Re-Assessing Non-Inducibility as Ablation Endpoint of Post-Infarction Ventricular Tachycardia: The Impact of Left Ventricular Function

Running title: De Riva et al.; Impact of LV function on ablation endpoint

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Abstract:

**Background** - Non-inducibility is frequently used as procedural endpoint of ventricular tachycardia (VT) ablation after myocardial infarction (MI). We investigated the influence of left ventricular (LV) function on the predictive value of non-inducibility for VT recurrence and cardiac mortality.

**Methods and Results** - Ninety-one patients (82 men, 67±10 years) with post-MI VT underwent ablation between 2009 and 2012. Fifty-nine (65%) had a LV ejection fraction (EF) >30%, (mean 41±7) and 32 (35%) a LVEF≤30% (mean 20±5). Thirty patients (51%) with EF>30% and 13 (41%) with EF≤30% were non-inducible after ablation (P=0.386). During a median follow-up of 23 (Q1-Q3 16-36) months, 35 patients (38%) experienced VT recurrences and 17 (18%) cardiac death. At one year follow-up, survival free from VT recurrence and cardiac death for patients with LVEF>30% was 80% (CI 95%, 70-90) compared to 42% (CI 95%, 33-51) for those with LVEF≤30% (P=0.001). Non-inducible patients with LVEF>30% had a recurrence free survival from cardiac death of 90% (CI 95%, 71-100) compared to 65% (CI 95% 47-83) for inducible patients (P= 0.015). In the subgroup of patients with LVEF≤30% the survival free from VT recurrence and cardiac death was 31% (CI 95%, 0-60%) for non-inducible compared to 39% (CI 95%, 2/-2) for those who remained inducible (P= 0.842).

**Conclusions** - Non-inducible patients with moderately depressed LV function have a favorable outcome compared to patients that remained inducible after ablation. On the contrary, patients with severely depressed LV function have a poor prognosis independent of the acute procedural outcome.

**Key words:** ventricular tachycardia, catheter ablation, myocardial infarction, ventricular function, non-inducibility

**Introduction**
In patients late after myocardial infarction (MI), non-inducibility of any sustained monomorphic ventricular tachycardia (VT) with programmed electrical stimulation (PES) after ablation has been associated with favorable long-term outcome (lower VT recurrence rate and mortality).\textsuperscript{1-5}

Non-inducibility is therefore currently used as procedural endpoint in many electrophysiology laboratories and the only endorsed by the current expert consensus.\textsuperscript{6} However, the predictive value of non-inducibility for VT recurrence is limited since up to 30\% of patients that are rendered non-inducible experience VT recurrences and more than half of the patients that remain inducible for non-clinical VTs do not present recurrence on short-term follow-up.\textsuperscript{5}

In line with prior recommendations, the majority of patients included in former studies of post-MI VT ablation had an advanced disease with poor left ventricular function, presenting with multiple VT episodes refractory to anti-arrhythmic drugs (AAD) including amiodarone.\textsuperscript{1-5,7} More recently, ablation early in the course of the arrhythmic disease has been recommended based on two randomized trials.\textsuperscript{8-9}

Due to the reported high recurrence rates despite non-inducibility, new ablation endpoints like elimination of late or abnormal potentials have been suggested for all patients with scar-related VT irrespective of baseline patient characteristics and clinical presentation. Achieving these endpoints may require more invasive and extensive procedures likely to be associated with patient discomfort and procedure related complications.\textsuperscript{10-12}

We hypothesize that differences between patients, in particular in left ventricular (LV) function may not only affect procedural and long term outcome but also the optimal procedural endpoint for an individual patient.

The main objective of this study was to analyze the influence of individual patient
characteristics on the predictive value of non-inducibility for VT recurrence and cardiac mortality in the population currently referred for VT ablation after MI.

