CARDIOVASCULAR MEDICINE

Enhanced vagal modulation and exercise induced ischaemia of the inferoposterior myocardium

T Kawasaki, A Azuma, T Kuribayashi, T Taniguchi, S Asada, T Kamitani, S Kawasaki, H Matsubara, H Sugihara

Heart 2006;92:325–330. doi: 10.1136/hrt.2005.063230

See end of article for authors' affiliations

Correspondence to:
Dr Tatsuya Kawasaki,
Department of Cardiology,
Matsushita Memorial
Hospital, Sotojima 5-55,
Moriguchi, Osaka 570-
8540, Japan; js-k@
wf6.so-net.ne.jp

Accepted 2 June 2005
Published Online First
6 June 2005

Objective: To determine whether the Bezold-Jarisch reflex or enhancement of vagal nerves, which are preferentially distributed in the inferoposterior myocardium, results from exercise induced ischaemia in this region.

Methods: On the basis of exercise myocardial scintigraphy and coronary angiography, 145 patients were classified as follows: group I, 34 patients with inferoposterior ischaemia; group A, 32 with anterior ischaemia; and control, 79 without ischaemia. The relation between ischaemic areas and ECG leads with ST segment changes and vagal modulation assessed by heart rate variability (HRV) (high frequency (HF) component (0.15–0.40 Hz) and coefficient of HF component variance (CCV_{HF}), which is the square root of HF divided by mean RR interval) were assessed.

Results: The rate of ST segment depression in any lead did not differ between group I and group A. HF and CCV_{HF} were similar before exercise but higher in group I than in group A and the control group after exercise (mean (SEM) HF: 94 (17) ms², 41 (7) ms², and 45 (6) ms², respectively, $p = 0.021$; CCV_{HF}: 1.18 (0.09)%, 0.81 (0.07)%, and 0.89 (0.05)%, $p = 0.0053$). Furthermore, the percentage change in CCV_{HF} before and after exercise was higher in group I than in group A or controls (mean (SEM) 22 (10)%, –24 (4)%, and –21 (3)%, $p < 0.0001$). The optimal cut off for diagnosis of inferoposterior ischaemia was –5% with a sensitivity of 74%, specificity 75%, and accuracy 75%.

Conclusions: Vagal modulation as assessed by HRV analysis was enhanced in association with exercise induced inferoposterior ischaemia. Exercise ECG testing combined with HRV analysis would increase accuracy in the diagnosis of ischaemic areas in selected patients with angina pectoris.

Acute myocardial infarction in the left ventricular (LV) inferoposterior wall is often associated with transient hypotension along with sinus bradycardia.^{1–3} The cardioinhibitory response or Bezold-Jarisch reflex has been thought to be induced by enhanced afferent vagal activities, as the vagal nerves are preferentially distributed in the inferoposterior wall of the LV.^{3–5} This phenomenon has been reproduced by experimental coronary occlusion in animals.^{6–7}

Heart rate is under the influence of the balance between vagal and sympathetic nerve activities in the cardiovascular system. Analysis of heart rate variability (HRV) has attracted special attention in the estimation of vagal modulation.^{8–12} We determined the site of ischaemia based on exercise technetium-99m-tetrofosmin myocardial scintigraphy and coronary angiography. Then, by using HRV, we analysed the alteration of vagal modulation associated with exercise induced ischaemia of the LV inferoposterior wall in comparison with that of the LV anterior wall. We further compared the regional difference in HRV with ST segment changes on the ECG.

METHODS

Study population

We enrolled 283 consecutive outpatients who were suspected of having angina pectoris and had undergone exercise testing with ^{99m}Tc-tetrofosmin myocardial scintigraphy at Matsushita Memorial Hospital from November 2001 to August 2003. No patient had either a documented history of myocardial infarction or abnormal Q waves on ECG at rest. We excluded 32 patients with diabetes mellitus, 23 who were taking any cardiovascular medications, four with non-sinus rhythm, one with left bundle branch block, two with right

bundle branch block, three with LV hypertrophy with strain on ECG at rest because the ECG change during exercise was equivocal,¹³ three with uraemia because of interference with HRV,^{10–14} 12 with cardiac arrhythmias $\geq 1\%$, five with a technically inadequate ECG tracing for HRV analysis during the exercise test,¹⁵ two who chose not to undergo cardiac catheterisation study, and eight with no angiographically detectable coronary stenosis consistent with reversible defects on scintigraphy. We further excluded 21 patients with reversible scintigraphic defects in multiple sites: eight with reversible defects in the LV lateral wall and 14 with non-reversible defects possibly caused by silent myocardial infarction.

