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Predictive Value of Programmed Ventricular Stimulation After Catheter Ablation of Post-Infarction Ventricular Tachycardia

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ABSTRACT

BACKGROUND A recent meta-analysis demonstrated a survival benefit in post-infarction patients whose ventricular tachycardia (VT) was rendered noninducible by catheter ablation. Furthermore, patients with noninducible VT had a lower VT recurrence rate than did patients whose VT remained inducible after ablation.

OBJECTIVES The purpose of this multicenter cohort study was to assess whether noninducibility after VT ablation is independently associated with improved survival.

METHODS Data from 1,064 patients who underwent VT ablation for post-infarction VT at seven international centers were analyzed. The ablation procedure was considered successful if no VT was inducible at the end of the procedure and unsuccessful if VT remained inducible or if programmed stimulation was not performed at the end of the ablation.

RESULTS Median follow-up time was 633 days. Noninducibility was independently associated with lower mortality (adjusted hazard ratio: 0.65; 95% confidence interval: 0.53 to 0.79; $p < 0.001$). Atrial fibrillation, diabetes, and age were other independent predictors of higher mortality. Ablation of only the clinical VT in patients who also had inducible, nonclinical VTs was not associated with improved survival.

CONCLUSIONS Noninducibility after VT ablation in patients with post-infarction VT is independently associated with lower mortality during long-term follow-up. (J Am Coll Cardiol 2015;65:1954–9) © 2015 by the American College of Cardiology Foundation.

The optimal endpoint for catheter ablation of post-infarction, sustained, monomorphic ventricular tachycardia (VT) is not known. A recent meta-analysis demonstrated that the mortality risk may be lower in patients whose VT is rendered noninducible at procedure completion (1). However, the meta-analysis was on the basis of cohort studies and yielded unadjusted estimates of risk.

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The purpose of this study was to assess whether noninducibility of VT is an independent predictor of improved survival after catheter ablation in patients with post-infarction VT.

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METHODS

Seven centers experienced in catheter ablation of VT provided data from consecutive patients who underwent VT ablation for post-infarction VT between 2004 and 2012. Baseline demographic and clinical data were collected. Eligible patients had prior myocardial infarction by history and objective testing.

MAPPING AND ABLATION. After informed consent was obtained from each patient, a multipolar catheter was positioned in the right ventricle. Programmed ventricular stimulation was performed from multiple sites in an attempt to induce VT. The induced VTs were compared to each patient's clinical VT using 12-lead electrocardiograms whenever available or the electrogram morphology of VT episodes recorded by an implantable cardioverter-defibrillator. If these were unavailable, the cycle lengths of the clinical and induced VTs were compared. The protocol of programmed stimulation included up to 4 extra stimuli from 2 ventricular locations with coupling intervals down to 200 ms or refractoriness, whichever occurred first. An irrigated-tip catheter was used for mapping and ablation in conjunction with a 3-dimensional mapping system. If the VT was hemodynamically tolerated, entrainment mapping was performed and radiofrequency energy was delivered at sites with concealed entrainment. In the case of hemodynamically unstable VT, ablation was performed during sinus rhythm in areas with matching pace-maps or areas with fragmented electrograms. Post-ablation, programmed ventricular stimulation was repeated using the same stimulation protocol.

The procedure was classified as successful if no sustained VT (lasting ≥30 s or requiring termination) was inducible when pacing was performed from 2 ventricular sites with up to 4 extra stimuli. The procedure was considered unsuccessful if any clinical or nonclinical sustained, monomorphic VT was inducible or if programmed stimulation was not performed at the end of the ablation procedure. The latter was "unsuccessful" because programmed ventricular stimulation was not performed at procedure completion if patients were unstable. If VT was not inducible at the beginning of the procedure and remained noninducible at the conclusion of the procedure, an ablation was not considered successful. For sensitivity analysis, we also assessed the relationship between noninducibility of VT post-ablation and mortality after excluding patients whose VT was noninducible before ablation. Induction of only polymorphic VT or ventricular fibrillation at the end of the procedure was not considered as a failed ablation procedure.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

NYHA = New York Heart Association

VT = ventricular tachycardia

After the ablation procedure, treatment with antiarrhythmic medications was at the discretion of the attending physician. Follow-up data were obtained from the implantable cardioverter-defibrillator clinics or from the referring physician.

