

exercise and the heart

Initial and Final Exercise Heart Rate Transients*

Influence of Gender, Aerobic Fitness, and Clinical Status

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Study objectives: To compare the independent and additive data provided by initial and final heart rate (HR) exercise transients, and to analyze both according to gender, aerobic fitness, clinical status, and medication usage.

Design: Retrospective study.

Setting: Exercise medicine clinic.

Patients: A total of 544 subjects (363 men) with a mean (\pm SD) age of 50 ± 14 years (age range, 10 to 91 years), including asymptomatic and coronary artery disease patients.

Measurements and results: HR transients were obtained from the following two exercise protocols: 4-s exercise test (4sET) followed by a maximal cardiopulmonary cycling exercise test (CPET). The initial HR transient was represented by the cardiac vagal index (CVI), which was obtained by the 4sET, and the final transient (*ie*, HR recovery [HRR]) was determined by the following equation: CPET maximal HR – the 1-min postexercise HR. Transients were modestly related ($r = 0.22$; $p < 0.001$) when adjusted for age, aerobic fitness, clinical status, and negative chronotropic action drug usage. The transients were unrelated to gender (vs CVI, $p = 0.10$; vs HRR, $p = 0.15$). Subjects with a measured maximum oxygen uptake ($\dot{V}O_{2\max}$) exceeding 100% of the predicted maximal aerobic power showed higher CVIs than those in less aerobically fit subjects ($\dot{V}O_{2\max} < 50\%$ subgroup, $p = 0.009$; $\dot{V}O_{2\max} < 75\%$ subgroup, $p = 0.034$). Both transient results differed for asymptomatic and cardiac subjects (CVI, 1.32 ± 0.02 vs 1.42 ± 0.02 , respectively [$p = 0.001$]; HRR, 33 ± 1 beats/min (bpm) vs 37 ± 1 bpm, respectively [$p = 0.009$]).

Conclusions: The initial and final HR transients were modestly related, suggesting a potentially complementary clinical role for both measurements in the assessment of autonomic function in patients with coronary artery disease. Although both HR transients tended to behave similarly under the influence of several variables, the initial HR transient, measured during 4sET, was more likely to discriminate distinct subgroups compared with the final HR transient.

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Key words: autonomic nervous system; exercise; 4-s exercise test; heart rate recovery; heart rate transient; vagal tone

Abbreviations: ANOVA = analysis of variance; bpm = beats per minute; CI = confidence interval; CPET = cardiopulmonary exercise test; CVI = cardiac vagal index; 4sET = 4-s exercise test; HR = heart rate; HRR = heart rate recovery; MET = metabolic equivalent; NCAD = negative chronotropic action drug; $\dot{V}O_2$ = oxygen uptake; $\dot{V}O_{2\max}$ = maximal oxygen uptake

The heart rate (HR) response to dynamic exercise follows a well-defined pattern, which is primarily modulated by the autonomic nervous system.^{1–3} During the first few seconds of exercise, there is a rapid HR increase, known as the *initial transient*, that is exclusively mediated by vagal inhibition, regardless of exercise intensity.⁴ As the exercise continues, there is increasing sympathetic activity,

proportional to the intensity of the exercise, which progressively accelerates the HR. Immediately after exercise, a final transient represented by a decreasing HR response is observed. This is a result of vagal reactivation and a reduction in the sympathetic stimulation, with the latter contributing more effectively to the slow or late deceleration phase of postexercise HR.⁴

While the physiologic basis of HR transients in exercise has been studied for some decades through selective pharmacologic blockade of both branches of the autonomic nervous system, it is only in the last years that these HR responses have been linked to clinical outcomes. Numerous studies have now shown that adults with autonomic dysfunction, manifested as reduced cardiac vagal tone,⁵⁻⁹ have higher all-cause and cardiovascular mortality rates.^{5,10-12} This impaired vagal-dependent cardioprotection can be assessed through varied patterns of HR behavior at rest^{5,11} and during the initial exercise transients (rest to exercise)⁴ and the final exercise transients (exercise to rest).¹²⁻¹⁴ Exercise-related HR modulation indexes have been widely used to analyze cardiac autonomic function, and to provide a powerful and independent prognostic indicator of mortality in adults.¹⁵

Since the pioneering studies undertaken at the Cleveland Clinic,^{12,16,17} and later independently confirmed by other authors,^{13,14,18} it has been demonstrated that a slower HR final transient, as measured during the first 1 or 2 min of the postexercise period, both during maximal exercise¹² and submaximal exercise,¹⁹ significantly increases the relative risk of death. However, these studies were not designed to investigate the possible underlying physiologic mechanisms (eg, parasympathetic dysfunction). Interestingly, while the initial fast transient (ie, the first 4 s) is exclusively vagus dependent, this is probably not the case with the final transient, especially if a longer period of 1 min, which proved its prognostic value in clinical studies, is considered. As previously discussed, during the final HR transient, an important and simultaneous participation of both branches of the autonomic nervous system is expected.

