

Chronotropic incompetence and autonomic dysfunction in patients without structural heart disease

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Aims

An attenuated heart rate response to exercise, termed chronotropic incompetence (CI), has been reported to be an independent predictor of cardiovascular mortality. We examined the change in autonomic function during exercise testing and correlated the results with CI.

Methods and results

Exercise testing using a bicycle ergometer was performed in 172 patients who had no evidence of cardiac disease. Chronotropic incompetence was defined as the failure to achieve 85% of the age-predicted maximum heart rate, heart rate reserve <80%, or chronotropic response index <0.80. We analysed the relationship between CI and the change in two components of heart rate variability during exercise testing: high-frequency (HF) component (0.15–0.40 Hz) as an index of vagal modulation and the ratio of low-frequency (LF) component (0.04–0.15 Hz) to HF component as an index of sympathovagal balance. Heart rate variability indexes before exercise were similar in patients with and without CI. Percentage changes after exercise in the ratio of LF to HF component were higher in patients with CI than in those without CI (84 ± 15 vs. $41 \pm 16\%$, $P < 0.05$), whereas percentage changes in an HF component were similar in the two groups.

Conclusion

Our data suggested that CI in patients without structural heart disease was mainly caused by a pathophysiological condition in which sympathetic activation was not well translated into heart rate increase. Further study is needed to determine the post-synaptic sensitivity of the beta-adrenergic receptor pathway in relation to CI.

Keywords

Chronotropic incompetence • Autonomic function • Heart rate variability

Introduction

Heart rate generally increases in response to exercise, although the maximum heart rate decreases with age.¹ In the early 1970s, a 7-year follow-up study in middle-aged men exhibited that the lack of appropriate heart rate response to exercise was associated with cardiac death.² A subsequent study resulted in a similar finding, following 2700 subjects after maximum treadmill stress testing.³ The attenuated heart rate response to exercise was termed as chronotropic incompetence (CI) by Ellestad and Wan,³ which has been accepted as an independent predictor of cardiovascular mortality.^{4–6}

Heart rate is under the influence of autonomic function, namely sympathovagal balance. The initial heart rate increment during

exercise is considered to be mainly provoked by vagal withdrawal, and the subsequent heart rate increment seems to be due to sympathetic activation.⁷ Thus, autonomic dysfunction was suspected to be a possible mechanism of CI, but there has so far been no good evidence showing that CI is caused by impaired autonomic function.⁸ In the present study, we examined the change in autonomic function during exercise testing and correlated the results with CI.

Methods

Study population

On the basis of the data on routine medical examinations of exercise testing in Matsushita Memorial Hospital between 2003 and 2005, we

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enrolled 172 consecutive patients who had no evidence of cardiac disease. All of them had normal findings on physical examination and 12-lead electrocardiography. Furthermore, all patients had normal echocardiographic ventricular dimensions and function and had no detectable coronary artery disease on coronary angiography or exercise testing with scintigraphy. We excluded athletes and patients having diabetes (with a fasting glucose >110 mg/dL, self-reported to be physician-diagnosed, or taking an hypoglycaemic agent), because of possible interference with an assessment of autonomic function using heart rate variability.⁹

Exercise testing

All patients had undergone exercise testing with a sitting electrically operated bicycle ergometer (ERGOMED 840L, SIEMENS, Erlangen, Germany) under continuous monitoring with 12-lead electrocardiography (ML-4500, FUKUDA DENSHI, Tokyo, Japan). All medications were withdrawn just before exercise testing for at least five half-lives; 37 (21.5%) patients received calcium antagonist and 8 (4.7%) received beta-blockers. Resting heart rate in the sitting position was averaged for 5 min before exercise. Blood pressure was measured using an arm-cuff sphygmomanometry every 2 min or more frequently (STBP-780B, COLIN, Aichi, Japan). The maximum heart rate was the highest value during exercise testing. The exercise workload began with 25 W and was increased by 25 W every 2 min. The workload was discontinued when 85% of the maximum predicted heart rate was achieved or because of physical exhaustion, additional horizontal or down sloping ST-segment depression ≥ 0.2 mV or systolic BP ≥ 250 mmHg. After the workload was ceased, all subjects had a 1 min cool-down period maintained at exercise grade of 30 W.