STATISTICAL ANALYSIS. Continuous variables are expressed as mean ± SD. Comparisons of baseline demographic, clinical, and procedure-related characteristics between patients with noninducible VT post-ablation versus patients with inducible VT (or in whom inducibility was not tested after ablation) were performed using the Fisher exact test or chi-square test, as appropriate for discrete variables, and the 2-group Student *t* test for continuous variables. For mortality comparisons, time-to-event analyses were done. Log-rank tests were done to assess the relationship between each baseline variable and mortality. A Kaplan-Meier survival curve was plotted by noninducibility versus inducibility of VT or inability to perform stimulation post-ablation. Cox regression was used to assess whether successful ablation was independently associated with mortality after adjustment for other baseline variables that were either associated with a p value <0.1 on bivariate analyses or known to be associated with mortality. Robust standard errors were used to adjust for potential correlation of outcomes within each study center. Nonproportional hazards were checked by including an interaction term of time by noninducibility post-ablation in the Cox model. For robustness of the finding, we also obtained an estimate stratified by study center, which allows for different baseline hazards for each study center. Results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Analyses were done using Stata 13.1 (StataCorp LP, College Station, Texas). A p value <0.05 was considered statistically significant.

RESULTS

Data from a total of 1,064 consecutive patients from seven centers were included in the study (Table 1). Data regarding inducibility at onset were available in 1,011 patients and, of these, VT was inducible in 948 patients (93.8%). Radiofrequency energy was delivered for a mean of 50 ± 44 min (range 1.1 to 253 min),

TABLE 1 Patient Characteristics

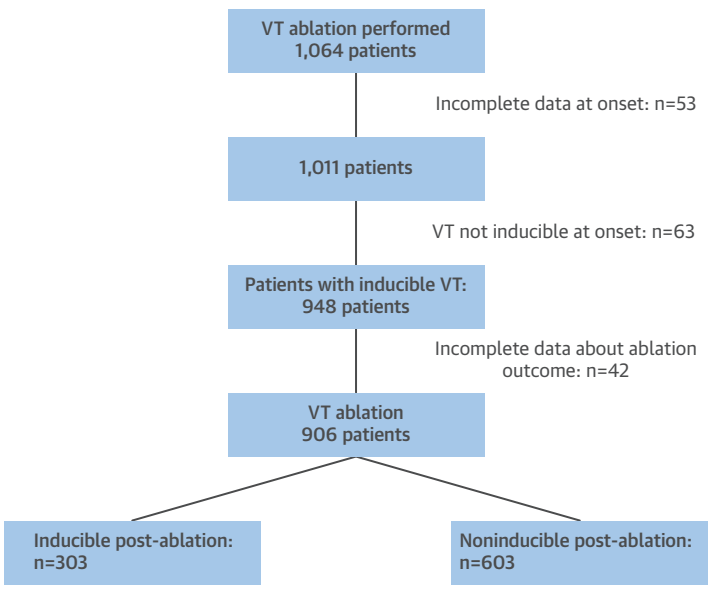
	Study Groups			
	Inducible or No Stimulated Procedure After Ablation (n = 349)	Noninducible (n = 643)	p Value	All Patients (N = 992)
Age, yrs	67.9 ± 9.2	68.1 ± 9.8	0.71	68.1 ± 9.6
Male	94	93	0.4	94
LVEF	30.3 ± 11.3	31.5 ± 11.5	0.12	31.1 ± 11.4
Risk factors				
Heart failure	86.5	84.9	0.52	85.4
Hypertension	75.4	76.7	0.63	76.3
History of AF	38.9	38.0	0.81	38.3
CRI	37.0	38.7	0.63	38.1
Diabetes	30.1	29.7	0.91	29.9
PVD	16.4	17.3	0.73	17.0
COPD	15.3	14.7	0.80	14.9
VT history				
VT storm	30.1	30.8	0.81	30.6
Incessant VT	17.5	18.3	0.74	18.0

Values are mean ± SD or %. Data listed at the procedure's end for patients included in the mortality analysis (N = 998).

