Case Report

Heart Rate Recovery and Tissue Doppler Echocardiography in Heart Failure

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ABSTRACT

Background: Previous research has demonstrated the prognostic value of echocardiography with tissue Doppler imaging (TDI) in the heart failure (HF) population. Heart rate recovery (HRR) has also recently shown promise as a prognostic marker.

Hypothesis: We hypothesize echocardiography with TDI and HRR will be significantly correlated and both will provide prognostic information.

Methods: A total of 243 subjects underwent echocardiography with TDI and maximal exercise testing to determine: (1) the ratio between mitral early (E) to mitral annular (E′) and E to mitral late (A) velocity; (2) left ventricular ejection fraction (LVEF); (3) left ventricular (LV) mass; (4) LV end-systolic volume (LVESV); and (5) HRR at 1 minute postexercise (HRR_1).

Results: HRR_1 was significantly correlated with LVEF ($r = 0.14$, $P = .03$), LV mass ($r = -0.30$, $P < .001$), E/A ($r = -0.22$, $P = .001$), and E/E′ ($r = -0.49$, $P < .001$). Multivariate Cox regression analysis revealed HRR_1 was the strongest predictor of cardiac mortality (χ^2: 55.5, $P < .001$); LV mass (residual χ^2: 13.1, $P < .001$), E/E′ (residual χ^2: 11.2, $P = .001$), and LVESV (residual χ^2: 5.9, $P = .015$) all added significant prognostic value and were retained in the regression while LVEF was removed (residual χ^2: 0.008, $P = .93$).

Conclusions: To our knowledge, this is the first investigation demonstrating an association between HRR and variables obtained from echocardiography with TDI in subjects with HF. The combination of both assessment techniques provides improved prognostic discrimination.

Introduction

Heart rate recovery (HRR) following aerobic exercise reflects the reintroduction of vagal tone with faster reductions reflecting better cardiovascular health.[1,2] Moreover, a number of investigations have found that HRR is highly prognostic in populations not diagnosed with heart failure (HF).[3] Initial investigations on the prognostic value of HRR indicates this applies to the HF population[4,5] although the samples assessed in these studies are small and further analysis is required.

Echocardiography with tissue Doppler imaging (TDI) has likewise demonstrated robust prognostic value.[6,7] Initial investigations also indicate variables obtained from echocardiography with TDI, which reflect diastolic function, are significantly associated with aerobic capacity in patients with HF.[8] To our knowledge, no investigation has explored the relationship between HRR and measures obtained from echocardiography with TDI in patients with HF. Furthermore, the complementary prognostic value of these important measures has not been explored. Given the ability of HRR and echocardiography to reflect pathophysiology, we hypothesize these variables from these assessments will be correlated and provide complementary prognostic information. The purpose of the present investigation was to address these associations and their prognostic utility in a HF cohort.

Methods

A total of 243 patients with compensated HF, undergoing evaluation at San Paolo Hospital in Milano, Italy, were enrolled in this study. All were receiving stable pharmacologic management prior to initiation of the study. All authors have read and approved the manuscript. Informed consent and institutional review board approval was obtained prior to study initiation and this investigation was in accordance with the Declaration of Helsinki.

Standard M-mode, 2-dimensional echocardiography, and Doppler blood flow measurements were performed (Philips

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iE33 Echocardiography System, Philips, Eindhoven, The Netherlands) in agreement with the American Society of Echocardiography Guidelines.[9] Septal and posterior left ventricular (LV) wall thickness was obtained from the parasternal long-axis view. LV end-systolic volumes (LVESV) were obtained from 2-dimensional apical images. LV ejection fraction (LVEF) was calculated according to Simpson's method from 2-dimensional apical images. LV mass was calculated according to the formula proposed by Devereux et al.[10] Mitral inflow measurements included peak early (E) and peak late (A) flow velocities and the E/A ratio. The TDI of the mitral annulus was obtained from the apical 4-chamber view. A 1.5 sample was placed sequentially at the lateral and septal annular sites. Analysis was performed for the early (E′) diastolic peak velocity. The ratio of early transmitral flow velocity to annular mitral velocity of the lateral LV wall (E/E′) was taken as an estimate of LV filling pressure.[11]