Lastly, we divided the remaining 145 patients into three groups based on scintigraphic findings: group I, 34 patients with reversible defects located in the LV inferoposterior wall; group A, 32 patients with reversible defects located in the LV anterior wall; and a control group comprising 79 patients with no reversible defects in the LV. All patients of group I and group A underwent selective coronary angiography. This study was approved by our institutional ethic committees, and informed consent for the study was obtained from all participants.

Exercise test

An electrically operated bicycle ergometer (Ergomed 840L; Siemens, Erlangen, Germany) was used under continuous

Abbreviations: CCV_{HF}, coefficient of high frequency component variance; HF, high frequency; HRV, heart rate variability; LV, left ventricular; RMSSD, root mean square of the differences between adjacent RR intervals; SPECT, single photon emission computed tomography

monitoring with 12 lead ECG (ML-4500; Fukuda Denshi, Tokyo, Japan). Blood pressure was measured with an arm cuff sphygmomanometer every two minutes or more (STBP-780B; Colin, Aichi, Japan). The exercise workload began with 25 W and was increased by 25 W every two minutes. The exercise test was finished at the achieved target heart rate, defined as 85% of the maximum predicted heart rate,¹⁶ or because of leg fatigue, chest pain, dyspnoea, ST segment depression ≥ 2 mm, or systolic blood pressure ≥ 250 mm Hg.¹³ After having achieved the peak workload, all patients cooled down for one minute at an exercise grade of 30 W.

Every exercise induced displacement of the ST segment was measured at 0.08 seconds after the J point over three consecutive beats. A positive exercise ECG was defined as horizontal or downsloping ST segment depression ≥ 1 mm or ST segment elevation ≥ 1 mm.¹⁷ A negative exercise ECG was defined as ST segment changes < 1 mm in achieving the target heart rate. The exercise ECG was inconclusive when patients did not reach the target heart rate in the absence of ischaemic ST segment changes.

HRV analysis

A single lead ECG (lead II) during exercise testing was obtained on line from the continuous monitoring equipment for 12 lead ECG. Beat to beat heart rate data were sampled at a frequency of 500 Hz by a personal computer and software (MemCalc/Tarawa; GMS, Tokyo, Japan). This system can compute five spectral components by means of the maximum entropy method according to the data obtained¹⁸: ultralow frequency component (< 0.003 Hz), very low frequency component (0.003–0.04 Hz), low frequency component (0.04–0.15 Hz), high frequency (HF) component (0.15–0.40 Hz), and low frequency to HF ratio. Of these, HF was used in the estimation of vagal modulation.^{8–12}

Our system requires ≥ 30 seconds, preferably ≥ 1 minute,¹⁰ to determine the HF component. Hence, HF was extracted every minute and averaged for five minutes immediately before exercise and immediately after a cool down period following exercise. For the HF component we used the absolute value of power (ms^2) without normalisation because normalisation requires the very low frequency component, a dubious measure on a short term recording for ≤ 5 minutes.¹⁰

We adjusted the magnitude of the HF component every minute by the average RR interval to determine the coefficient of HF component variance (CCV_{HF}), which is the square root of HF divided by mean RR interval.^{19–20} Furthermore, by using measured RR intervals, we calculated the root mean square of the differences between adjacent RR intervals (RMSSD), which also can be obtained from a short term recording and predominantly reflects vagal modulation.¹⁰

Single photon emission computed tomography

^{99m}Tc-tetrofosmin of 370 MBq or 740 MBq was injected intravenously one minute before the termination of exercise or four hours later after exercise, respectively. Single photon emission computed tomography (SPECT) was obtained 30 minutes after injection of a tracer with a digital gamma camera (Starcam 3000XC/T; GE Medical Systems, Waukesha, Wisconsin, USA). SPECT images were estimated on the short axis slices at the apical, mid, and basal LV levels in combination with the apical long axis views.^{21–22} The apical short axis section was divided into four segments (anterior, septal, inferior, and lateral), and two other short axis sections were divided into six segments (anterior, anterosseptal, inferoseptal, inferior, inferolateral, and anterolateral).

