EDITORIAL COMMENT

Postexercise Severe Ventricular Ectopy in Heart Failure Patients

New Marker for Aggregate Risk*

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In our current era marked with the beneficial addition of implantable cardiac defibrillators (ICDs) and beta-adrenergic receptor blockade to our therapeutic strategies, it is increasingly difficult to identify the individual with advanced systolic heart failure (HF) at high mortality risk (1). Traditionally, the peak maximum oxygen consumption identified during symptom-limited, metabolic exercise treadmill testing has been considered one of the best criteria as originally identified by Mancini et al. (2). However, in the current era of beta-blocker treatment for advanced HF, there are developing concerns regarding the interpretation of this marker in identifying the high-risk individual. For example, Shaker et al. (3), in a retrospective analysis, demonstrated that the traditional peak oxygen-consumption cut-off value of 14 ml/kg/min does not predict survival free of cardiac transplant in patients who tolerate chronic treatment with beta-adrenergic receptor blockers. Therefore, it is both important and relevant to identify new clinical markers of aggregate risk to assist in this decision-making process.

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In a retrospective, cohort study in this issue of the *Journal*, O'Neill et al. (4) demonstrate that the presence of complex ventricular ectopy during the recovery period after symptom-limited metabolic exercise treadmill testing identifies patients with advanced HF at increased risk for all-cause mortality. In a total of 2,123 consecutive patients undergoing routine symptom-limited metabolic exercise treadmill testing at the Cleveland Clinic, the three-year mortality ascertained from the Social Security Death Index was greater in patients who developed severe ventricular ectopy during recovery compared with those who did not (37% vs. 22%; p ≤ 0.0001). 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 prevalence of severe ventricular ectopy during recovery from exercise was relatively low, as only 140 of 2,123 (7%) of the consecutive patients who were analyzed experienced this phenomenon. The groups with and without ventricular ectopy during recovery from metabolic exercise treadmill testing were reasonably balanced with regards to potential confounders. The group with severe ventricular ectopy during recovery was significantly older (57 vs. 54 years) and had more chronic obstructive pulmonary disease (15% vs. 9%). Medical therapy was balanced with the exception of less use of amiodarone in the group with severe ectopy during recovery (14% vs. 22%). Importantly, beta-blocker use was not significantly different (38% vs. 44%) between the groups. The etiology of advanced HF appeared balanced based on the presence of known coronary artery disease (50% vs. 51%). Moreover, the severity of HF also appeared balanced between those with and without severe ventricular ectopy during recovery, as suggested by similar mean ejection fractions (19% vs. 20%), systolic blood pressure (108 mm Hg vs. 109 mm Hg), and peak oxygen consumption (16.5 ± 4.3 ml/kg/min vs. 16.5 ± 5.2 ml/kg/min) in patients with severe ventricular ectopy compared with those without severe ventricular ectopy during recovery from exercise.

The association of severe ventricular ectopy during recovery from exercise persisted in adjusted analysis (hazard ratio [HR] 1.48; 95% confidence interval [CI] 1.10 to 1.97; p = 0.0089). In stratified analyses, the association of ventricular ectopy was observed in those using (HR 1.81; 95% CI 1.00 to 3.28) and not using beta-blockers (HR 1.68; 95% CI 1.21 to 2.34), patients with a nonischemic (HR 1.99; 95% CI 1.32 to 2.99) and ischemic etiologies (HR 1.63; 95% CI 1.08 to 2.46), as well as those with (HR 2.25; 95% CI 1.16 to 4.35) and without (HR 1.45; 95% CI 1.00 to 2.11) severe ventricular ectopy *during* exercise. The only hint for interaction (p = 0.05) was demonstrated when the analysis was stratified by peak oxygen consumption using the traditional cut-off value for transplant consideration. The association of severe postexercise ventricular ectopy with increased mortality risk was most robust in those with a peak oxygen consumption ≥14 ml/kg/min (HR 2.28; 95% CI 1.57 to 3.32) as compared with those <14 ml/kg/min (HR 1.26; 95% CI 0.80 to 1.99).

