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Severe Frequent Ventricular Ectopy After Exercise as a Predictor of Death in Patients With Heart Failure

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OBJECTIVES The study was done to determine the prognostic importance of frequent ventricular ectopy in recovery after exercise among patients with systolic heart failure (HF).

BACKGROUND Although ventricular ectopy during recovery after exercise predicts death in patients without HF, its prognostic importance in patients with significant ventricular dysfunction is unknown.

METHODS Systematic electrocardiographic data during rest, exercise, and recovery were gathered on 2,123 consecutive patients with left ventricular systolic ejection fraction ≤35% who were referred for symptom-limited metabolic treadmill exercise testing. Severe ventricular ectopy was defined as the presence of ventricular triplets, sustained or nonsustained ventricular tachycardia, ventricular flutter, polymorphic ventricular tachycardia, or ventricular fibrillation. The primary end point was all-cause mortality, with censoring for interval cardiac transplantation.

RESULTS Of 2,123 patients, 140 (7%) had severe ventricular ectopy during recovery. There were 530 deaths (median follow-up among survivors 2.9 years). Severe ventricular ectopy during recovery was associated with an increased risk of death (three-year death rates 37% vs. 22%, hazard ratio [HR] 1.76; 95% confidence interval [CI] 1.32 to 2.34, $p < 0.0001$). After adjustment for ventricular ectopy at rest and during exercise, peak oxygen uptake, and other potential confounders, severe ventricular ectopy during recovery remained predictive of death (adjusted HR 1.48; 95% CI 1.10 to 1.97; $p = 0.0089$), whereas ventricular ectopy during exercise was not predictive of death in this cohort.

CONCLUSIONS Severe ventricular ectopy during recovery after exercise is predictive of increased mortality in patients with severe HF and can be used as a prognostic indicator of adverse outcomes in HF cohorts. (J Am Coll Cardiol 2004;44:820–6) © 2004 by the American College of Cardiology Foundation

Ventricular ectopy at rest is common in patients with depressed left ventricular (LV) systolic function, and sudden death is responsible for 30% to 50% of mortality in heart failure (HF) patients (1). Among patients without HF, frequent ventricular ectopy during and/or after exercise has been shown to predict a higher death risk (2,3). The prognostic importance of ventricular ectopy during or after exercise among patients with advanced HF is unclear.

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As autonomic abnormalities that predispose to ventricular arrhythmias are common in severe HF (4), we hypothesized that ventricular ectopy during or after exercise would also be predictive of increased risk in this setting. Furthermore, as recovery immediately after exercise is thought to be a time when vagal reactivation should be rapidly occurring, we hypothesized that ventricular ectopy during recovery would be more predictive.

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In this study, we analyzed the prognostic value of exercise-related ventricular ectopy in patients with HF referred for metabolic gas exchange exercise testing.

METHODS

Patients. Consecutive Cleveland Clinic Foundation patients with LV systolic ejection fraction ≤35% who were referred for metabolic treadmill exercise testing between January 1995 and December 2002 were considered for inclusion. Patients were excluded for the following reasons: age <20 years, absence of U.S. social security number, congenital or primary valvular heart disease, end-stage renal disease, or history of cardiac transplantation. In patients with more than one metabolic exercise test, only the initial study was included in the analysis. Data were prospectively recorded on a customized computer database, which was approved by the Institutional Review Board of the Cleveland Clinic Foundation. The requirement for obtaining informed consent was waived.

Clinical and exercise data. Before each metabolic stress test, a structured interview and chart review yielded prospectively obtained data on demographics, LV ejection fraction, medications, etiology of HF, and various other clinical parameters as defined previously (5). Symptom-limited metabolic stress testing was performed using the Naughton protocol and recorded on a MedGraphics car-

Abbreviations and Acronyms

CI	= confidence interval
HF	= heart failure
HR	= hazard ratio
LV	= left ventricular
VCO_2	= carbon dioxide production (in ml/kg/min)
VE	= minute ventilation
VE/VCO_2	= ratio of minute ventilation to carbon dioxide production
VO_2	= oxygen consumption (in ml/kg/min)

diopulmonary system. Data were prospectively collected during each stage of exercise on symptoms, rhythm, and blood pressure. Measurements of oxygen consumption (VO_2), carbon dioxide production (VCO_2), heart rate, minute ventilation (VE), tidal volume, and respiratory rate were made after steady state at rest and after every 30 s during exercise and recovery. The ventilatory response to exercise was defined as the value of ratio of minute ventilation to carbon dioxide production (VE/VCO_2) at peak exercise (5). Anaerobic threshold was determined by the V-slope method (6) or by inspection of ventilatory equivalents (7).

