Table 3. Spectral Components Obtained from Wavelet Analysis (Maximum Response)

	Asymptomatic n = 9	Symptomatic n = 12	*P*
Respiratory components			
DBP (mm Hg^2/Hz)			
Control	0.089 ± 0.034	0.096 ± 0.048	NS
Hypercapnia	0.28 ± 0.11 *	0.37 ± 0.14 *	NS
Inst ventilation (L^2/Hz)			
Control	0.0060 ± 0.0011	0.0068 ± 0.0011	NS
Hypercapnia	0.030 ± 0.0053 *	0.029 ± 0.0045 *	NS
MSNA (%^{2}/Hz)			
Control	20.5 ± 4.7	20.1 ± 2.4	NS
Hypercapnia	52.1 ± 15.1 *	44.6 ± 5.9 *	NS
Pulse-synchronous components			
MSNA (%^{2}/Hz)			
Control	33.3 ± 6.1	30.8 ± 3.8	NS
Hypercapnia	61.7 ± 9.1 *	92.4 ± 8.9 *	<.05
Resp/resp+H-beat			
MSNA			
Control	0.37 ± 0.02	0.40 ± 0.02	NS
Hypercapnia	0.44 ± 0.04 *	0.33 ± 0.03 *	<.05

*$P < .05$.

Values are mean ± standard error at the mean .

DBP, diastolic blood pressure; NS, not significant; Inst, instantaneous; MSNA, muscle sympathetic nerve activity; Resp, respiratory components; H-beat, pulse-synchronous components.

for a comparable increase in minute ventilation than the asymptomatic patients. Although the mechanisms for the predominant sympathetic chemoreflex over ventilatory chemoreflex remain unclear, they could involve several possibilities. First, the rapid sympathetic and ventilatory responses within 1 minute of CO_2 exposure are assumed to be mediated through the peripheral hypercapnic chemoreflex, which has the short time constant of about 10 seconds.[16,17] The preservation of these responses with respiratory suppression of MSNA indicates that the peripheral chemoreflex could be operative even under the hyperoxic conditions. Somers et al.[18] demonstrated in normal humans that intact baroreflex effectively suppressed peripheral chemoreflex-mediated sympathoexcitation. An experimental study also documented that sympathetic stimuli could augment peripheral hypoxic chemoreflexes.[19] Baroreflex desensitization and sympathoexcitation, which are characteristic in heart failure, could contribute to an increase in baseline sympathetic tone and attenuate within-breath suppression of sympathetic nerve activity. Second, after 1 minute of CO_2 exposure, central hypercapnic chemoreflex, with the time constant of about 100 seconds,[17] could become to play a predominant role. A greater influence on the sympathetic limb than on the ventilatory limb might attributed to the reduced susceptibility of the central chemoreflex to lung stretch reflex in the advanced heart failure. Third, despite a greater increase in minute ventilation in the symptomatic patients, the increase in tidal volume was similar to that in the asymptomatic patients. Because the symptomatic patients had a greater cardiac size than the asymptomatic patients, their lung expansion is assumed to be limited. Under these conditions, ventilatory demand had to be kept pace with by increasing respiratory rate. Consequently, the limited increase in tidal volume could result in a ceiling of the respiratory sympathoinhibition and relative augmentation of pulse-synchronous burst power in the symptomatic patients.

Clinical Implications

A greater sympathoexcitation during submaximal exercise has been well documented in heart failure.[20] Principal mechanism for sympathoexcitation during exercise is attributable to central command and muscle metaboreflex in normal subjects.[21] In heart failure, however, muscle metaboreflex is attenuated as compared with that in normal subjects.[22] Even under these conditions, a greater accumulation of metabolic byproducts during exercise may contribute to a greater metaboreflex-mediated sympathoexcitation in heart failure.[23] Alternatively, the enhanced sensitivity of hypercapnic chemoreceptors might mediate potent sympathoexcitation during exercise in heart failure. Although augmentation of the chemoreflex gain has been documented during exercise in normal subjects,[24] it remains unclear whether exercise could enhance hypercapnic chemoreflex further in patients with heart failure.

Limitations

The present study was limited for several reasons. First, the lack of normal control is a shortcoming of this study. Narkiewicz et al.[5] have already shown ventilatory and sympathetic responses to hypercapnia in normal humans using the same methods as in the present study. They found 21%

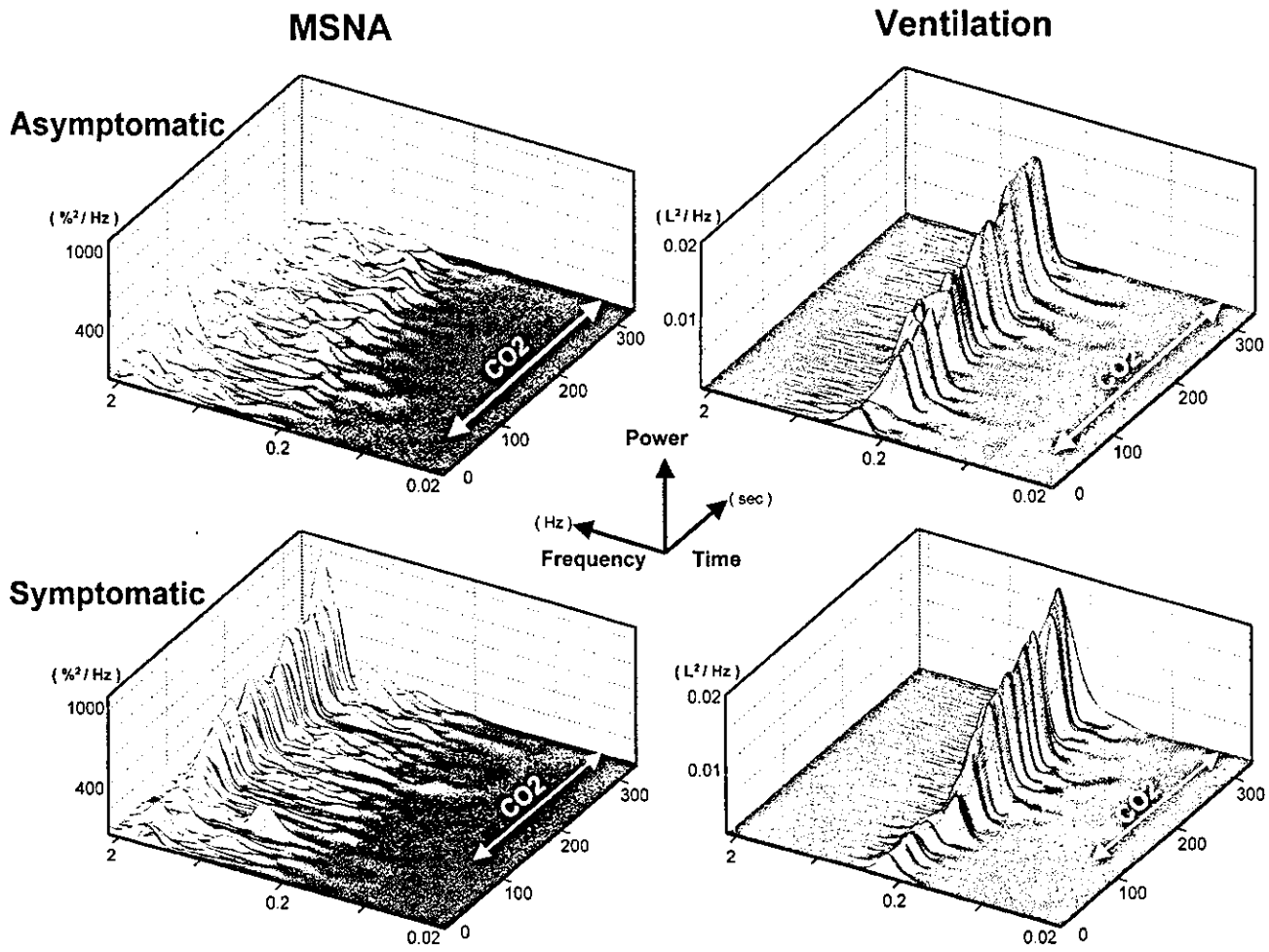

Fig. 2. Time-varying spectral plots of instantaneous ventilation (right) and muscle sympathetic nerve activity (MSNA, left). The instantaneous ventilatory power rose gradually in both groups with a shift toward higher frequencies (increase in respiratory rate) as CO_2 rebreathing time elapsed. In the asymptomatic patient, the increase in instantaneous ventilation was accompanied by a parallel augmentation of respiratory spectral components (0.15–0.5 Hz) of MSNA with a similar magnitude as in the pulse-synchronous components (0.51–2.0 Hz). In the symptomatic subject, however, the pulse-synchronous components of MSNA power predominated over the respiratory components. CO_2, carbon dioxide rebreathing.

increase in MSNA burst area during CO_2 exposure in normal subjects, whereas patients with heart failure showed a significantly higher increase in MSNA burst area (+58 %). In the present study, increases in MSNA burst area were 27% in the asymptomatic patients and 82% in the symptomatic patients, where the average increase of both groups was 58% and quite concordant with the data found by Narkiewicz et al.[5] From these findings, the normal sympathetic responses to hypercapnia are assumed to be considerably lower than those in patients with heart failure. Second, because of the heterogeneity of our patients and drug usage, the data could contain a modest quantitative error. However, there was no significant difference in the prevalence in etiology of heart failure between the 2 groups. Angiotensin-converting enzyme inhibitors and digitalis, which are known to suppress MSNA,[25,26] had been used frequently in the symptomatic patients. Nevertheless, these patients demonstrated predominant sympathoexcitatory response to CO_2 inhalation. Third, we included patients with mildly and moderately severe heart failure for reasons of subject safety. Thus it remains unknown whether the present findings can be extrapolated to patients with more advanced heart failure. Finally, MSNA could be modulated through arterial baroreflexes in response to respiratory variations of arterial pressure because dynamic baroreflex control of sympathetic nerve activity is preserved in heart failure.[27] During hypercapnic ventilation, diastolic blood pressure varied similarly in the asymptomatic and symptomatic patients. Therefore, the input to arterial baroreceptors was not assumed to be different in both groups. Recent study by Borne et al.[28] demonstrated that hyperventilation attenuates arterial baroreflex control of MSNA. Exaggerated ventilation found in the symptomatic patients might alter the arterial baroreflex gain and be partly responsible for attenuated respiratory components of MSNA.