Methods

Patient population

The study population consisted of consecutive patients with prior MI and spontaneous symptomatic sustained monomorphic VT who underwent a first catheter ablation procedure at the Leiden University Medical Centre between January 2009 and December 2012. Diagnosis of MI was based on the presence of wall motion abnormalities, non-reversible perfusion defects and/or subendocardial or transmural late gadolinium enhancement areas in the perfusion territory of a significant stenotic coronary artery (>75%). Patients who underwent surgical ablation or presented with frequent premature ventricular contractions (PVC) or non-sustained VT without documented spontaneous sustained VT were excluded. All patients provided informed consent and were treated according to the institutional clinical protocol.

Preprocedural evaluation

Prior to the procedure patients underwent a comprehensive clinical evaluation. VT clinical presentation was classified as electrical storm (≥3 implantable cardioverter defibrillator [ICD] shocks/24 hours), incessant VT (recurrent sustained VT despite repeated intervention for termination), recurrent ICD therapies, VT below detection of ICD and first episode of VT. A special effort was taken to obtain 12-lead documentation of the spontaneous VTs.

All patients underwent two-dimensional and color Doppler echocardiography to assess LV ejection fraction (LVEF). LV end-diastolic and end-systolic volumes were obtained from the apical 2- and 4-chamber views and LVEF was calculated according to the biplane Simpson’s
method. Echocardiographic analyses were performed by an experienced observer, blinded to all clinical and procedural data.

In 25 patients without ICD, contrast-enhanced magnetic resonance imaging (CE-MRI) was performed. Seventy-nine patients (87%) underwent coronary angiography and in 23 (25%) percutaneous coronary intervention was performed prior to catheter ablation.

**Electrophysiological study**

Studies were performed in the fasting state under conscious sedation. In stable patients, all AAD with the exception of amiodarone (n=39, 43%) were discontinued for 5 half-lives before the study.

The PES protocol consisted of burst pacing and extrastimulation with 3 drive cycle lengths (CL) (600, 500 and 400ms) from at least two sites (right ventricular apex and right ventricular outflow tract) with one, two and three extrastimuli until 200ms or refractoriness.

Positive endpoint for stimulation was considered the induction of a sustained monomorphic VT lasting for >30s or requiring termination because of hemodynamic instability. Induced VTs where classified as: 1) Clinical when there was a 12/12 electrocardiographic (ECG) morphology match with a previously documented VT, 2) Presumptive clinical when the cycle length (CL) was ± 30ms of an ICD recorded VT or 3) Non clinical VT when the previous criteria where not fulfilled.

**Electroanatomical mapping and catheter ablation**

The initial approach was endocardial in all but one patient (after two failed attempts of endocardial ablation in another center). If non-inducibility could not be achieved from the endocardium and an epicardial site of origin was assumed based on endocardial activation and substrate mapping, epicardial mapping as secondary approach was considered depending on VT
clinical presentation and patient preference. Electroanatomical (EAM) LV mapping was performed through a retrograde aortic approach (n=88) or a combination of retrograde and transeptal approach (n=3) during sinus or paced rhythm (n=9). Bipolar voltage maps were created with a 3.5mm irrigated-tip catheter with a 2-5-2mm interelectrode spacing (NaviStar ThermoCool, Biosense Webster, Inc., Diamond Bar, CA, USA) and the CARTO system. EG were filtered at 30-400Hz (bipolar) and 1-240Hz (unipolar). The area with bipolar voltages under 0.5mV was defined as dense scar (DS). The area with bipolar voltages between 0.5-1.5mV was defined as scar border zone (BZ). Re-entry isthmus sites were identified with entrainment and activation mapping for stable VTs and with substrate mapping for unstable VTs. Potential ablation targets based on EG characteristics and pace mapping (≥10/12 morphology match with induced VT and stimulus-to-QRS delay > 40ms) were tagged on the map. Once the area of interest was localized, VT was re-induced. Whenever possible, poorly tolerated VTs were at least briefly mapped during VT to either perform entrainment mapping or slow and terminate VT during radiofrequency (RF) application. Only areas specifically related to induced VTs based on entrainment and/or pace-mapping were targeted. RF energy was delivered between 35 and 50W with a temperature limit of 43ºC and a flow rate of 20-30ml/min until the capture threshold post-ablation was > 10mA/2ms.