Chronotropic incompetence was defined to be a diminished heart rate response to exercise on the basis of the following three criteria:^{10,11} failure to achieve 85% of the maximum age-predicted heart rate, <80% heart rate reserve, or chronotropic response index of <0.80 at a submaximum workload. Maximum age-predicted heart rate was calculated as (220 – age). The percentage of heart rate reserve was calculated as (maximum heart rate during exercise – resting heart rate)/(maximum age-predicted heart rate – resting heart rate) $\times 100$.¹² We determined chronotropic response index at the submaximum workload which was considered to be 100 W, according to the following formula: [(heart rate at fixed submaximum work – heart rate at rest)/(maximum age-predicted heart rate – heart rate at rest)]/[(metabolic equivalents (METs) at fixed submaximum work – METs at rest)/(METs at maximum work – METs at rest)]; METs were replaced by watts to simplify the equation of chronotropic response index because the workload at rest was explicitly 0 W.¹¹ The criterion on the basis of chronotropic response index <0.80 workload was not applied to patients with the maximum workload <100 W.

Autonomic function

In general, RR intervals during recovery are non-stationary time series, which trend will have influences on heart rate variability indexes.^{13,14} Heart rate variability indexes calculated by the geometric pattern are relatively insensitive to the analytical quality of the time series of RR intervals.¹⁵ The geometric analysis, however, needs a reasonable number of RR intervals to construct the geometric pattern.⁹ In practice, the geometric analysis should be performed through recordings of heart rate at least 20 min but preferably 24 h,⁹ suggesting that the current geometric methods are inappropriate to assess short-term changes in heart rate variability, such as exercise-related alterations. Thus, we employed heart rate variability indexes calculated by frequency-domain methods. Archived data of RR intervals during

Table 1 Baseline characteristics and CI during exercise testing

	CI	
	With (n = 72)	Without (n = 100)
Age (years)	59.9 \pm 10.0	58.9 \pm 9.9
Women	31 (43.1%)	42 (42.0%)
Body mass index (kg/m ²)	23.9 \pm 3.2	23.5 \pm 4.6
Hypertension	40 (55.6%)	42 (42.0%)
Dyslipidaemia	37 (51.4%)	46 (46.0%)
Current smoker	30 (41.7%)*	18 (18.0%)
Left ventricular ejection fraction (%)	71.2 \pm 9.8	71.5 \pm 7.4
Left ventricular end-diastolic volume (mL)	79.1 \pm 24.1	77.2 \pm 22.0
Exercise testing		
Maximum workload (W)	81.3 \pm 26.1*	98.2 \pm 34.4
Maximum rate–pressure product	20 470 \pm 5408*	22 373 \pm 5687
Before exercise		
Averaged heart rate (bpm)	73.7 \pm 10.4*	78.1 \pm 11.5
Averaged systolic blood pressure (mmHg)	154.1 \pm 23.2	151.1 \pm 22.6
During exercise		
Maximum heart rate (bpm)	120.5 \pm 12.8*	140.8 \pm 7.8
Maximum systolic blood pressure (mmHg)	198.7 \pm 25.3*	210.4 \pm 29.2
After exercise		
Averaged heart rate (bpm)	86.1 \pm 10.0*	96.1 \pm 9.2
Averaged systolic blood pressure (mmHg)	159.9 \pm 26.4	158.8 \pm 23.2

Data are mean \pm standard deviation or number (%). CI, chronotropic incompetence.

* $P < 0.05$ vs. patients without CI.

exercise testing were sampled at a frequency of 500 Hz and heart rate variability was analysed using personal computer and software (MemCalc/Tarawa, GMS, Tokyo, Japan) as described previously.¹⁶ Low-frequency (LF) component (0.04–0.15 Hz) and high-frequency (HF) component (0.15–0.40 Hz) were extracted every 1 min and averaged for 5 min before exercise and immediately after a cool-down period following exercise. We employed for HF component the absolute value of power (m s²) without normalization, because the normalization needs the value of very LF component, a dubious measure on a short-term recording for ≤ 5 min.⁹ The magnitude of these indexes were adjusted every 1 min by the average RR interval to determine the coefficient of component variance (CCV) (square root of the component/mean RR interval)^{17,18} because of a reduction in the influence of RR trend. Tulppo et al.¹⁴ studied beat-to-beat heart rate dynamics by plotting each RR interval (Poincaré plot) during exercise with the help of pharmacological autonomic nerve blockades. They reported that quantitative two-dimensional vector analysis of the Poincaré plot, based on geometric methods and useful for relatively short-term recordings, could provide meaningful information on autonomic function. The change in CCV indexes seemed to be similar to that in two-dimensional vector analysis of Poincaré plot.¹⁹