The anterior and septal segments at the apical level and the anterior and anterosseptal segments at the mid and basal LV levels were assigned to the territory of the left anterior descending artery; the inferior segments at the apical level and the inferior and inferoseptal segments at the mid and basal LV levels were assigned to the territory of the right coronary artery; and the lateral segments at the apical level and the anterolateral and inferolateral segments at the mid and basal LV levels were assigned to the territory of the left circumflex artery.²¹ A perfusion defect was restricted in one territory or covered multiple territories, reflecting multiple coronary lesions.^{21–23}

Two experienced observers who had no information on HRV analysis semiquantified the degree of tracer uptake in each segment by means of a four point scoring system: 0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced. Disagreements between these observers were resolved by consensus. A score of ≥ 2 on stress images was considered abnormal; abnormal perfusion with complete or partial normalisation on rest images was classified as a reversible defect; and abnormal perfusion with no change was classified as a non-reversible or fixed defect.^{21–24} Furthermore, a summed stress score and a summed rest score were calculated by adding the 16 segment scores of the stress and rest images, respectively. A summed difference score was derived as the difference between stress and rest scores.

Coronary angiography

The Judkins technique was used. The mean (SD) interval between the exercise test and coronary angiography was 6 (3) weeks. Coronary artery stenosis was quantified by means of edge detection software (Advantx DLX; GE Medical Systems); a diameter reduction $\geq 50\%$ was considered significant.

Statistical analysis

Categorical variables were compared by the χ^2 test or Fisher's exact test as appropriate. Continuous variables were expressed as mean (SD) and compared between the three groups by one way analysis of variance followed by Scheffe's multiple comparison test. HRV variables were expressed as mean (SEM) and compared by the Kruskal-Wallis test followed by the Bonferroni correction for multiple comparison test. Furthermore, analysis of covariance was applied to correct the influencing factors on intergroup differences of HRV; the variables with $p < 0.1$ in analysis of variance were used as possible influencing factors. Spearman correlation coefficients were used to determine the correlations of HRV variables with scintigraphic scores. Receiver operating characteristic curves were analysed to determine the best cut off point. A probability value of $p < 0.05$ was considered significant.

RESULTS

Basic features and haemodynamic measurements

Table 1 shows that the three groups were well matched with respect to baseline characteristics, except that systemic hypertension was more common in group I and group A. The maximum workload tended to be lower in group I and group A than in the control group, with no statistical difference. Mean systolic blood pressure was significantly higher both before and after exercise testing in group I and group A than in controls. Mean and maximum heart rates during exercise were both lower in groups I and A than in controls. Haemodynamic parameters did not differ significantly between group I and group A during the exercise test.

Table 1 Baseline characteristics and haemodynamic parameters during exercise testing of patients with inferoposterior ischaemia (group I) and with anterior ischaemia (group A) compared with controls