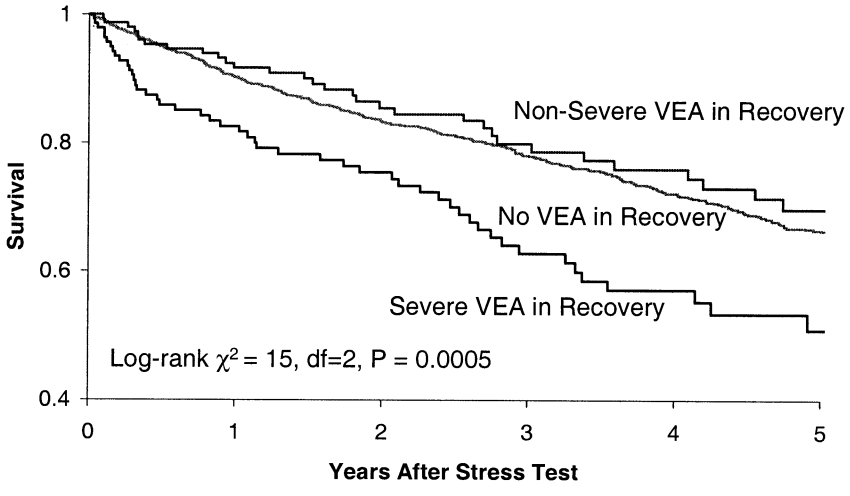
Because of the inclusion of patients with atrial fibrillation and patients actively receiving beta-blocker therapy, chronotropic response (previously documented to have prognostic significance in exercise testing [8]) was not included in the analyses. In addition, because of the inclusion of patients with permanent pacemakers, heart rate recovery (also known to be of prognostic importance [9]) was also not considered. The Duke treadmill score was not included for the above reasons and because of the prevalence of abnormal resting electrocardiograms in this population.

Ventricular ectopy. Ventricular ectopy was previously defined (10). Briefly, systematic data were gathered on the electrocardiogram and during rest, exercise, and recovery and analyzed according to prespecified definitions. Frequent ventricular ectopy was defined as the presence of seven or more ventricular premature beats/min, frequent ventricular couplets, ventricular bigeminy or trigeminy, or any other form of ventricular tachycardia (either monomorphic or polymorphic) or ventricular fibrillation.

Patients with frequent ventricular ectopy were subdivided into less severe and more severe categories based on the Lown classification (11). Severe ventricular ectopy was defined as the presence of ventricular triplets, sustained or nonsustained ventricular tachycardia, ventricular flutter, polymorphic ventricular tachycardia, or ventricular fibrillation. Sustained ventricular arrhythmias were defined as ventricular flutter, polymorphic ventricular tachycardia, or ventricular fibrillation.

End points. The primary end point was all-cause mortality, which was determined with reference to the Social Security Death Index (12,13). We have previously shown that this method has a sensitivity of 97% for detecting death in Cleveland Clinic Foundation exercise laboratory patients (8). Cross-referencing our unified transplant database identified patients later undergoing orthotopic heart transplantation. Patients who underwent cardiac transplant during the period of the study were censored at the time of transplantation.

Statistical analyses. For descriptive purposes, patients were divided into three groups: (1) no frequent ventricular ectopy in recovery, (2) nonsevere frequent ventricular ectopy in recovery, and (3) severe ventricular ectopy in recovery. The Kruskal-Wallis test was used for comparisons of



Number at Risk						
No VEA	1833	1425	1108	813	569	366
Non-severe	150	120	89	64	54	37
Severe	140	99	79	50	39	21

Figure 1. Kaplan-Meier analysis of survival according to the absence or presence of nonsevere frequent ventricular ectopy or severe frequent ventricular ectopy during recovery after exercise. VEA = ventricular ectopic activity.

