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. 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 involving the inferoposterior wall of the left ventricle and its reperfusion, such as those that occur with acute 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...
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-vascular 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; Esotec, 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 V2, aVF, and V5 were continuously monitored from rest through the recovery period. Arte-

Hypertension, n
LVEF, %
Previous MI,

Men/women, n
Age, yr

H1180 PRONOUNCED HR VARIABILITY IN INFERIOR ISCHEMIA

<table>
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<th>Table 1. Patient characteristics</th>
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<td>RCA</td>
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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.

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 resulted 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/τ, where A and B are constants, 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 Scheffe’s test for intergroup and intragroup comparisons. Student’s unpaired and paired t-tests, linear regression analysis, multiple linear regression analysis, and χ2-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

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<th>Table 2. Exercise test results</th>
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<td>RCA</td>
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<td>Exercise time, s</td>
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Values are means ± SD. HR, heart rate; SBP, systolic blood pressure; n, no. of subjects.
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. 3A). %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. 3B).

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,
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 $\Delta$RR 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 $\Delta$RR 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 ($58 \pm 11$ vs. $64 \pm 8$ yr, $P < 0.01$) and had a significantly lower HR at rest ($61 \pm 10$ vs. $70 \pm 12$ beats/min, $P < 0.01$) and peak HR ($117 \pm 19$ vs. $139 \pm 18$ beats/min, $P < 0.01$) compared with those without this phenomenon.

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 $\Delta$RR 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 $\Delta$RR (60–90 s).

![Fig. 4](image1.png)

**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; $n = 51$).

![Fig. 5](image2.png)

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

![Fig. 6](image3.png)

**Fig. 6.** Scatterplots of $\Delta$RR at 60–90 s plotted separately for each patient in the RCA (left) and LAD (right) stenosis groups. Pronounced HRV (defined as $\Delta$RR $>12$ 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, $\Delta RR$ early after exercise was significantly attenuated (from $22 \pm 14$ to $9 \pm 5$ ms for $60–90$ s, from $25 \pm 12$ to $11 \pm 5$ ms for $90–120$ s, and from $27 \pm 13$ to $13 \pm 5$ ms for $120–150$ s, all $P < 0.05$; Fig. 7). The time constant was concordantly prolonged (from $73 \pm 21$ to $96 \pm 30$ 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 or local 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 $\Delta RR$ and $\%\Delta RR$ 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 “refusion 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 toward 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 ARR > 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 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., 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.

REFERENCES


GRANTS

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