Table 1 Characteristics of the Patients With AMI According to Their ACE Genotype

	II	ID	DD	p value
N	75	67	26	
F, %	14	14	19	0.851
Age, years	59±1	56±1	60±2	0.139
BW, kg	61.3±1.2	65.4±1.4	61.7±2.1	0.068
BMI, kg/m²	23.1±0.4	24.1±0.4	23.0±0.6	0.160
DM, %	55	40	59	0.102
HLP, %	60	61	59	0.970
HT, %	61	54	50	0.540
Smoking, %	64	63	81	0.164
LVEF, %	45±1	48±1	47±2	0.129
Heart rate, beats/min	72±2	76±2	74±3	0.336
ACE inhibitor, %	58	51	59	0.679
β-blocker, %	32	27	11	0.078

AMI, acute myocardial infarction; BW, body weight; BMI, body mass index; DM, diabetes mellitus; HLP, hyperlipidemia; HT, hypertension; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme. Values are mean±SE.

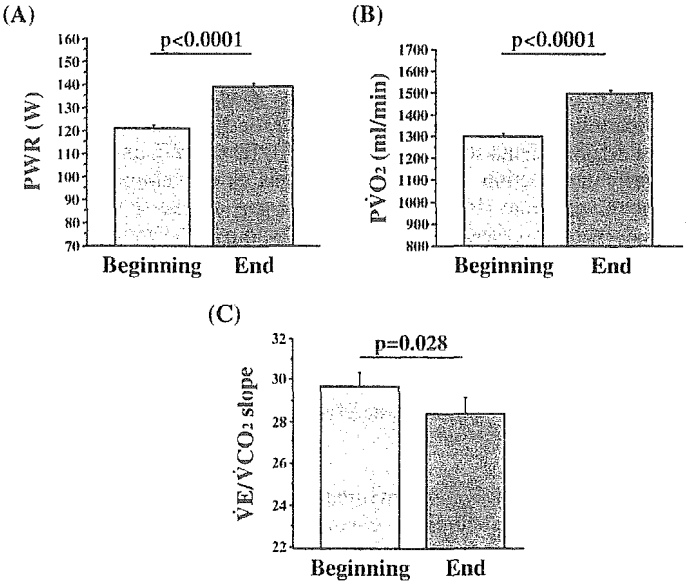

Fig 1. Changes in the cardiopulmonary exercise parameters after 3-month cardiac rehabilitation in 168 patients. (A) peak work rate (PWR), (B) peak oxygen consumption ($P\dot{V}O_2$), and (C) the slope of minute ventilation–carbon dioxide production relationship ($\dot{V}E/\dot{V}CO_2$ slope). Bars represent mean±SE.

week: 2–3 times in hospital under supervision and the remaining 2–3 times at home. Exercise consisted of aerobic dance and stationary bicycle riding in hospital and brisk walking at home. The training heart rate (HR) was determined according to the HR reserve method or Karvonen's equation (k=0.5–0.6): training HR=(peak HR−rest HR)×k+rest HR, where peak and rest HR were obtained in a symptom-limited exercise test at the beginning of the program.[13] Six patients failed to complete the 3-month CR program and so the total number of subjects was 162.

Cardiopulmonary Exercise Testing (CPX)

All patients underwent symptom-limited incremental CPX on a bicycle ergometer at the beginning and end of the 3-month CR program. Breath-by-breath respiratory gas exchange measurements were performed using a computerized metabolic cart (Minato Products, Japan). Details of the test protocol have been published elsewhere![14]

Assessment of LV Systolic Function

LV ejection fraction (LVEF) was determined as an index of LV systolic function by contrast left ventriculography at the beginning of the CR program (approximately 3 weeks after AMI onset). LVEF <45% was considered as LV dysfunction.

Blood Tests

Genomic DNA was isolated from peripheral leukocytes as previously reported![15] The ACE genotypes were determined by polymerase chain reaction as previously reported![15]

The institutional ethics committee approved the study and written informed consent was obtained from each patient before participation.

Statistics

The ANOVA method was used to assess the statistical significance of differences in means across genotype groups. All data are expressed as the mean value±SD. A p-value <0.05 was considered significant. All statistical analyses were performed with the JMP statistical package (SAS Institute Inc, Cary, NC, USA).

Results

Patient Characteristics

The 168 patients were divided into 3 groups according to

Table 2 Exercise Capacity at the Beginning and End of Cardiac Rehabilitation of the Patients With AMI According to Their ACE Genotype

	II (n=74)	ID (n=62)	DD (n=26)	p value
Beginning				
PWR	118±3	125±4	119±6	0.285
$P\dot{V}O_2$	1,262±42	1,370±46	1,292±71	0.218
$\dot{V}E/\dot{V}CO_2$	30.1±0.9	27.9±1.1	30.1±1.6	0.243
End				
PWR	136±4	141±4	133±6	0.452
$P\dot{V}O_2$	1,465±49	1,562±53	1,414±82	0.229
$\dot{V}E/\dot{V}CO_2$	27.7±0.7	27.5±0.8	27.8±1.2	0.960
Increase rate				
%PWR	13.6±1.5	12.9±1.6	12.0±2.5	0.863
$\%P\dot{V}O_2$	14.5±1.9	14.3±2.0	10.4±3.2	0.507
$\%\dot{V}E/\dot{V}CO_2$	−4.4±2.4	−1.7±2.8	−5.1±4.3	0.704

AMI, acute myocardial infarction; ACE, angiotensin converting enzyme; PWR, peak work rate; $P\dot{V}O_2$, peak oxygen consumption; $\dot{V}E/\dot{V}CO_2$, minute ventilation carbon dioxide production relationship. Values are mean±SE.

Table 3 Exercise Capacity at the Beginning and End of Cardiac Rehabilitation of the Patients With AMI and LV Dysfunction (LVEF <45%) According to Their ACE Genotype

	II (n=31)	ID (n=21)	DD (n=8)	p value
Beginning				
PWR	113±5	124±6	105±10	0.192
$P\dot{V}O_2$	1,210±60	1,331±73	1,123±119	0.259
$\dot{V}E/\dot{V}CO_2$	30.9±1.2	28.3±1.7	28.7±3.2	0.428
End				
PWR	127±6	136±7	114±11	0.225
$P\dot{V}O_2$	1,354±73	1,501±90	1,202±141	0.170
$\dot{V}E/\dot{V}CO_2$	29.9±1.1	27.4±1.4	25.8±2.4	0.228
Increase rate				
%PWR	7.7±1.9	11.2±2.3	9.2±3.5	0.509
$\%P\dot{V}O_2$	8.5±3.1	12.4±3.7	7.8±5.8	0.681
$\%\dot{V}E/\dot{V}CO_2$	2.0±3.6	0.1±4.8	−10.1±8.8	0.453

AMI, acute myocardial infarction; LV, left ventricular; LVEF, LV ejection fraction; ACE, angiotensin converting enzyme; PWR, peak work rate; $P\dot{V}O_2$, peak oxygen consumption; $\dot{V}E/\dot{V}CO_2$, minute ventilation carbon dioxide production relationship. Values are mean±SE.

their ACE genotype, the frequencies of which were in a Hardy-Weinberg equilibrium in this population. Baseline characteristics of the 3 groups are summarized in Table 1. Sex, mean age, body weight, body mass index and risk factors did not differ significantly among the genotypes. No significant difference in either resting LVEF or HR was detected. Although the subjects with the DD genotype had a trend toward a lower percentage of β-blocker treatment, no significant difference was observed.

Effects of CR on Exercise Capacity

Fig 1 shows the effects of 3-month CR on the CPX parameters in all subjects. The peak work rate (PWR), $P\dot{V}O_2$ and the slope of the minute ventilation–carbon dioxide production relationship ($\dot{V}E/\dot{V}CO_2$ slope) improved significantly after 3 months of CR (12.1%, 13.3%, −3.9% from baseline, respectively).

Exercise Capacity and Effects According to ACE Genotype

Table 2 shows the CPX data at the beginning and end of the 3-month CR stratified by the ACE genotype. It also shows the increase rate ((end−beginning)/beginning×100; %). No significant differences in PWR, $P\dot{V}O_2$ or $\dot{V}E/\dot{V}CO_2$ slope were observed among the 3 genotype groups at either time point. All parameters improved by a similar magnitude across the genotypes after 3-month CR as demonstrated by the increase rate.

Subanalysis was performed in patients with LV dysfunction (LVEF <45%, n=60), which is shown in Table 3. The pattern of the genotype distributions did not differ significantly between the patients with or without LV dysfunction (chi-square test, p=0.269). No significant differences in the 3 exercise parameters were observed among the 3 genotype groups at either the beginning or the end. Also, there were no significant differences in the increase rate of the 3 parameters among the 3 groups. Similar results were obtained in the subanalysis of male patients (63II/54ID/22DD) (data not shown).

Discussion

In the present study, based upon the hypothesis that the ACE genotype may have an association with the exercise capacity, we investigated this association in patients with AMI participating in CR for 3 months. However, we found no association between ACE I/D polymorphism and exercise capacity in this patient group, even in those with LV dysfunction. Furthermore, the ACE genotype may have no influence on the training effects of CR after AMI. Although many studies have explored the relationship of ACE geno-

type with the exercise capacity or training effects in athletes or healthy persons, this is the first study to examine the association between them in patients after AMI. In particular, because CR obviously provides improved exercise tolerance and quality of life and decreased mortality in patients with CHF or after AMI, it is important to clarify whether it is genetic factors, such as the ACE genotype, that are causing the training effects of CR.