To assess the relative contribution of vagal activity, Araújo et al²⁰ proposed and validated a 4-s exercise test (4sET) protocol, in which predominantly vagal activity at rest is suddenly withdrawn by fast unloaded cycling exercise. Although Araújo et al²¹ have recently demonstrated the reliability of 4sET, its prognostic value for cardiovascular and all-cause mortality remains unknown. Thus, our major aims in this study were as follows: (1) to compare the

independent and additive data provided by initial and final HR exercise transients; and (2) to analyze both HR transients according to gender, aerobic fitness, clinical status, and medication usage.

MATERIALS AND METHODS

Sample

We reviewed our laboratory data from nonathletes who were voluntarily submitted to a detailed medical and functional evaluation between 1995 and 2003. From a total of 2,198 assessments, we were able to select 544 subjects (363 men; mean [\pm SD] age, 50 ± 14 years; age range, 10 to 91 years) who had performed a 4sET followed by a maximal cardiopulmonary exercise test (CPET) utilizing a ramp protocol,²² both on a cycle ergometer. A single physician (C.A.) evaluated and supervised all exercise tests. Before the procedures, all subjects read and signed a specific informed consent form approved by the institutional research committee. Nearly all subjects (98%) were white and represented a higher socioeconomic class.

Clinical Data

A functional evaluation was preceded by clinical anamnesis and physical examination, a 12-lead supine resting ECG, and spirometry. Relevant clinical features as well as the regular use of negative chronotropic action drugs (NCADs), such as amiodarone, β -blockers, and calcium-channel blockers, were carefully recorded.

Exercise Protocols

4sET: The 4sET was pharmacologically validated²⁰ for the isolated assessment of the integrity of cardiac vagal tone through the analysis of HR initial transient (ie, the rest-to-exercise transition), as reported by our group^{20,23,24} and others.²⁵ Briefly, the 4sET consists of unloaded pedaling as fast as possible on a cycle ergometer (EC-1600; Cat Eye; Tokyo, Japan) from the fourth to the eighth seconds of a 12-s maximal inspiratory apnea. The subject remains seated on the cycle ergometer, and, after the HR stabilizes, the verbal commands of four evaluators guide the actions to be sequentially performed at 4-s intervals, as follows: (1) a fast maximal inspiration, primarily through the mouth; (2) as fast as possible pedaling; (3) sudden cessation of pedaling; and (4) expiration.^{20,21,26} A continuous recording of a single ECG lead, usually CC₅ or CM₅, for 35 s at 25 mm/s, beginning 5 s before the command for maximal inspiration was obtained with two different ECG systems (Cardiolife TEC 7100; Nihon-Kohden; Tokyo, Japan; or Elite Ergo PC 3.2.1.5; Micromed; Brasília, Brazil).

To quantify cardiac vagal tone, the following ECG R-R intervals (identified and measured with 10-ms resolution) were recorded: the longest R-R interval (ie, either the interval obtained immediately before the onset of exercise or the first one after the onset of exercise); and the shortest R-R interval during the 4-s exercise (generally, the last one). Two maneuvers were typically carried out, with a dimensionless index (the greatest ratio between the aforementioned intervals obtained during both 4sET maneuvers) being chosen to represent the cardiac vagal index (CVI).

Previous studies have shown that the CVI magnitude is not dependent on the presence or absence of resistance to pedal

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movement,⁴ on active or passive execution,^{26,27} on whether the exercise is undertaken with the lower or upper limbs,²⁸ or even without a ergometer usage, in the orthostatic position.²⁹ Moreover, within-day and between-day reliability have been shown to be very high.²¹

Maximal CPET: The CPETs were conducted using a cycle ergometer with direct collection and analysis of expired gases (VO₂₀₀₀; MedGraphics; St. Paul, MN), immediately after the 4sET, according to an individualized ramp protocol, to achieve a duration of between 8 and 12 min.^{22,30} The subjects were verbally encouraged to exercise to volitional fatigue (*ie*, exhaustion), regardless of the maximal HR attained.

For the 4sET and the CPET, both feet remained fixed to the pedals so as to enhance motor performance and to improve mechanical efficiency. The ECG was continuously monitored via a single lead (CC₅ or CM₅) from pretest rest to at least 5 min postexercise. Immediately after the test, subjects were helped off the cycle ergometer and placed on an adjacent stretcher in the supine position, generally within 20 to 40 s.

Procedures for HR Analysis: HR transients were obtained from the following two exercise protocols: 4sET; and CPET. On the 4sET, the initial transient was represented by the CVI, as previously described. On CPET, the final transient (*ie*, the HR

recovery [HRR]) was determined by the following equation: maximal measured HR – the 1-min postexercise HR. Both values were obtained from averaging seven R-R interval durations at respective times. For comparative purposes, the predicted maximal HR was calculated according to the following equation: $210 - 0.65 \times \text{age (in years)}$.³¹

The relationship between both HR transients expressed as CVI and HRR was initially quantified and adjusted according to the following variables: age; aerobic fitness; clinical status; and NCAD use.