AF = atrial fibrillation; COPD = chronic obstructive lung disease; CRI = chronic renal insufficiency; LVEF = left ventricular ejection fraction; PVD = peripheral vascular disease; VT = ventricular tachycardia.

and the mean procedure duration was 236 ± 136 min (range 50 to 755 min). At the conclusion of the procedure, programmed stimulation was not repeated in 106 patients, and no VTs were inducible in 663 patients. Of the 948 patients with VTs inducible before the ablation procedure, VT was no longer inducible after ablation in 603 patients. In 254 patients, the clinical VT was no longer inducible, but other nonclinical VTs remained inducible. The procedure failed in 49 patients in whom the clinical VT remained inducible (Figure 1).

FIGURE 1 Study Flow



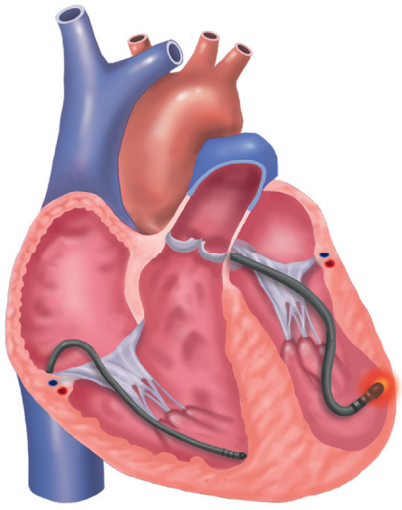
The number of patients undergoing ventricular tachycardia (VT) ablation is shown. On electrophysiological testing after ablation, nearly twice as many patients were noninducible.

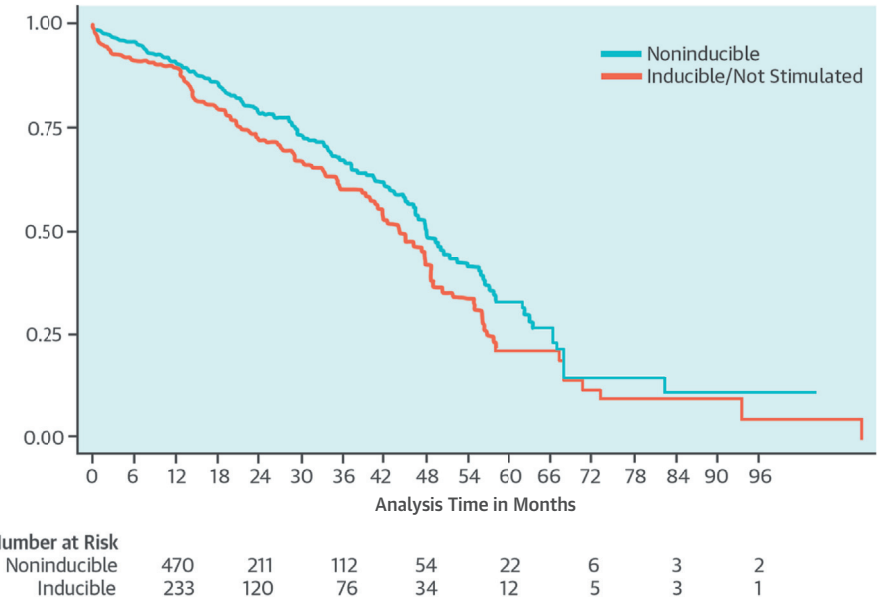
Mortality analysis included data from 998 patients, after the exclusion of 24 patients without mortality data and 42 patients with missing data regarding both the success of the ablation procedure and whether programmed stimulation was performed at the end of the ablation. Patients were at risk for a total of 700,367 days, with a median of 634 days per patient. Of the 998 patients, VT was noninducible after the ablation in 649 patients. Median survival time was 1,467 days (48.1 months) in patients with noninducible VT versus 1,349 days (44.2 months) in patients with inducible VT or in whom programmed stimulation was not performed at the conclusion of the procedure. The difference corresponded to an estimated 4.7 months of life gained at 6 years. The patients whose VT was noninducible had a 0.77-fold (95% CI: 0.61 to 0.97) lower risk for death compared with patients in whom VT remained inducible or in whom programmed stimulation was not performed. Kaplan-Meier survival curves were significantly different between the groups (log-rank: p = 0.02) (Central Illustration).