	Control (n = 79)	Group I (n = 34)	Group A (n = 32)	p Value
Age (years)	60 (7)	61 (10)	61 (10)	0.68
Men	66 (84%)	28 (82%)	27 (84%)	0.98
Body mass index (kg/m ²)	24.0 (5.1)	24.6 (2.6)	24.1 (3.1)	0.76
Systemic hypertension	23 (29%)	19 (56%)*	18 (56%)*	0.0044
Hyperlipidaemia	43 (54%)	16 (47%)	20 (63%)	0.45
Current smoking	22 (28%)	15 (44%)	8 (25%)	0.16
Maximum workload (W)	104 (30)	91 (31)	91 (22)	0.057
Maximum rate–pressure product ($\times 10^3$)	27.6 (4.6)	26.1 (4.3)	26.4 (4.9)	0.27
Before exercise				
Mean heart rate (beats/min)	75 (11)	75 (13)	74 (11)	0.85
Mean systolic BP (mm Hg)	146 (17)	158 (21)*	158 (28)*	0.0032
Mean diastolic BP (mm Hg)	91 (11)	90 (16)	89 (14)	0.89
During exercise				
Mean heart rate (beats/min)	109 (10)	103 (12)*	104 (11)*	0.01
Maximum heart rate (beats/min)	137 (14)	124 (14)**	125 (16)**	<0.0001
Maximum systolic BP (mm Hg)	202 (24)	211 (24)	210 (24)	0.11
Maximum diastolic BP (mm Hg)	104 (17)	106 (21)	104 (17)	0.66
After exercise				
Mean heart rate (beats/min)	88 (12)	84 (15)	88 (15)	0.25
Mean systolic BP (mm Hg)	151 (24)	170 (31)**	170 (29)**	0.0004
Mean diastolic BP (mm Hg)	87 (14)	90 (12)	93 (18)	0.16

Data are mean (SD) or number (%).

*p<0.05, **p<0.01 compared with control group.

BP, blood pressure.

Exercise ECG

Among all 145 patients, 130 (90%) had a normal ECG at rest and 15 (10%) had slight ST segment depression. Only one patient had ST segment elevation during exercise. The rate of positive exercise ECG did not differ between group I and group A (65% v 66%), although it was significantly higher in the two groups than in the control group (32%, $p = 0.0006$). Exercise ECG enabled us to detect myocardial ischaemia as shown by SPECT with a sensitivity of 80%, specificity 59%, accuracy 69%, positive predictive value 63%, and negative predictive value 77%. The rate of ST segment depression ≥ 1 mm during exercise did not differ between group I and group A in leads II, III, aVF (71% v 75%, $p = 0.69$), leads I and aVL (0% v 6%, $p = 0.25$), leads V1–4 (71% v 53%, $p = 0.14$), and leads V5 and V6 (71% v 66%, $p = 0.67$).

Coronary angiography

Of 34 patients in group I who had significant stenosis in the right coronary artery, three also had stenosis in the left anterior descending coronary artery (58%, 65%, and 72% diameter stenosis) and two had stenosis in the left circumflex coronary artery (56% and 68%). These five patients were not excluded from group I because reversible defects were located in the LV inferoposterior wall on exercise scintigraphy and all HRV variables of the five patients did not differ significantly from those of the remaining 29 patients (for example, CCV_{HF} before exercise: 1.13 (0.21)% v 1.15 (0.14)%; CCV_{HF} after exercise: 1.17 (0.12)% v 1.18 (0.10)%).

Of 32 patients in group A who had significant stenosis in the left anterior descending coronary artery, three had stenosis in the right coronary artery (62%, 78%, and 68%)

Figure 1 Root mean square of the differences between adjacent RR intervals (RMSSD), high frequency (HF) component, and coefficient of HF component variance (CCV_{HF}) before and after exercise in patients with inferoposterior ischaemia (group I) and with anterior ischaemia (group A). Data are mean (SEM). * $p < 0.05$, ** $p < 0.01$ compared with controls or group A.

Figure 2 Absolute changes in RMSSD, HF, and CCV_{HF} from before to after exercise. Medians and 10th, 25th, 75th, and 90th centiles are shown. * $p < 0.01$ compared with controls or group A.

Figure 3 Percentage changes in RMSSD, HF, and CCV_{HF} from before to after exercise. Medians and 10th, 25th, 75th, and 90th centiles are shown. * $p < 0.05$, ** $p < 0.01$ compared with controls or group A.

and three had stenosis in the left circumflex coronary artery (54%, 81%, and 62%). These six patients were not excluded from group A; they had reversible defects in the LV anterior wall and their HRV did not differ significantly from the others' (for example, CCV_{HF} before exercise: 1.08 (0.14)% ν 1.06 (0.10)%; CCV_{HF} after exercise: 0.83 (0.12)% ν 0.80 (0.08)%).

