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EDITORIAL COMMENT

Long-Term Mortality After Ablation of Ischemic Ventricular Tachycardia

Not Inducible Is Not Enough*

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Ventricular tachycardia (VT) following myocardial infarction (MI) arises from surviving muscle fibers that traverse the border and penetrate more deeply into the scar core. Typically, these fibers are interconnected but insulated from one another along much of their course, separated by collagen and fibrous tissue. This architecture disrupts the normal pattern and sequence of rapid ventricular activation and can produce critical regions of slow conduction. In post-MI VT, these critical areas are typically subendocardial but also occur in intramural and epicardial scar. VT results when conduction block occurs at one of these sites, with slow conduction around the block site and reentry of the activation wave front from the opposite direction at the original site of block. Circuit dimensions are large (>2 cm^2). In a given patient, multiple and widely separated areas of slow conduction usually coexist, giving the potential for multiple circuits and differing QRS configurations on the surface electrocardiogram.

Catheter ablation for post-MI VT has been utilized for more than 3 decades to decrease the risk for VT recurrence, improve quality of life, and reduce health care costs associated with treating recurrent episodes. The goal of VT ablation is to eliminate areas of slow conduction where block and initiation of reentry are most likely to occur. During the procedure, programmed ventricular stimulation (PVS) is used to reproduce VTs in the laboratory at onset and confirm ablation success by demonstrating that VT can no longer be induced at the end. Potential limitations of noninducibility as a procedural endpoint include the probabilistic nature of VT induction (variability in the pacing sequence and ease of induction over varying time periods, dependence on site of PVS and proximity to circuits), the inability to induce VT at procedure onset in some patients, and a high rate (20% to 40%) of spontaneous VT recurrence despite post-procedure noninducibility (1-3). Additionally, the risk for repeated induction and termination of VT in marginally stable patients after a long procedure may lead physicians to forgo post-procedure PVS in the interest of a patient's safety. These limitations have prompted many investigators to advocate additional or alternative endpoints for VT ablation, including complete elimination of fragmented and delayed potentials in sinus rhythm (4,5) or extensive ablation of the entire scar (6).

Despite the limitations of PVS as a guide to ablation endpoints, a recent meta-analysis of eight observational studies evaluated post-MI VT ablation outcomes, stratified by the results of post-procedure PVS (7). The investigators reported a substantial reduction in the risks for both recurrent VT and death in patients in whom inducible VT was rendered noninducible by ablation. The study did not examine mortality as a time-dependent variable or adjust for differences in other risk predictors. Thus, the possibility could not be excluded that the ability to render VT noninducible may simply reflect a less extensive electroanatomical substrate associated with better long-term outcomes.

SEE PAGE 1954

It is within this context that we can interpret the findings from the study by Yokohawa et al. (8), published in this issue of the *Journal*. This study,

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involving 7 international centers, provides a retrospective analysis of long-term mortality following ablation in a consecutive cohort of 1,064 patients with post-MI VT who underwent ablation between 2004 and 2012. The study population's mean age was 68 years and mean ejection fraction was 31%. The proportion of patients in whom the index procedure represented the first attempt at VT ablation, versus a repeat procedure, is unclear. The burden of VT episodes before the index ablation also is unknown, although prior amiodarone use in 55% of patients and a history of VT storm in 31% suggest that a substantial portion of patients had more advanced disease. The approach to ablation largely reflected current practices, including use of three-dimensional mapping systems and irrigated-tip ablation catheters, and a multifaceted strategy that included both entrainment mapping and substrate-guided approaches. The study's major goal was to determine whether noninducibility post-ablation independently predicted survival.

Of the 1,011 patients with inducibility data available, 6% of patients had no VT induced at the beginning of the procedure. At the procedure's end, of the 948 patients with initially inducible VT, 70% had no VT induced, 19% still had inducible VT, and the remaining 11% did not undergo post-ablation PVS due to instability. Long-term follow-up data regarding both the outcome of the index ablation and subsequent mortality were available in 998 patients. Overall, at 6 years, survival was 10% to 15%. Patients without inducible VT at the end of the procedure had significantly better survival (unadjusted hazard ratio [HR]: 0.77; 95% confidence interval [CI]: 0.61 to 0.97), with an estimated 4.7 months of life gained compared with those in patients with persistently induced VT or in whom post-ablation PVS was not performed. Exclusion of patients without baseline inducible VT negligibly affected this outcome. As expected, there was a trend toward higher mortality in patients who did not undergo post-procedure PVS due to instability, but this finding was not statistically significant (HR: 1.23; 95% CI: 0.84 to 1.82).

Multivariate Cox regression was used to determine whether post-procedure noninducibility was an independent predictor of mortality relative to other potential baseline comorbidities. An important study limitation was that approximately one-third of the initial cohort was excluded from analysis due to missing data on predictor variables. Noninducibility post-procedure remained an independent predictor of long-term mortality (adjusted HR: 0.65; 95% CI: 0.53 to 0.79). Age, history of atrial fibrillation, diabetes, and presentation with incessant VT were also independent predictors. In this dataset, New York Heart Association functional class and left ventricular ejection fraction did not independently predict mortality. This finding is surprising given previous data indicating that ejection fraction is a strong predictor of mortality in patients with post-MI VT following ablation (2,9). This finding remains unexplained and may reflect unrecognized collinearity among variables, and undetected residual confounders.