Exclusion of the 51 patients whose VT was noninducible at the onset of the procedure did not change the results with respect to improved survival in the patients with noninducible VT. Specifically, in the subset of patients whose VT was rendered noninducible, mortality was lower compared with that in the group in whom VT was still inducible or programmed stimulation was not performed (HR: 0.79; 95% CI: 0.63 to 0.99). With respect to mortality, in 295 patients in whom data were available regarding whether the clinical VT was ablated, successfully ablated clinical VT was associated with a numerically lower hazard, but the HR was not significantly lower than 1.0 (HR: 0.70; 95% CI: 0.33 to 1.49).

The group whose VT was rendered noninducible had significantly greater freedom from VT recurrences compared with that in the group in whom VT remained inducible (61.3% vs. 45.4%, respectively; p < 0.001). The group in whom the clinical VT was ablated but other VTs remained inducible had a recurrence rate similar to that in the group in which the clinical VT remained inducible (56% vs. 55%; p = 0.92). On unadjusted analysis, VT recurrence was not predictive of mortality (HR: 1.20; 95% CI: 0.77 to 1.88; p = 0.42). No difference was found in mortality between those 51 patients (5.1%) whose VT was not

CENTRAL ILLUSTRATION **Survival in Patients With Ablated VT**





Yokokawa, M. et al. J Am Coll Cardiol. 2015; 65(18):1954–9.

In patients who have experienced a myocardial infarction, catheter ablation can render ventricular tachycardia (VT) noninducible and produce lower VT recurrence rates than in patients who remain inducible. The **left panel** illustrates catheters positioned in the right ventricle for programmed stimulation and in the left ventricle for ablation of VT with in scar tissue. The **right panel** shows the Kaplan-Meier survival curve for those with noninducible VT compared with those with inducible VT or in whom programmed stimulation was not performed. Noninducibility post-ablation was independently associated with lower mortality (log-rank: p = 0.02).

inducible at baseline and patients with inducible VT (HR: 0.93; 95% CI: 0.42 to 2.06; p = 0.85). Not performing programmed stimulation after ablation was not significantly associated with higher mortality (HR: 1.23; 95% CI: 0.84 to 1.82; p = 0.28).

Before the ablation procedure, 583 of 1,064 patients (55%) were on amiodarone. Post-ablation, 473 patients were on amiodarone (44%) and 118 patients were on sotalol (11%). A total of 924 patients (88%) were discharged on beta-blocker therapy. Patients with inducible VT were more likely to have been discharged on amiodarone compared with patients whose VT was noninducible at the end of the ablation procedure (56% vs. 37%; p < 0.0001). This was not the case for sotalol, which was used in 10% of the patients whose VT was noninducible compared with 13% of the patients whose VT continued to be inducible at the end of the ablation (p = 0.21). Finally, use of post-ablation amiodarone was more prevalent in patients with a history of atrial fibrillation (AF) than in patients without AF (49% vs. 41%; p = 0.02).