HRV analysis

All HRV variables were similar in the three groups before exercise but were significantly higher in group I than in group A and in controls after exercise (fig 1). Figure 2 shows absolute changes (value after exercise minus value before exercise) and fig 3 shows percentage changes (absolute change divided by value before exercise, expressed as a percentage) in HRV parameters. The absolute change in CCV_{HF} and the percentage change in RMSSD, HF, and CCV_{HF} were higher in group I than in group A and in controls, who had the greatest percentage change in CCV_{HF} (mean (SEM) 22 (10)%, -24 (4)%, and -21 (3)%, respectively, $p \leq 0.0001$). Analysis of covariance, with maximum workload and mean systolic blood pressure after exercise as covariates, showed significant intergroup differences in the percentage change in CCV_{HF} ($p = 0.024$). The percentage change in CCV_{HF} was not significantly correlated with summed stress score ($r_s = -0.033$, $p = 0.85$), summed rest score ($r_s = 0.14$, $p = 0.42$), and summed difference score ($r_s = 0.15$, $p = 0.39$). The receiver operating characteristic curve of the percentage change in CCV_{HF} for the detection of inferoposterior ischaemia showed that the optimal cut off was -5% (fig 4). This cut off point yielded good diagnostic value of the presence of inferoposterior ischaemia with a sensitivity of 74%, specificity 75%, accuracy 75%, positive predictive value 47%, and negative predictive value 91%.

DISCUSSION

The present study showed that HRV variables were altered in association with exercise induced ischaemia of the LV inferoposterior wall. HRV analysis can partially distinguish vagal modulation from autonomic nervous control in the

cardiovascular system; vagal activities are the major contributor to the HF component and RMSSD.¹⁰⁻¹² Accordingly, we may safely consider that vagal modulation was enhanced by exercise induced inferoposterior ischaemia. A similar cardioinhibitory response or Bezold-Jarisch reflex has been observed in cardiac events injuring the inferoposterior wall such as acute myocardial infarction,^{1,2} experimental coronary occlusion,⁴⁻⁶ coronary spasm,³ ischaemia induced by dobutamine stress testing,²⁵ or intracoronary injection of contrast media.²⁶ This reflex has been explained by the preferential distribution of cardiac receptors and afferent vagal pathways in the LV inferoposterior wall.³⁻⁵

Few data on the vagal enhancement associated with ischaemia during exercise are available. Miller *et al*²⁷ reported that seven patients with significant narrowing of the right coronary artery displayed sinus deceleration defined as ≥ 5 beats/min during exercise in about 40 000 consecutive exercise tests. Considering that Miller *et al*²⁷ in their study

Figure 4 Receiver operating characteristic curve for the detection of inferoposterior ischaemia obtained from exercise related percentage changes in CCV_{HF} . The optimal cut off point was -5%.

must have enrolled far more patients with right coronary lesions, the prevalence of sinus deceleration during exercise may be very low in general, even in patients with right coronary lesions. In our study, no patients exhibited sinus deceleration during exercise, which suggests the difficulty in estimating vagal activities by means of heart rate change. This difficulty may be explained by the physiological conditions during exercise—that is, a decrease in heart rate by enhanced vagal activities may be offset by simultaneous sympathetic activation provoked by exercise.²⁸

Cole *et al*²⁹ examined heart rate recovery after exercise in 2428 adults referred for their first symptom limited exercise test and suggested that recovery by ≤ 12 beats during the first minute was a potent predictor of overall mortality independent of standard cardiovascular risk factors, medications, exercise capacity, etc. Imai *et al*³⁰ used pharmacological autonomic nerve blockades to clarify that vagal reactivation was the principal determinant of post-exercise heart rate recovery during the first 30 seconds in healthy adults. In our study, however, heart rate after exercise did not differ significantly between the three groups, although vagal modulation in group I was more activated after exercise. Another finding in the study by Cole *et al*²⁹ was that abnormal ST segment response or angina during exercise was not associated with the delay of heart rate recovery; however, in their study they did not classify the patients into subgroups according to ischaemic areas. Heart rate recovery may not be sensitive enough to detect enhanced vagal activities caused by inferoposterior ischaemia, suggesting that there is room for examining the vagal modulation by means of HRV analysis during exercise test.