The ACE genotype affects both serum and tissue ACE levels and many studies have investigated the associations with various cardiovascular diseases. As ACE is involved in the metabolism of substances that affect vascular and cardiac remodeling, it may account for the cardiopulmonary fitness of individuals and for the differences among individuals in response to physical training. Recent studies have shown higher frequencies of the ACE I allele among endurance athletes compared with non-athlete controls[9,10] Moreover, Hangberg et al reported an association between the ACE I allele and higher $P\dot{V}O_2$ levels in postmenopausal women.[11] However, there also have been conflicting reports about this association. Some studies failed to find an association between the ACE I allele and exercise capacity and did not support the hypothesis that ACE I/D polymorphism plays a major role in cardiopulmonary endurance.[16] Others reported that the ACE DD allele is associated with higher levels of $P\dot{V}O_2$ and that a greater strength gain in cardiac and skeletal muscles in response to resistance training program is found in the D allele carriers.[17,18]

The present study demonstrated that in post-AMI patients, the ACE genotype did not affect either the baseline exercise capacity or the training effects of a 3-month CR program, and there are several possible explanations. The subjects investigated were not healthy and the intensity of the exercise training was much less than that of endurance training in athletes. It is also well known that ethnic differences can affect genetic associations. However, at present, a physiological explanation for any association between the cardiorespiratory phenotype and ACE polymorphism has not been found and requires further investigation.

Recently, Abraham et al reported an association of the ACE DD genotype with decreased exercise tolerance 57 patients with CHF.[12] They observed that those with the ACE DD genotype had more restrictive pulmonary changes and a reduced lung diffusing capacity, and they attributed this to the poorer exercise capacity in the patients with CHF. Huwang et al reported that the ACE DD genotype might be a marker of a more severe condition in Chinese Han patients with CHF.[19] However, it remains controversial whether ACE polymorphism is associated with CHF.[20] In a subanalysis of the present study, we demonstrated no impact of ACE I/D polymorphism on exercise capacity in patients with LV dysfunction after AMI. As we did not assess the pulmonary function, we could not confirm Abraham's observations precisely in the current study. Also, we defined LV dysfunction as LVEF <45% and Abraham et al used LVEF <35%, which might explain the different results between the 2 studies. Exercise tolerance is a multifactorial phenotype and training benefits may be attributed to adaptations in cardiac and pulmonary performances, as well as those in the peripheral circulation and skeletal muscles. Although ACE I/D polymorphism does not appear to bean important modulator of the exercise capacity of patients with LV dysfunction after AMI, further studies are necessary to clarify the contribution of other important genetic factors in the decreased exercise capacity of CHF/LV dysfunction patients.

Study Limitations

We did not assess the effect of genotype on circulating markers of the renin–angiotensin system. However, because the association of the ACE D allele with increased plasma ACE activity has been consistently demonstrated in many previous studies, our observation suggests there is no relationship between plasma ACE activity and exercise capacity. In addition, the analysis and findings of this study are limited by the retrospective design. Finally, the study population was relatively small, especially in the subanalysis of patients with LV dysfunction. Any negative finding could thus be caused by a low statistical power. A larger study will be required if associations of the ACE genotype are to be investigated further.

Acknowledgments

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Pronounced HR variability after exercise in inferior ischemia: evidence that the cardioinhibitory vagal reflex is invoked by exercise-induced inferior ischemia

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Pronounced HR variability after exercise in inferior ischemia: evidence that the cardioinhibitory vagal reflex is invoked by exercise-induced inferior ischemia

Nobuhiro Tahara,[1] Hiroshi Takaki,[2] Atsushi Taguchi,[1] Kazuhiro Suyama,[1] Takashi Kurita,[1] Wataru Shimizu,[1] Shunichi Miyazaki,[1] Toru Kawada,[2] and Kenji Sunagawa[2]

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Tahara, Nobuhiro, Hiroshi Takaki, Atsushi Taguchi, Kazuhiro Suyama, Takashi Kurita, Wataru Shimizu, Shunichi Miyazaki, Toru Kawada, and Kenji Sunagawa. Pronounced HR variability after exercise in inferior ischemia: evidence that the cardioinhibitory vagal reflex is invoked by exercise-induced inferior ischemia. *Am J Physiol Heart Circ Physiol* 288: H1179–H1185, 2005. First published October 21, 2004; doi:10.1152/ajpheart.00045.2004.—Potent cardioinhibitory vagal reflex resulting in bradycardia and hypotension has been observed under particular conditions of transmural inferior ischemia and its reperfusion, such as those observed with acute infarction. However, whether exercise-induced ischemia with ST depressions that is subendocardial and that might be recurrently experienced in daily activities can evoke this reflex remains unknown. In patients with exercise-induced ST depressions due to either inferior [right coronary artery stenosis (RCA), $n = 52$] or anterior ischemia [left anterior descending artery stenosis (LAD), $n = 51$], we evaluated postexercise vagal activity (from 0 to 6 min) by the time constant of heart rate (HR) decay and HR variability by 30-s averages of the absolute values of successive RR interval differences (ΔRR). Exercise parameters were similar between groups. The time constant was slightly but significantly shorter in RCA than LAD patients (79 ± 24 vs. 93 ± 29 s, $P < 0.01$). More significantly, ΔRR early after exercise (0.5–2.5 min) was approximately twofold greater in RCA than LAD patients (from +76 to +118%, $P < 0.001$), indicating pronounced vagal activity stimulated by inferior ischemia. Revascularization prolonged the time constant ($P < 0.05$) and attenuated recovery ΔRR in RCA patients ($P < 0.05$, $n = 10$) but did not change both parameters in LAD patients ($n = 12$). As well as acute inferior infarction, exercise-induced inferior subendocardial ischemia, which might recurrently occur in daily activities, activates the cardioinhibitory reflex. These new findings must be taken into account in interpreting vagal activity in patients with coronary artery disease.

heart rate variability; vagus nerve; coronary artery disease

EXPERIMENTAL STUDIES in animals have demonstrated that excitation of vagal sensory nerve endings from myocardial ischemia involving the inferoposterior wall of the left ventricle activates potent cardioinhibitory reflex resulting in bradycardia and hypotension (7, 24). In humans, similar observations have been made under particular conditions of severe transmural inferior ischemia and its reperfusion, such as those that occur with myocardial infarction, vasospastic angina, or angioplasty of the right coronary artery (12, 15, 21, 22, 28). For example, in the first hour of the onset of acute myocardial infarction, patients with inferior infarction often (~75%) show sinus bradycardia and/or hypotension, which generally responds to intravenous administration of atropine. This observation contrasts with that in patients with anterior infarction, about 50% of whom show sinus tachycardia and/or hypertension (15).

Despite these well-recognized clinical observations, little attention has been paid to the question as to whether this reflex could be evoked by exercise-induced ischemia that is usually subendocardial with the manifestation of ST depressions and that might be recurrently experienced during daily activities. If it does occur in this condition, this hitherto-unrecognized possibility must be taken into account in the clinical interpretation of vagal activity in patients with coronary artery disease (CAD). It is widely accepted that the higher the estimated measure of vagal activity, the better the patient status and the prognosis according to various reports examining the clinical significance of estimating vagal activity with the use of heart rate (HR) variability (HRV) analysis from 24-h Holter recording (1, 11, 13, 23a) or HR recovery after exercise testing (5, 18, 26). It is possible that vagal activity may be adversely augmented under a certain pathological condition, i.e., in the presence of inducible inferior ischemia, and that vagal estimation may be erroneously interpreted in patients with inducible inferior ischemia. In view of the diagnostic utility of exercise testing, the identification of the pronounced vagal activity induced by exercise may serve as an additive measure for detecting and localizing the presence of inferior ischemia.

On the basis of these considerations, the present study was designed to test the hypothesis that inferior ischemia, even that evoked by physiological stress such as exercise, may invoke the cardioinhibitory reflex, which would in turn influence postexercise HR decay and HRV through a reflex enhancement of vagal activity. The postexercise condition may more readily unmask this phenomenon than during exercise, because vagal activity is physiologically depressed during exercise but markedly reactivated after exercise (2, 20), although this reflex should be activated both during exercise-induced ischemia and after postexercise reperfusion. Thus we compared HR decay and HRV after exercise in patients with exercise-induced inferior ischemia and those with anterior ischemia and then evaluated the effects of revascularization on these parameters.

METHODS

Study population. From consecutive patients who underwent both coronary angiography and conventional treadmill exercise ECG testing within 3 wk for the evaluation of CAD, a total of 103 patients who were documented to have either inducible inferior ischemia due to

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Table 1. *Patient characteristics*

	RCA	LAD
n	52	51
Age, yr	60±10	63±8
Men/women, *n*	45/7 (87/13)	45/6 (88/12)
Previous MI, *n*	25 (48)	26 (51)
LVEF, %	53±11	52±9
Hypertension, *n*	30 (58)	28 (55)
Diabetes mellitus, *n*	16 (31)	18 (35)
Medication		
β-Blockers, *n*	21 (40)	23 (45)
Ca antagonists, *n*	30 (58)	33 (65)
Nitrates, *n*	34 (65)	30 (59)

Values are means ± SD; *n*, no. of subjects. Values in parentheses are percentages. RCA, right coronary artery stenosis; LAD, left anterior descending coronary artery stenosis; MI, myocardial infarction; LVEF, left ventricular ejection fraction by contrast left ventriculography.

right coronary artery (RCA) stenosis (n = 52, RCA group) or anterior ischemia due to left anterior descending artery (LAD) stenosis (n = 51, LAD group) were enrolled in the study in a prospective fashion (Table 1). Significant coronary stenosis was defined as >50% luminal narrowing. All had significant exercise-induced ST segment depressions on treadmill ECG. Fifty-one (50%) patients had previous myocardial infarction. The majority (75%) had a single-vessel disease of either RCA stenosis (69%) or LAD stenosis (84%). In 24 patients with multiple vessel disease, exercise single-photon emission computed tomographic thallium-201 scintigraphy was performed to confirm that exercise-inducible ischemia was exclusively localized to either the inferior or anterior wall of the left ventricle. Exclusion criteria included the presence of atrial fibrillation, frequent premature beats (>5 beats/min) during the exercise test, and exercise-induced ST segment elevations (≥1.0 mm).

Clinical characteristics, including age, sex, prevalence of prior infarction, left ventricular ejection fraction (by contrast left ventriculography), and drug regimens, were quite similar between the two groups (Table 1). β-Blockers, calcium antagonists, and nitrates were taken in 44 (43%), 63 (61%), and 64 (62%) patients, respectively. No patient was taking digitalis at the time of the study. Drug regimens were neither altered nor stopped for the exercise test. The study protocol was approved by the ethics committee of our institution. All patients gave informed consent to participate in the study.