Recurrent VT during follow-up was significantly more likely in patients in whom VT remained inducible as well as in patients who did not undergo post-procedural testing (65% vs. 39%). Recurrence of any VT post-ablation did not predict mortality in the unadjusted analysis and was only marginally significant when included as a time-fixed variable in Cox regression analysis (adjusted HR: 1.51; $p = 0.05$), with little impact on the better survival associated with noninducibility. This finding contrasts with those from prior studies that reported a significant association between post-ablation VT recurrence and mortality (2,9). Reduction in the number of recurrent VT episodes following ablation, rather than complete elimination, occurs in a substantial proportion of patients (2) and could also confer mortality benefit. As the authors acknowledge, data regarding the number and timing of post-ablation VT recurrences may have provided a more robust evaluation of the independent impact of VT recurrence per se on mortality, as the impact on time to death may depend on the timing and number of VT recurrences.

Of greater importance, additional time-dependent events during follow-up may substantially influence mortality. These include: 1) changes in drug therapy, including antiarrhythmic drugs; 2) intercurrent heart failure (HF) decompensation or change in functional class; and 3) changes in ischemic burden (progression of coronary disease, new MI, coronary revascularization). Data from a substudy of MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) demonstrated that in a large cohort of patients with prior MI and left ventricular ejection fraction ≤30%, hospitalization for new ischemic events or HF exacerbation during follow-up was associated with a substantial increase in the risks for VT and death relative to patients without these events (10). Recurrent HF hospitalizations during follow-up were the most powerful predictor of mortality (11). We do not know how many patients underwent additional ablation during follow-up or whether such procedures affected VT recurrence and death. The cumulative impact of these events during long-term follow-up (and their distribution between groups) may overwhelm the predictive value of variables

gathered at the time of VT ablation, including inducibility status. They also may potentially explain the relatively limited impact of noninducibility on long-term survival in this population.

What is most sobering in the data reported by Yokokawa et al. (8) is the relentless nature of mortality risk following VT ablation in a post-MI population, irrespective of the outcome of PVS. The survival curves separate after 1 year and remain relatively parallel for the next 5 years, with an approximately 5% difference in estimated survival between groups at most points in time. Survival after 6 years was uncommon in either group. This does not negate the value of ablation in this population, which included a substantial portion of patients with relatively advanced heart disease and drug-refractory VT and in whom the primary therapeutic objective was the reduction of symptoms and VT burden. Survival in this population without ablation is unknown and could have been considerably worse.

Enrollment was recently completed in a randomized trial comparing VT ablation to continued antiarrhythmic drug therapy in a post-MI population with characteristics similar to those described in the present study (VANISH [VT Ablation Versus Enhanced Drug Therapy]; NCT00905853); completion of a planned 5-year follow-up is underway. This trial will likely provide additional insight into the potential survival benefit of VT ablation in the subgroup of post-MI patients with more advanced substrate abnormalities and recurrent VT.

Patient characteristics and approaches to VT ablation in this study reflect current clinical practice in high-volume, experienced centers. The authors are to be congratulated on an important contribution that provides relatively complete mortality data and a contemporary snapshot of factors influencing mortality risk in one of the largest cohorts of post-infarction VT assembled to date. Rendering baseline inducible VT noninducible following ablation is associated with a modest survival benefit, independent of most baseline risk factors. Thus, continued use of noninducibility as one endpoint for VT ablation seems reasonable. Whether improvements in the rate of post-procedure noninducibility alone will lead to significant improvements in survival is much less clear. The results of this study should not discourage the exploration of new additional/alternative endpoints for ablation. Developing better methods to comprehensively address the arrhythmogenic substrate present at the time of ablation remains a high priority, including the use of high-resolution imaging (12,13) and more effective catheter technology to eliminate intramural and subepicardial VT sources (14,15). However, it is likely that a substantial portion of mortality risk (as well as risk for recurrent VT) in the patient with post-MI VT ablation is determined by events and therapies that occur during follow-up. We need to increase our focus on the treatment and prevention of HF progression and new ischemic events, continued beta-blockade, judicious use of antiarrhythmic drug therapy, and the role of heart replacement therapy.

Finally, a strategy of early intervention soon after the initial VT episode (and earlier in the clinical course of ischemic VT) may provide a better test of whether VT ablation can contribute to lower mortality. Two small randomized trials of treatment after the first VT episode in post-MI patients have demonstrated significantly reduced VT recurrences following ablation compared with conventional medical therapy, but no difference in mortality during 2-year follow-up (16,17). Of interest, the mortality at 2 years in both early intervention trials was approximately 10% compared to 25% in the present study, highlighting the potential adverse impact of disease progression and multiple VT recurrences. Whether earlier ablation can alter the prognosis of ischemic VT and improve survival compared with comprehensive medical therapy over extended follow-up remains uncertain and is being evaluated in 2 recently initiated randomized clinical trials (NCT01547208 and NCT02130765).

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