Procedural endpoint

All clinical and non-clinical sustained monomorphic VTs were targeted for ablation. Only non-clinical fast VTs, defined as VTs with a VTCL close to ventricular refractory period, that were not reproducible inducible were considered to be of unknown clinical relevance and were not targeted. Safety was taken into major consideration, therefore the procedure was stopped if multiple electrical cardioversions were required or the patient had prolonged hemodynamic
instability.

**Acute procedural outcome**

After the last RF application, the entire PES protocol was repeated. Complete acute success was defined as non-inducibility of any sustained monomorphic VT; partial success as elimination of all clinically documented VTs but inducibility of any non-clinical VT independent from VTCL and morphology also including non-targeted fast VTs and failure as persistent inducibility of any clinical VT.

**Post-procedural management**

An ICD was offered to all patients regardless of acute procedural outcome. Pre-ablation AAD were maintained until the first follow-up visit. Thereafter the AAD regimen was left at the discretion of the referring cardiologist.

**Follow-up**

Patients were followed at the outpatient clinic 3 and 6 months after the procedure and every 6 months afterwards including a careful history regarding symptoms for VT and ICD interrogation. For patients followed at other institutions and in case of death, the referring cardiologist or general physician was contacted for VT recurrence and cause of death. VT recurrence was defined as occurrence of any documented VT after ablation, independently of CL or clinical presentation. In-hospital recurrences were also included in the analysis. During follow-up, VT recurrence was classified as: electrical storm (≥3 ICD shocks/24h), incessant VT (recurrent sustained VT despite repeated intervention for termination), VT terminated by ICD shock, VT terminated by ATP, VT in monitor zone or ECG-documented VT. A clinically relevant VT recurrence was defined as any VT that was treated with ICD shock or led to hospitalization, re-ablation or modification of the anti-arrhythmic therapy.
Statistical analysis

Continuous variables are reported as mean±SD or medians with upper and lower quartiles (Q1-Q3). Categorical variables are presented as numbers and frequencies (%). Categorical variables were compared using the Chi-squared test or the Fisher exact test and continuous variables with the Student t test or the Mann-Whitney U test when appropriate. The VT and ICD shock frequency before and after ablation, and the CL of the spontaneous, remaining and recurrent VTs were compared with the Wilcoxon signed rank test. Freedom from VT recurrence and cardiac death was estimated by Kaplan-Meier method and compared by log-rank test between groups. Predictors of acute procedural outcome, VT recurrence and mortality were assessed with univariate logistic regression and Cox regression analysis respectively. For the regression analysis of predictors of mortality on follow-up, VT recurrence was treated as time-dependent variable. Independent predictors of acute procedural outcome and VT recurrence were analysed with multivariable models using a backward stepwise selection. Variables with a p value < 0.10 were initially included. At each step the least significant variable was removed from the model, until all variables reached a p value <0.20. All tests were 2-sided and a p value < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 20.0 (SPSS Inc, Chicago, IL).

Results

During the study period, 116 patients with prior MI and symptomatic ventricular arrhythmias were referred for ablation. Twenty patients (17%) with non-sustained VT and/or PVC, 4 (3 %) who underwent surgical ablation and one (1%) with pleomorphic VT at presentation were excluded. Finally, 91 patients (82 men, 67±10 years) with remote MI and history of spontaneous
sustained monomorphic VT comprised the study population. Ten (11%) patients had previously undergone ≥1 failed endocardial VT ablation in another center. Fifty-seven patients (63%) had an ICD implanted before the procedure. Fifteen patients (17%) presented with electrical storm and 14 (15%) with incessant VT. Twenty-eight patients (31%) were referred for ablation after the first documented VT episode.

