ventilation during the hyperpneic phase of CSR-CSA exceeds that during CO2 administration (Figure 4), which suggests that sympathetic activation might be higher as well. Alternatively, it suggests that CSR-CSA itself facilitates ventricular ectopy over and above the effects of respiratory drive by overwhelming the ability of the ventricular myocardium to adapt to constant oscillations in autonomic activity or by other, as yet undetermined, mechanisms. Finally, while administering CO2 to a subject during regular breathing will increase sympathetic activity, this may not be true when CO2 is administered to a subject with CSR-CSA. Sympathetic stimulation during CSR-CSA arises through multiple mechanisms, including the sympathetic effects of CO2 retention, decreases in PO2 and, possibly, CSR-CSA itself. Thus, although CO2 administration will tend to stimulate sympathetic activity, elimination of apneas and hypopneas may have countervailing effects that would tend to inhibit sympathetic outflow.

Severe hypoxia is a recognized cause of ventricular arrhythmias, and previous authors have suggested that VPB during CSR-CSA were related to hypoxic dips. However, several observations suggest that, in our subjects, hypoxia was not a critical mechanism by which CSR-CSA provoked VPB during the hyperpneic phase.
hyperpneic phase. First, during room-air breathing, the frequency of VPB increased during the hyperpneic phase, even though the SaO₂ fell by only 2% to 3% and did not drop below 90% in most subjects (Figures 1 and 3). Such a small decrement is unlikely to account for the differences in the frequency of VPB observed. Second, mean and mean nadir SaO₂ were not significantly different between periods of CSR-CSA and spontaneous regular breathing, even though there was a 2-fold difference in the frequency of VPB. It is not surprising that this minor degree of hypoxia seemed not to play an important role in triggering VPB in our subjects, since previous investigators have found that ventricular ectopy during sleep was increased only as a result of much more severe degrees of hypoxemia (SaO₂ < 60%-70%).20 Finally, in a subset of our subjects, administration of supplemental O₂ to maintain the SaO₂ above 92% during CSR-CSA did not reduce the frequency of VPB compared to room air (Figure 4).

Our study has some limitations. In particular, administration of CO₂ and O₂ was restricted to a subset of 4 subjects with particularly severe CSR-CSA who did not manifest any periods of spontaneous regular breathing. Thus, these specific findings may not be generalizable to all patients with CSR-CSA. Moreover, it is possible that with a larger number of patients, a significant reduction in VPB frequency with correction of hypoxia might have been found. However, in our 4 patients, we did not find such a reduction with administration of O₂, though we did find a significantly reduced frequency of VPB with administration of CO₂. Despite the small number of subjects, differences in the frequency of VPB were significant using stringent statistical analyses. In addition, by using patients as their own controls on the same night, any possible confounding by changes in clinical status, medication use, or level of consciousness has been excluded.

In summary, our findings support the work of previous investigators10,11,17 in suggesting that CSR-CSA provokes ventricular ectopy. Our novel observation that VPB occur preferentially during the hyperpneic phase of CSR-CSA may offer additional insight into the mechanisms involved. We speculate that this increase in ventricular ectopy arises mainly as a result of surges in cardiac sympathetic outflow coupled to the intense respiratory drive during the hyperpneic phase of CSR-CSA,2,22,26,21 or to stretch of the myocardium during generation of large tidal volumes.22 All of our subjects had HF, due mainly to ischemic cardiomyopathy, and had more than 30 VPB per hour. Since the presence of VPB at a rate of as little as 10 per hour is a risk factor for both arrhythmic and nonarrhythmic death in patients with ischemic cardiomyopathy,6 increased ventricular ectopy at the frequency we observed in our subjects may contribute to the increased mortality observed in patients with CSR-CSA.3–5 This suggests that reversal of CSR-CSA in patients with HF has the potential to reduce ventricular arrhythmias and, therefore, to improve survival.5,11 Long-term randomized trials will be required to test this hypothesis.

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