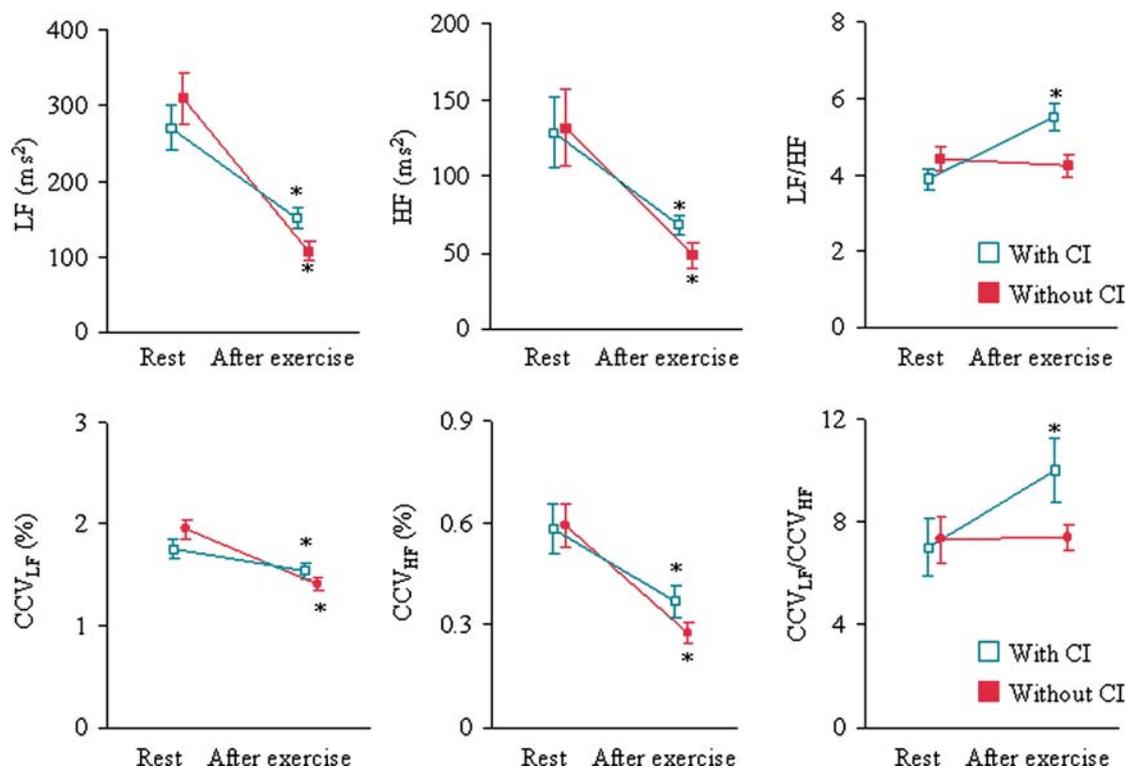


Figure 1 Changes in low-frequency component, high-frequency component, and coefficient of component variance from at rest to after exercise in patients with and without chronotropic incompetence. * $P < 0.05$ vs. resting values.

In addition, the ratio of LF to HF component was measured. We then determined exercise-induced percentage changes of these three indexes as [(the value before exercise – the value after exercise/the value before exercise) \times 100].

Statistical analysis

Categorical variables were compared by χ^2 test. Continuous variables were expressed as mean \pm standard deviation and compared using Student's *t*-test. Heart rate variability indexes were expressed as mean \pm standard error and compared using the Mann–Whitney *U* test. Wilcoxon matched pairs signed ranks test was used to analyse heart rate variability indexes within each group. A $P < 0.05$ was considered statistically significant.

Results

Exercise was discontinued because of physical exhaustion in 66 patients, systolic blood pressure ≥ 250 mmHg in 1, and ST-segment depression ≥ 0.2 mV in another. Of 172 patients, 72 were diagnosed as having CI and the remaining 100 as not having CI. The two groups were well matched with respect to baseline characteristics, except that the current smoking was more common in patients with CI (Table 1). Exercise capacity and heart rate during exercise testing were lower in patients with CI than in those without CI. In patients with CI, 87.5% of patients had any chest symptoms in the daily rife (e.g. dyspnoea, atypical chest pain, or palpitation), whereas the incidence of

chest symptoms was slightly low in patients without CI (75.0%, $P = 0.059$).