Fifty-nine patients (65%) had a moderately depressed LVEF (defined as LVEF>30%, mean 41±7) and 32 (35%) a severely depressed LVEF (defined as LVEF≤30%, mean 20±5). Patients with severely depressed LVEF were younger (64±13 vs 69±8 years-old, P=0.048) and had more frequently a history of an anterior MI (53% vs 29%, P=0.026), atrial fibrillation (47% vs 22%, P=0.018), heart failure hospitalizations (72% vs 29%, P<0.0001), ICD implantation prior to the procedure (84% vs 51%, P=0.002), a previous VT ablation in another center (22% vs 5%, P=0.030) and slower VTs at presentation (438±69 vs 353±77ms, P<0.0001). Patients with LVEF>30% were more often referred for ablation after the first episode of a symptomatic VT (42% vs 9%, P=0.001). In most of these patients the procedure was performed clinically, before ICD implantation. Baseline characteristics of the patients according to LVEF are displayed in table 1.

Ablation procedure

Eighty-five patients (93%) were either inducible (median 3 VTs per patient, Q1-Q3 2-5; mean CL 355±87ms) or in VT at the beginning of the procedure. Clinical VTs were present or induced in 75 patients (82%). VT was classified as “clinical” based on the 12 lead-ECG in 60 patients (66%) and on ICD recordings in 15 (16%). Ten patients (11%) were only inducible for non-clinical VTs. Sixty-four (70%) had at least one hemodynamically unstable VT inducible.

Compared to patients with LVEF>30%, patients with LVEF≤30% were inducible for a
higher number of VTs (2.8±2.0 vs 5.0±2.9, P<0.0001) which were slower (mean CL 323±63 vs 409±97ms, P<0.0001) and had more often left bundle branch block morphology (51% vs 78%, P=0.033). Procedural data according to LVEF are summarized in table 2.

All patients underwent endocardial mapping and ablation. In 8 of 52 patients (15%) that remained inducible after endocardial ablation, an epicardial approach was attempted. Of the 7 patients who finally underwent epicardial mapping (one was not successful due to pericardial adherences) only in 4 epicardial RF was applied. Three patients were rendered non-inducible and one remained inducible for non-clinical VTs only after combined endo-epicardial approach.

At the end of the procedure, all patients underwent PES. Complete acute success was achieved in 43 patients (47%) and partial in 44 (49%). Procedural failure occurred in 4 patients (4%). Of note, there was no difference between patients with severely and moderately depressed LV function regarding the acute procedural success rate (non-inducibility was achieved in 30 patients (51%) with EF>30% vs 13 (41%) with EF≤30%: P=0.386).

The majority of inducible patients after ablation (41/48, 85%) had remaining VTs which were faster than all spontaneous VTs (mean CL 280±59 vs 389±89ms, P<0.0001), 35/48 patients (73%) had only VTs with a CL≤300ms). Importantly, in 38 of 48 patients (79%), remaining fast VTs were not targeted because they were considered to be of unknown clinical relevance (mean CL 263±42ms).

Complications

There was no procedure related mortality. One patient with multiple ICD shocks and a basoseptal central isthmus site developed anticipated complete AV block after ablation. Ten patients had vascular access related complications. None of them needed surgical intervention. Cardiac tamponade requiring percutaneous drainage after endocardial ablation occurred in one
patient and late tamponade after an epicardial approach in one other patient. There was no difference in the occurrence of procedural related complications according to baseline LVEF (EF>30%: 18% vs EF≤30%: 6%, P=0.129).

**Predictors of acute outcome**

Non-complete acute success was associated with a higher number of induced VTs (odds ratio 1.42 per additional VT induced: CI 95% 1.15-1.76; P=0.001) and the induction of faster (odds ratio 2.79 per 50ms decrease in minimum VT CL: CI 95% 1.66-4.72; P<0.0001) and hemodynamically unstable VTs (odds ratio 6.55: CI 95% 2.11-20.32; P=0.001) (Figure 1). On multivariate analysis, the number of induced VTs (odds ratio 1.23 per additional VT induced: CI 95% 1.00-1.57; P=0.047) and the CL of the fastest induced VT (odds ratio 2.78 per 50ms decrease in minimum VT CL: CI 95% 1.60-4.76; P<0.0001), remained independently associated with the acute procedural outcome.