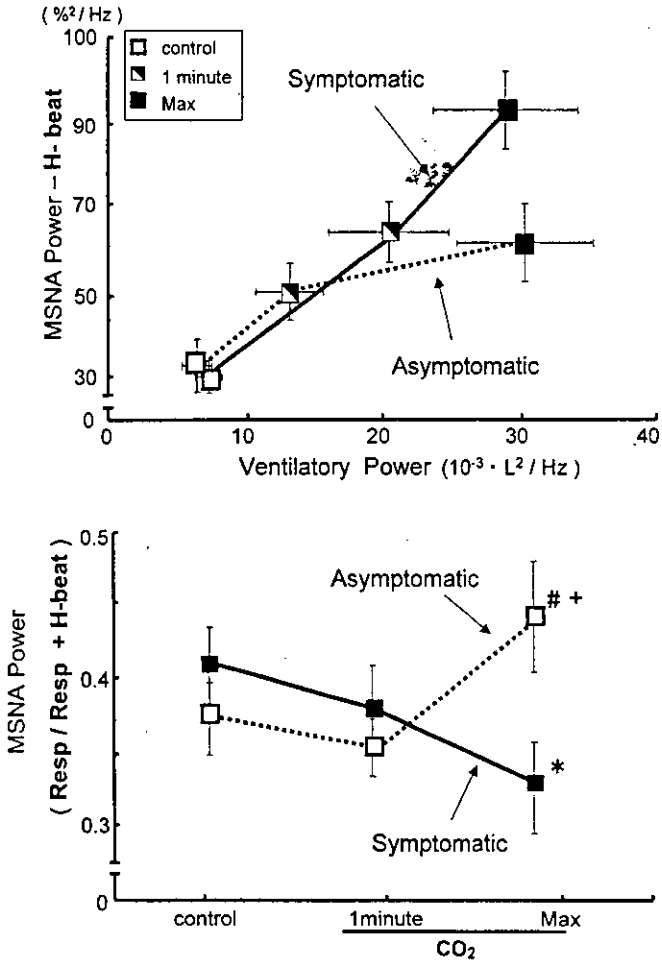

Fig. 3. Changes in pulse-synchronous (H-beat, top) spectral components of muscle sympathetic nerve activity (MSNA) as a function of instantaneous ventilatory power during hypercapnia. In the late phase (>1 minute) of hypercapnia, the pulse-synchronous components of MSNA power progressively increased in the symptomatic patients (solid line), whereas it reached a plateau in the asymptomatic patients (broken line). In contrast, relative magnitude of respiratory components as the ratio to the total MSNA power (Resp/Resp+H-beat, bottom) rose significantly in the asymptomatic patients, whereas it fell in the symptomatic patients ($P < .05$ for group-by-time interaction). Data are mean ± standard error of the mean; Max, maximum time of hypercapnia; CO_2, carbon dioxide; *, $P < .05$ versus control; #, $P < .05$ versus 1 minute; +, $P < .05$ versus Max of symptomatic.

Conclusions

Chemoreflex-mediated sympathoexcitation predominated over chemoreflex-mediated ventilatory drive in heart failure. During hypercapnic chemoreflex activation, ventilatory counteraction could not work sufficiently enough to suppress MSNA in patients with moderately severe heart failure. This abnormality would contribute to exaggerated sympathoexcitation when these patients are exposed to CO_2 during exercise or sleep apnea.

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Pulse-synchronous sympathetic burst power as a new index of sympathoexcitation in patients with heart failure

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Oda, Yoshitaka, Hidetsugu Asanoi, Hiroshi Ueno, Kunihiro Yamada, Shuji Joho, Tomoki Kameyama, Tadakazu Hirai, Takashi Nozawa, Shutaro Takashima, and Hiroshi Inoue. Pulse-synchronous sympathetic burst power as a new index of sympathoexcitation in patients with heart failure. *Am J Physiol Heart Circ Physiol* 287: H1821–H1827, 2004. First published June 3, 2004; 10.1152/ajpheart.00252.2003.—The upper limit of incidence of muscle sympathetic neural bursts can lead to underestimation of sympathetic activity in patients with severe heart failure. This study aimed to evaluate the pulse-synchronous burst power of muscle sympathetic nerve activity (MSNA) as a more specific indicator that could discriminate sympathetic activity in patients with heart failure. In 54 patients with heart failure, the pulse-synchronous burst power at the mean heart rate was quantified by spectral analysis of MSNA. Thirteen patients received a central sympatholytic agent (guanfacine) for 5 days to validate the feasibility of this new index. Both burst incidence and plasma norepinephrine level showed no significant difference between patients in New York Heart Association functional class III (94 ± 6 per 100 heartbeats and 477 ± 219 pg/ml, respectively) and class II (79 ± 14 per 100 heartbeats and 424 ± 268 pg/ml, respectively). In contrast, the burst power was useful for discriminating patients in class III from those in class II (61 ± 8% vs. 39 ± 10%; $P < 0.05$). Inhibition of sympathetic nerve activity by guanfacine was more sensitively reflected by the change of burst power (−36 ± 25%) than by that of burst incidence (−12 ± 14%; $P < 0.001$). The sympathetic burst power reflects both burst frequency and amplitude independently of the absolute values and provides a sensitive new index for interindividual comparisons of sympathetic activity in patients with heart failure.

muscle sympathetic nerve activity; α_2-adrenoceptor agonist; spectral analysis

ALTHOUGH THE FUNDAMENTAL MECHANISMS involved remain unclear, sympathoexcitation is not merely a marker of a poor prognosis in patients with heart failure but plays a causative role in its development (2, 4, 7, 12). Muscle sympathetic nerve activity (MSNA), the most specific marker of sympathetic tone in humans, has provided direct evidence of increased central sympathetic outflow in patients with heart failure (4, 8, 9). However, one of the crucial problems with this parameter is quantification of MSNA for interindividual comparisons, because neural bursts are influenced not only by the number and firing rate of active sympathetic fibers but also by proximity to the recording electrodes (15). Therefore, interindividual comparisons have been traditionally based on the burst count per minute (burst frequency) or per 100 heartbeats (burst incidence). A major problem with applying the burst count to assessment of the severity of heart failure is that the maximum value could be limited by the heart rate. Consequently, the burst count is not useful for quantifying sympathetic tone in patients with moderately severe heart failure because most of these patients have a relatively high burst incidence that is close to the upper limit of 100 per 100 heartbeats. Recently, Sverrisdóttir et al. (16, 17) reported that the distribution of burst amplitude was a useful quantitative index for interindividual comparisons. This measure focused on the proportion of large bursts because the amplitude distribution tended to be more even in subjects with a high burst incidence (15).

In the present study, we quantified pulse-synchronous neural bursts by spectral analysis of MSNA in patients with chronic heart failure. The pulse-synchronous burst power was defined as the normalized spectral power of MSNA at the heart rate of each patient. This new index was used based on the hypothesis that when sympathetic activity is high, as in patients with severe heart failure, every heartbeat is accompanied by a neural burst with a similar amplitude. Consequently, power spectral analysis should reveal a single peak at the heart rate. In contrast, several spectral peaks would exist when sympathetic neural bursts are less frequent with variable amplitude, as in the case of normal young subjects. Since this method takes both the frequency and the amplitude of MSNA bursts into account, it does not require measurement of the amplitude of each burst for comparison.

METHODS

Patients. The present study included 54 patients with asymptomatic or symptomatic cardiac dysfunction (43 men and 11 women, aged 56 ± 13 yr). The underlying cardiac disease was dilated cardiomyopathy in 25 patients, ischemic heart disease in 19, valvular heart disease in 4, and other conditions in 6. The New York Heart Association (NYHA) functional class was I in 24 patients, II in 21, and III in 9. The specific activity scale (13) determined from an interview about daily physical activities was 6.1 ± 1.3 metabolic equivalents. Left ventricular ejection fraction (determined by radionuclide or contrast ventriculography) was 38 ± 17% (Table 1). Patients with atrial fibrillation or frequent premature beats were excluded because spectral analysis would yield a broad band in the presence of these conditions. Patients with lung disorders, anemia, severe hypoxemia (arterial oxygen partial pressure <80 mmHg), diabetes mellitus, or autonomic neuropathy due to other causes were also excluded from the present study. Angiotensin-converting enzyme inhibitors had been given in 33 patients, angiotensin-II receptor antagonists in 3 patients, β-blockers in 9 patients, diuretics in 23 patients, and digitalis in 15 patients. Medications for heart failure were continued throughout the study. None of the subjects had a history of more than occasional alcohol consumption. Informed consent was obtained from each subject.