Exercise test. Conventional symptom-limited or submaximal (up to 90% age-predicted maximum HR) graded treadmill exercise testing was performed using a commercially available treadmill system (Formula; Esaote, Italy) equipped with an analog-to-digital converter and hard disk according to our protocol (23), being similar to the modified Bruce protocol. ECGs in lead V_2, aV_F, and V_5 were continuously monitored from rest through the recovery period. Arterial blood pressure was measured at rest, at the end of each stage, peak exercise, and at 1, 2, 4, and 6 min after exercise by a sphygmomanometer. Throughout the test, eight leads of the ECG, including lead I, II, and V_{1-6}, were continuously digitized at 500 Hz (12 bit) and stored on a computer hard disk for subsequent analysis. The standard 12-lead ECGs were hardcopied at rest, at the end of each stage, at peak exercise, immediately after exercise, and at every minute of the recovery period. A significant ST segment depression was defined by the following criteria: *1*) a horizontal or downsloping ST segment displacement at J point ≥ 0.1 mV and *2*) an upsloping ST segment displacement at 80 ms after J point ≥ 0.15 mV in at least three consecutive beats at peak exercise.

Assessment of revascularization effects. In 22 patients who subsequently received successful revascularization, we repeated the exercise test within 1 mo after the procedure. Eighteen patients received successful percutaneous transluminal coronary angioplasty either on the RCA (n = 8) or LAD (n = 10). Coronary artery bypass graft surgery was undertaken in the other four patients (RCA n = 2, LAD n = 2).

On the basis of consideration that a higher attainment of peak HR resulting from increased exercise capacity after the intervention (i.e., different exercise time) and its possible influences on vagal activity would make it difficult to estimate the true effect of revascularization on postexercise HR analysis, the exercise test after revascularization was terminated at the same exercise duration as that before the revascularization. Drug regimens were also kept constant.

Data analysis. Off-line analysis was performed on a personal computer using our custom-made software. We first determined the beat-by-beat RR intervals throughout the test from rest to recovery period by detecting the peak of R wave deflections. In patients with premature beats, we corrected RR intervals by linear interpolation with the previous and following beats.

Using the time series of RR intervals during recovery periods of 6 min, we computed the time constant of HR decay. We fitted the HR data to a monoexponential curve ($HR = A + Be^{-t/\tau}$, where A and B are constants, t is the elapsed time after peak exercise, and τ is the time constant of recovery) by nonlinear least-squares regression analysis. We then estimated the time course of HRV by time-domain and frequency-domain analysis as follows. Instead of parameters such as the standard deviation of the average interval between normal beats, which is substantially influenced by dynamic changes in overall trend, serial changes in HRV were assessed by 30-s averages of the absolute values of successive beat-to-beat differences in the RR interval (ΔRR). Serial changes in HRV were also evaluated by 30-s averages of the beat-to-beat percent changes [absolute successive differences relative to instantaneous RR interval (%ΔRR)] to eliminate the effect of the individual variation in HR.

Power spectral analysis of RR interval changes was also performed by fast Fourier transformation. We serially computed the spectrum of RR interval data of 1-min duration with 50% overlapping of each segment (0–1 min, 0.5–1.5 min, ... , 4.5–5.5 min, 5–6 min; 11 segments in all). The linear trend in the data was subtracted from the data set in each segment. A Blackman-Harris window was applied to reduce spectral leakage.

Statistical analysis. Data are presented as means ± SD. Serial changes in variables were evaluated by repeated-measures ANOVA followed by Scheffè's test for intergroup and intragroup comparisons. Student's unpaired and paired t-tests, linear regression analysis, multiple linear regression analysis, and χ^2-analysis were used when applicable. A P value of <0.05 was considered statistically significant.

RESULTS

All exercise tests were completed without any unfavorable events or serious complications. Exercise test parameters including exercise duration, resting and peak HR, resting and peak systolic blood pressure, the maximum magnitude of ST segment depression, and the occurrence of exercise-induced angina were consistently similar between the RCA and LAD groups (Table 2). Only peak HR tended to be lower in the RCA

Table 2. *Exercise test results*

	RCA	LAD
Exercise time, s	507±159	497±133
HR, beats/min		
Resting	65±12	65±11
Peak	126±22	135±21
SBP, mmHg		
Resting	129±13	130±18
Peak	158±24	160±20
ST depression, mm	−2.0±0.8	−1.7±1.5
Angina, *n*	22/30	25/26

Values are means ± SD. HR, heart rate; SBP, systolic blood pressure; *n*, no. of subjects.

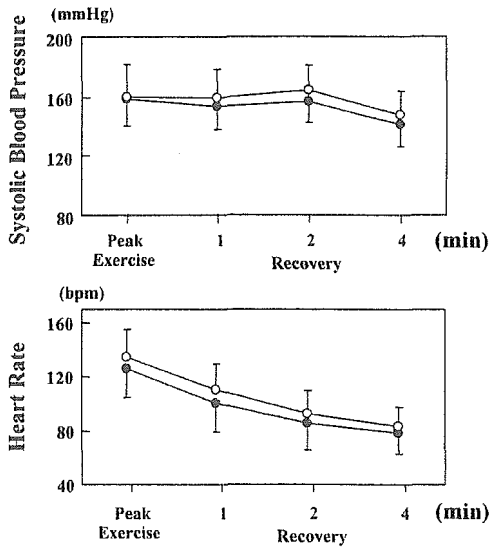

Fig. 1. Time course of systolic blood pressure (*top*) and heart rate [HR, in beats/min (bpm); *bottom*] in right coronary artery (RCA) stenosis (closed circles) and left anterior descending artery (LAD) stenosis (open circles) patients. No differences were observed in either parameter. Values are expressed as means ± SD.

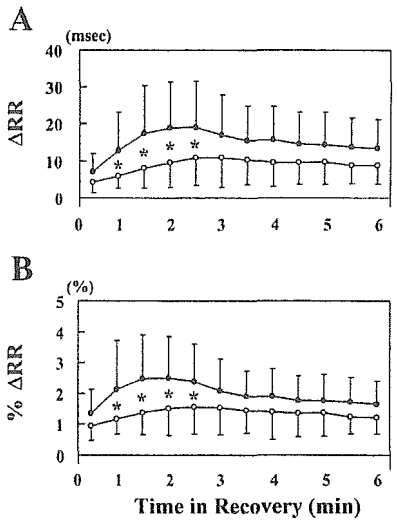

Fig. 3. Comparisons of the HRV time course expressed by ΔRR (*A*) and absolute successive differences relative to instantaneous RR interval (%ΔRR; *B*). Closed circles depict the RCA stenosis group, and open circles depict the LAD stenosis group. Values are expressed as means ± SD. *$P < 0.01$, RCA stenosis patients vs. LAD stenosis patients.

group (126 ± 22 beats/min) than in the LAD group (135 ± 21 beats/min), but this difference did not reach statistical significance.

Postexercise systolic blood pressure and HR. There was no significant difference between the groups with respect to postexercise systolic blood pressure and HR at 1, 2, and 4 min of recovery (Fig. 1).

Postexercise HR decay and HRV. Shown in Fig. 2 are representative examples of the time series of beat-by-beat HR and absolute value of the successive RR interval changes throughout the exercise test. A patient with RCA stenosis (Fig. 2, *left*) showed a transient increase in RR variability soon after the termination of exercise, whereas such findings were not observed in a patient with LAD stenosis (Fig. 2, *right*). The time constant was shorter in the former (92 s) than in the latter (112 s).

When pooled data were compared between the two groups, the time constant of postexercise HR decay was slightly but significantly shorter in RCA than LAD patients (79 ± 24 vs. 93 ± 29 s, $P < 0.01$). More significantly, postexercise HRV expressed by ΔRR (average over every 30 s) early after exercise was markedly greater in RCA than LAD patients for a period of 1.0–2.5 min ($P < 0.001$ for all; Fig. 3*A*). %ΔRR was similarly greater in RCA patients than in LAD patients in the same period of 1.0–2.5 min after exercise ($P < 0.001$ for 1.0–2.0 min and $P < 0.01$ for 2.5 min; Fig. 3*B*).

Figure 4, *top*, shows serial changes in the power spectrum of RR intervals in the recovery period analyzed in the same two patients shown in Fig. 2. As can be seen, unlike the patient with LAD stenosis (Fig. 4, *right*), the patient with RCA stenosis (Fig. 4, *left*) showed substantial amounts of power spectra in the frequency range between ~0.30 and 0.60 Hz. When these data were pooled (Fig. 4, *bottom*), total power within the frequency range between 0.25 and 0.60 Hz (corresponding to the respiratory rates after exercise) was significantly higher in the RCA group than in the LAD group in the four time window segments early after exercise, i.e., 0.5–1.5 min, 1.0–2.0 min,

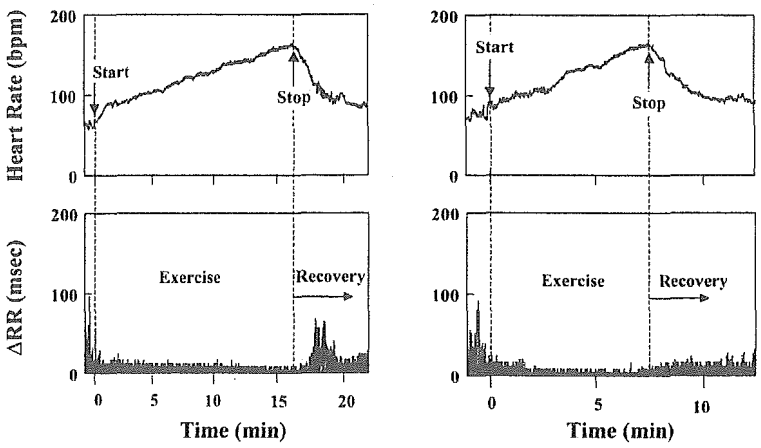

Fig. 2. Representative trends of beat-by-beat HR (*top*) and absolute values of successive beat-to-beat differences in the RR interval (ΔRR; *bottom*) from rest to recovery in a patient with RCA stenosis (*left*) and in a patient with LAD stenosis (*right*). A transient increase in HR variability (HRV) can be seen soon after exercise in the patient with RCA stenosis.