Each patient performed a supervised, standard, progressively increasing (individualized ramp protocol) work rate to maximum tolerance on an electromagnetically braked cycle ergometer (Corival, Lode B.V., Groningen, The Netherlands). Test termination criteria consisted of patient request, ventricular tachycardia, $\geq$2.0 mm of horizontal or downsloping ST-segment depression, or a drop in systolic blood pressure $\geq$20 mm Hg during exercise. HRR, determined by electrocardiography (CardioSoft, GE Medical Systems, Milwaukee, WI), was defined as the difference between HR at maximal exercise and HR at 1 minute during an active cool-down (HRR_1). Cool-down consisted of zero load pedaling at 40 rpm. Subjects were followed for cardiac-related mortality for 4 years following echocardiography with TDI and exercise testing via hospital and outpatient medical chart review. Subjects were followed by the HF program at San Paolo Hospital providing for the high likelihood that all events were captured. Any death with a cardiac-related discharge diagnosis was considered an event.

Pearson product moment correlation was used to assess the relationship between echocardiography with TDI and HRR_1. Unpaired *t* testing compared differences in resting and peak exercise HR as well as HRR_1 and age according to β-blocker use. Univariate and multivariate Cox regression analysis assessed the ability of Doppler echocardiography and HRR_1 to predict cardiac mortality. Univariate Cox regression also assessed the prognostic characteristics of HRR_1 as a continuous variable in subgroups according to β-blocker use. Multivariate Cox regression determined the combined prognostic value of HRR_1 and age in β-blocker subgroups. The forward stepwise method was used for the multivariate analyses with entry and removal *p* values set at 0.05 and 0.10, respectively. Receiver operating characteristic (ROC) curves were constructed to determine the ability of HRR_1 to identify subjects with an unfavorable E/E′. This statistical technique was also used to determine the optimal prognostic threshold value (highest combination of sensitivity/specificity) for variables retained in the multivariate regression. Kaplan-Meier analysis was used to assess differences in cardiac-related events using threshold values defined by ROC curves. The log-rank test was used to determine if the difference in event-free survival was significant between subjects falling into different categories. Statistical differences with a p value $<.05$ were considered significant.

Results

Baseline echocardiography with TDI and HRR_1 characteristics for the overall group are listed in the Table. A majority of the subjects were male with ischemic HF. An angiotensin-converting enzyme inhibitor was prescribed to the majority of patients. Prescription of an antialdosterone agent or β-blocker was less prevalent.

Table 1. Baseline, Echocardiography with TDI, and Heart Rate Recovery Characteristics

Baseline Variables	
Age, years	62.2±9.7
Sex, M/F	190/53
Etiology, Ischemic/Nonischemic	152/91
NYHA class	2.2±0.80
Echocardiography with TDI	
LVEF, %	35.6±11.1
LVESV, mL	111.5±27.7
LV mass, grams	227.1±24.6
E/A ratio	1.2±0.44
E/E′ ratio	9.0±3.3
Therapy Distribution, %	
ACE inhibitor	79.4%
Antialdosterone	42.0%
β-Blocker	57.2%
Heart Rate Characteristics, Beats per Minute	
Resting HR	74.0±9.1
Peak HR	129.2±16.4
HRR_1	18±3.3

Age, NYHA (New York Heart Association) class, echocardiography with tissue Doppler imaging, and heart rate data all presented as mean ± standard deviation.
Sex and heart failure etiology data presented as number of patients.
Therapy distribution presented as percentage of patients prescribed a given agent.

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Table 2. Kaplan-Meier Analysis Results Illustrated in Figure 1

Group	Characteristics	Subjects Meeting Criteria	Cardiac Death	Percent Alive
A	0-1 Risk Factors [a]	151	4	97.4%
B	2 Risk Factors [b]	40	10	75.0%
C	3-4 Risk Factors [c]	52	29	44.2%

Log-rank = 101.8, $P < .001$.
[a] 1 event: no risk factors.
1 event: E/E′ abnormal.
2 events: HRR_1 abnormal.
[b] 6 events: HRR_1 and E/E′ abnormal.
2 events: HRR_1 and LV mass abnormal.
2 events: LV mass and LVESV abnormal.
[c] 5 events: HRR_1, LV mass, and LVESV abnormal.
5 events: HRR_1, E/E′, and LV mass abnormal.
3 events: HRR_1, E/E′, and LVESV abnormal.
E/E′: ratio of early transmitral flow velocity to annular mitral velocity of the lateral LV wall
— *HRR: Heart rate recovery *
— *LV mass: Left ventricular mass*
— *LVESV: Left ventricular end-systolic volume*
16 events: All 4 variables abnormal.