The values related to the initial and final HR transients then were compared according to the following six features: (1) gender-specific absolute aerobic fitness (< 5 metabolic equivalents [METs]; 5 to 7.9 METs; 8 to 11 METs; and > 11 METs)³²; (2) predicted aerobic fitness (expressed as a percentage, and for age and gender)³³; (3) HRR (cutoff point, 23 beats/min [bpm])³⁴; (4) the presence or absence of NCAD use; (5) chronotropic incompetence, defined as the inability to reach 85% of the predicted maximal HR ($220 - \text{age in years}$) during maximal exercise testing³⁵; and (6) clinical status, distinguishing between patients with coronary artery disease and asymptomatic subjects. Accordingly, we analyzed HR transients from several different perspectives.

Table 1—Characteristics of the Study Sample (n = 544) With Specific Reference to Gender, Demographics, Cardiopulmonary Variables, Clinical Status, and Medications Usage*

Variables	All (n = 544)	Men (n = 363)	Women (n = 181)	p Value	95% CI†
Demographics					
Age, yr	50 ± 1 (10–91)	50 ± 1 (11–91)	50 ± 1 (10–82)	1.00	–2.20–2.20
Weight, kg	77 ± 1 (28–162)	83 ± 0.9 (48–184)	66 ± 1 (28–128)	< 0.001	14.98–19.02
Height, cm	169 ± 0.4 (137–195)	174 ± 0.4 (148–195)	160 ± 0.5 (137–178)	< 0.001	13.07–14.93
Body mass index	26.8 ± 0.22 (15.1–57.6)	27.4 ± 0.3 (18.4–57.6)	25.6 ± 0.4 (15.1–48.6)	< 0.001	1.09–2.50
HR					
CVI	1.37 ± 0.01 (1.01–2.62)	1.37 ± 0.01 (1.04–2.62)	1.37 ± 0.02 (1.01–2.20)	1.00	–0.03–0.03
Predicted HR, bpm	177 ± 0.38 (151–203)	177 ± 0.5 (151–203)	178 ± 0.6 (157–204)	0.087	–2.15–0.14
Maximum HR, bpm	160 ± 1 (82–207)	160 ± 1 (82–207)	159 ± 2 (96–198)	0.479	–1.77–3.77
HRR, bpm	34 ± 1 (2–76)	34 ± 1 (2–76)	35 ± 1 (8–75)	0.371	–3.20–1.20
Aerobic fitness					
Estimated $\dot{V}O_2$, mL/(kg × min)	26.1 ± 0.36 (9.2–55.5)	27.6 ± 0.4 (10.6–55.5)	23.1 ± 0.6 (9.2–51.5)	< 0.001	3.60–5.50
$\dot{V}O_{2\text{max}}$, mL/(kg × min)	27 ± 0.45 (4.8–61)	29.9 ± 0.5 (9.5–61.1)	22.4 ± 0.7 (4.8–56.2)	< 0.001	6.30–8.70
METs	7.8 ± 0.1 (1.4–17.5)	8.1 ± 0.2 (2.7–17.5)	6.4 ± 0.2 (1.4–16.1)	< 0.001	1.26–2.14
$\dot{V}O_2$, % predicted	87.3 ± 1.22 (20.0–211.0)	93.4 ± 1.2 (30.6–211)	75.2 ± 1.9 (20–185.8)	< 0.001	15.2–21.2
Clinical status					
Asymptomatic	132 (24)	81 (23)	51 (28)		
Coronary artery disease	115 (21)	103 (28)	12 (7)		
Other diseases and mixed cases	297 (55)	179 (49)	118 (65)		
NCADs					
No	396 (73)	252 (69)	144 (80)		
Yes	148 (27)	111 (31)	37 (20)		

*Values given as mean ± SEM (minimum–maximum) or No. (%), unless otherwise indicated.

†Related to difference of means.

To investigate between-group differences, *t* tests and one-way and two-way analysis of variance (ANOVA) were used, followed by Bonferroni *post hoc* comparisons where appropriate. Both linear and stepwise regressions, and partial and Pearson product-moment correlations were used to assess the relationship between variables. Partial correlations were adjusted according to the aforementioned variables. The significance level was defined at $p < 0.05$, and the 95% confidence intervals (CIs) were calculated for demographic and cardiorespiratory variables. A statistical software package (SPSS, version 11; SPSS; Chicago, IL) was used for the statistical analyses.

RESULTS

Descriptive statistics of the major variables are presented in Table 1. CVI and HRR results were only modestly related, as shown in Figure 1. This association was even smaller after adjustments for age, aerobic capacity, clinical status, and NCAD use ($r = 0.22$; $p < 0.001$), with age being the most influential variable.