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Table 1. *Patient characteristics*

	All Patients (n = 54)	Patients Treated with Guanfacine (n = 13)
Age, yr	56 ± 13	57 ± 13
Sex (male/female)	43/11	11/2
NYHA class (I / II / III)	24/21/9	4/5/4
SAS (METs)	6.1 ± 1.3	5.7 ± 1.5
Etiology		
DCM	25	8
IHD	19	2
VHD	4	0
Others	6	3
Drugs		
ACEI	33	11
ARB	3	1
β-Blockers	9	2
Diuretics	23	7
Digitalis	15	4
CTR, %	53 ± 7	52 ± 6
LVDd, mm/m^2	36 ± 7	40 ± 7
LVEF, %	38 ± 17	36 ± 9
NE, pg/ml	340 ± 226	350 ± 291
BNP, pg/ml	188 ± 233	123 ± 67
Heart rate, beats/min	69 ± 9	71 ± 13
Mean BP, mmHg	91 ± 18	91 ± 13
MSNA		
Bursts/min	52 ± 13	53 ± 13
Bursts/100 heartbeats	76 ± 18	77 ± 14

Data are expressed as means ± SD or number of patients. NYHA, New York Heart Association; SAS, specific activity scale; MET, metabolic equivalents; DCM, dilated cardiomyopathy; IHD, ischemic heart disease; VHD, valvular heart disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonist; CTR, cardiothoracic ratio; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; NE, plasma norepinephrine; BNP, brain natriuretic peptide; MSNA, muscle sympathetic nerve activity.

Measurements. All measurements were performed with the subjects resting in the supine position, as reported previously (5, 6). Blood pressure was determined by noninvasive tonometry (Jentow 7700; Colin, Komaki, Japan). Respiratory flow was measured continuously on a breath-by-breath basis with a thermal dissipation technique (AE-300; Minato, Osaka, Japan). Multiunit recordings of efferent postganglionic sympathetic nerve activity to the skeletal muscle district were obtained with a microelectrode inserted directly into the left peroneal nerve posterior to the fibular head. The signal was amplified 100,000-fold, fed through a band-pass filter (500–5,000 Hz), and integrated with a custom nerve traffic analysis system (NeuropackΣ MEB-5504; Nihon Koden, Tokyo, Japan). Integrated neural activity, analog blood pressure tracing, ECG, and respiratory flow were digitized at 1,000 Hz per channel by an analog-digital converter (DT9804-USB; Data Translation, Marlboro, MA) and stored directly in a hard drive memory system (Latitude C600; Dell, Round Rock, TX). To evaluate baseline cardiac function, chest radiographs and two-dimensional echocardiograms were obtained in all patients. A blood sample for measurement of the plasma concentration of norepinephrine was drawn from the antecubital vein with the subject at rest. To examine the reproducibility of pulse-synchronous burst power, measurement of MSNA was repeated after ≥1 h in 10 patients resting in the supine position.

In 13 patients, the α_2-adrenoceptor agonist guanfacine (0.25 mg/day), which inhibits central sympathetic outflow, was administered orally for a mean of 5 days (4–6 days; Table 1). Measurement of sympathetic nerve activity and plasma norepinephrine level was then repeated.

Data analysis. Baseline recordings of the ECG, blood pressure, and MSNA were performed for 10 min while patients were breathing room air in the supine position. Sympathetic neural bursts were identified in the integrated signals by their characteristic appearance and their relationship to the R wave of the ECG. The burst frequency was determined for each patient and expressed as bursts per 100 heartbeats. Slow baseline fluctuations of the integrated burst signals caused by transient electromyographic or motor and sensory nerve activity sometimes produced prominent low-frequency spectral artifacts. Therefore, the baseline drift caused by such noise was detected and subtracted from the original integrated nerve activity (Fig. 1). Fast Fourier transformation was then applied to the MSNA time series to distinguish the spectral components of burst signals. This transformation generated power spectra from 29,952-point epochs of data (29.952 s) with 50% overlap. A Hanning window in the time domain

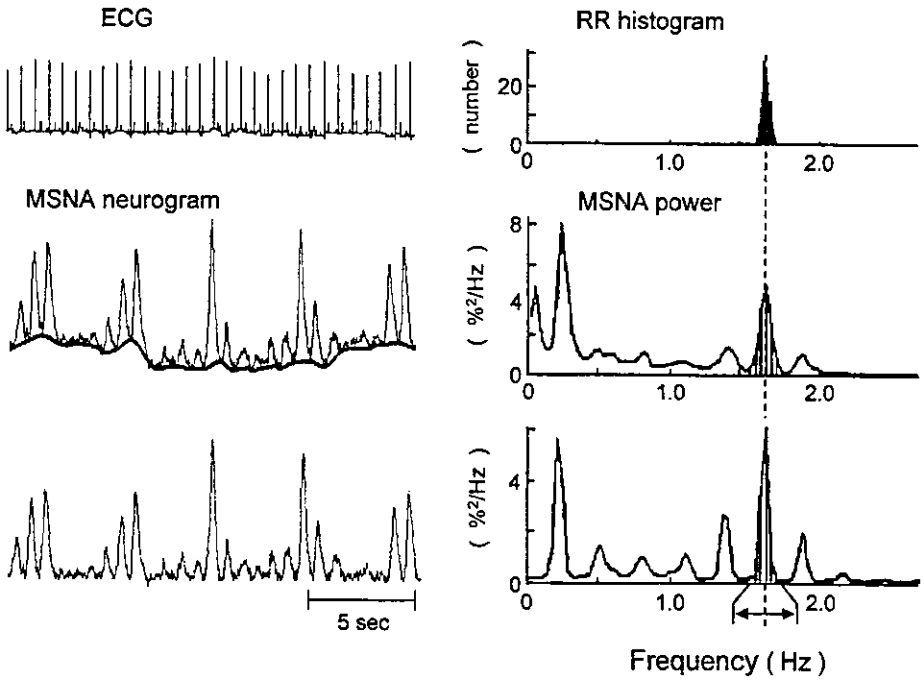

Fig. 1. Spectral analysis of muscle sympathetic nerve activity (MSNA). The baseline of integrated MSNA bursts was automatically detected in the original integrated neural activity recording (*middle left*). Baseline fluctuations of the neural activity caused an increase of low-frequency components (*middle right*). After subtraction of these fluctuations (*bottom left*), the spectral density showed several discrete peaks (*bottom right*). Arrow indicates the range of the pulse-synchronous neural frequencies. ECG recording (*left*) and R-R interval histogram (*right*) are shown at *top*.

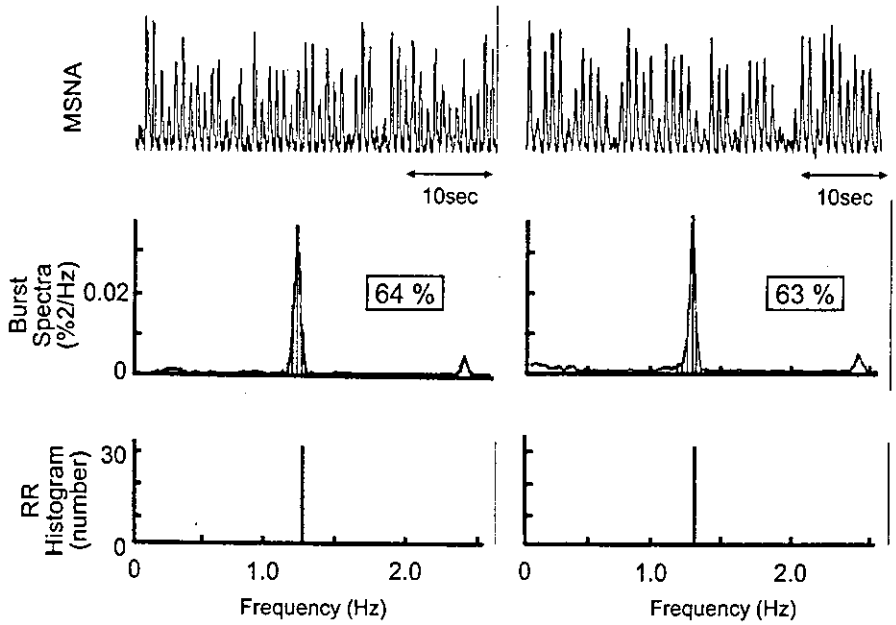

Fig. 2. Reproducibility of the burst power of MSNA. Baseline measurement of MSNA burst, power burst spectra, and R-R interval histogram are shown on *left*. Measurement of MSNA burst power was repeated after >1 h while the patient lay quietly in the same position (*right*). A similar spectral pattern was obtained by the 2 measurements. There is no variation of the R-R interval in this patient because of cardiac pacing.

was used to attenuate the leakage effect. The mean burst frequency synchronized with the heartbeat was determined in each patient based on the mean frequency of the R-R interval (Fig. 1). In all patients, the R-R intervals were distributed within the frequency range of 0.183 Hz (average ± 2SD) around the mean R-R interval frequency. This frequency range was used for measurement of the spectral area of the pulse-synchronous burst power, and the burst power was then expressed as a percentage of the total power. We defined the total MSNA spectral power as the spectral area ranging from 0.04 to 2.5 Hz because most components of MSNA were within this frequency range. When there are no MSNA bursts, the pulse-synchronous burst power is theoretically 0%, whereas when the sympathetic system is maximally activated with all heartbeats accompanied by neural bursts with the same amplitude, the pulse-synchronous burst power is close to 100% with a single spectral peak at the heart rate. However, even when all heartbeats are accompanied by neural bursts, the variations in amplitude caused by respiratory modulation or blood pressure fluctuation generate several other peaks away from the heart rate frequency, resulting in a decrease of the pulse-synchronous burst power. Thus the pulse-synchronous burst power could potentially discriminate sympathetic tone between patients who have the same burst incidence but a different amplitude distribution. Because of normalization by the total power, measurement of the individual burst amplitudes was unnecessary. To determine the optimum period for acquisition of MSNA data for spectral analysis, the influence of a period of 1–5 min on the spectral power was examined in 11 patients before administration of guanfacine and in 6 patients after administration of guanfacine.