Methodological considerations

RR intervals during recovery are non-stationary time series, and this trend influences HRV variables.^{10 15 31} In general, HRV is evaluated by time domain methods consisting of statistical and geometric patterns or frequency domain methods. HRV variables calculated by the geometric pattern are relatively insensitive to the analytical quality of the time series of RR intervals.³² Geometric analysis, however, needs a reasonable number of RR intervals to construct the geometric pattern.¹⁰ In practice, geometric analysis should be based on recordings of heart rate of at least 20 minutes but preferably 24 hours,¹⁰ suggesting that the current geometric methods are inappropriate to assess short term changes in HRV, such as exercise related alterations. Thus, we used HRV variables calculated by time domain methods of statistical pattern and frequency domain methods. These selected variables can be calculated from short term recordings and predominantly reflect vagal modulation.¹⁰

Tulppo *et al*³¹ studied beat to beat heart rate dynamics by plotting each RR interval (Poincaré plot) during exercise with the help of pharmacological autonomic nerve blockade. They reported that quantitative two dimensional vector analysis of the Poincaré plot, based on geometric methods and useful for relatively short term recordings, may provide meaningful information on vagal modulation of RR interval dynamics. The present change in CCV_{HF}, determined by adjustment of the HF component by the RR interval, seemed to be similar to that in two dimensional vector analysis of a Poincaré plot.¹⁵ Furthermore, in our present study, the influence of the trend that RR intervals are non-stationary time series after exercise may have been reduced by analysing the HRV after a post-peak workload cool down period and by shortening the time interval by up to one minute.

Clinical implications

ST segment depression on an exercise ECG suggests the presence of coronary artery disease.¹³ However, whether ST

segment depression during exercise testing provides information as to which myocardial portion was involved seems controversial.^{33 34} In our patients with angina pectoris, the ST segment was not necessarily depressed in the ECG leads reflecting the area of ischaemia as shown by ^{99m}Tc-tetrofosmin myocardial scintigraphy. On the other hand, the present study showed that alterations of HRV variables, such as percentage change in CCV_{HF}, were exclusively associated with exercise induced ischaemia of the LV inferoposterior wall. Thus, exercise testing combined with HRV analysis will improve the accuracy of ECG diagnosis of ischaemic areas in selected patients with angina pectoris.

Study limitations

This study cohort was highly selected; patients with myocardial infarction or lateral ischaemia who had diabetes mellitus or were taking any medication were excluded. This selectiveness may have influenced the predictive accuracy of the percentage change in CCV_{HF}. Furthermore, the percentage change in CCV_{HF} had good negative predictive value for the detection of inferoposterior ischaemia but the positive predictive value was not high enough. We did not measure respiratory parameters; the altered respiratory pattern associated with exercise may have important neural and non-neural effects on the HRV signal, which cannot be distinguished even by cross spectral analysis of RR intervals and the respiratory signal.^{10 35} We analysed post-exercise HRV for five minutes immediately after a one minute cool down period after peak exercise was achieved; the optimal timing or period of extracted HRV variables after exercise remains to be elucidated. Enhancement of vagal modulation was not associated with a significant blood pressure decrease. We measured blood pressure at least every two minutes; more frequent measurement may have detected transient hypotension induced by afferent vagal enhancement. Control subjects were determined not to have myocardial ischaemia by means of exercise myocardial scintigraphy but not always in conjunction with coronary angiography. Exercise myocardial scintigraphy, however, has been reported to have good predictive value for the presence of coronary stenosis.²¹

Conclusion

Vagal modulation as assessed by HRV analysis was enhanced through exercise induced myocardial ischaemia of the LV inferoposterior wall. Exercise testing combined with HRV analysis will improve the accuracy of ECG diagnosis of ischaemic areas in selected patients with angina pectoris.

ACKNOWLEDGEMENTS

We thank Jun Maniwa, Nobuyuki Tanaka, and Kenji Takaki for their technical support with scintigraphic acquisitions.

Authors' affiliations

T Kawasaki, T Taniguchi, S Asada, T Kamitani, S Kawasaki, H Sugihara, Department of Cardiology, Matsushita Memorial Hospital, Osaka, Japan
A Azuma, H Matsubara, Department of Cardiovascular Medicine, Kyoto Prefectural University Graduate School of Medicine, Kyoto, Japan
T Kuribayashi, Kuribayashi Clinic of Cardiology, Fukuoka, Japan

Grants and disclosures: Neither sources of support nor conflicts of interest that require acknowledgement.