Men and women with a lower measured maximal aerobic power, expressed as METs, generally demonstrated slower initial and final HR transients as shown by CVI and HRR data (Fig 2). One-way ANOVA revealed differences ($p < 0.05$) among some of the subsets that had been stratified according to aerobic fitness, more specifically at the ends of the continuum (ie, < 5 vs 8 to 11 METs, < 5 vs > 11 METs, and 5 to 7.9 vs > 11 METs) for the female HR initial transient. Although statistical analysis showed differences ($p = 0.036$) for the final HR

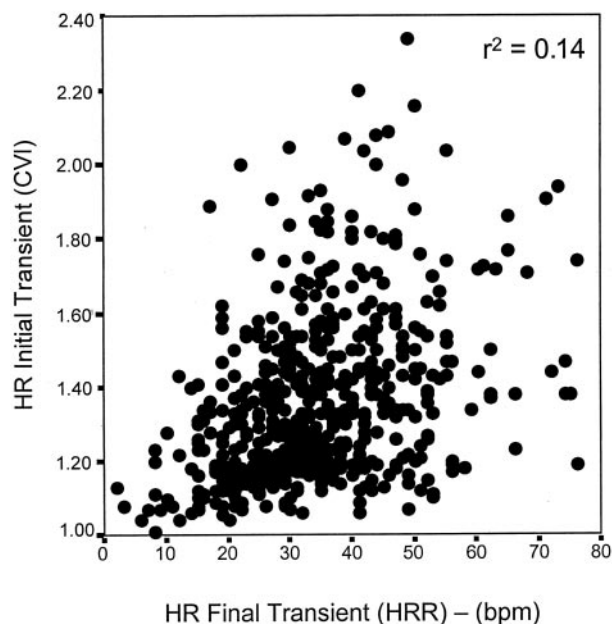


FIGURE 1. Nonadjusted relationship between CVI and HRR.

transient, *post hoc* analysis failed to identify them. For male subjects, the transients differed in the subsets for initial and final HR transients, except for < 5 vs 5 to 7.9 METs, and for 8 to 11 vs > 11 METs, respectively.

Age-adjusted two-way ANOVA showed that the transients were unrelated to gender (CVI, $p = 0.10$; HRR, $p = 0.15$). When within-group analyses performed according to aerobic fitness were carried out, differences between men and women in the cohort with < 5 METs for CVI (1.20 ± 0.02 vs 1.30 ± 0.02 , respectively; $p = 0.01$) and in the groups with < 8 METs for HRR (ie, < 5 METs, $p < 0.001$ [21 vs 32 bpm, respectively]; and 5 to 7.9 METs, $p = 0.025$ [32 vs 36 bpm, respectively]) were observed. However, there were nearly twice as many more women than men (67 vs 35, respectively) in the < 5 METs group. Additionally, the associations adjusted for age, clinical status, and NCAD use between both transients and directed measured maximal aerobic power expressed as METs were $r = 0.19$ ($p < 0.001$) for the initial transient and $r = 0.08$ ($p = 0.056$) for the final transient, when collective data from both sexes were considered.

Subjects with $< 50\%$ of age-predicted and gender-predicted maximal aerobic power tended to show slower initial and final HR transients (Fig 3). Although no statistically significant differences ($p = 0.052$) for HRR were detected among the subsets of subjects, such differences were noted for CVI in the groups with $< 50\%$ of aerobic power vs those with $> 100\%$ of aerobic power ($p = 0.009$), and in the groups with $< 75\%$ of aerobic power vs those with $> 100\%$ of aerobic power ($p = 0.034$). The correlation coefficients between the HR transients and the percentages of predicted maximal aerobic power, adjusted for age, clinical status, and medication usage, were $r = 0.17$ ($p < 0.001$) for CVI, and $r = 0.09$ ($p = 0.031$) for HRR, which are similar to the values obtained for absolute values of measured maximal oxygen uptake ($\dot{V}O_{2\max}$), expressed as METs. However, only 7% of the study sample (28 women and 8 men) had aerobic capacity values that were $< 50\%$ of the age-predicted and gender-predicted values.

By using the percentage of predicted HR achieved with CPET (reference value, 85%) to divide the sample according to the presence or absence of chronotropic incompetence in NCAD nonusers, those with chronotropic incompetence demonstrated slower HR transients, which is especially evident in the initial transient (Table 2). Approximately 17% of the subjects demonstrated an abnormal HR descent at 1 min after exercise (ie, < 23 bpm). The analysis of the initial transient of these individuals revealed significantly lower CVI values