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Table 1. Clinical and Cardiovascular Characteristics of the Study Patients According to the Absence or Presence of Ventricular Ectopy During Recovery After Exercise

Variable	No Frequent Ventricular Ectopy (n = 1,833)	Frequent Non-Severe Ventricular Ectopy (n = 150)	Frequent Severe Ventricular Ectopy (n = 140)	p Value
Demographic characteristics				
Age (yrs)	54 ± 11	54 ± 12	57 ± 10	0.0008
Male gender, no. (%)	1,354 (74)	117 (78)	122 (87)	0.0004
Black, no. (%)	199 (11)	15 (10)	17 (12)	0.78
Clinical history, no. (%)				
Diabetes, insulin-treated	161 (9)	11 (7)	5 (4)	0.03
Diabetes, non–insulin-treated	306 (17)	16 (11)	16 (11)	0.03
Hypertension	898 (49)	67 (45)	69 (49)	0.73
Tobacco use	399 (22)	34 (25)	33 (24)	0.86
Known coronary artery disease	928 (51)	81 (54)	70 (50)	0.84
Prior myocardial infarction	709 (39)	51 (34)	51 (36)	0.35
Prior coronary artery bypass grafting	468 (26)	41 (27)	41 (29)	0.29
Prior percutaneous coronary intervention	342 (19)	24 (16)	21 (15)	0.20
Pacemaker	346 (19)	21 (14)	21 (15)	0.11
Implantable defibrillator	350 (19)	39 (26)	34 (24)	0.03
Atrial fibrillation	99 (5)	7 (5)	18 (13)	0.002
Peripheral vascular disease	79 (4)	5 (3)	6 (4)	0.84
Carotid artery disease	101 (6)	8 (5)	10 (7)	0.50
COPD	161 (9)	15 (10)	21 (15)	0.02
Asthma	124 (7)	8 (5)	7 (5)	0.32
Prior stroke	87 (5)	11 (7)	3 (2)	0.52
Prior TIA	80 (4)	5 (3)	5 (4)	0.52
Medication use, no. (%)				
Beta-blocker	800 (44)	74 (49)	53 (38)	0.53
ACE inhibitor	1,511 (82)	118 (79)	118 (84)	0.99
Angiotensin receptor blocker	155 (8)	15 (10)	14 (10)	0.41
Amiodarone	395 (22)	22 (15)	20 (14)	0.009
Sotalol	14 (1)	2 (1)	2 (1)	0.62
Calcium channel blocker	27 (1)	2 (1)	2 (1)	0.93
Aspirin	749 (41)	66 (44)	54 (30)	0.87
Statin	530 (29)	46 (31)	39 (29)	0.96
Spirinolactone	360 (20)	19 (13)	23 (16)	0.09
Digoxin	1,442 (79)	113 (75)	118 (84)	0.32
Loop diuretic	1,534 (84)	121 (81)	125 (89)	0.25
Thiazide diuretic	219 (12)	21 (14)	22 (16)	0.15
Cardiovascular assessment				
Body mass index	28 ± 6	28 ± 5	28 ± 5	0.73
Resting heart rate (beats/min)	79 ± 15	74 ± 15	79 ± 15	0.003
Resting blood pressure (mm Hg)				
Systolic	109 ± 18	110 ± 17	108 ± 17	0.44
Diastolic	74 ± 11	73 ± 11	72 ± 11	0.18
Left ventricular ejection fraction (%)	20 ± 7	20 ± 6	19 ± 7	0.42
Peak oxygen consumption (ml/kg/min)	16.5 ± 5.2	18.0 ± 5.7	16.5 ± 4.3	0.007
VE/VCO_2	33.3 ± 9.7	31.9 ± 8.8	34.3 ± 9.5	0.22
Nonsevere ventricular ectopy (rest), no. (%)	14 (1)	37 (25)	22 (16)	0.0001
Severe ventricular ectopy (rest), no. (%)	12 (1)	2 (1)	18 (13)	0.0001
Severe ventricular ectopy (exercise), no. (%)	34 (2)	20 (13)	51 (36)	0.0001
Nonsevere ventricular ectopy (exercise), no. (%)	67 (4)	63 (42)	28 (20)	0.0001

ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack; VCO_2 = carbon dioxide production; VE = minute ventilation.

continuous variables, whereas the chi-square test for trend was used to test for comparisons of categorical variables.

Kaplan-Meier curves were constructed (Fig. 1) and Cox stepwise selection proportional hazards modeling was performed to analyze the association of recovery ventricular ectopy and death. The proportional hazards assumption was confirmed by testing an interaction with follow-up time as a time-dependent covariate. Three proportional hazards models were generated. The simplest model considered only severe and nonsevere frequent ventricular ectopy in recovery. The next model considered severe and nonsevere frequent ventricular ectopy in recovery, in exercise, and at rest. Finally, we added to all six of the ventricular ectopy variables a number of potential confounders including all the variables listed in Table 1.