Statistical analysis. Data are expressed as means ± SD. Simple exponential fitting was applied to the relationship between MSNA burst power and burst incidence. Interindividual comparisons of sympathetic parameters were performed with one-way ANOVA fol-

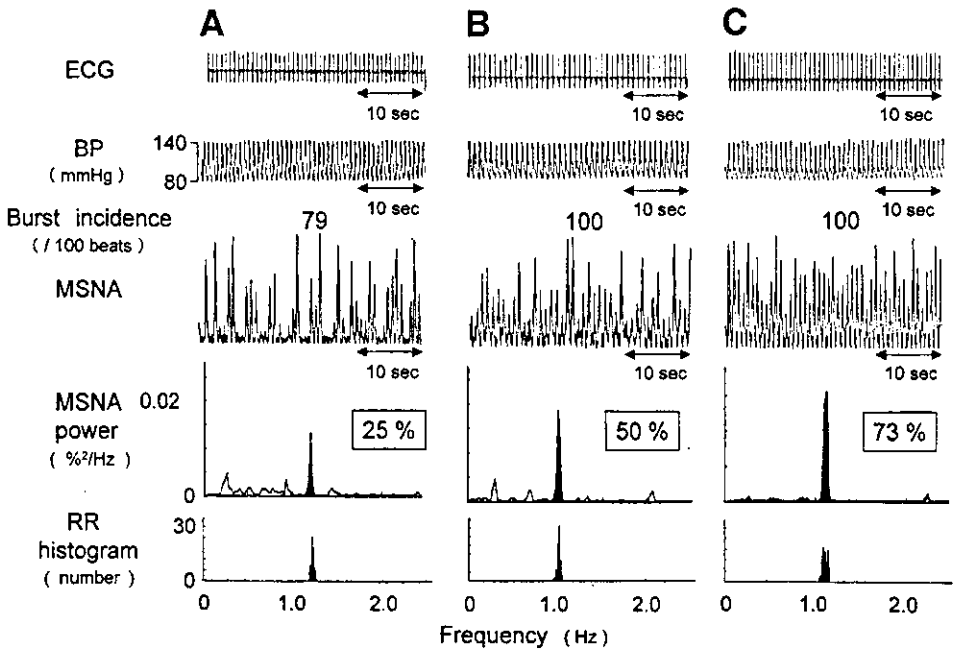

Fig. 3. Comparison between the burst incidence and pulse-synchronous burst power of MSNA in 3 patients with different severity of heart failure. *Patient A* (mild heart failure; *left*) has a lower burst incidence and power than the others. *Patients B* and *C* (moderately severe heart failure; *center* and *right*) have the same burst incidence of 100 per 100 heartbeats despite a different burst amplitude distribution. The uniform amplitude of neural bursts in *patient C* is reflected by a single spectral peak at the heart rate, resulting in a larger pulse-synchronous burst power. In contrast, *patient B* shows greater variation of burst amplitude, which has several spectral peaks with different frequencies, leading to a relative reduction of the pulse-synchronous burst power. BP, blood pressure.

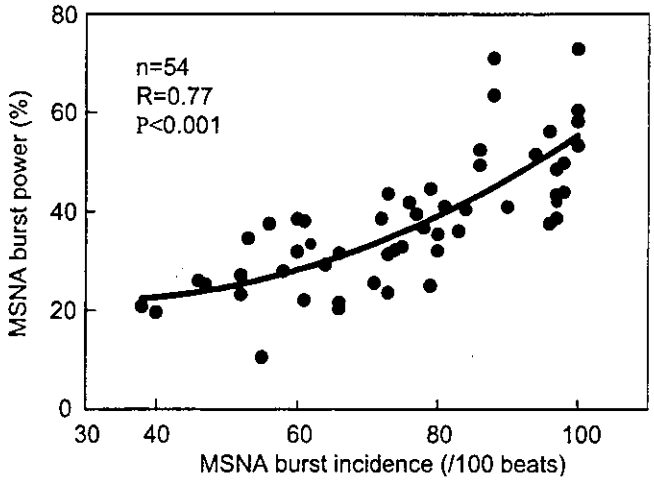

Fig. 4. Relationship between the pulse-synchronous burst power and burst incidence of MSNA. There was a significant correlation between the burst incidence and pulse-synchronous burst power. In patients with a higher burst incidence (>85 per 100 heartbeats), the incidence was close to the maximum level of 100 per 100 heartbeats but the burst power varied substantially.

lowed by Bonferroni's test for multiple comparisons. The effect of guanfacine was tested by paired *t*-test. Analyses were performed with SigmaStat software (version 2.03; SPSS, Chicago, IL), and the level of significance was set at $P < 0.05$.

RESULTS

Sympathetic burst power. The reproducibility of pulse-synchronous burst power data was examined in 10 patients with widely differing burst powers ranging from 24 to 73% (43 ± 17%). For patients lying quietly in the same position, the difference in burst power between two measurements obtained >1 h apart was quite small (3 ± 3%, Fig. 2). The pulse-synchronous burst power derived from different measurement periods (1–5 min) also showed no significant difference. The burst power measured before administration of guanfacine was 41 ± 10%, 41 ± 10%, 40 ± 9%, 40 ± 9%, and 39 ± 9% with 1, 2, 3, 4, and 5 min of data, respectively. After suppression of sympathetic activity with guanfacine, there was no significant difference (2 ± 3%) in the spectral power derived from 1 and 5 min of data. Thus the burst power determined from 1 min of data was used for all analyses in the present study.

Figure 3 shows the MSNA time series, burst spectra, and frequency histograms of the R-R interval for representative patients with different severity of heart failure. The MSNA power spectra displayed several peaks within the frequency range of 0.04–2.5 Hz. The major spectral band was located at the same frequency as that of the mean heart rate. In *patient A* with mild heart failure, within-breath variation of bursts created a spectral peak at 0.25 Hz that was separated from the pulse-synchronous burst spectra. In *patients B* and *C* with moderately severe heart failure, all heartbeats were accompanied by neural bursts, i.e., the burst incidence was 100 per 100 heartbeats. However, the burst amplitude was more uniform in *patient C* than in *patient B*. The differences in variations of burst amplitude resulted in different burst spectra; the power spectra of *patient B* were distributed widely with several peaks, whereas *patient C* showed a prominent single peak with the same frequency as the heart rate. Consequently, the pulse-synchronous burst power was significantly greater in *patient C* than in *patient B* despite the same burst incidence. There was a significant correlation between burst incidence and pulse-synchronous burst power, as shown in Fig. 4. In the patients with a higher burst incidence (>85 per 100 heartbeats), the incidence reached a plateau of 100 per 100 heartbeats (Figs. 4 and 5), but the burst power still differed substantially among these patients.

Interindividual and longitudinal comparisons. Figure 5 illustrates the pulse-synchronous burst power, burst incidence, and plasma norepinephrine levels in the subgroups of patients from NYHA functional classes I, II, and III. Although all of the sympathetic parameters increased along with the deterioration of functional capacity, the differences in the burst incidence and plasma norepinephrine level did not reach statistical significance for comparison between NYHA classes II and III. In contrast, burst power was more discriminatory, because patients in NYHA class III had a significantly higher burst power than those in class II.

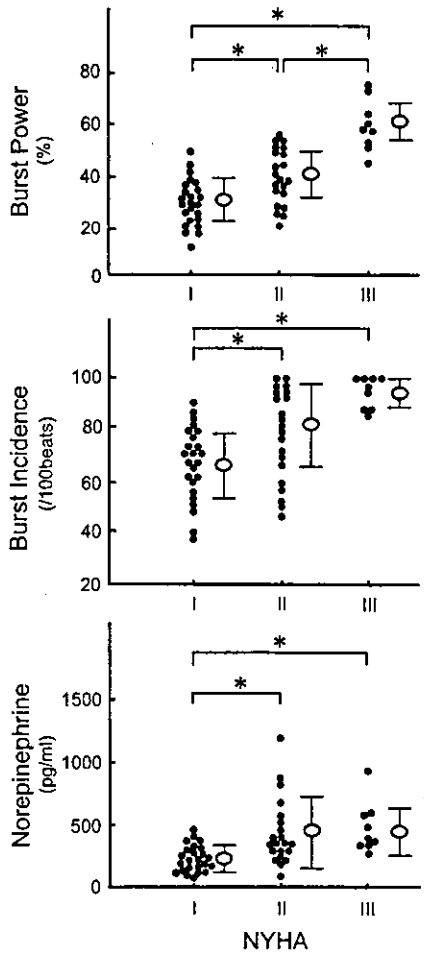

Fig. 5. Comparison of three parameters of sympathetic activity for different severity of heart failure. Although each parameter increases with the deterioration of functional capacity, the burst incidence of MSNA (*middle*) and the plasma norepinephrine level (*bottom*) do not show a significant difference between New York Heart Association (NYHA) classes II and III. In contrast, the pulse-synchronous burst power (*top*) was more discriminatory, with patients in NYHA class III having a significantly higher burst power than those in class II. *$P < 0.05$.