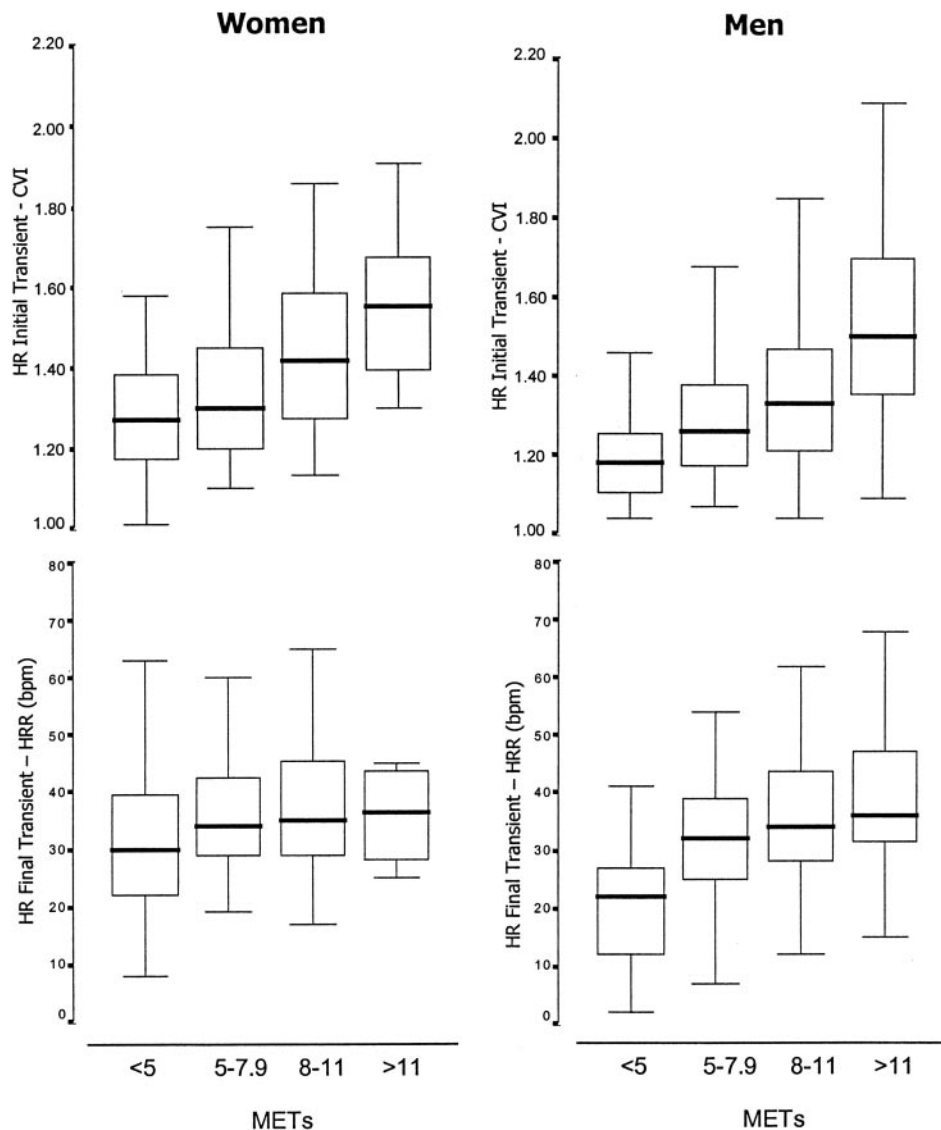


FIGURE 2. Measured aerobic fitness ($\dot{V}O_2\max$) and initial HR transients (*top*) and final HR transients (*bottom*) for women and men.

(mean CVI, 1.23 ± 0.02 vs 1.40 ± 0.01 , respectively; $p = 0.001$; 95% CI, -0.27 to 0.66).

Interestingly, in the 27% of the subjects who were regularly receiving NCADs, their use did not substantially influence the HR transients, despite the presence of marginal statistically significant differences (Table 3). When the sample was divided according to clinical status, mean differences for both transients were found between the coronary artery disease group and the asymptomatic group (CVI, 1.32 ± 0.02 vs 1.42 ± 0.02 , respectively [$p = 0.001$; 95% CI, -0.16 to -0.04]; HRR, 33 ± 1 vs 37 ± 1 bpm, respectively [$p = 0.009$; 95% CI, -7 to -1]) [Fig 4]; however, those with coronary artery disease were older by comparison (mean age, 58 ± 1 vs 44 ± 1 years, respectively; $p < 0.001$; 95% CI, 7 to 11).

DISCUSSION

Relationship Between Initial and Final Transients

Our results demonstrated a small, albeit significant, association among age-adjusted, medication-adjusted, aerobic fitness-adjusted, and clinical status-adjusted initial and final HR transients, as shown by linear and partial regression coefficients. These results underlie the assumption that, although both coefficients are dependent, at least in part, on the autonomic nervous system,⁴ different physiologic mechanisms are responsible for the initial and final HR transients. Thus, it seems that the information obtained from both transients is complementary, as only 4% of variation of one of them may account for the variation in the other.