We tested for possible interactions by means of prespeci-

fied subset analyses and interaction terms. Specifically, we stratified patients according to age, gender, prior implantable defibrillator placement, peak V_{O_2}, ventilatory response to exercise, body mass index, use of medications (including aspirin, beta-blockers, and metolazone), known carotid disease, and known chronic lung disease. All analyses were performed with SAS software (version 8.2, SAS Institute, Cary, North Carolina).

RESULTS

There were 2,123 patients eligible for analysis. Of this cohort, 290 patients (14%) had frequent ventricular ectopy in recovery, of whom 140 (48%) had severe ventricular ectopy in recovery. Five patients (0.2%) developed sustained ventricular arrhythmias during recovery after exercise.

Clinical and metabolic exercise data according to presence or absence of ventricular ectopy in recovery are shown in Table 1. Patients with frequent ventricular ectopy during recovery were older and more likely to be male, to have a history of atrial fibrillation or chronic obstructive pulmonary disease, and were less likely to be taking amiodarone. The presence of severe ventricular ectopy at rest was correlated with severe ventricular ectopy during recovery.

There were 530 deaths during a median follow-up of 2.9 years (25th and 75th percentiles, 1.4 and 4.9 years, respectively); during that time, 198 (9%) underwent cardiac transplantation. Among patients with severe ventricular ectopy in recovery, there were 51 deaths, and among those with nonsevere frequent ventricular ectopy in recovery, there were 34 deaths. Severe frequent ectopy in recovery predicted a higher mortality (hazard ratio [HR] 1.76; 95% confidence interval [CI] 1.32 to 2.34; $p < 0.0001$) compared to no frequent ventricular ectopy or nonsevere frequent ventricular ectopy during recovery after exercise (Fig. 1).

In a model that included severe ventricular ectopy in recovery, nonsevere ventricular ectopy in recovery, severe ventricular ectopy during exercise, nonsevere ventricular ectopy during exercise, severe ventricular ectopy at rest, and nonsevere ventricular ectopy at rest, the only variable predictive of mortality was severe ventricular ectopy during recovery (adjusted HR 1.55; 95% CI 1.12 to 2.15; $p = 0.009$).

Using a subsequent multivariable Cox regression model, after adjustment for baseline clinical and cardiovascular variables, severe frequent ventricular ectopy in recovery remained predictive of death (adjusted HR 1.48; 95% CI 1.10 to 1.97; $p = 0.0089$). The strongest predictor overall was peak V_{O_2}. Other independent predictors included male gender, concomitant thiazide diuretic use, lower resting diastolic blood pressure, carotid artery disease, chronic obstructive lung disease, and lower body mass index. Beta-blocker and aspirin therapy were protective (Table 2).

In addition to stepwise modeling, a multivariate model was created that forced in age, chronic obstructive lung disease, amiodarone, and atrial fibrillation, in addition to the six ventricular ectopy variables (nonsevere and severe, during rest, exercise, and recovery). The only ventricular ectopy variable that was a significant predictor of death was severe ventricular ectopy during recovery (adjusted HR 1.43; 95% CI 1.03 to 1.99; $p = 0.035$). Other variables in this nonstepwise model that were significant predictors of death were age (adjusted HR 1.03; 95% CI 1.02 to 1.04; $p < 0.0001$), chronic obstructive pulmonary disease (adjusted HR 1.52; 95% CI 1.18 to 1.96; $p = 0.0011$), and amiodarone therapy (adjusted HR 1.45; 95% CI 1.19 to 1.77; $p = 0.0002$).

Table 2. Predictors of Mortality by Multivariable Analysis: Variables Are Shown in the Order They Entered a Stepwise Cox Regression Model

Variable*	Adjusted Hazard Ratio (95% CI)	p Value
Peak oxygen consumption (decrease of 5 ml/kg/min)	2.07 (1.85–2.31)	0.0001
Male gender	2.00 (1.56–2.55)	0.0001
Beta-blocker therapy	0.64 (0.52–0.77)	0.0001
Thiazide diuretic	1.69 (1.36–2.10)	0.0001
Resting diastolic blood pressure	0.98 (0.98–0.99)	0.0001
Carotid artery disease	1.64 (1.21–2.20)	0.0013
Severe ventricular ectopy in recovery	1.48 (1.10–1.97)	0.0089
Aspirin therapy	0.79 (0.66–0.95)	0.013
Chronic obstructive lung disease	1.39 (1.08–1.79)	0.011
Body mass index (decrease of 5 kg/m^2)	1.12 (1.04–1.22)	0.005
Implantable defibrillator	0.78 (0.619–0.98)	0.038