REFERENCES

- 1 Wei JY, Markis JE, Malagold M, *et al*. Cardiovascular reflexes stimulated by reperfusion of ischemic myocardium in acute myocardial infarction. *Circulation* 1983;67:796–801.
- 2 Webb SW, Adgey AA, Pantridge JF. Autonomic disturbance at onset of acute myocardial infarction. *BMJ* 1972;ii:89–92.
- 3 Mark AL. The Bezold-Jarisch reflex revisited: clinical implications of inhibitory reflexes originating in the heart. *J Am Coll Cardiol* 1983;1:90–102.

- 4 Zucker IH, Cornish KG. The Bezold-Jarisch in the conscious dog. *Circ Res* 1981;**49**:940-8.
- 5 Perez-Gomez F, Martin de Dios R, Rey J, et al. Prinzmetal's angina: reflex cardiovascular response during episode of pain. *Br Heart J* 1979;**42**:81-7.
- 6 Thoren PN. Activation of left ventricular receptors with nonmedullated vagal afferent fibers during occlusion of a coronary artery in the cat. *Am J Cardiol* 1976;**37**:1046-51.
- 7 Bishop VS, Peterson DF. The circulatory influences of vagal afferents at rest and during coronary occlusion in conscious dogs. *Circ Res* 1978;**43**:840-7.
- 8 Stein PK, Bosner MS, Kleiger RE, et al. Heart rate variability: a measure of cardiac autonomic tone. *Am Heart J* 1994;**127**:1376-81.
- 9 Stein PK, Ehsani AA, Domitrovich PP, et al. Effect of exercise training on heart rate variability in healthy older adults. *Am Heart J* 1999;**138**:567-76.
- 10 Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996;**93**:1043-65.
- 11 Pomeranz B, Macaulay RJ, Caudill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985;**248**:H151-3.
- 12 Koizumi K, Terui N, Kollai M. Effect of cardiac vagal and sympathetic nerve activity on heart rate in rhythmic fluctuations. *J Auton Nerv Syst* 1985;**12**:251-9.
- 13 Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on exercise testing). *J Am Coll Cardiol* 1997;**30**:260-311.
- 14 Akselrod S, Lishner M, Oz O, et al. Spectral analysis of fluctuations in heart rate: an objective evaluation of autonomic nervous control in chronic renal failure. *Nephron* 1987;**45**:202-6.
- 15 Tulppo MP, Mäkilä TH, Seppänen T, et al. Vagal modulation of heart rate during exercise: effects of age and physical fitness. *Am J Physiol* 1998;**274**:H424-9.
- 16 Sheffield LT. Graded exercise test for ischemic heart disease in exercise testing and training of apparently healthy individuals: a handbook for physicians. Texas: American Heart Association, 1975.
- 17 Colby J, Hakki AH, Iskandrian AS, et al. Hemodynamic, angiographic and scintigraphic correlates of positive exercise electrocardiograms: emphasis on strongly positive exercise electrocardiograms. *J Am Coll Cardiol* 1983;**2**:21-9.
- 18 Saito K, Koyama A, Yoneyama K, et al. A recent advance in time series analysis by maximum entropy method. Sapporo: Hokkaido University Press, 1994.
- 19 Hayano J, Sakakibara Y, Yamada M, et al. Decreased magnitude of heart rate spectral components in coronary artery disease: its relation to angiographic severity. *Circulation* 1990;**81**:1217-24.
- 20 Hayano J, Sakakibara Y, Yamada A, et al. Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. *Am J Cardiol* 1991;**67**:199-204.
- 21 Azzarelli S, Galassi AR, Foti R, et al. Accuracy of 99m Tc-tetrofosmin myocardial tomography in the evaluation of coronary artery disease. *J Nucl Cardiol* 1999;**6**:183-9.
- 22 Garcia EV, Van Train K, Maddahi J, et al. Quantification of rotational thallium-201 myocardial tomography. *J Nucl Med* 1985;**26**:17-26.
- 23 Kahn JK, McGhie I, Akers MS, et al. Quantitative rotational tomography with 201Tl and 99mTc 2-methoxyisobutyl-isonitrile: a direct comparison in normal individuals and patients with coronary artery disease. *Circulation* 1989;**79**:1282-93.
- 24 Chouraqui P, Maddahi J, Ostrzega E, et al. Quantitative exercise thallium-201 rotational tomography for evaluation of patients with prior myocardial infarction. *Am J Cardiol* 1990;**66**:151-7.
- 25 Emre A, Ersek B, Gursurer M, et al. Myocardial perfusion and angiographic findings in patients with paradoxical sinus deceleration during dobutamine technetium-99m sestamibi-gated SPECT imaging. *Cardiology* 1999;**92**:183-8.
- 26 Eckberg DL, White CW, Kioschos JM, et al. Mechanisms mediating bradycardia during coronary arteriography. *J Clin Invest* 1974;**54**:1455-61.
- 27 Miller TD, Gibbons RJ, Squires RW, et al. Sinus node deceleration during exercise as a marker of significant narrowing of the right coronary artery. *Am J Cardiol* 1993;**71**:371-3.
- 28 Stratton JR, Pfeifer MA, Halter JB. The hemodynamic effects of sympathetic stimulation combined with parasympathetic blockade in man. *Circulation* 1987;**75**:922-9.
- 29 Cole CR, Blackstone EH, Pashkow FJ, et al. Heart-rate recovery immediately after exercise as a predictor of mortality. *N Engl J Med* 1999;**341**:1351-7.
- 30 Imai K, Sato H, Hori M, et al. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *J Am Coll Cardiol* 1994;**24**:1529-35.
- 31 Tulppo MP, Mäkilä TH, Takala TE, et al. Quantitative beat-to-beat analysis of heart rate dynamic during exercise. *Am J Physiol* 1996;**271**:H244-52.
- 32 Malik M, Xia R, Odemuyiwa O, et al. Influence of the recognition artefact in automatic analysis of long-term electrocardiograms on time-domain measurement of heart rate variability. *Med Biol Eng Comput* 1993;**31**:539-44.
- 33 Mark DB, Hlatky MA, Lee KL, et al. Localizing coronary artery obstructions with the exercise treadmill test. *Ann Intern Med* 1987;**106**:53-5.
- 34 Robertson D, Kostuk WJ, Ahuja SP. The localization of coronary artery stenoses by 12 lead ECG response to graded exercise test: support for intercoronary steal. *Am Heart J* 1976;**91**:437-44.
- 35 Hayano J, Mukai S, Sakakibara M, et al. Effects of respiratory interval on vagal modulation of heart rate. *Am J Physiol* 1994;**267**:H33-40.