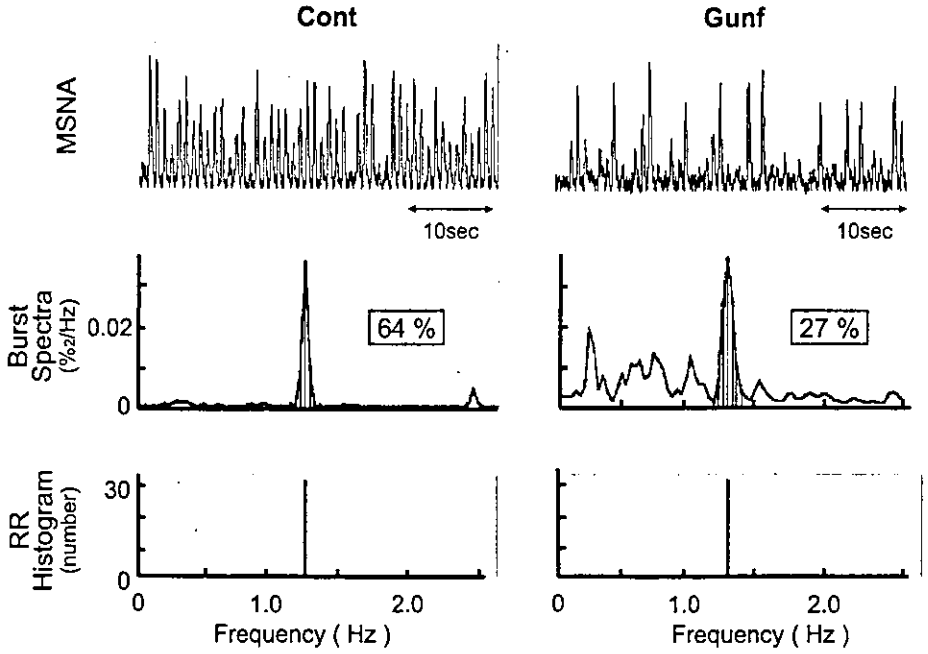

Fig. 6. Influence of a central sympatholytic agent (guanfacine) on MSNA burst incidence and pulse-synchronous burst power. *Left*: baseline burst incidence was >90 per 100 heartbeats, with a prominent pulse-synchronous peak at the heart rate. Cont, control. *Right*: guanfacine (Gunf) decreased the number of bursts and produced within-breath variation of MSNA bursts. Consequently, several other components and a prominent low-frequency peak around the respiratory frequency appeared in addition to the pulse-synchronous component. There were no variations of the R-R interval in this patient because of cardiac pacing.

Figure 6 shows the changes of MSNA and pulse-synchronous burst power after administration of a central sympatholytic agent (guanfacine) in a representative patient. Before administration of guanfacine, the burst incidence was >90 per 100 heartbeats and a single power spectral peak was seen at the frequency of the mean heart rate. Guanfacine decreased the number of bursts and increased the within-breath variation of MSNA. Consequently, several other spectral components appeared in addition to the pulse-synchronous component, where a prominent low-frequency component was seen at the respiratory frequency. After administration of guanfacine, the plasma norepinephrine level tended to decline, but this change did not reach statistical significance. Although the burst incidence decreased by $-12 \pm 14\%$ ($P < 0.05$) after guanfacine, the inhibition of sympathetic activity was more sensitively reflected by the change of burst power ($-36 \pm 25\%$; $P < 0.001$, Fig. 7).

DISCUSSION

The major findings of this study are as follows. First, the pulse-synchronous burst power of MSNA could discriminate sympathetic tone between patients with heart failure who had similar burst frequencies. Second, assessment of the burst power detected central sympathetic inhibition more sensitively than measurement of the burst incidence or the plasma norepinephrine concentration. Another advantage of the pulse-synchronous burst power is that this parameter is independent of the absolute value of each burst amplitude. Therefore, the MSNA burst power may serve as a sensitive new index for interindividual or longitudinal comparisons of sympathetic activity, especially in patients with moderately severe or severe heart failure.

Because of the dependence on proximity to the recording electrode, the burst amplitude cannot be used for interindi-

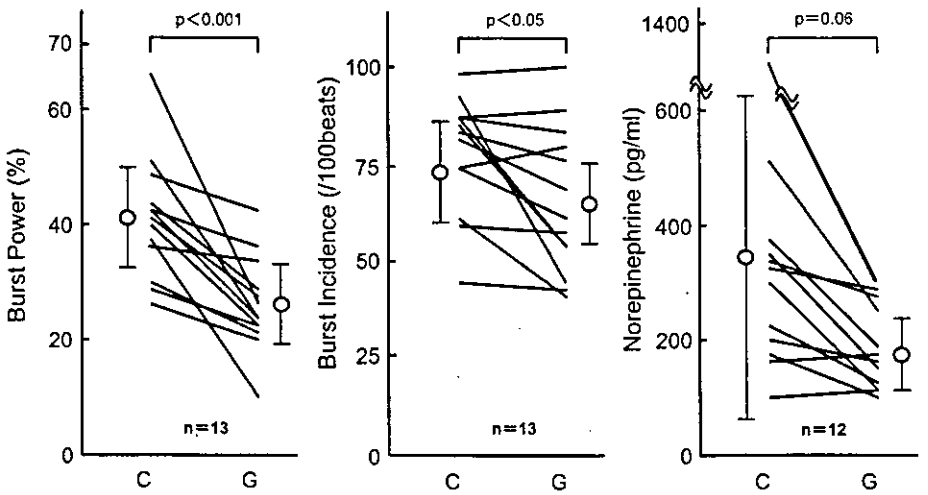

Fig. 7. Inhibitory effects of guanfacine on sympathetic activity. Guanfacine reduced the burst power (*left*) and burst incidence (*middle*) of MSNA, with a greater reduction for burst power. The plasma norepinephrine level (*right*) also tended to decline, but the change did not reach the statistical significance. C, control; G, guanfacine.

vidual comparisons of MSNA. To normalize differences in the electrode position, several neural indexes have been introduced in the clinical setting (11, 16–18). Burst rate and burst incidence, the traditional indexes used for interindividual comparisons, focus only on the frequency by ignoring differences in amplitude. Consequently, interindividual differences in sympathetic tone could be underestimated as the burst incidence reaches its plateau of 100 per 100 heartbeats. Recently, Sverrisdóttir et al. (17) proposed the usefulness of amplitude distribution of neural bursts. This was based on the observation that the proportion of high-amplitude bursts tends to increase along with an increase in burst incidence, resulting in a more even amplitude distribution (15). As a specific indicator of sympathetic nerve activity, these investigators derived the median from a histogram of the normalized amplitudes of all neural bursts. Therefore, the determination of the highest burst amplitude is crucial to normalize each burst amplitude and a large number of bursts, such as 1,000–2,000 cardiac cycles in animals (10) or 5-min data in humans (17), are required to determine the 0% and 100% levels of the burst amplitude.

In contrast, the burst power used in the present study does not require measurement of the amplitude of each burst and can be determined from only 1 min of MSNA data. The similarity of the pulse-synchronous burst power obtained from 1-min and 5-min data could be related to the fact that the burst incidence was relatively high in our patients with heart failure and sufficient to assess sympathetic nerve activity. Even when sympathetic activity was suppressed with guanfacine, the burst power showed no significant difference between 1 min and 5 min of data. However, a short data acquisition period might not be feasible in normal subjects with a lower burst incidence. Generally, most of the spectral components of MSNA are found within the frequency range from 0.03 Hz up to that of the heart rate in normal subjects. One of the typical factors causing variation of the burst amplitude is respiratory modulation of sympathetic activity (1, 3, 5, 6, 10, 14). Sympathetic neural silence during the inspiratory phase produces a large spectral peak at the respiratory frequency around 0.25 Hz (Fig. 1; Ref. 5). A well-defined peak related to low-frequency blood pressure variation is also found near 0.1 Hz (6). As sympathetic tone increases with the development of heart failure, the pulse-synchronous peak of the neural bursts becomes predominant over the other spectral components. Consequently, beat-by-beat activation of neural bursts with a similar amplitude results in a single spectral peak at the same frequency as the heart rate. When sympathetic neural bursts have variations in frequency and amplitude, a variety of spectral peaks other than the pulse-synchronous peak can be produced. Thus the pulse synchronicity and shape uniformity of the neural bursts are faithfully reflected by the burst power.

In the present study, the difference in the discriminatory ability between burst incidence and burst power did not seem so striking (Fig. 5) because few of our patients had severe heart failure. When sympathetic activity is low and is largely reflected by the number of neural bursts, both burst frequency and burst power can be useful and will show parallel changes. However, when sympathetic activity is high, it is largely reflected by the distribution of the amplitude of neural bursts. Spectral analysis is more effective in such situations because it can sensitively assess the uniformity of the burst amplitude.

In conclusion, assessment of the pulse-synchronous burst power of MSNA does not require measurement of amplitude of each burst and can be obtained from a relatively short data recording. This parameter is a more sensitive discriminator of sympathetic nerve activity than the traditional burst count or the plasma norepinephrine level and could be useful for interindividual comparisons of sympathetic tone in patients with heart failure.