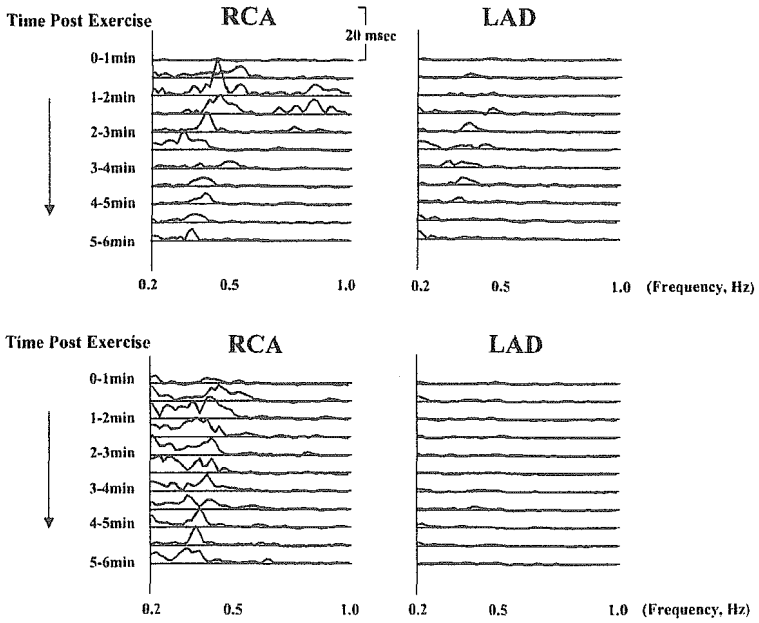

Fig. 4. *Top*: representative data of power spectrum analysis of HRV obtained in the same 2 patients shown in Fig. 2 (*left*, RCA stenosis patient; *right*, LAD stenosis patient). Horizontal lines depict the frequency (in Hz). The data series of power spectrum for 1 min are shown serially from the top (0–1 min) downward with time of recovery (overlapping 30 s). The spectral component of RR intervals for each segment is shown as the square root of the power (i.e., amplitude). *Bottom*: pooled data of power spectrum analysis in the RCA stenosis group (*left*; n = 52) and LAD stenosis group (*right*; n = 51).

1.5–2.5 min, and 2.0–3.0 min ($P < 0.005$ for the first 3 segments and $P < 0.02$ for 2.0- to 3.0-min segment).

Figure 5 shows scatterplots of ΔRR at 1.5 min (60–90 s) versus the time constant for all patients. There was a relatively close relationship ($r = -0.50$, $P < 0.001$) between these parameters. When ΔRR at 1.5 min (60–90 s) for each patient was plotted separately in RCA and LAD patients (Fig. 6), the prevalence of pronounced HRV (exceeding 12 ms) was much more frequently found in RCA patients (58%) than in LAD patients (16%, $P < 0.001$). Subgroup analysis of RCA patients showed that those with enhanced HRV were significantly younger (58 ± 11 vs. 64 ± 8 yr, $P < 0.01$) and had a significantly lower HR at rest (61 ± 10 vs. 70 ± 12 beats/min, $P < 0.01$) and peak HR (117 ± 19 vs. 139 ± 18 beats/min, $P < 0.01$) compared with those without this phenomenon.

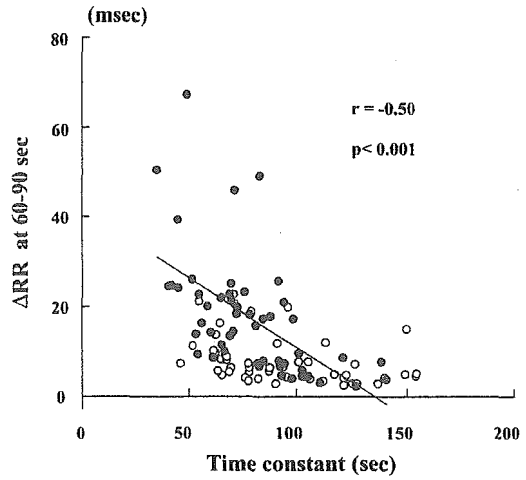

Fig. 5. Graph showing the relationship between ΔRR (60–90 s) and the time constant. Closed circles, RCA stenosis patient; open circles, LAD stenosis patient.

There was no significant difference with respect to sex, left ventricular ejection fraction, the use of cardiovascular drugs (β-blockers, calcium antagonists, or nitrates), prevalence of previous myocardial infarction, history of diabetes mellitus, exercise time, magnitude of ST depression, occurrence of exercise-induced angina, or resting ΔRR level. When multiple linear regression analysis that included clinical, angiographic, and exercise variables was used in the overall population, age ($P = 0.02$), resting HR ($P = 0.04$), and peak exercise HR ($P = 0.02$) together with the location of ischemia ($P < 0.0001$) were independently associated with ΔRR (60–90 s).

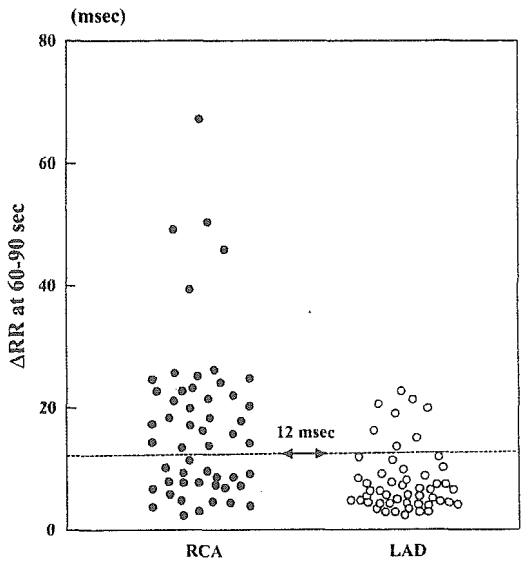

Fig. 6. Scatterplots of ΔRR at 60–90 s plotted separately for each patient in the RCA (*left*) and LAD (*right*) stenosis groups. Pronounced HRV (defined as ΔRR >12 ms; dotted line) was observed in 58% of RCA stenosis patients, whereas it was found in 16% of LAD stenosis patients ($P < 0.001$).

Effects of revascularization on postexercise HR decay and HRV. In either the RCA or LAD patient group, HR at both rest and the end of exercise were not significantly different before and after revascularization (note that the second test was terminated at the same duration as was achieved at the first test). In RCA patients, HR at 1 and 2 min of recovery were significantly higher (both $P < 0.05$) after than before revascularization, whereas no such significant differences were observed in LAD patients.

After revascularization, in RCA patients, ΔRR early after exercise was significantly attenuated (from 22 ± 14 to 9 ± 5 ms for 60–90 s, from 25 ± 12 to 11 ± 5 ms for 90–120 s, and from 27 ± 13 to 13 ± 5 ms for 120–150 s, all $P < 0.05$; Fig. 7). The time constant was concordantly prolonged (from 73 ± 21 to 96 ± 30 s, $P < 0.05$). Both parameters in RCA patients changed toward the same level as those in LAD patients, in whom both parameters remained unchanged after the revascularization procedure. There was no significant difference in systolic blood pressure at any time point in both RCA and LAD patient groups.

DISCUSSION

Although potent cardioinhibitory vagal reflex stimulated by inferior ischemia (the so-called Bezold-Jarisch reflex) has been recognized under particular conditions of transmural ischemia in animal and human studies (7, 12, 15, 21, 22, 24, 28), whether exercise-induced transient subendocardial ischemia could evoke this reflex has received little attention and has not been previously examined. The present study indicated that exercise-induced inferior ischemia with ST depressions reflecting subendocardial ischemia, which might be recurrently experienced in daily activities, activates the cardioinhibitory reflex as evidenced by a faster postexercise HR decay and more pronounced HRV in RCA patients compared with LAD patients. In addition, removal of inferior ischemia by revascularization prolonged the time constant and reduced pronounced HRV in the early recovery in RCA patients, whereas revascularization did not significantly change these parameters in LAD patients. These findings, indicative of the direct role of "localized inferior ischemia" on the appearance of this phenomenon, support the validity of our hypothesis that transmural severe ischemia is not a prerequisite for the manifestation of this reflex.

Estimation of vagal activity. Numerous previous studies have indicated the clinical importance of estimating the vagal activity regulating the cardiovascular system in patients with heart disease by noninvasive methods such as HRV analysis (1, 11, 13, 23a) and baroreflex sensitivity measurements with phenylephrine injection (3, 13, 14). After a report of Imai et al. (10) demonstrating that the rate of HR decay after exercise is a function of the reactivation of vagal activity, recent studies have shown the postexercise HR fall is a useful marker for predicting mortality in subjects with suspected CAD (5, 18, 26). In the present study, to assess the dynamic changes in vagal activity, serial HRV analysis during recovery was conducted by calculating ΔRR and %ΔRR every 30 s along with the evaluation of the HR decay (time constant). As a result, both HRV parameters in RCA patients markedly increased from 0.5 to 1 min of recovery, remained rather constant up to 2.5 min, and thereafter decreased nearly to the level of those in LAD patients. The group difference was more striking compared with that of the time constant. The characteristic overshooting of the HRV parameters suggests a transiently enhanced vagal activity as a "reperfusion reflex" after the resolution of exercise-induced ischemia. In agreement with its observed time course, frequency analysis also revealed a transient augmentation of power spectrum of RR intervals in high-frequency ranges early after exercise, supporting the validity of reperfusion-stimulated vagal overactivation.

It should be of importance that, in the present study, the exercise duration after revascularization was matched to that before the procedure. This is because a higher level of exercise intensity, as a consequence of the removal of critical stenosis, would alter the postexercise autonomic activity, possibly making it difficult to estimate the direct effects of revascularization.