IMAGES IN CARDIOLOGY

doi: 10.1136/hrt.2005.069138

Left coronal ostium to right atrium fistula causing right ventricular failure and pulmonary hypertension

A 68 year old woman was hospitalised because of dyspnoea and chest tightness. She had chronic atrial fibrillation. Left cardiac catheterisation revealed coronary arteries without significant stenoses and no impaired left ventricular function (ejection fraction 66%). A fistula from the left coronal ostium to the right atrium was visualised during coronary and aorta arteriography. Right cardiac catheterisation showed mild tricuspid valve insufficiency, pulmonary hypertension of 54/22 mm Hg (mean 35 mm Hg), right ventricular pressure of 54/8 mm Hg, mean pulmonary capillary wedge pressure of 10 mm Hg, and 80.0% saturation of the superior vena cava. Echocardiography showed an increased left atrial diameter (48 mm) and normal dimensions and thickness of the left ventricle (end systolic diameter of 28 mm and end diastolic diameter of 53 mm). Cardiac magnetic resonance imaging in longitudinal projection showed an abnormal structure passing across the aortic wall and into the right atrium (length 77.4 mm, width 13.1 mm—see panel). In this case, the Qp/Qs ratio was 2.1 and we performed fistula closure surgically, using the heart-lung machine.

M Yoda
K Minami
R Koerfer
masatakayoda@aol.com