All indexes of heart rate variability before exercise were similar in patients with CI and without CI (Figure 1). After exercise, LF component and HF component decreased in both groups. The ratio of LF to HF component increased after exercise in patients with CI (3.87 ± 0.28 to 5.49 ± 0.35 , $P < 0.05$) but did not differ in patients without CI (4.41 ± 0.31 to 4.23 ± 0.29). As shown in Figure 2, percentage changes in LF component were $-18\% \pm 7\%$ in patients with CI and $-51\% \pm 5\%$ in patients without CI; the ratios of LF component to HF component were $84\% \pm 15\%$ and $41\% \pm 16\%$, respectively, with the difference being more marked in percentage changes of CCV indexes (CCV_{LF}, -4.3 ± 4.4 vs. $-22.8 \pm 3.5\%$, $P < 0.01$; CCV_{LF}/CCV_{HF}, 94.8 ± 24.9 vs. 30.8 ± 9.3 , $P < 0.01$, respectively), although these changes in HF component and CCV_{HF} were similar in the two groups. These results were not altered even in a subgroup analysis in which the different incidence of smoking was taken into account (Figure 3).

Discussion

In the present study, CI was associated with higher values of LF component, the ratio of LF to HF component, and these CCV indexes after exercise, but not with exercise-induced changes in HF component and CCV_{HF}. The vagal activity is recognized to be a major contributor to HF component.^{20–22} Disagreement exists regarding the interpretation of LF component: a marker of

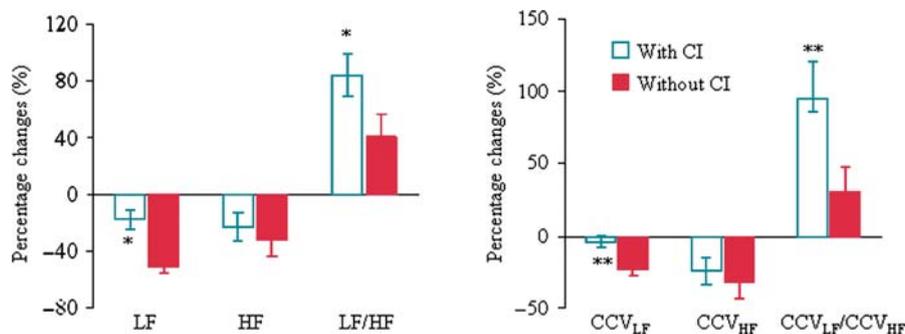


Figure 2 Percentage changes in low-frequency component, high-frequency component, and coefficient of component variance from at rest to after exercise in patients with and without chronotropic incompetence. ** $P < 0.01$, * $P < 0.05$ vs. patients without CI.

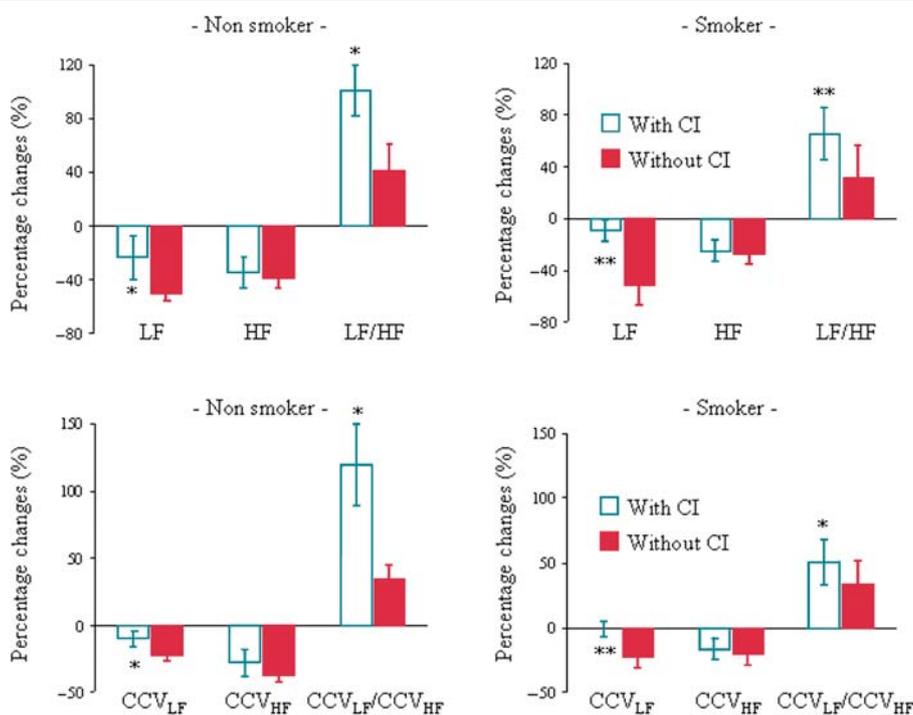


Figure 3 Percentage changes in low-frequency component, high-frequency component, and coefficient of component variance from at rest to after exercise in subgroups of smoker and non-smoker. ** $P < 0.01$, * $P < 0.05$ vs. patients without chronotropic incompetence.