Cardioinhibitory reflex activated by exercise-induced ischemia. To the best of our knowledge, no previous study has been systematically conducted to evaluate the possible role of exercise-induced ischemia with ST depressions on this reflex phenomenon. Miller et al. (16) reported on seven patients who developed sinus deceleration during exercise testing, all of whom had angiographically documented RCA lesions. The authors speculated the role of Bezold-Jarisch reflex in this mechanism and stated that the prevalence of deceleration during exercise appears to be very low, which is in agreement with our experiences in the exercise laboratory. Sinus deceleration during exercise may be an extreme example caused by an ischemia-mediated reflex (4, 6).

Thus this reflex phenomenon is presumably operative during exercise-induced ischemia as well as during postexercise reperfusion; however, we focused on postexercise HR dynamics for the following reasons. Because vagal activity is physiologi-

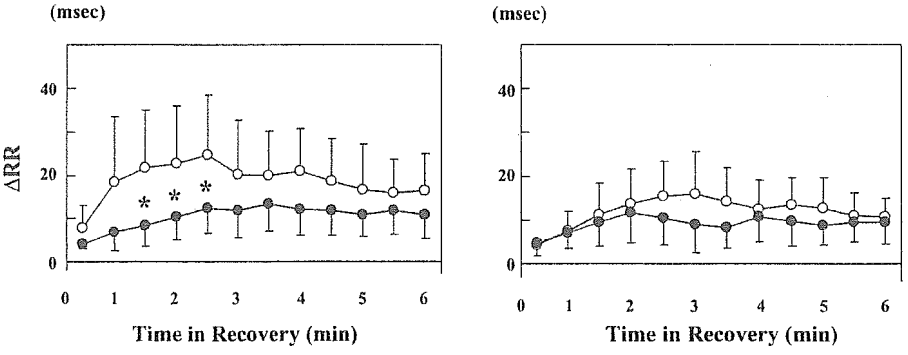

Fig. 7. Changes in the HRV (ΔRR) time course after revascularization in the RCA (*left*; $n = 52$) and LAD (*right*; $n = 51$) stenosis groups. Open circles depict the values before the procedure, and closed circles depict the values after the procedure. Values are expressed as means ± SD. *$P < 0.05$, before vs. after revascularization.

cally attenuated in proportion to the increase in exercise intensity, this reflex might be masked during exercise. In contrast, potent reactivation of vagal nerve activity after exercise may accelerate the appearance of this reflex under a higher vagal condition after exercise. In practice, several cases among RCA patients showed a pronounced HRV and marked impairment of HR increase even during exercise indicative of the operation of this reflex during exercise; however, we also found a markedly rapid HR decay and more profound increase in HRV during recovery almost without exception.

The physiological implication of this reflex, namely, what role this reflex may play, is unknown. The possibility that the reflex cardioprotectively works thorough the reduction in myocardial oxygen demand or that the resultant high vagal tone prevents the development of serious ventricular arrhythmias is of interest (9, 19); however, there are few available data to support this so far.

Pronounced HRV after exercise (defined as $\Delta RR > 12$ ms) was observed in 58% of RCA patients but in only 16% of LAD patients. These prevalences are very similar to those during the observation of the "bradycardia-hypotension" pattern observed in patients early after acute inferior and anterior myocardial infarction, respectively (27). The difference probably indicates that the vagal nerves involving this reflex are preferentially distributed in the inferior area but some mounts of fibers are distributed in the anterior area of the left ventricle.

In RCA patients, none of the clinical, angiographic, and exercise parameters differed between patients with and without this phenomenon except in regard to age, resting HR, and peak HR. All of these three parameters were independently associated with HRV early after exercise in our multiple regression analysis. Vagal activity is known to be strongly associated with age and resting HR. Thus it is suggested that the presence or absence of this phenomenon would depend on the basal level of vagal activity rather than other parameters such as severity of ischemia or the presence of previous myocardial infarction.

Clinical implications. The findings demonstrated in the present study should provide a new insight into the interpretation of estimated vagal activity in patients with CAD. It is widely accepted that autonomic imbalance, i.e., vagal withdrawal and coexisting sympathetic activation, is associated with poor prognosis and pathophysiology in various types of heart disease (25). In other words, we believe that the higher the vagal activity, the better the patient prognosis and status. However, present data suggest that this is not necessarily the case in some patients under certain conditions. For example, studies using Holter recordings showed that a considerable number of patients with documented CAD frequently experience episodes of transient myocardial ischemia in their daily life (17). In such patients, transient enhancement of HRV provoked by inferior ischemia may often occur, leading to an erroneous interpretation of HRV. In addition, there are several studies (5, 18, 26) that related a poor prognosis to attenuated HR recovery after exercise testing on the assumption that a fall in HR recovery immediately after exercise is a function of vagal reactivation. These findings might be true in the overall population; however, it should be noted that a rapid HR decrease after exercise may occur under a pathological condition through an ischemia-mediated cardioinhibitory reflex. HRV measures might be affected not by the patient status but by the presence of inferior ischemia.

We did not analyze postexercise parameters in subjects without CAD. This is because they should be capable of exercising far longer than our patients with exercise-induced ischemia, which may considerably influence the postexercise vagal activity. At present, we can consider that the vagal overactivation after exercise may be useful in predicting the presence of inferior ischemia when significant exercise-induced ST depressions are observed. It may also be useful in patients after angioplasty of RCA disease to predict restenosis or to confirm the therapeutic effects.

Study limitations. It is generally considered that anterior ischemia is more deleterious than inferior ischemia in terms of hemodynamics, leading to a more severe autonomic impairment, i.e., a more depressed vagal activity in LAD patients. Thus the observed differences in vagal activity between the groups might be caused not only by the cardioinhibitory reflex evoked by inferior ischemia but also by the differences in hemodynamic impairment. For this reason, we evaluated the changes in vagal parameters (time constant and ΔRR) after revascularization and found that these parameters were significantly altered in RCA patients but not in LAD patients. This strongly supports the notion that the differences in estimated vagal activity between the groups are determined primarily by the presence or absence of inferior located ischemia. Nevertheless, we cannot completely exclude the possible contribution of the different sympathetic tone between the groups, because anterior located ischemia, although rare, can stimulate this reflex.

In conclusion, as well as transmural myocardial ischemia with ST elevations such as that occurring with acute inferior myocardial infarction, exercise-induced transient inferior subendocardial ischemia with ST depressions, which might be recurrently experienced in daily activities, activates cardioinhibitory reflex by stimulating vagal nerve endings in humans. This hitherto-unknown findings must be taken into account in the estimation of vagal function conducted in various clinical settings, especially when evaluating patients with CAD.

GRANTS

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Response of beat-by-beat QT variability to sympathetic stimulation in the LQT1 form of congenital long QT syndrome

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OBJECTIVES The purpose of this study was to test the hypothesis that the lability of beat-by-beat QT variability is prominent during sympathetic stimulation in LQT1 patients. We analyzed beat-by-beat QT variability using a newly developed program and applied cross-correlation methods in LQT1 patients before and after epinephrine infusion.

BACKGROUND Studies suggest that cardiac events associated with sympathetic stimulation are more common in the LQT1 form than the LQT2 and LQT3 forms of congenital long QT syndrome (LQTS). Although beat-by-beat alternation of T-wave morphology is observed in LQTS, its objective estimation is difficult because of complicated T-wave morphology.

METHODS Twelve-lead ECG was recorded under baseline conditions and during epinephrine infusion (0.1 μg/kg/min) in 14 LQT1 and five control patients. We measured beat-by-beat QT interval by a cross-correlation technique. Mean of successive changes in RR (ΔRR), QT (ΔQT), standard deviation of ΔRR (SD-ΔRR), ΔQT (SD-ΔQT), and QTI (QT/ RR) before and after epinephrine were compared between the two groups.

RESULTS No significant differences in any parameters were observed between the two groups under baseline conditions. ΔQT, SD-ΔQT, and QTI were increased in LQT1 but not in control patients during epinephrine (LQT1: ΔQT 2.3–4.2 ms, SD-ΔQT 2.2–4.1, QTI 0.10–0.22, $P < .005$ vs baseline; Control: ΔQT 2.5–2.4 ms, SD-ΔQT 1.9–2.1, QTI 0.08–0.09: P = NS vs baseline).

CONCLUSIONS Beat-by-beat QT variability analyzed by the cross-correlation method was greater in LQT1 patients during epinephrine infusion, suggesting sympathetic stimulation accentuates beat-by-beat alternation of repolarization in LQT1 patients.

KEYWORDS Long QT syndrome; Epinephrine; Sympathetic activity; QT interval; T-wave alternans

(Heart Rhythm 2005;2:149–154)

Introduction

The congenital long QT syndrome (LQTS) is a hereditary disorder associated with prolonged ventricular repolarization and the life-threatening polymorphic ventricular tachycardia torsades de pointes (TdP).[1,2] Genetic studies have shown that congenital LQTS is a primary electrical disease caused by mutation in specific ion channel genes.[3,4] Seven forms of congenital LQTS have been identified.

Among the seven forms, cardiac events associated with sympathetic stimulation are more common in the LQT1 form than in the other forms of congenital LQTS.

T-wave alternans (TWA), an ECG phenomenon characterized by beat-by-beat alternation of the morphology, amplitude, and/or polarity of the T wave, often is associated with congenital LQTS. TWA is an important prognostic indicator because it is commonly observed just preceding episodes of TdP.[5–7] Although beat-by-beat alternation of repolarization somewhere in the heart is presumed to underlie TWA, its objective estimation is difficult because of complicated T-wave morphology.

The present study used a novel method "cross-correlation technique" to assess beat-by-beat QT variability. The aim of the study was to test the hypothesis that the lability

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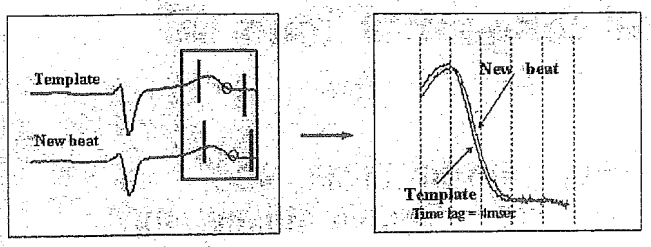

Figure 1 Algorithm of QT measurement by the cross-correlation method. See text for details.

of beat-by-beat QT variability is prominent during sympathetic stimulation in LQT1 patients in whom cardiac events often occur during sympathetic stimulation.