*Only variables with $p < 0.05$ are shown. The following variables were rejected from the model, using a criterion of $p < 0.05$ for model entry and retention: age, race, resting pulse rate, resting systolic blood pressure, ejection fraction, history of atrial fibrillation, ischemic heart disease, diabetes, hypertension, smoking history, family history, prior myocardial infarction, prior coronary artery bypass grafting, prior percutaneous intervention, pacemaker, peripheral vascular disease, asthma, prior stroke, prior transient ischemic attack, V_E/V_{CO_2}, angiotensin-converting enzyme inhibitor, digoxin, angiotensin-II antagonists, loop diuretics, spironolactone, nitrates, statins, fibrates, inhaled beta-2 agonists, amiodarone, and sotalol.
CI = confidence interval.

The results of prespecified subgroup analyses are shown in Table 3 Severe ventricular ectopy in recovery was associated with higher death rates in nearly all subgroups. Of note, a borderline interaction was noted whereby severe ventricular ectopy in recovery was a stronger predictor of risk among patients with an V_{O_2} of ≥14 ml/kg/min.

DISCUSSION

In a large cohort of patients with severe LV dysfunction and HF, the presence of severe ventricular ectopy during recovery was independently predictive of risk of death even after accounting for maximum V_{O_2}, ejection fraction, ventricular ectopy at rest or during exercise, and other potential confounders. Our findings in this group of very ill patients parallel our previous report of the prognostic power of ventricular ectopy during recovery after exercise among a very large cohort of patients without HF (2).

Despite advances in therapy, HF continues to carry a 59% five-year age-adjusted mortality (14). Cardiac transplantation has a median survival of 10 years (15). Organ availability limits the number of transplants to approxi-

Table 3. Association Between Severe Ventricular Ectopy During Recovery and Mortality in Prespecified Subgroups

Stratifying Variable	No Severe Ventricular Ectopy During Recovery Deaths/No. of Patients (%)	Severe Ventricular Ectopy During Recovery Deaths/No. of Patients (%)	Relative Risk (95% CI)	p Value for Interaction
Age				
<60 yrs	270/1,343 (20)	22/77 (29)	1.51 (0.98–2.33)	0.53
>60 yrs	209/640 (33)	29/63 (46)	1.83 (1.24–2.71)	
Implantable defibrillator				
Yes	77/389 (20)	11/34 (32)	1.91 (1.01–3.60)	0.90
No	402/1,594 (25)	40/106 (38)	1.75 (1.26–2.42)	
Gender				
Male	391/1,471 (27)	44/122 (36)	1.56 (1.15–2.14)	0.29
Female	88/512 (17)	7/18 (39)	2.46 (1.14–5.30)	
Etiology of heart failure				
Ischemic	279/1,009 (28)	25/70 (36)	1.63 (1.08–2.46)	0.52
Nonischemic	200/974 (21)	26/70 (37)	1.99 (1.32–2.99)	
Peak oxygen consumption				
<14 ml/kg/min	244/676 (36)	20/42 (48)	1.26 (0.80–1.99)	0.05
≥14 ml/kg/min	235/1,307 (18)	31/98 (32)	2.28 (1.57–3.32)	
VE/VCO_2				
≥35	238/747 (32)	29/57 (51)	1.73 (1.18–2.55)	0.81
≤35	241/1,236 (20)	22/83 (27)	1.64 (1.06–2.54)	
Body mass index				
≤25	161/617 (26)	16/40 (40)	1.93 (1.15–3.23)	0.68
≥25	318/1,366 (23)	35/100 (35)	1.70 (1.20–2.41)	
Aspirin therapy				
Yes	173/815 (21)	18/54 (33)	1.74 (1.07–2.83)	0.94
No	306/1,168 (26)	33/86 (38)	1.76 (1.23–2.53)	
Beta-blocker therapy				
Yes	124/874 (14)	12/53 (23)	1.81 (1.00–3.28)	0.84
No	355/1,109 (32)	39/87 (45)	1.68 (1.21–2.34)	
COPD				
Yes	64/176 (36)	9/21 (43)	1.49 (0.74–3.01)	0.69
No	415/1,807 (23)	42/119 (35)	1.75 (1.27–2.40)	
Severe ventricular ectopy with exercise				
Yes	15/54 (28)	22/51 (43)	2.25 (1.16–4.36)	0.29
No	464/1,929 (24)	29/89 (33)	1.45 (1.00–2.11)	