It has been pharmacologically demonstrated that

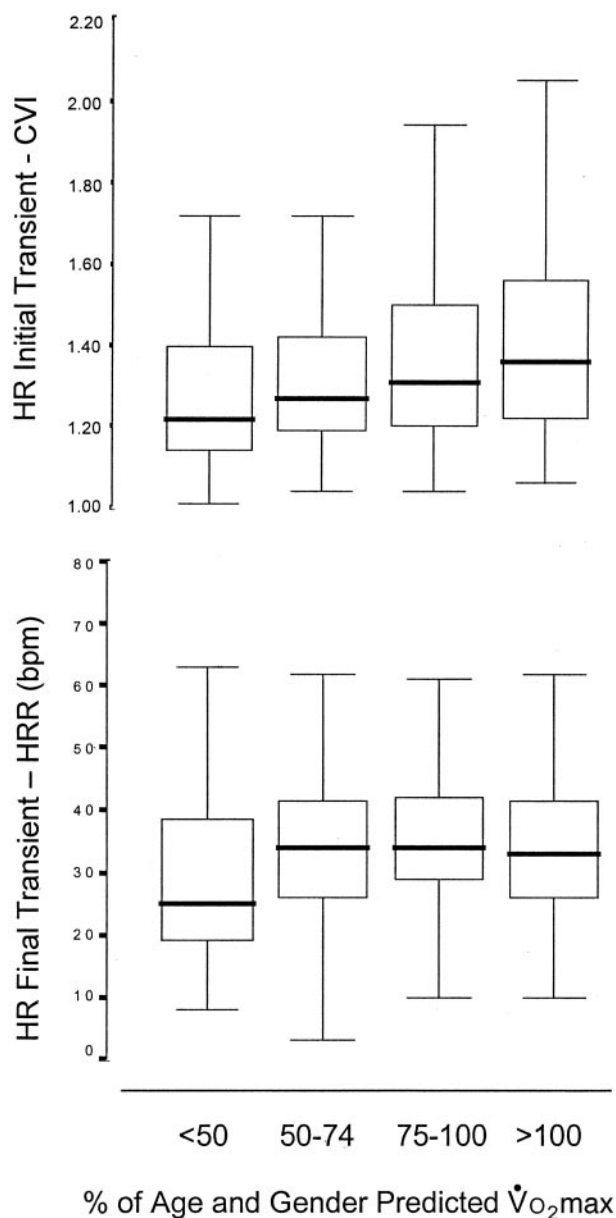


FIGURE 3. Aerobic fitness according to age-predicted and gender-predicted $\dot{V}O_2\max$ and initial HR transients (*top*) and final HR transients (*bottom*).

the rapid initial HR transient is exclusively mediated by vagal inhibition.²⁰ On the other hand, the physiologic mechanisms involved in the final or immediate postexercise transient are unclear. Imai et al³⁶ demonstrated that the first 30 s of recovery are primarily mediated by vagal reactivation, regardless of age and exercise intensity in healthy adults, athletes, and individuals with heart failure. Nevertheless, it seems that the adrenergic component reduction plays a greater role in the subsequent HR decrement.

Although the prognostic clinical usefulness of

HRR presents strong epidemiologic evidence under different situations and methods, it would seem to be an oversimplification to assume that the HR descent during the postexercise period, mainly when observed for > 30 s, was primarily due to a parasympathetic activity recovery. The great diversity of methods used to investigate HRR after exercise made the comparison of the various studies tenuous at best. Selected methodological differences were as follows: (1) test characteristics (maximal¹² vs submaximal¹⁹); (2) type of ergometer (cycle³⁷ vs treadmill^{14,38,39}); (3) different recovery times (from 30 s³⁶ to 5 min³⁹); (4) recovery format (active¹² vs passive³⁴); and (5) recovery position (standing,¹³ sitting,¹⁸ supine,³⁸ or lateral decubitus,³⁴), as well as other variations in protocol such as the time spent to adopt the resting position, respiratory rate, and tidal volume,⁴⁰ and whether the subject was allowed to talk or move during this period.

In order to achieve a generalized use in clinical practice, a given clinical or physiologic measurement must be repeatable in the same individual under the same controlled conditions. Recently, an analysis of previously published studies⁴¹ on the methods of quantitating the initial and final HR transients suggested that HRR measurements may be unreliable in men and women (90 patients; age range, 30 to 80 years) with or without symptoms. Conversely, the intraday and interday CVI calculations were highly reliable in a large and heterogeneous sample (1,699 patients; age range, 8 to 85 years),²¹ under a variety of clinical statuses. Therefore, in contrast to CVI, the widespread use of HRR measurements may present an additional challenge (*ie*, low reliability), potentially compromising the clinical analysis and implications.