Atrial fibrillation, New York Heart Association (NYHA) functional class, ejection fraction, hyperlipidemia, diabetes, and chronic renal failure were all associated with increased mortality by bivariate analysis, as were VT inducibility post-ablation and advanced age (Table 2). By multivariate analysis, advanced age (HR: 1.03), a history of AF (HR: 1.83), and a history of diabetes (HR: 1.58) were independently associated with increased mortality post-ablation. Noninducibility of VT post-ablation was independently associated with a lower mortality (HR: 0.65). Noninducibility of VT post-ablation was independently predictive of survival (HR: 0.72; 95% CI: 0.54 to 0.96; p = 0.03), even in the subgroup excluding patients in whom programmed stimulation was not performed post-ablation. Although NYHA functional class did not influence mortality on multivariate analysis, increased NYHA functional class was associated with an increased mortality, with an adjusted HR of 1.68 for NYHA functional class III versus I and an adjusted HR of 1.77 for NYHA functional class IV versus I, after control for other covariates and noninducibility. No adjustment for VT recurrence was performed in the main Cox regression model (Table 2) because time-to-recurrence data were not available to appropriately adjust for its time-varying nature. However, in another Cox model in

TABLE 2 Adjusted HR Mortality Estimates

	HR	95% CI	p Value
Age	1.03	1.01–1.06	0.001
Noninducible post-ablation*	0.65	0.53–0.79	<0.001
NYHA functional class†			
II	0.89	0.39–2.03	0.78
III	1.68	0.79–3.56	0.18
IV	1.77	0.69–4.54	0.24
History of AF	1.83	1.14–2.93	0.01
Diabetes	1.58	1.17–2.13	<0.01
Noninducible at onset	0.54	0.29–1.01	0.06
Incessant VT	1.31	1.09–1.57	<0.01

Cox regression model (n = 671; included patients in whom all data were available for analysis). *Compared with inducible or no stimulation performed post-ablation. †Reference = I.

CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association; other abbreviations as in Table 1.

which VT recurrence was added as a time-fixed covariate, along with other patient characteristics, the adjusted HR estimate remained similar to that of the main model for noninducibility post-ablation (HR: 0.69; p = 0.002) and other covariates, while VT recurrence was marginally significant (HR: 1.5; p = 0.05).

Proportional hazards assumption was checked and considered met, as indicated by the lack of evidence for a significant interaction of time by noninducibility (p = 0.09). Cox model stratified by study center yielded an adjusted HR estimate for noninducibility of VT post-ablation of 0.66 (95% CI: 0.46 to 0.95; p = 0.03), which was similar to the adjusted HR accounting for within-study center correlation using robust standard errors.

DISCUSSION

Noninducibility of VT post-ablation in this large-scale, multicenter cohort of patients with prior myocardial infarction who underwent VT ablation was independently associated with lower mortality (**Central Illustration**). Ablation of only the clinical VT was not associated with a reduction in either mortality or recurrent VT.

A recent meta-analysis demonstrated an association of noninducibility after VT ablation procedures with better survival (1). The findings from the present cohort study support the findings of the meta-analysis and identify other factors associated with higher mortality, including AF and diabetes. These factors have been described in a prior report (2). Most likely, these factors contribute to mortality through progression of the underlying cardiac disease process, or they may be markers of disease severity. VT recurrence is associated with a higher risk for death, and the association of an effective VT ablation procedure with lower mortality in the present study supports a potential contribution of VT recurrence to mortality. Further studies, however, are necessary to confirm that lower mortality is indeed due to a lower VT recurrence. The difference in mortality becomes apparent only after 1 year of follow-up, which could be why studies with smaller sample sizes and shorter follow-up durations did not detect a mortality benefit after VT ablation (2).