Arrhythmias in the setting of left ventricular dysfunction may be due to re-entry, may be triggered after-depolarizations, or due to enhanced automaticity. It is more likely that alterations in autonomic tone may explain the frequency and type of arrhythmia observed in patients during the recovery phase of stress testing. High vagal tone has long been associated with a decreased propensity to malignant ventricular tachyarrhythmias and a prolonged survival in patients with cardiac disease (5). Heart rate response during the recovery period of stress testing is believed to be a marker of autonomic tone and has been shown to be predictive of mortality (6). In a study of more than 29,000 patients without a history of HF or arrhythmias,

ventricular arrhythmias during the recovery phase of stress testing also were found to be a good predictor of mortality (7). The current study extends this finding to patients with congestive HF. Finally, interventricular and intraventricular conduction delay may contribute to impaired autonomic tone as suggested by improvements in heart rate variability after cardiac resynchronization therapy (8).

One may question the relevance of these data to current practice because many of the patients in this study with an ischemic etiology would now be candidates for ICDs based of the results of the Multicenter Automatic Defibrillator Implantation Trial (MADIT), the Multicenter UnSustained Tachycardia Trial (MUSTT) and the MADIT-II studies. Moreover, given the recently released results of Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT), it appears that ICD therapy will be recommended for all patients with symptomatic HF, including those with a nonischemic etiology. Diminishing the clinical relevance of the present study by O'Neill et al. (4) based on this line of reasoning assumes, however, that severe ventricular ectopy during recovery from metabolic exercise testing identifies patients with an increased risk for arrhythmic death that would be substantially reduced by an ICD. However, the association of severe ventricular ectopy during recovery from metabolic exercise testing with an increased risk for mortality was demonstrated in patients *with* (HR 1.91; 95% CI 1.01 to 3.60) and *without* (HR 1.75; 95% CI 1.26 to 2.42) an ICD. What does this suggest? It is likely that the presence of severe ventricular ectopy during recovery is not a marker of future arrhythmic risk as much as an aggregate measure of HF severity that identifies patients at higher risk for disease progression. Impaired baroreceptor function certainly is expected to contribute to arrhythmic risk, but its presence also reflects a globally disturbed pathophysiologic milieu that likely increases overall mortality risk. For example, reduced heart rate variability, another measure of impaired baroreceptor function, predicts not only sudden but also all-cause mortality in patients with HF (9,10). Moreover, a precise understanding of the mechanism(s) involved is not necessary for it to function as a useful "summary index" of risk. In addition, although there are a myriad of markers that have been associated with an increased *relative* risk for adverse outcomes in HF, the clinician caring for a patient needs to have an estimate of *absolute* risk. The three-year mortality rate experienced by the overall group of patients that developed severe ventricular ectopy during recovery was greater than what would be expected with cardiac transplantation. However, because this included all the patients that experienced severe ventricular ectopy during recovery from exercise, it is not certain from the data presented that this poor actuarial survival was experienced by the group with a peak oxygen consumption >14 ml/kg/min.

The increasing challenge to clinicians managing patients who have advanced HF is to improve our capacity to risk stratify these patients in the era of cardiac defibrillators, cardiac resynchronization therapy, and the addition of beta-blockers to the therapeutic armamentarium. Another challenge is to determine the best management for patients tolerating beta-blocker therapy who have peak oxygen consumption values that ordinarily would trigger consideration for a cardiac transplant. Ideally, one would like to see these data confirmed in a cohort of patients receiving contemporary management of their heart failure. In particular, it would be desirable to validate these findings in patients with a peak oxygen consumption >14 ml/kg/min, a group that is usually considered to have a good prognosis. However, although acknowledging the inherent weaknesses in a retrospective analysis of a cohort assembled over a time period of evolving changes in HF therapy, these data are intriguing and appear to identify a novel and easily ascertained aggregate risk marker with the capacity to improve our ability to identify the high-risk patient with advanced HF. It seems reasonable to conclude that presence or absence of complex ventricular ectopy during recovery after metabolic exercise testing identifies the individual patient who warrants more frequent follow-up than would otherwise be considered, in particular those with a peak oxygen consumption >14 ml/kg/min, optimization of pharmacological treatment, and possibly cardiac resynchronization therapy (8) if significant interventricular or intraventricular conduction delay is present. Finally, the presence of this aggregate risk marker might be useful to adjudicate clinical equipoise in patients who are otherwise at the threshold of consideration for cardiac transplantation.

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