Methods

Study population

Fourteen LQT1 patients with *KCNQ1* mutation and five healthy volunteers used as controls were included in the study. The five healthy volunteers had no symptoms, and no abnormal T-wave morphologies were observed on 12-lead ECG. LQTS-affected individuals were noted based on the ECG diagnostic criteria of Keating et al.[8] The criteria include corrected QT (QTc) ≥470 ms in asymptomatic individuals and QTc >440 ms for men and >460 ms for women associated with one or more of the following: (1) stress-related syncope, (2) documented TdP, or (3) family history of early sudden cardiac death. Genotyping of LQTS was reviewed and approved by the Ethical Review Committee. Written informed consent was obtained from all patients.

Recording of standard 12-lead ECG

Standard 12-lead ECG was recorded using an FDX6521 (Fukuda Denshi Co., Tokyo, Japan) with the patient in the supine position without antiarrhythmic medications, including beta-blockers. ECG data were digitized using analog-to-digital converters at a sampling rate of 1,000 samples/second per channel.

ECG measurements

We measured QT interval beat by beat in the most stable lead to analyze T-wave morphology among precordial leads. The beat-by-beat changes of the QT interval were assessed during the latter half of T wave (Figure 1).

Specifically, the steps involved in analyzing a digitized ECG record included the following. (1) The operator selected a lead to analyze and the beginning and the end of the template T wave as an average of consecutive five beats. (2) The time of each R wave was identified using an automated peak detection algorithm. (3) For each of the other new beats, the time lags between the new beat and the template were calculated for comparison with the templates of QT morphology by a *cross-correlation method.* The templates were resampled as successive five beats before the newest analyzed beat.

We also analyzed beat-by-beat QT interval using a semi-automated digitizing program simultaneously. QT interval was defined as the time interval between QRS onset and the point at which the isoelectric line intersected a tangential line drawn at the maximal downslope of the T wave *(tangential method).*

Epinephrine administration

The epinephrine test was conducted as part of the clinical evaluation of LQTS.

A bolus injection of epinephrine 0.1 μg/kg was followed immediately by continuous infusion at 0.1 μg/kg/min. Twelve-lead ECG was recorded continuously during sinus rhythm under baseline conditions and usually for 5 minutes after start of epinephrine infusion. The effect of epinephrine on RR and QT intervals usually reached steady-state conditions 2 to 3 minutes after epinephrine was started. Epinephrine infusion for more than 5 minutes was avoided. ECG monitoring was continued for another 5 minutes after finishing epinephrine infusion to detect any occurrence of TdP. ECG data were collected under baseline conditions and at steady-state epinephrine effect 3 to 5 minutes after epinephrine was started.

Analyzed parameters

The following five ECG parameters were calculated from all RR and QT intervals recorded for 30 seconds during baseline conditions and at steady-state epinephrine conditions and then compared between the two groups (Figure 2): (1) ΔRR, the average of successive RR interval changes; (2) ΔQT, the average of successive QT interval changes; (3) SD-ΔRR, the standard deviation of RR interval; (4) SD-ΔQT, the standard deviation of the QT interval; and (5) QT index (QTI), the rate of change of QT interval

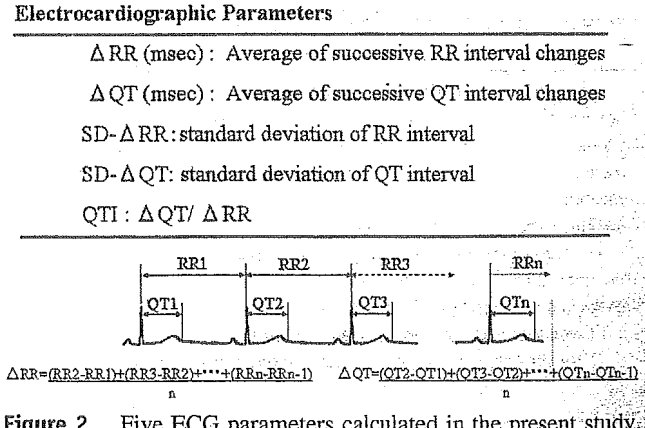

Figure 2 Five ECG parameters calculated in the present study. See text for details.

Table 1 Baseline ECG characteristics

	LQT1 (n = 14)	Control (n = 5)
Age	28 ± 20	29 ± 10
HR (bpm)	71 ± 10	68 ± 7
QT (ms)	454 ± 59*	387 ± 13
QTc (ms)	504 ± 76*	410 ± 36
$T_{peak-end}$ (ms)	102 ± 16	91 ± 19
QTD (ms)	71 ± 25*	45 ± 11

Values are reported as mean ± SD.

HR = heart rate; QTc = corrected QT interval; $T_{peak-end}$ = interval between T_{peak} and T_{end}; QTD = QT dispersion (maxQT-minQT).

*$P < .05$ vs control.

to RR interval, defined as the beat-by-beat value of ΔQT divided by ΔRR.

We examined the relationship between QT variability (ΔQT, SD-ΔQT) analyzed by cross-correlation methods and QT interval or heart rate before and after epinephrine infusion.

Statistical analysis

Data are expressed as mean ± SD. Paired and unpaired t-tests were used for couple observation. Correlation between continuous variables was tested by linear regression. For all tests, $P < .05$ was considered significant.

Results

Table 1 lists baseline ECG characteristics. No significant differences were observed regarding age and baseline heart rate between the LQT1 and control groups. The baseline QT and QTc intervals and QT dispersion, which were analyzed by the tangential method, were all significantly greater in the LQT1 group than in control group.

Beat-by-beat T wave variability before and after epinephrine

Figure 3 illustrates representative examples of superimposed QT complexes before and after epinephrine. The consecutive 10 beats of eight-lead ECGs were drawn temporally. In the control patient, no significant difference of beat-by-beat T-wave morphology was observed before and after epinephrine. In contrast, more significant beat-by-beat lability of the T wave was recognized after epinephrine in the LQT1 patient, although no significant change of beat-by-beat T-wave morphology was observed under baseline.

Beat-by-beat QT variability

The analyzed ECG leads were lead V_5 in three controls and six LQT1 patients, lead V_6 in two controls and five

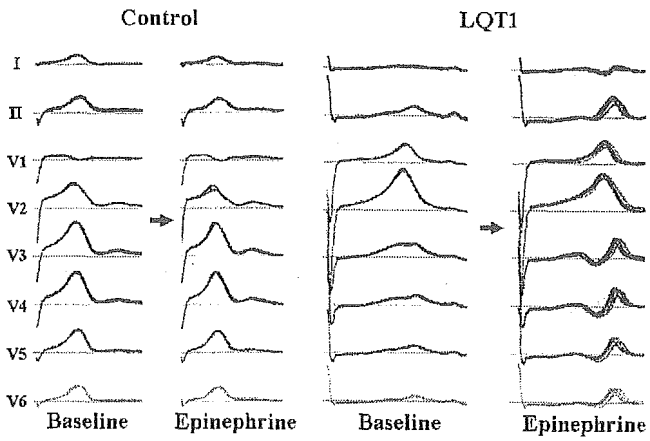

Figure 3 Representative example of superimposed QT complexes before and after epinephrine. The consecutive 10 beats of eight-lead ECGs are drawn temporally. In a control patient, no difference of beat-by-beat T-wave morphology is observed before and after epinephrine. However, more significant beat-by-beat alternans of T wave and change to biphasic T-wave pattern were observed after epinephrine in an LQT1 patient.

LQT1 patients, and lead V_2, V_3, and V_4 in each of the remaining LQT1 patients.

Figure 4 illustrates beat-by-beat change of the RR, QT, and the ΔRR and ΔQT in a control patient. The RR interval was decreased after bolus infusion of epinephrine, and remained decreased less than before epinephrine at the steady state condition. The ΔRR, which is heart rate variability, became small following the start of epinephrine. The QT interval was prolonged when the RR was decreased after bolus epinephrine, however the QT interval was slightly shortened compared before epinephrine at steady-state. The ΔQT was not changed before and after epinephrine infusion.

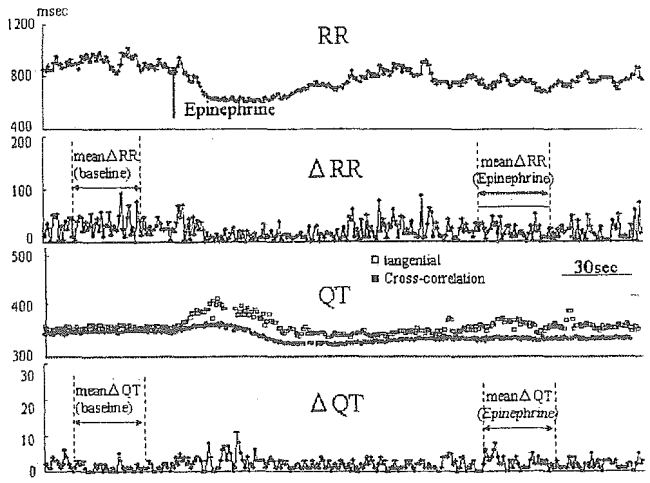

Figure 4 Beat-by-beat change of RR, QT, ΔRR, and ΔQT in a control patient. RR interval was decreased after bolus infusion of epinephrine and remained decreased less than before epinephrine at the steady-state condition. ΔRR became small after epinephrine was started. QT interval was prolonged when RR was decreased after bolus epinephrine but was slightly shortened compared with before epinephrine at the steady-state epinephrine effect. ΔQT was not changed before and after epinephrine infusion.