ACKNOWLEDGMENTS

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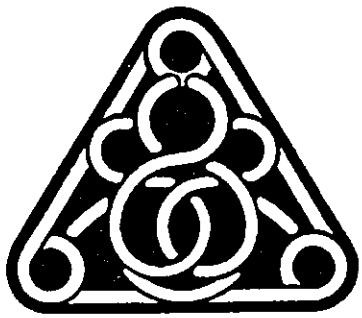

Role of central sympathoexcitation in enhanced hypercapnic chemosensitivity in patients with heart failure

Kunihiro Yamada, MD, Hidetsugu Asanoi, MD, Hiroshi Ueno, MD, Shuji Joho, MD, Junya Takagawa, MD, Tomoki Kameyama, MD, Tadakazu Hirai, MD, Takashi Nozawa, MD, and Hiroshi Inoue, MD *Toyama, Japan*

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Background Enhanced central hypercapnic chemosensitivity is known to mediate excessive exercise ventilation and to indicate a poor prognosis in patients with chronic heart failure. The present study was designed to elucidate the role of central sympathetic activity in the enhancement of hypercapnic chemosensitivity.

Methods Central hypercapnic chemosensitivity and plasma norepinephrine were measured in 99 patients with chronic heart failure. In 40 patients, the α index was derived from simultaneous analysis of R-R interval and systolic blood pressure variability. The effects of a central sympatholytic agent, guanfacine (0.25 mg/day), on hypercapnic chemosensitivity and exercise ventilatory response were studied in 20 of these patients.

Results Hypercapnic chemosensitivity was enhanced in 76% of the patients and correlated significantly with plasma norepinephrine levels ($r = 0.49$, $P < .01$) at rest. There was a significant inverse relationship between central chemosensitivity and the α index ($r = -0.41$, $P < .01$). Guanfacine significantly reduced plasma norepinephrine levels by 29% ($P < .01$) and chemosensitivity by 31% ($P < .01$). The beneficial effect of central sympathoinhibition with guanfacine was observed specifically in patients who had enhanced chemosensitivity prior to drug administration. Similarly, the patients with excessive exercise ventilation showed a greater reduction in exercise ventilation with this agent.

Conclusions The present findings suggest that central sympathoexcitation could play an important role in the pathogenesis of enhanced hypercapnic chemosensitivity and a resultant increase in exercise ventilation in chronic heart failure. (Am Heart J 2004;148:964–70.)

Shortness of breath is a major symptom of congestive heart failure. The origin of dyspnea is multifactorial in optimally treated patients, but the excessive ventilation seen during exercise may play a role in inducing this symptom. An abnormal increase in physiological dead space has been proposed as the primary mechanism responsible for exercise hyperpnea in heart failure.[1,2] Recently, Chua et al[3] demonstrated that central and peripheral chemosensitivity is augmented and correlated significantly with the increased ventilatory response to exercise in patients with heart failure. They also demonstrated that administration of dihydrocodeine suppressed chemosensitivity and improved excessive exercise ventilation in patients with heart failure.[4] The mechanisms for this beneficial effect of dihydrocodeine remain unclear but could include a reduction in sympathetic activity or resultant improvement in hemodynamics. Recently, Narkiewicz et al[5] demonstrated a parallel augmentation of sympathetic and ventilatory responses to central chemoreflex activation in heart failure. These findings suggest that autonomic dysregulation is closely linked to peripheral and central chemoreflexes in heart failure.[6] However, there have been no clinical studies that examined the causative relationship between sympathetic activation and enhanced chemosensitivity in patients with chronic heart failure.

The present study was therefore undertaken to determine whether sympathetic activation is responsible for enhanced hypercapnic chemosensitivity in chronic heart failure. For this purpose, we assessed 1) the relationship between central hypercapnic chemosensitivity and neurohumoral and ventilatory factors and 2) the effects of central sympathoinhibition on chemosensitivity in patients with chronic heart failure.

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Table I. Patient characteristics

	All patients (n = 99)	Patients treated with guanfacine (n = 20)
Age (y)	57 ± 12	54 ± 13
Sex (male/female)	77/22	17/3
Body weight (kg)	61 ± 11	61 ± 11
NYHA functional class		
I	47	10
II	18	3
III	34	7
SAS (METs)	5.6 ± 1.8	5.3 ± 1.8
Peak Vo_2 (mL/kg/min)	20.2 ± 4.2	20.2 ± 4.0
VE-Vco_2 slope	33.7 ± 5.2	35.5 ± 8.6
Underlying heart disease		
DCM	51	14
Prior MI	12	3
VHD	15	1
Miscellaneous	21	2
LVEDD (mm/m^2)	36 ± 6	36 ± 6
LVEF (%)	39 ± 18	33 ± 14
NE (pg/mL)	320 ± 202	357 ± 209
BNP (pg/mL)	157 ± 229	190 ± 275
ANP (pg/mL)	64 ± 68	59 ± 52
Treatment		
ACE inhibitor	56	13
β-Blocker	16	3
Diuretics	54	14
Digoxin	28	7

Values are mean ± SD. *ACE*, Angiotensin-converting enzyme; *ANP*, atrial natriuretic peptide; *BNP*, brain natriuretic peptide; *DCM*, dilated cardiomyopathy; *LVEF*, left ventricular ejection fraction; *LVEDD*, left ventricular end-diastolic diameter; *MI*, myocardial infarction; *NE*, plasma norepinephrine; *NYHA*, New York Heart Association; *SAS*, specific activity scale; Vco_2, carbon dioxide output; *VE*, minute ventilation; *VHD*, valvular heart disease; Vo_2, oxygen uptake.

Table II. Correlations with hypercapnic chemosensitivity

	R	P	n
SAS	−0.29	<.01	99
AT	−0.13	NS	99
Peak Vo_2	−0.11	NS	99
VE-Vco_2 slope	0.54	<.01	99
$Paco_2$	−0.36	<.01	90
Pao_2	−0.18	NS	90
LVEDD	0.09	NS	86
LVEF	−0.15	NS	86
PCWP	0.07	NS	59
LVEDP	0.02	NS	59
NE	0.49	<.01	99
BNP	0.07	NS	99
ANP	0.21	<.05	99

AT, Anaerobic threshold; *LVEDP*, left ventricular end-diastolic pressure; *NS*, not significant; $Paco_2$, arterial partial pressure of carbon dioxide; Pao_2, arterial partial pressure of oxygen; *PCWP*, pulmonary wedge pressure. See Table I for other abbreviations.

Methods

Study patients

Ninety-nine patients with stable chronic heart failure (77 men, 22 women) were studied (Table I). The causes of cardiac disease were dilated cardiomyopathy in 51 patients, prior myocardial infarction in 12, valvular heart disease in 15, and miscellaneous causes in 21. Functional status was New York Heart Association (NYHA) functional class I in 47 patients, class II in 18, and class III in 34. Specific activity scales[7] obtained from interviewing daily physical activities were 5.6 ± 1.8 metabolic equivalents. Fifteen patients had chronic atrial fibrillation and the others were in sinus rhythm. Patients with anemia, primary lung disease, or angina pectoris were excluded from this study. Angiotensin-converting enzyme inhibitors had been given in 56 patients, diuretics in 54 patients, β-blockers in 16 patients, and digoxin in 28 patients. These medications were maintained during the examination. All patients gave informed consent for their participation in the study as approved by our institutional committee on human research.

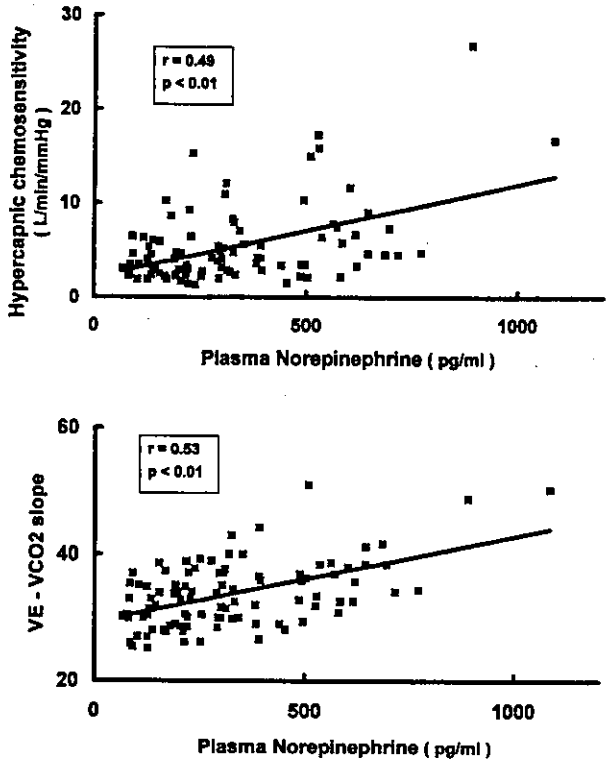
Study protocol

Hypercapnic chemosensitivity at rest and ventilatory response to exercise were assessed in all patients. Functional capacity and humoral factors including plasma norepinephrine were also examined in these patients. Because of safety, a lower dose of α_2-adrenoceptor agonist, guanfacine (0.25 mg/day, orally), which inhibits central sympathetic neural outflow, was administered for 4 to 6 days in 20 patients (Table I). Measurements of the hypercapnic chemosensitivity, humoral factors, cardiopulmonary exercise testing, and 2-dimensional echocardiography were performed before and after the drug administration.