Aerobic Fitness

The methodological strengths of the present study include discrimination between genders and a direct measurement of expired gases during maximal exercise, which was supervised and analyzed by the same experienced physician. Individuals with a lower aerobic fitness, expressed as a measured value or as a percentage of the age-predicted and gender-predicted $\dot{V}O_2\max$, also had slower initial and final HR transients. Similar results had been reported previously in epidemiologic studies that compared aerobic fitness,³² HR transients,^{12,13} and cardiovascular mortality. Theoretically, because the slower HR initial transient is due to vagal dysfunction, these individuals would be expected to demonstrate a higher mortality rate, due to loss of vagal-dependent cardioprotection and increased vulnerability to malignant ventricular arrhythmias.¹⁵

Table 2—HR Transients According to Chronotropic Incompetence Without NCAD Utilization*

Variable	< 85% (n = 54)	> 85% (n = 342)	p Value	95% CI
HR, % predicted	77 ± 0.8 (59–84)	96 ± 0.3 (85–112)	< 0.001	–23.05–14.95
Initial transient (CVI)	1.22 ± 0.02 (1.01–2.62)	1.42 ± 0.01 (1.04–2.34)	0.003	–0.23–0.09
Final transient (HRR), bpm	25 ± 1 (2–53)	37 ± 1 (3–76)	0.062	–24.62–0.62

*Values given as mean ± SEM (minimum–maximum), unless otherwise indicated.

Our data suggest that the initial HR transient tends to stratify the absolute or relative aerobic fitness better than HRR, regardless of gender. In contrast to CVI, which showed a clear differentiation, the final HR transient basically divided the four groups in two (*ie*, < 5 and > 5 METs, or < 50% and > 50% of predicted oxygen uptake ($\dot{V}O_2$). This becomes even clearer when aerobic fitness is analyzed according to the percentage of the predicted $\dot{V}O_{2max}$, in which ANOVA failed to identify any difference among the groups in the final HR transient. Thus, the use of HRR as a marker of aerobic fitness seems to lack precision,^{42,43} since different physiologic mechanisms are involved. However, our study sample included a relatively low prevalence of subjects with aerobic fitness of < 50% of predicted.

Our data showed weak associations between aerobic fitness, whether expressed in METs or in percentages of predicted $\dot{V}O_{2max}$, and the initial and final HR transients. Although statistically significant, the correlations were relatively low, which is in agreement with the findings of other studies.⁴ In contrast, CVI performed better when compared with HRR, suggesting an inability to predict HR transient responses from aerobic fitness and *vice versa*. This is relevant because it is well-documented that aerobic fitness alone, whether measured directly or estimated, is an excellent predictor of cardiovascular and all-cause mortality.^{32,44} Thus, as has been previously demonstrated by Cole et al,¹² the HRR (*ie*, the final transient) provides independent clinical prognostic information. It is possible that the initial HR transient, which was widely discussed in this study, also may provide a relevant, complementary prognostic indicator, based on its more objective dependence

on cardiac vagal integrity, high reliability, and modest association with the final transient.

Both HR transients seemed to be gender independent, which is in agreement with what we have previously described for CVI,⁴⁵ at least in adults. On the other hand, there were differences in HRR among boys and girls undergoing submaximal exercise protocols.⁴⁶ Considering the present data for categories of low aerobic fitness (*ie*, < 8 METs and < 75% predicted $\dot{V}O_2$), women showed higher and more normal values for HR transients than did men. These provocative data thus suggest that women with low aerobic fitness tend to better preserve their autonomic function and, accordingly, maintain a higher degree of cardioprotection.⁴⁷

Chronotropic Incompetence

A lower maximal HR during exercise testing is associated with a greater risk of cardiovascular events and all-cause mortality.³⁵ Chronotropic incompetence may be a marker of autonomic modulation, reflecting the underlying cardiovascular disease. Our results suggest that individuals with blunted values for initial and final HR transients often also had concomitant evidence of chronotropic incompetence, with an even higher discriminatory power derived from the former.

HRR

Although most study subjects had a chronic clinical status that may have influenced autonomic activity, only 17% showed abnormal HRR responses according to the cutoff criteria used (23 bpm). Thus, the use of absolute cutoffs, as originally proposed,

Table 3—HR Transients According to NCAD Usage*

Variable	Without NCAD (n = 396)	With NCAD (n = 148)	p Value	95% CI
Initial transient (CVI)	1.39 ± 0.01 (1.01–2.34)	1.30 ± 0.02 (1.04–2.62)	< 0.001	0.04–0.13
Final transient (HRR), bpm	35 ± 1 (2–76)	32 ± 1 (6–76)	0.008	0.82–5.57

*Values given as mean ± SEM (minimum–maximum), unless otherwise indicated.