While subjects prescribed a β-blocking agent demonstrated a significantly lower resting (70.6 ± 8.4 vs 78.5 ± 7.9 beats per minute, $P<.001$) and peak exercise HR (123.6 ± 14.5 vs 136.5 ± 15.9 beats per minute, $P<.001$), HRR_1 was similar between subgroups (17.7 ± 3.1 vs 18.4 ± 3.4, $P>.05$). There were 24 cardiac-related deaths in the 139 subjects prescribed a β-blocking agent. HRR_1 was a significant univariate prognostic maker in this subgroup (χ^2: 22.9; hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.61–0.82, $P<.001$). The remaining 19 cardiac-related deaths were in the 104 subjects not prescribed a β-blocking agent. HRR_1 was again a significant univariate prognostic maker in this second subgroup (χ^2: 32.2; HR: 0.70; 95% CI: 0.61–0.80, $P<.001$). While age was significantly higher in subjects receiving β-blockage (63.9 ± 9.2 vs 60.0 ± 10.0 y, $P = .002$), it was not a significant predictor of events in either subgroup (residual $\chi^2 \leq 3.3, P \geq .07$).

HRR_1 was significantly correlated with LVEF ($r = 0.14$, $P = .03$), LV mass ($r = -0.30$, $P<.001$), and E/A ($r = -0.22$, $P = .001$), but with a weak association. The significant correlation between HRR_1 and E/E′ ($r = -0.49$, $P<.001$) reached moderate strength. The correlation between LVESV and HRR was not statistically significant ($r = 0.13$, $P = .05$). Receiver operating characteristic curve analysis revealed a HRR_1 threshold of ≤/>17 beats per minute optimally indentified subjects with an E/E′ ≤/>10 (lower value reflecting normal; area under curve: 0.75; 95% CI: 0.68–0.82, 78% sensitivity/73% specificity, $P<.001$).

There were 43 cardiac-related deaths during the 4 year tracking period (annual cardiac mortality rate: 9.4%). HRR_1 (χ^2: 55.5, $P<.001$), E/E′ (χ^2: 46.1, $P<.001$), LV mass (χ^2: 36.0, $P<.001$), E/A (χ^2: 17.1, $P<.001$), and LVESV (χ^2: 8.2, $P = .004$) were all significant univariate predictors of survival. Multivariate Cox regression analysis revealed HRR_1 was the strongest predictor of cardiac mortality (χ^2: 55.5, $P<.001$), LV mass (residual χ^2: 13.1, $P<.001$), E/E′ (residual χ^2: 11.2, $P = .001$), and LVESV (residual χ^2: 5.9, $P = .015$) all added significant prognostic value and were retained in the regression while E/A (residual χ^2: 1.2, $P = .28$) and LVEF (residual χ^2: 0.008, $P = .93$) were removed. Receiver operating characteristic curve analysis revealed the optimal prognostic thresholds for HRR_1, E/E′, LV mass, and LVESV were ≤/>17 beats per minute (higher value normal; area under curve: 0.83; 75% sensitivity/90% specificity; HR: 21.8, 95% CI: 7.8–61.4, $P<.001$), ≤/>10 (lower value normal; area under curve: 0.76; 80% sensitivity/72% specificity; HR: 6.7, 95% CI: 3.4–13.0, $P<.001$), ≤ />232 grams (lower value normal; area under curve: 0.69; 73% sensitivity/65% specificity; HR: 5.4, 95% CI: 2.9–10.1, $P<.001$), and ≤ />113 milliliters (lower value normal; area under curve: 0.64; 64% sensitivity/65% specificity; HR: 4.4, 95% CI: 2.3–8.4, $P<.001$), respectively. Using these thresholds, Kaplan-Meier analysis revealed the percentage of subjects surviving with the presence of 0 or 1, 2, and 3 or 4 abnormal values were significantly different (Figure).