Cardiopulmonary exercise test

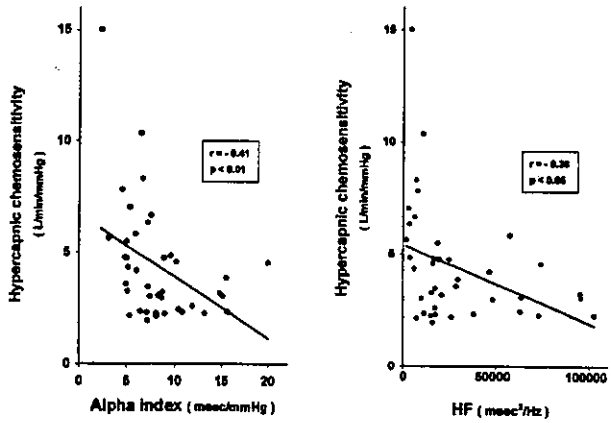
Each subject was evaluated at least 2 hours after a meal. Patients were asked to perform progressive maximal symptom-limited exercise while seated upright on an electronically braked cycle ergometer (Corival-400, Lode, The Netherlands). Initially, patients performed unloaded cycling for 3 minutes. Then, the work rate was increased progressively by 3 to 15 watts every minute. The work rate increment was individualized on the basis of the subject's exercise capacity. Every subject terminated progressive exercise because of leg fatigue or dyspnea. Heart rate was monitored together with blood pressure, which was measured by the cuff method at 1-minute intervals throughout the test. Oxygen uptake (Vo_2), carbon dioxide production (Vco_2), minute ventilation (VE), tidal volume, and respiratory rate were continuously measured on breath-by-breath basis using a metabolic measurement cart equipped with an oxygen and carbon dioxide analyzer (Minato AE-280, Osaka, Japan). Respiratory flow was measured by the thermal dissipation technique. Exercise tolerance was evaluated using the peak Vo_2 and the anaerobic threshold. In the present study, the exercise ventilatory response was assessed by the regression slope between VE and the corresponding Vco_2 below the level of respiratory compensation required for metabolic acidosis. In all subjects, VE correlated with Vco_2 in a highly linear fashion ($r >$ 0.96).

Figure 1



Correlations between plasma norepinephrine levels and hypercapnic chemosensitivity (upper panel) and between plasma norepinephrine levels and ventilation (VE)-carbon dioxide output (V_{CO_2}) regression slope (lower panel). There were significant positive correlations between these parameters.

Figure 2



Correlations between central hypercapnic chemosensitivity and the α index and between central chemosensitivity and high-frequency spectral power of R-R interval variability (HF). Chemosensitivity had an inverse relationship with HF and the α index.

Measurements of central hypercapnic chemosensitivity

All subjects were exposed to a hyperoxic hypercapnic gas mixture (7% carbon dioxide + 93% oxygen) to activate the central hypercapnic chemoreflex, where the peripheral hypoxic and hypercapnic chemoreflexes were minimized by hyperoxia.[8] Measurements were taken during 3-minute periods of stable ventilation while subjects breathed room air with a mask. Then patients were exposed to the hypercapnic stressor for 4 minutes, while oxygen and carbon dioxide concentrations of respiratory gases and minute ventilation were measured on breath-by-breath basis. Hypercapnic chemosensitivity was assessed by the regression slope between minute ventilation and end-tidal carbon dioxide. The slope was expressed in terms of liters per minute per mm Hg (L/min/mm Hg). The test was continued for 4 minutes unless the subject complained of moderately severe breathlessness.

Neurohumoral and hemodynamic measurements

All measurements were performed with subjects in resting supine conditions, as reported previously.[9] In 40 patients, a stationary 6-minute period of blood pressure tracing with noninvasive tonometry (Jentow 7700, Colin, Komaki, Japan) and electrocardiogram (ECG) were digitized at 1000 Hz per channel by an analog-digital converter (DT9804-USB, Data Translation, Marlboro, Mass) and directly stored on a hard-disk memory system (Latitude C600, Dell, Round Rock, Tex). Beat-to-beat R-R interval and systolic blood pressure were interpolated at 4 Hz to ensure equidistant sampling in each time series and subject to the maximum entropy method, with 50 as a model order to derive the power spectra of R-R interval and systolic blood pressure variability. After subtraction of the very low-frequency power, the frequency contents were then classified as high-frequency (HF; 0.12-0.5 Hz) and low-frequency (LF; 0.04-0.11 Hz) power. The simultaneous analysis of R-R interval and systolic blood pressure variabilities allows us to determine α index, calculated as the square root of the ratio of the R-R interval power to the corresponding systolic blood pressure power.[10] In all 99 patients, blood sample was drawn at rest from the antecubital vein for measurements of plasma concentrations of norepinephrine and atrial and brain natriuretic peptides. Concentration of the resting arterial blood gases were examined in 90 patients. Two-dimensional echocardiography was performed in 86 patients and cardiac catheterization in 59 patients to evaluate the baseline cardiac function.

Statistical analysis

Values are expressed as mean ± SD. Correlation between ventilatory and hemodynamic variables and central chemosensitivity was examined by the linear regression analysis. The effects of guanfacine were examined by paired t test. Values of $P < .05$ were considered to be statistically significant.

Table III. Effects of guanfacine

	Baseline	Guanfacine	P
Rest HR (beats/min)	82 ± 16	74 ± 19	<.05
Rest MBP (mm Hg)	85 ± 10	81 ± 9	NS
Peak HR (beats/min)	153 ± 28	152 ± 33	NS
Peak MBP (mm Hg)	105 ± 17	107 ± 13	NS
AT (mL/kg/min)	12.2 ± 2.9	12.9 ± 2.6	NS
Peak Vo_2 (mL/kg/min)	20.2 ± 4.0	21.1 ± 3.9	NS
VE-Vco_2 slope	35.5 ± 8.6	33.4 ± 6.6	<.01
VE-$ETco_2$ slope (L/min/mm Hg)	5.7 ± 3.2	3.9 ± 2.0	<.01
LVEF (%)	32.7 ± 14.0	34.7 ± 13.2	NS
LVEDD (mm/m^2)	36.3 ± 6.1	35.0 ± 6.5	NS
NE (pg/mL)	357 ± 209	252 ± 202	<.01
BNP (pg/mL)	190 ± 275	204 ± 337	NS
ANP (pg/mL)	59 ± 52	57 ± 52	NS
pH	7.44 ± 0.02	7.44 ± 0.02	NS
PaO_2 (mm Hg)	90.2 ± 9.4	92.0 ± 12.7	NS
$PaCO_2$ (mm Hg)	39.4 ± 3.9	40.6 ± 4.1	<.05

Values are mean ± SD. *$ETCO_2$*, End-tidal carbon dioxide concentration; *HR*, heart rate; *MBP*, mean blood pressure; VE-ETCO2 slope represents hypercapnic chemosensitivity. See Tables I and II for other abbreviations.

Results

Hypercapnic chemosensitivity and functional impairment

The relationship between hypercapnic chemosensitivity and ventilatory, cardiac, and neurohumoral variables is summarized in Table II. Although hypercapnic chemosensitivity did not correlate with exercise capacity assessed by peak Vo_2 and the anaerobic threshold, there was a significant inverse correlation between chemosensitivity and ordinary physical activity assessed by the specific activity scale. A close positive correlation was found between chemosensitivity and exercise ventilatory response assessed by the VE-Vco_2 slope. Enhanced chemosensitivity was also accompanied by a fall in arterial partial pressure of carbon dioxide at rest. Figure 1 illustrates the relationship between plasma norepinephrine levels and chemosensitivity and the relationship between plasma norepinephrine levels and VE-Vco_2 slope. The patients with increased sympathetic tone showed a greater chemosensitivity and a resultant augmentation in exercise ventilation. In contrast, chemosensitivity had an inverse relationship with HF power of heart rate variability ($r = -0.38$, $P < .05$) and the α index ($r = -0.41$, $P < .01$) (Figure 2). There were no significant correlations between hypercapnic chemosensitivity and left ventricular function and between chemosensitivity and exercise capacity.

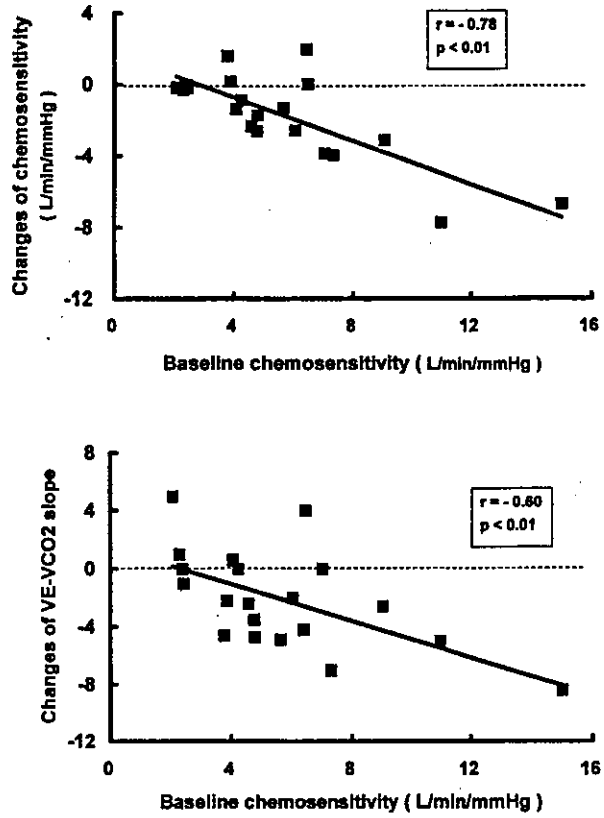
Effects of central sympatholytic agent

Table III summarizes the effects of guanfacine. Despite a small dose of guanfacine, plasma norepinephrine levels fell significantly by 29% after drug administration. Guanfacine significantly suppressed both hypercapnic chemosensitivity and the VE-Vco_2 slope by 31% and 6%, respectively. These changes were accompanied by a significant increase in arterial carbon dioxide tension. However, the magnitude of the reduction in hypercapnic chemosensitivity and the VE-Vco_2 slope after guanfacine varied depending on chemosensitivity prior to the drug administration. Patients with a higher hypercapnic chemosensitivity showed a greater reduction in chemosensitivity after guanfacine (Figure 3, upper panel). Similarly, patients with a greater hypercapnic chemosensitivity showed a greater decrease in VE-Vco_2 slope with this drug (Figure 3, lower panel). The resting heart rate fell significantly with guanfacine, whereas blood pressure remained unchanged (Table III). There were no significant changes in left ventricular function and plasma natriuretic peptide levels after guanfacine. Similarly, exercise capacity assessed by anaerobic threshold and peak oxygen consumption remained unchanged.