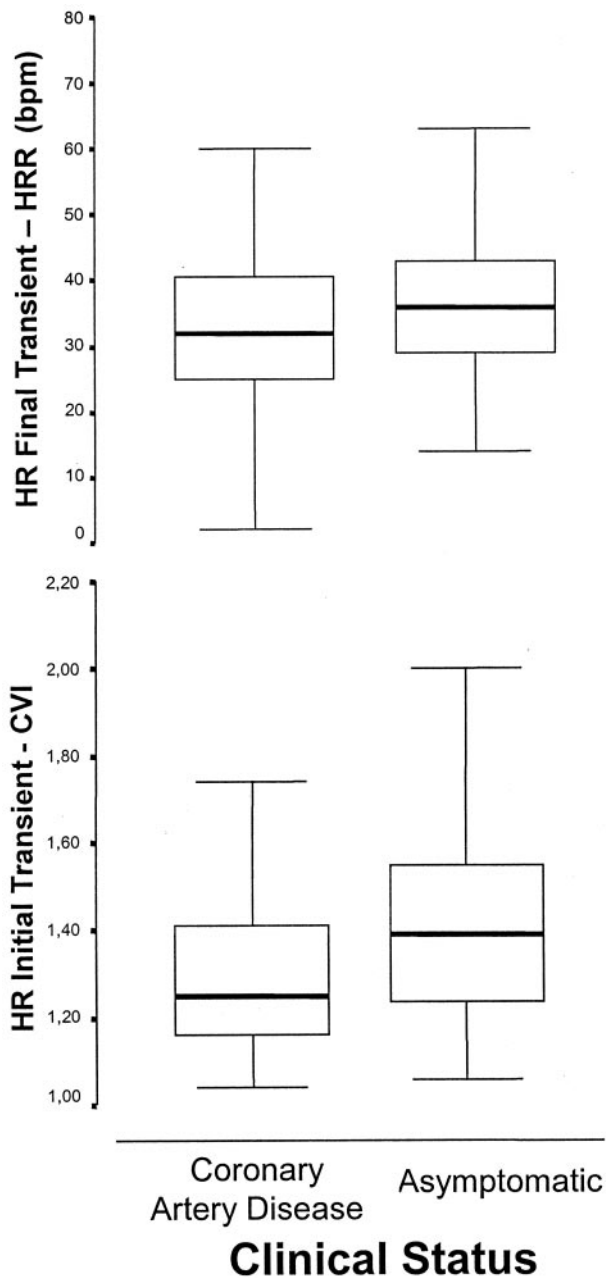


FIGURE 4. Final and initial HR transients according to clinical status.

may not be an adequate discriminator.³⁷ Alternatively, one might explore the use of a percentage of maximal exercise HR obtained at the first minute of recovery as an index of subsequent mortality. Another clinically relevant analysis might be the quantification of HRR in relation to HR reserve (*ie*, maximum HR – resting HR), that is, the percentage of the subject's HRR to which the HR is reduced at 1 min after maximal exercise testing.

More recently, Raymond⁴⁸ challenged the mechanisms responsible for postexercise HRR, even con-

testing its prognostic value. Currently, it seems that the HRR requires additional study before definitive criteria for its clinical use and interpretation can be adopted.

NCADs

Individuals receiving NCADs were more likely to exhibit slower HR transients. Because these drugs act primarily on the sympathetic nervous system, which is largely unrelated to the initial transient as studied on 4sET,²⁰ the differences found may reflect disease-related autonomic impairment rather than a drug effect *per se*.

Clinical Status

As expected, individuals with known coronary artery disease, compared with their healthy counterparts, demonstrated a more blunted HR response for both the initial and final HR transients. Once again, however, the initial transient, as assessed by 4sET, showed greater discriminatory power compared with HRR. The difference between the groups is probably due to the fact that, in addition to being composed of older individuals,^{49–51} the group of patients with coronary artery disease had greater autonomic dysfunction, a feature that is inherent in their clinical status.^{5,52,53}

Limitations, Clinical Applications, and Future Research

The present study has potentially confounding variables, such as the severity and duration of the cardiovascular disorders presented, and the magnitude and location of any residual ischemic myocardium or fibrotic areas. The results suggest that the physiologic mechanisms underlying the initial and final HR transients are partially distinct, as measured by 4sET and CPET. Moreover, the clinical prognostic value of cardiac vagal activity, as assessed by the 4sET and how it compares with HRR, remains unresolved.

Considering the limitations of the standardization of postexercise HRR measurement, and the simplicity, potentially greater safety, and time required for the performance and analysis of 4sET, it seems that the latter procedure should be additionally investigated and quantified. The simultaneous analysis of both HR transients may be complementary, augmenting the clinically relevant and prognostic value of the chronotropic response to exercise. Finally, methodologic improvements may be needed for future studies. These may include standardizing the time that the subject takes to assume a supine resting

position after exercise and incorporating the concept of HR reserve into the interpretation of the final HR transient.

CONCLUSION

We found the following: (1) that the initial and final HR transients are significantly, albeit modestly, related, suggesting a potentially complementary clinical role for both measurements in the assessment of autonomic function and coronary artery disease; and (2) that both HR transients tended to behave similarly under the influence of several variables, although the initial HR transient, measured during 4sET, was more likely to discriminate distinct subgroups compared with the final HR transient.

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