Although the findings from the prior meta-analysis suggested that ablation of the clinical VT also reduced VT recurrence (1), this idea could not be confirmed in the present study. However, elimination of the clinical VT appears to be beneficial, as indicated by a numerically low HR, although this finding was not statistically significant, likely due to the small sample size. In a recent consensus statement (3), eliminating the clinical VT was recommended as a minimal goal, with the idea that abolition of recurrent, spontaneously occurring VTs results in a decrease of the arrhythmia burden in most patients. This issue remains complex because most patients have multiple morphologies of inducible VT, and whether those that have not been observed to occur spontaneously, referred to as *nonclinical,* should be targeted for ablation is controversial. Confirmation that an ablated VT actually was a clinical VT may be difficult because a 12-lead electrocardiogram of the clinical VT is rarely available at the time of the ablation procedure. The VT cycle length has been used as a surrogate for QRS morphology, but a prior study has demonstrated that different VTs can have identical cycle lengths, making it impossible to distinguish clinical from nonclinical VTs (4). Therefore, the assumption that the clinical VT has been eliminated might also be erroneous. Larger-scale studies are required to establish the value of targeting and ablating only the clinical VT.

A prior study that assessed the outcome of VT ablation reported that heart failure was associated with increased mortality (2). Although we were not able to demonstrate that NYHA functional class was associated with a statistically significant increase in mortality after adjusting for other covariates, our data are consistent with those from published results showing an adjusted hazard of mortality of about 70% higher for NYHA functional classes III and IV compared to NYHA functional class I.

Even patients whose VT is rendered noninducible after ablation continue to have an appreciable rate of recurrent VT; hence, the value of programmed stimulation has been debated (5). Several factors might contribute to VT recurrence after an apparently

successful ablation procedure. A new VT substrate may emerge with further evolution of the infarct region and ventricular remodeling (6). Alternately, a VT may not have been inducible during the index procedure, resulting in no ablation to an area of arrhythmogenic scar (6). More thorough ablation has been associated with an incremental benefit with respect to VT recurrence when areas of late potentials were ablated in addition to rendering a patient's VT noninducible (7). Another mechanism of VT recurrence despite an apparently successful ablation rendering all VTs noninducible is a transient effect due to local edema induced by radiofrequency ablation. Once the edema resolves, VT may recur (8). Therefore, noninducibility of VT is not a perfect endpoint. However, because it is associated with decreased mortality, it does seem to be a desirable endpoint.

STUDY LIMITATIONS. Although the findings from the present study support attempts to achieve noninducibility of all monomorphic VTs, we cannot rule out the possibility that noninducibility post-ablation is a marker of less severe heart disease. Patients in whom programmed stimulation was not repeated post-ablation were pooled with the inducible group. Consistent results after excluding these patients from the analysis give us confidence in our findings, but it remains to be determined whether another procedure, once a patient is more stable, can help to further reduce VT recurrence in patients deemed too unstable to undergo programmed stimulation post-ablation. Antiarrhythmic drug therapy was left to the treating physicians and might have affected the outcomes. Due to the retrospective design of the study, the protocol of programmed stimulation was not identical at all centers; however, all centers did perform programmed stimulation from 2 ventricular sites with up to 4 extra stimuli and coupling intervals down to 200 ms or refractoriness, whichever occurred first. Data on the impact of the number of inducible VTs were not analyzed, and data on the timing of VT recurrence were not available.

CONCLUSIONS

Noninducibility of VT after an ablation procedure is independently associated with lower mortality in patients with prior myocardial infarction. These findings support the elimination of all inducible monomorphic VTs as an endpoint of post-infarction VT ablation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with post-infarction VT, inability to induce VT post-ablation is associated with improved survival compared to patients in whom VT remains inducible, supporting elimination of inducible VTs as an appropriate endpoint for VT ablation procedures.

TRANSLATIONAL OUTLOOK: Better characterization of reentry circuits in the infarct zone may reduce recurrence of VT and improve the clinical outcomes associated with post-infarction VT ablation procedures.

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KEY WORDS ablation, mortality