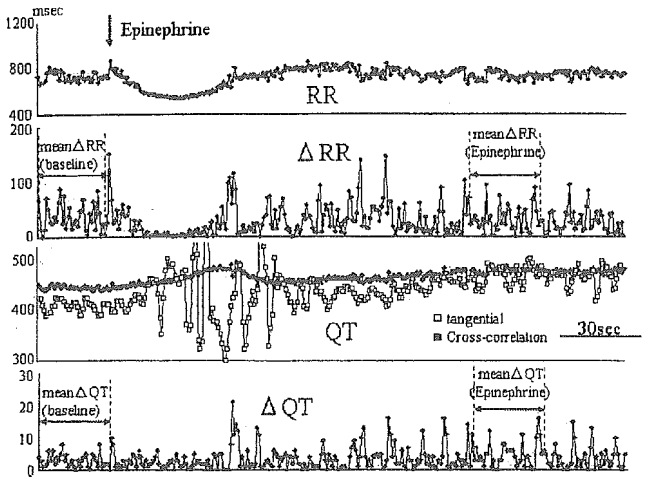

Figure 5 Beat-by-beat change of RR, QT, ΔRR, and ΔQT in an LQT1 patient. RR interval was decreased following bolus infusion of epinephrine and remained decreased at steady-state condition. ΔRR became small after bolus infusion of epinephrine. QT interval was prolonged after bolus infusion of epinephrine and remained prolonged at steady-state epinephrine effect compared with before epinephrine. Of note, ΔQT was significantly increased at steady-state epinephrine effect compared with before epinephrine.

Figure 5 illustrates beat-by-beat change of RR, QT, ΔRR, and ΔQT in an LQT1 patient. Similar to the control patient, the RR interval also was decreased following bolus infusion of epinephrine and remained decreased at steady-state epinephrine effect in the LQT1 patient. ΔRR became small after bolus infusion of epinephrine. QT interval was prolonged following the bolus infusion of epinephrine and remained prolonged at steady-state epinephrine effect compared before epinephrine. It is noteworthy that ΔQT was significantly increased at steady-state epinephrine effect compared with before epinephrine.

Table 2 lists composite data of the five ECG parameters before and at steady-state epinephrine effect in the LQT1 and control groups.

No significant differences in ΔRR, ΔQT, SD-ΔRR, SD-ΔQT, and QTI were observed between the two groups under baseline conditions. Epinephrine increased ΔQT (2.3 ± 0.3 to 4.2 ± 2.3 ms, $P < .005$), SD-ΔQT (2.2 ± 1.9 to 4.1 ± 2.2 ms, $P < .005$), and QTI (0.10 ± 0.06 to 0.22 ± 0.16, $P < .005$) in LQT1 group but not in control group (ΔQT 2.5 ± 1.5 to 2.4 ± 0.5 ms, SD-ΔQT 1.9 ± 0.9 to 2.1 ± 0.6 ms, QTI 0.08 ± 0.02 to 0.09 ± 0.06, P = NS) (Figure 6).

ΔQT and SD-ΔQT showed significant correlation with QTc after epinephrine (r = 0.61; $P < .05$ and r = 0.65; $P < .05$, respectively) but not before epinephrine. On the other hand, the values were not correlated with heart rate either before or after epinephrine. No significant differences in the five ECG parameters were observed between patients with (n = 8) and patients without (n = 6) a history of syncope or cardiac arrest.

Discussion

Quantification of ventricular repolarization

Several methods have been proposed to quantify abnormalities of repolarization[9,10]; however, few of the techniques are suitable for routine clinical use. Thus, assessment of ventricular repolarization still is based largely on QT and QTc measurements and on qualitative description of morphologic alterations such as presence of notched, bifid, or biphasic T waves. A set of new morphologic ECG parameters proposed by Merri et al,[11] Benhorin et al,[12] and Priori et al[13] could provide a better description of repolarization and be more reproducible than QT interval duration, but these parameters have not yet obtained widespread application in clinical practice.

RT interval, the duration between the peak of R and T wave, was used to analyze the repolarization period to minimize the observer bias in manual acquisition of data.[14] Experimental studies[15,16] using arterially perfused canine left ventricular wedges suggest both the peak and the end of the T wave on the ECG are coincident with repolarization of epicardial and maximal M-cell action potentials, respectively, so that the interval between the T_{peak} and T_{end} reflects transmural dispersion of repolarization. The transmural dispersion of repolarization, the latter part of the T wave, is linked to ventricular arrhythmias such as TdP under long QT conditions. Therefore, the RT interval cannot detect the

Table 2 ECG parameters before and after epinephrine in LQT1 and control groups

	LQT1 (n = 14)		Control (n = 5)	
	Baseline	Epinephrine	Baseline	Epinephrine
ΔRR	33 ± 28	36 ± 39	39 ± 20	34 ± 25
ΔQT	2.3 ± 0.3	4.2 ± 2.3*,†	2.5 ± 1.5	2.4 ± 0.5
SD-ΔRR	23 ± 18	27 ± 27	30 ± 17	36 ± 27
SD-ΔQT	2.2 ± 1.9	4.1 ± 2.2*,†	1.9 ± 0.9	2.1 ± 0.6
QTI	0.10 ± 0.06	0.22 ± 0.16*,†	0.08 ± 0.02	0.09 ± 0.06

Values are reported as mean ± SD.
*$P < .05$ vs baseline.
†$P < .05$ vs control.

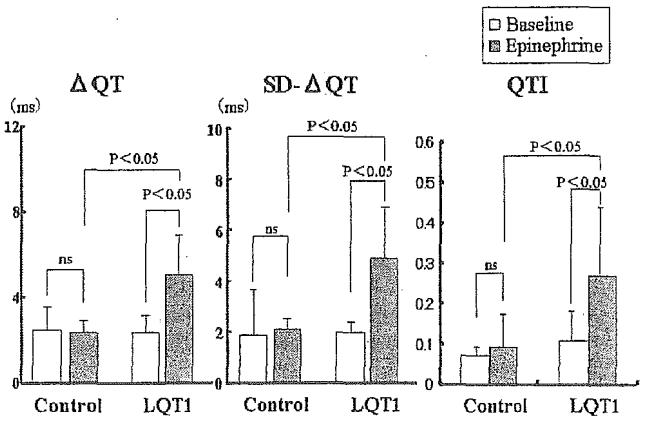

Figure 6 Comparison of ΔQT, SD-ΔQT, and QTI before and after epinephrine infusion between LQT1 and control groups. No significant differences in ΔQT, SD-ΔQT, and QTI were observed between the two groups under baseline conditions. Epinephrine increased ΔQT, SD-ΔQT, and QTI in the LQT1 group but not in the control group.

important part of the T wave and may underestimate a repolarization abnormality in patients with LQTS.

Our novel method, the cross-correlation method, analyzed beat-by-beat "time-lag" comparing the template of the latter part of the T wave, thus better description of QT interval could be assessed independently of complicated TU wave morphology. Beat-by-beat T-wave and QT variability measured by the cross-correlation method is not synonymous with T-wave alternans and could be analyzed more stably than with the standard tangential method even during epinephrine infusion in the two patient groups (Figures 4 and 5).

Variability of repolarization in LQT1 syndrome

Physical exercise and strong emotion precipitate syncope and sudden cardiac death in patients with congenital LQTS.[2] Experimental models[17,18] of LQTS and clinical studies[19] suggest catecholamine-enhanced early afterdepolarization and triggered activity play a pivotal role in the genesis of QT prolongation and TdP.

TWA is a well-known ECG phenomenon often associated with the development of cardiac arrhythmias,[20] particularly in the setting of acquired and congenital LQTS.[6,7] The phenomenon previously was described as QT interval variability or T-wave lability by the pronounced changes in T-wave morphology.[21,22] The mechanism underlying catecholamine-provoked T-wave lability is unclear. It also is clearly different from microvolt (μV-TWA). The μV-TWA shows no definite periodicity of the T-wave changes on surface ECG. Exercise-induced μV-TWA was not significantly different between genotype carriers and noncarriers in a study involving a large single kindred with LQTS.[21,23]

An experimental study by Shimizu and Antzelevitch[7] suggested that TWA observed at rapid rates under long QT conditions largely results from alternation of the M-cell action potential duration, leading to exaggeration of transmural dispersion of repolarization during alternating beats and thus the potential for development of TdP. Their data also suggested that unlike transient forms of TWA that damp out quickly and depend on electrical restitution factors, the steady-state electrical and mechanical alternans appears to largely result from beat-to-beat alternans of intracellular calcium cycling.

Our study showed that beat-by-beat QT variability was accentuated by epinephrine infusion only in LQT1 patients, indicating that variability of repolarization is made pronounced by sympathetic stimulation in patients of LQT1 but not in normal controls. Our result supports the clinical manifestation that life-threatening arrhythmia, such as TdP, often is observed under increased sympathetic activity in LQTS, especially in LQT1 patients.[23]

However, the numbers of families and individuals in the present study were small and limited the number of LQT1 patients. Therefore, our data may be limited to LQT1 and not applicable to LQTS patients with other genotypes.

Relationship among QT variability, QT interval, and heart rate

In the present study, QT variability after epinephrine was correlated with QTc interval after epinephrine but not with heart rate. The μV-TWA is a highly heart rate-dependent parameter and can be assessed invasively by arterial pacing or noninvasively by exercise. Heart rate threshold for induction of the μV-TWA was reported at 110 bpm in healthy adults.[24] No relationship between QT variability and heart rate after epinephrine was observed in this study, probably because of the lesser increase in heart rate in both groups.

Conclusion

Our data showed that beat-by-beat QT variability analyzed by the cross-correlation method was greater in LQT1 patients during sympathetic stimulation, suggesting that sympathetic stimulation accentuates beat-by-beat alternans of repolarization in the LQT1 syndrome.

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Artificial Baroreflex

Clinical Application of a Bionic Baroreflex System

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Background—We proposed a novel therapeutic strategy against central baroreflex failure: implementation of an artificial baroreflex system to automatically regulate sympathetic vasomotor tone, ie, a bionic baroreflex system (BBS), and we tested its efficacy in a model of sudden hypotension during surgery.