Discussion

Based on recent investigations, HRR appears to be a valuable prognostic marker in patients with HF.[4,5] These previous findings are confirmed in the present study, further supporting the clinical use of this easily derived exercise test variable in patients with HF. HRR furthermore was a superior prognostic marker compared to variables obtained

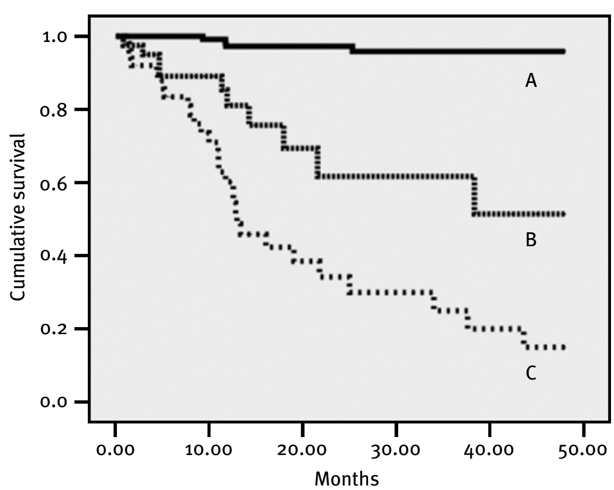

Figure 1. Kaplan-Meier analysis for 4-year cardiac mortality according to combined HRR_1, E/E′, LV mass, and LVESV dichotomous thresholds.

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from echocardiography with TDI, although combining these variables provided better predictive power for risk of cardiac death. It also appears that HRR is moderately and inversely associated with E/E′, an accurate gauge of LV filling pressure,[11] which has previously demonstrated a significant correlation with aerobic capacity in patients with HF.[8]

We are unaware of any previous investigation reporting on the relationship between HRR and measures obtained from echocardiography with TDI. Of the correlations reported in the current analysis, the strongest was demonstrated between E/E′ and HRR_1. Stein et al[12] recently demonstrated a relationship between diastolic and autonomic dysfunction in patients with HF. Given the relationship between HRR and autonomic tone,[13] the correlation of this exercise variable to E/E′, a marker of diastolic dysfunction, is not surprising. Moreover, ROC analysis in the present study indicates an HRR_1 threshold of $\leq/>17$ beats per minute was optimal in identifying an E/E′ threshold of $\leq/>10$. This relationship should be considered when performing exercise testing in patients with HF in the absence of echocardiography with TDI data.

β-Blockade, a well-accepted pharmacologic intervention in patients with HF that is known to dramatically blunt the HR response during exercise, appears to have no impact on HRR.[14] The present study supports this notion, demonstrating similar HRR_1 values between subgroups based upon β-blocker use. Furthermore, subgroup analysis in this investigation indicates HRR_1 was prognostically significant, irrespective of β-blocker use. Previous studies along with the present findings therefore suggest this drug class has no impact on the clinical value of HRR, supporting its clinical application irrespective of pharmacotherapy.

While expression of HRR at 1 minute postexercise is an accepted approach, others have proposed a 2 minute calculation, which also demonstrates prognostic value.[15] We unfortunately did not capture HRR at 2 minutes postexercise in the present investigation. Future research should compare the diagnostic and prognostic value of HRR at different time intervals in patients with HF. Furthermore, the majority of subjects in the present study were male, potentially limiting extrapolation of these findings to females with HF. Future investigations should therefore include a larger number of female patients allowing for gender-based comparisons.

In conclusion, HRR has demonstrated great promise as a marker of adverse events in non-HF cohorts. Initial evidence indicates HRR is also prognostic in patients with HF. The results of the present study confirm the value of HRR and also demonstrate an association between HRR and diastolic dysfunction as measured by echocardiography with TDI. Heart rate recovery and echocardiography with TDI also provide complementary prognostic information when evaluating patients with HF. Additional work in this area is warranted to more accurately determine the clinical role of these assessment techniques.

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