Discussion

The present study revealed the causative relationship between sympathetic nerve activity and enhanced hypercapnic chemosensitivity in patients with chronic heart failure. Another important finding of this study is that the effect of the sympatholytic agent on hypercapnic chemosensitivity depends on the baseline chemosensitivity. Patients with a higher hypercapnic chemosensitivity benefited more from the central sympatholytic agent guanfacine. Similarly, central sympathoinhibition resulted in a greater decline in VE-Vco_2 slope in patients with excessive exercise ventilation. These findings suggest that a heightened central sym-

Figure 3



Changes in central hypercapnic chemosensitivity and ventilation (VE)-carbon dioxide (V_{CO_2}) regression slope with guanfacine were plotted against baseline hypercapnic chemosensitivity. Patients with a higher baseline hypercapnic chemosensitivity showed a greater improvement in chemosensitivity with this agent (upper panel). Similarly, guanfacine reduced VE-V_{CO_2} slope more in patients with a higher baseline chemosensitivity before the drug administration (lower panel).

pathetic activity could play a role in enhancing hypercapnic chemosensitivity in chronic heart failure.

Although mechanisms causing altered hypercapnic chemosensitivity remain obscure, several factors are known to influence hypercapnic ventilatory drive. At sea level, carbon dioxide is believed to be the major chemical drive for autonomic respiratory control. However, when hypoxia occurs, the overall gain of this controller is multiplied; the lower the arterial oxygen tension, the greater the hypercapnic chemosensitivity.[11,12] Exercise is assumed to be another factor that alters central chemoreflex sensitivity. Weil et al [13] found a clear increase in hypercapnic chemosensitivity during the transition from rest to the first low level of exercise. Conversely, sleep, in which the behavioral control of respiration disappears, is accompanied by a depression of hypercapnic chemosensitivity in normal subjects.[14] In anesthetized cats, cooling of the ventral surface of the medulla in putative chemosensitive areas causes similar changes in the ventilatory carbon dioxide response.[15] These findings suggest that central chemosensitivity is subject to brain mechanisms, including brain oxygen tension and behavioral inputs.

Opiate and morphine are centrally active by depressing respiration and relieving breathlessness. The respiratory depression with these drugs is considered to be due to the reduced responsiveness of chemoreceptors to arterial blood gas. Chua et al[4] demonstrated that dihydrocodeine suppressed central hypercapnic chemosensitivity in patients with heart failure. They suggested a potential benefit of pharmacologic modulation of chemosensitivity for patients with heart failure because the chemoreflex suppression in these patients was accompanied by an improvement in exercise tolerance and excessive exercise ventilation. Milsom and Sadig[16] have shown in anesthetized rabbits that norepinephrine infusion significantly augmented afferent fiber discharge from carotid chemoreceptors in a dose-dependent manner. This response was abolished sufficiently by propranolol, suggesting that a β-adrenergic mechanism is involved in the excitation of the peripheral chemoreceptors. However, it remains unknown whether the suppression of sympathetic activation could reduce the hypercapnic chemosensitivity in humans. Central mechanisms for sympathetic nerve activation have received considerable attention in heart failure.[17,18] Hemodynamic and sympathetic responses to mental stress are augmented in heart failure and effectively suppressed with α_2-adrenergic agonists.[18] The present study indicates that central sympathoinhibition also has a potential benefit in the modulation of enhanced hypercapnic chemosensitivity in patients with chronic heart failure.

In the present study we demonstrated significant inverse relationships between central chemosensitivity and baroreflex sensitivity, calculated as the α index and between the chemosensitivity and HF power of heart rate variability. A similar relationship between peripheral chemosensitivity and baroreflex sensitivity has already been reported in animals, healthy humans, and patients with heart failure.[19-23] The peripheral chemoreflex-baroreflex interactions have been explained by interneuronal antagonistic connection in the solitary and paramedian reticular nuclei in the medulla.[24] However, these direct neuronal interactions are unlikely to be responsible for the inverse relationship between central chemoreflex and vagal tone or baroreflex, because the central chemoreflex is less sensitive to baroreflex activation in normal subjects.[23] Another possible mechanism could involve central factors that are related to both sympathetic and vagal tone. Several previous studies[25,26] suggested the central role of angiotensin II, which blunts the baroreflex sensitiv-

ity and stimulates sympathetic tone leading to an augmentation of the central chemoreflex.

Normalization of hypercapnic chemosensitivity could stabilize the respiratory system because both hypersensitivity of the signal detector and a delayed transmission of signals make the feedback system unstable. Therefore, stable and deep respiration could suppress sympathetic nerve activity, as previously reported.[27] On the other hand, chemoreflex-mediated respiratory instability is known to elicit central sleep apnea in heart failure.[28,29] Sleep apnea has detrimental effects on sleep quality and the autonomic nervous system by fragmenting sleep architecture. Frequent arterial oxygen desaturation caused by apneic period not only amplifies central chemosensitivity but activates the sympathetic nervous system in these patients.

Some limitations of the present study should be addressed. First, because of safety we included patients with mild heart failure; about half of them were in NYHA class I. A close correlation between sympathoexcitation and chemosensitivity suggests that patients with severe heart failure could benefit more from central sympatholytic agents. Second, despite a significant improvement in chemosensitivity, cardiac function and plasma BNP levels remained unchanged during a short period of the treatment. Further studies are required to assess effects of a long-term treatment on cardiac function of the patient with heart failure. Third, we cannot exclude the possibility that guanfacine improved central chemoreflex sensitivity indirectly through beneficial hemodynamic effects. In congestive heart failure, a reduction in sympathetic outflow with α_2-adrenoceptor agonist decreases preload, heart rate, and arterial pressure acutely without changing cardiac output.[30] As shown in the Moxonidine Congestive Heart Failure Trial (MOXCON) trial,[31] however, a large dosage of a central sympatholytic agent could be inappropriately sympathoablative,[32] leading to an insufficient cardiac support by residual sympathetic outflow and progressive pump failure. In the present study, cardiac function and brain natriuretic peptide did not change appreciably after treatment with a low dose of guanfacine. Although we did not measure the changes in intracardiac pressure and cardiac output invasively in these patients, it is less likely that this dose of guanfacine reduced the chemosensitivity indirectly by improving hemodynamics. Secondly, guanfacine might alter ventilatory response to carbon dioxide through suppression of peripheral hypercapnic chemoreflex because peripheral chemoreceptors are prone to be sensitized by sympathetic nerve activation.[16] However, this was assumed not to be the case, because peripheral chemoreceptors are suppressed under the hyperoxic conditions and only 12% of the ventilatory response to hypercapnia is mediated by peripheral chemoreceptors.[33]

In conclusion, the close relationship between sympathetic activation and enhanced chemosensitivity and the specific, beneficial effects of guanfacine suggest that central sympathoexcitation could play an important role in the pathogenesis of enhanced hypercapnic chemosensitivity and a resultant increase in exercise ventilation in chronic heart failure.

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Circadian Dynamics of Heart Rate and Physical Activity in Patients with Heart Failure

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The present study was designed to develop a method to continuously measure Holter electrocardiogram (ECG) and physical activity in terms of metabolic costs to examine circadian dynamics of RR intervals and physical activity in patients with heart failure. A total of 7 healthy subjects and 4 heart failure patients performed cardiopulmonary exercise test using three-stage graded treadmill walking at 0% grade to examine whether the acceleration signals in the vertical direction could reflect actual body energy expenditure during physical activity. Then, using this new method, 24-hr monitorings of ECG and physical activity were performed in 24 inpatients with heart failure while they were allowed to walk around freely. Our results showed the integral of rectified acceleration signals was closely correlated with actual metabolic cost in all subjects. Instantaneous changes in heart rate were quite concordant with physical activity. As compared with the asymptomatic patients (n = 12), the symptomatic patients (n = 12) had lower energy expenditure during 8-hr daytime periods but higher mean heart rate. Furthermore, a more prominent ultradian rhythm of circadian changes in heart rate and physical activity was found in 50% of all subjects studied. The simultaneous analysis of Holter ECG and physical activity as the same time series revealed that in patients with heart failure, sympathovagal balance shifted toward sympathotonic conditions and their physical activity could become subject to intrinsic ultradian dynamics of body's homeostasis.

Keywords accelerometer, heart failure, oxygen consumption, power spectral analysis, ultradian rhythm

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