Methods and Results—The BBS consisted of a computer-controlled negative-feedback circuit that sensed arterial pressure (AP) and automatically computed the frequency (STM) of a pulse train required to stimulate sympathetic nerves via an epidural catheter placed at the level of the lower thoracic spinal cord. An operation rule was subsequently designed for the BBS using a feedback correction with proportional and integral gain factors. The transfer function from STM to AP was identified by a white noise system identification method in 12 sevoflurane-anesthetized patients undergoing orthopedic surgery involving the cervical vertebrae, and the feedback correction factors were determined with a numerical simulation to enable the BBS to quickly and stably attenuate an external disturbance on AP. The performance of the designed BBS was then examined in a model of orthostatic hypotension during knee joint surgery (n=21). Without the implementation of the BBS, a sudden deflation of a thigh tourniquet resulted in a 17±3 mm Hg decrease in AP within 10 seconds and a 25±2 mm Hg decrease in AP within 50 seconds. By contrast, during real-time execution of the BBS, the decrease in AP was 9±2 mm Hg at 10 seconds and 1±2 mm Hg at 50 seconds after the deflation.

Conclusions—These results suggest the feasibility of a BBS approach for central baroreflex failure. (***Circulation.*** **2006; 113:634-639.)**

Key Words: baroreceptors ■ blood pressure ■ computers ■ electrical stimulation ■ nervous system, sympathetic

The arterial baroreflex acts to maintain cerebral perfusion by quickly attenuating the effect of an external disturbance, such as the assumption of an upright position, on arterial pressure (AP).[1–4] Therefore, functional restoration of dynamic properties of the arterial baroreflex is essential for the treatment of patients with various syndromes of baroreflex failure,[5] including Shy-Drager syndrome,[6–9] baroreceptor deafferentation,[10,11] and traumatic spinal cord injuries.[12,13] However, most commonly used interventions, including salt loading,[14,15] cardiac pacing,[16,17] and adrenergic agonists,[18,19] can neither restore nor reproduce the functioning of the native vasomotor center, and most affected patients remain bedridden.

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We recently developed a framework for identifying an operational rule of the vasomotor center and a prototype of a bionic baroreflex system (BBS) in rats.[20–22] The BBS consisted of a negative-feedback system controlled by a computer (ie, the artificial vasomotor center) that sensed AP and automatically computed the frequency of a pulse train required to stimulate sympathetic efferent nerves through a pair of wire electrodes placed in the celiac ganglion. Previous experimental work demonstrated that the BBS restored native baroreflex function in rats with central baroreflex failure; however, an applicable neural interface with quick and effective controllability of AP is required for application of this technology in the clinical setting. The goal of the present study was to determine the efficacy of a novel bionic technology for the intraoperative restoration of AP in the context of central baroreflex failure and to validate this technology in a clinical model of orthostatic hypotension.

Methods

All studies were approved by the institutional review committee, and all subjects gave informed consent.

Theoretical Considerations

As previously described,[20–22] the principle of the BBS is based on a negative-feedback mechanism (Figure 1). The instantaneous AP is measured by a pressure transducer connected to a computer that functions as a controller or artificial vasomotor center. Instead of the disabled native vasomotor center, the controller automatically exe-

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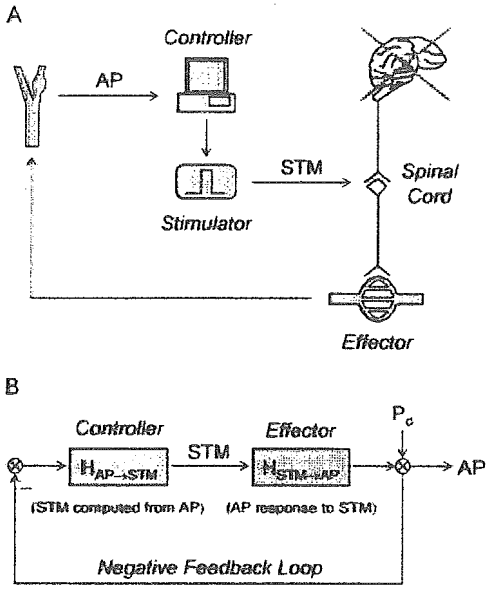

Figure 1. Schematic illustration (A) and block diagram (B) of a BBS. In the context of central baroreflex failure, the BBS automatically computes the frequency (STM) of a pulse train to stimulate sympathetic nerves through an epidural catheter placed at the level of lower thoracic spinal cord, while simultaneously sensing the change in AP. $H_{AP\rightarrow STM}$ denotes a transfer function for the controller functioning as an artificial vasomotor center. $H_{STM\rightarrow AP}$ is a transfer function showing the dynamic response of AP to STM. The overall transfer function of the BBS is given by $H_{AP\rightarrow STM}\times H_{STM\rightarrow AP}$. Therefore, the effect of an external disturbance (P_d) on AP is attenuated to $1/(1+H_{AP\rightarrow STM}\times H_{STM\rightarrow AP})$.

cutes real-time operations that determine the frequency of electrical stimulation (STM) required to minimize the effect of an external disturbance (P_d) on AP and then commands an electrical stimulator to deliver a stimulus of the same frequency to the vasomotor sympathetic nerves via epidural-catheter electrodes placed at the lower thoracic level of the spinal cord. The lower thoracic level was selected as the site for the neural interface of the BBS because the abdominal splanchnic vascular bed is a major effector mechanism for the arterial baroreflex.[23-25]

According to a classic feedback-control theory, ie, feedback correction with proportional and integral gain factors,[26,27] the following algorithm was used to program the controller for the calculation of STM in the frequency domain:

$$H_{AP\rightarrow STM}=K_p+\frac{K_i}{2\pi fj} \quad (1)$$

where $H_{AP\rightarrow STM}$ is a transfer function from AP to STM, K_p is the proportional correction factor, K_i is the integral correction factor, and j is the imaginary unit. The proportional factor determines the feedback amplification based on the absolute value of the instantaneous control error due to P_d, and the integral factor adjusts the feedback amplification based on the cumulative value of the instantaneous control error. Therefore, STM is computed as follows:

$$STM=-AP\cdot H_{AP\rightarrow STM} \quad (2)$$

and AP is also expressed as follows:

$$AP=STM\cdot H_{STM\rightarrow AP}+P_d \quad (3)$$

where $H_{STM\rightarrow AP}$ denotes the frequency response of AP to STM. From Equations 2 and 3, the effect of P_d on AP is estimated as follows:

$$AP=\frac{1}{1+H_{AP\rightarrow STM}\cdot H_{STM\rightarrow AP}}P_d \quad (4)$$

Thus, if $H_{AP\rightarrow STM}\cdot H_{STM\rightarrow AP}$ is far larger than unity, the BBS can nullify the effect of P_d on AP.

Subjects and Experimental Protocols

A total of 33 patients (46 to 84 years old, 19 males) who underwent orthopedic operations were enrolled in the present study. Ten patients had hypertension, and 4 had diabetes mellitus. None of the subjects had frequent ectopic beats or atrial fibrillation. After induction anesthesia with propofol, an endotracheal tube was introduced orally. The patients were mechanically ventilated with 67% nitrous oxide and 1.5% to 2% end-tidal sevoflurane in oxygen during experimental protocols, while end-tidal carbon dioxide was maintained at 35 to 38 mm Hg. An arterial catheter was placed in the radial artery for AP measurement. To record central venous pressure (CVP), a central venous catheter was placed in the femoral vein, and the tip of the catheter was advanced into the inferior vena cava just above the diaphragmatic level. Furthermore, an epidural catheter was placed percutaneously, and the tip, which contained a pair of electrodes (Unique Medical, Tokyo; interelectrode distance 15 mm), was placed at the level of Th_{9-11}. Placement of the central venous catheter and the epidural catheter was verified by chest radiograph.[28]

Before making an incision of affected areas, we performed 2 different protocols in separate groups of patients. In the first group of patients (n=12, 46 to 76 years old, 7 males) undergoing operations for cervical spondylosis and canal stenosis, the averaged $H_{STM\rightarrow AP}$ was estimated and the $H_{AP\rightarrow STM}$ was designed parametrically with Equation 1 to minimize the effect of P_d on AP. After we programmed the designed $H_{AP\rightarrow STM}$ into the computer, the efficacy of the BBS was tested against the rapid progressive hypotension induced by use of a thigh tourniquet[29-31] in the second group of patients (n=21, 64 to 84 years old, 12 males) undergoing operation for knee joint osteoarthritis. During each protocol, the muscle twitches induced by spinal cord stimulation were prevented by the intravenous administration of vecuronium bromide. Analgesia for the pain provoked by spinal cord stimulation and tourniquet inflation was provided by intravenous injection of fentanyl citrate. In a preliminary study, the validity of the analgesic preparation was confirmed for the experimental protocols, and the safety of spinal cord stimulation for 20 minutes was verified.

Estimation of Transfer Function From STM to AP

To characterize the dynamic nature of the AP response to STM, ie, $H_{STM\rightarrow AP}$, the lower thoracic sympathetic nerves were randomly stimulated for 15 minutes while we recorded AP. According to a white noise method for system identification, the STM was altered between 0 and 20 Hz every 4 seconds. The pulse width of electrical stimuli was fixed at 0.1 ms. The stimulation current was adjusted for each patient so as to produce a pressor response of ≈10 mm Hg at 20 Hz. This resulted in an average current of 15±4 (mean±SD) mA. The electrical signals of STM and AP were digitized at 100 Hz. As described previously,[20-22] the transfer function from STM to AP, $H_{STM\rightarrow AP}$, was estimated with a fast Fourier transform algorithm. Finally, the average of $H_{STM\rightarrow AP}$ among 12 patients was calculated.

Design of Artificial Vasomotor Center

With substitution of the averaged $H_{STM\rightarrow AP}$ for Equation 4, the instantaneous AP response to P_d was simulated numerically, and a stepwise decline with an amplitude of 20 mm Hg was imposed on the BBS. While the feedback parameters of $H_{AP\rightarrow STM}$, ie, K_p and K_i, were altered, the effect of the parameters on the AP response was investigated. Finally, the parameters that enabled the BBS to quickly and stably minimize the effect of P_d on AP were determined.

Efficacy of BBS in a Clinical Model of Transient Hypotension

The performance of the BBS was evaluated in a clinical model of rapid transient hypotension (n=21). Rapid hypotension was evoked by the sudden deflation of a thigh tourniquet, which is widely used to achieve bloodless dissection during total knee arthroplasty.[29-31] Acute hypotension immediately after tourniquet release is a well-