Abbreviations as in Tables 1 and 2.

mately 2,000 per year in the U.S., well below requirements and only a small fraction of the 5 million or so Americans with HF. Identifying patients at high risk of death is vital to appropriately select patients for referral for advanced therapies including heart transplantation. Conventional predictors of mortality include gender, LV and right ventricular ejection fractions, functional class, ischemic etiology, the presence of significant co-morbidities, and peak oxygen uptake levels determined on metabolic exercise testing (16).

Weber et al. (17) first described the use of peak VO_2 in ambulatory patients with HF as a means of formally assessing functional status. Exercise data from the first Veterans Administration Heart Failure Trial demonstrated that peak VO_2 independently predicted mortality (18). A study of 116 patients being considered for cardiac transplantation in the University of Pennsylvania program found that in patients with a peak VO_2 of <14 ml/kg/min, the freedom from death or urgent cardiac transplantation was only 48% at one year (19). Patients without significant co-morbidities and with a peak VO_2 of ≥14 ml/kg/min had a one-year survival of 94%. A consensus exists that an ejection fraction <20% and a peak VO_2 of <14 ml/kg/min should be present to warrant referral for cardiac transplantation (20). Some argue that there is an overreliance placed on this single end point for prognosis (21). Ventilatory and heart rate responses to exercise may be superior to peak VO_2 as predictors of mortality (5). The current report suggests that in a small number of patients the presence of severe ventricular ectopy during recovery may be an additional useful predictor of high risk.

Patients with HF have autonomic impairment at rest, manifested by reduced heart rate variability (22) and impaired baro-receptor responsiveness (4), both of which predict increased mortality in these patients. In addition, some HF patients have been shown to have blunted heart rate responses to exercise (23) and abnormal hyperventilation (24) as prognostically important manifestations of autonomic dysfunction. The presence of severe ventricular ectopy during recovery, a time when vagal reactivation ought to be occurring, may be a marker of a greater severity of autonomic disturbance and hence correlate with a greater risk of death.

Some important limitations of our study require mention.

Our data are derived from a cohort seen at a referral center with a high cardiac transplant volume; hence, there will be a need to confirm our results elsewhere. Use of the Social Security Death Index meant that we did not have data regarding the mechanism of death in these patients. Others and we have addressed in detail the issue of assessing cause of death in patients with cardiovascular disease and HF. Arguments have been made that attempting to classify cause of death may be problematic, whereas all-cause mortality is an objective, clinically relevant, and unbiased end point (25–27).

Resting ventricular ectopy was based only on a short pre-exercise recording, rather than a prolonged ambulatory monitor. We could not incorporate chronotropic response or heart rate recovery into our survival models because of the inclusion of patients with atrial fibrillation, pacemakers, and beta-blocker use. Indeed, beta-blocker use was only in the region of 44% of patients, reflecting the era of the data (January 1995 to December 2002). Contemporary practice now incorporates significantly higher use of beta-blocking therapy. This may limit somewhat the extrapolation of this data to the current heart failure cohort. In addition, we could not allow for the potential effects of interventions performed following the exercise stress test in patients who developed arrhythmias, which may have included changes in medications, a search for myocardial ischemia, or the implantation of cardioverter-defibrillators, which may have altered outcomes. Of note, though, only five patients developed sustained ventricular arrhythmias during recovery, suggesting that this is unlikely.

Cardiac transplantation was a competing event, which we treated by censoring; this seems a reasonable strategy as it is unlikely that patients were specifically chosen for transplant because of ventricular ectopy after exercise, which was not appreciated as a predictor of risk at the time these patients were exercised. Finally, even though it was an independent predictor of death, severe ventricular ectopy during recovery was a relatively uncommon finding.

Despite these limitations, our findings lend further credence to the potential clinical value of ventricular ectopy during recovery after exercise. In this cohort of HF patients, this finding was independently predictive of death, particularly among patients with an V_{O_2} >14 ml/kg/min, and hence may be useful for identifying previously unrecognized candidates for aggressive HF therapies. Future research will be needed to confirm these findings and to determine how best to incorporate the finding of recovery ventricular ectopy into exercise test interpretation among patients with and without HF.

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