sympathetic modulation^{22–24} or a marker including both sympathetic and vagal influences.^{20,25} Consequently, the LF/HF ratio seems to reflect sympathovagal balance^{22,26,27} with some exceptions.²⁸ Thus, we may safely consider that vagal withdrawal occurred after exercise to a similar extent irrespective of CI, whereas sympathetic activation was provoked after exercise in patients with CI.

In the study using treadmill exercise and autonomic blockades, early contributor to heart rate recovery after peak exercise was sympathetic withdrawal, with vagal reactivation behaving later.²⁹ Thus, sustained sympathetic activation with vagal withdrawal may synergistically lead to a higher heart rate than does the effect of sympathetic and vagal withdrawal. In the present study, however,

heart rate after exercise was lower in patients with CI despite an increased sympathetic activation. It is tempting, therefore, to consider that there may have been a pathological condition in which sympathetic activation was not well translated into the functional response, i.e. heart rate increase.

One of the pathophysiological conditions may be post-synaptic desensitization of the beta-adrenergic receptor pathway in the sinoatrial node. Frequent activation of sympathetic nerves will cause the down-regulation of beta-adrenergic receptors, leading to post-synaptic desensitization.^{30,31} Colucci et al.³² measured heart rate and nor-epinephrine level during exercise testing in 46 normal subjects and 59 patients with heart failure and found that

increments in heart rate during exercise were reduced in accordance with decreased exercise capacity, although increments in plasma nor-epinephrine during exercise were similar irrespective of exercise capacity. Further study will be needed to estimate the post-synaptic sensitivity of the beta-adrenergic receptor in relation to CI.

In the present study, cigarette smoking was more common in patients with CI. Lauer and co-workers^{33,34} reported a similar result that CI was associated with smoking in a healthy, population-based cohort. The mechanism linking smoking to CI remains unclear, but there may also underlie the post-synaptic desensitization of the beta-adrenergic receptor pathway. Cryer *et al.*³⁵ reported the smoking-associated increment of nor-epinephrine, which is released locally from adrenergic axon terminals in healthy subjects. Furthermore, smoking cessation has been reported to be associated with lower heart rate and improved autonomic function as assessed by heart rate variability in volunteer subjects.³⁶ Frequent activation of sympathetic nerves provoked by daily smoking may deteriorate post-synaptic sensitivity of the beta-adrenergic receptor pathway, possibly leading to CI during exercise testing. However, this speculation seems to be less tenable with our results demonstrating that similar autonomic dysfunction was observed in patients with CI irrespective of smoking.

Compensatory vagal hyperactivity has been proposed to be another possible physiological mechanism of CI.³⁷ Vagal activity is enhanced by left ventricular mechanoreceptor because of excessive contraction of the left ventricle^{38,39} and/or by chemoreceptor in the inferior myocardium of the left ventricle, the Bezold–Jarisch reflex.^{16,40} However, this vagal hyperactivity does not seem to have exerted a large effect on CI in our patients because vagal withdrawal after exercise occurred to the same degree in patients with and without CI. In addition, CI has been reported to be associated with left ventricular dilation and hypertrophy.⁴¹ However, they do not seem to be related to the present results either; none of our patients has left ventricular dilation or hypertrophy on echocardiography, although the left ventricular mass was not evaluated exactly in the present study.

Study limitations

Sick sinus syndrome is a possible mechanism of CI, but none of our patients had clinical evidence of sinus node dysfunction, although electrophysiological examination of sinus node function was not performed in our patients. The prevalence of CI was higher in the present study than in previous studies.^{11,33,41} Our patients were relatively old and underwent exercise testing with the use of a bicycle ergometer, not a treadmill, possibly leading to a relatively low level of maximum workload and/or higher prevalence of CI. The present study did not include a stress test using pharmacological autonomic nerve blockades.

Conclusion

Our data suggest that the main cause of CI in patients without structural heart disease is pathophysiological conditions in which sympathetic activation is not well translated into heart rate increase. Further study will be needed to determine the post-

synaptic sensitivity of the beta-adrenergic receptor pathway in relation to CI.

Conflict of interest: none declared.

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