This was observed for both patient groups, those with LVEF>30% and LVEF≤30% with the exception of the number of induced VTs, that was not associated with worse acute outcome for patients with LVEF≤30% (odds ratio 1.30 per additional VT induced: CI 95% 0.97-1.77; P=0.080).

**Post-procedural management**

Seventy-seven (85%) patients were discharged with an ICD. Fourteen (15%) patients refused ICD implantation. These patients were older (odds ratio 0.35 per 10 years increase: CI 95% 0.16-0.75; P=0.007), had better LVEF (odds ratio 0.69 per 5% increase EF: CI 95% 0.51-0.92; P=0.011, all but two EF>30%) and were more often non-inducible after ablation (odds ratio 20.37: CI 95% 2.53-163.82; P=0.005). Seventy-two (79%) patients were discharged on AAD other than conventional beta-blockers (44 (48%) on amiodarone and 28 (31%) on sotalol).
VT recurrence

During a median follow-up of 23 (Q1-Q3 16-36) months, 35 patients (38%) experienced any VT recurrence with a median time to recurrence of 133 (Q1-Q3 36-608) days (only one patient was lost for follow-up, all but 2 had a follow-up longer than 1 year, 9 patients died during the first year).

Patients with a LVEF>30% had a lower incidence of VT recurrence than patients with LVEF≤30% (34% vs 48%, HR 0.43: CI 95% 0.21-0.87; P=0.02).

The 1-year VT burden was reduced in the entire group from a median of 4 (Q1-Q3 2-14) episodes prior to ablation to a median of 0 (Q1-Q3 0-0) episodes after ablation (P<0.0001).

Sixty-five of 79 (82%) patients with a follow-up longer than 1 year had a ≥75% reduction of the VT burden (Figure 2A). In patients with ICD prior to ablation the frequency of shocks per year was reduced from a median of 3 (Q1-Q3 0-6) to a median of 0 (Q1-Q3 0-0) after ablation (P<0.0001) (Figure 2B). A significant reduction of the 1-year VT burden was observed in patients with both severely and moderately depressed LV function (Figure 3).

Mode and predictors of VT recurrence

Based on the provided definition, only 27 patients (29%) presented with clinically relevant VT recurrences (3 (3%) electrical storm, 5 (5%) incessant VT, 12 (13%) ≥ 1 ICD shock, 4 (4%) VT below detection of ICD, 3 (3%) frequent symptomatic ATP). Eight patients (9%) presented with sporadic ATP or asymptomatic self-terminating VTs in the monitor zone that did not require any intervention. Thirteen patients (42%) with LVEF≤30% presented with relevant VT recurrences compared to 14 (24%) with LVEF>30% (P=0.150). In 21 of 27 patients (81%) with relevant VT recurrences, these occurred during the first year of follow-up (18 (67%) in the first 6 months). No VT recurrence was documented in patients discharged without ICD.
Recurrent VTs were significantly slower than the remaining VTs in patients with non-complete acute procedural success (378±74 vs 285±63ms; p<0.0001). In fact, in 23 of 28 patients (82%) with non-complete acute success and recurrences on follow-up, the CL of the recurrent VT was at least 30ms longer than the CL of the slowest remaining VT after ablation, suggesting that remaining fast VTs were not the cause of recurrence in these patients. Figure 4 shows the CL of spontaneous, remaining and recurrent VTs in individual patients with partial acute success and VT recurrence during follow-up.

On multivariate analysis, after adjusting for age, sex, hypertension, ejection fraction, history of atrial fibrillation, renal failure, history of heart failure hospitalizations, electrical storm, incessant VT at presentation and amiodarone use after ablation, a higher number of induced VTs (HR 1.22 per additional VT induced; CI 95% 1.08-1.40; P=0.002) and inducibility after ablation (HR 2.49; CI 95% 2.49-5.61; P=0.028) were independently associated with VT recurrence for the entire population. Ablation after the first documented VT episode was independently associated with lower VT recurrence (HR 0.30; CI 95% 0.10-0.89; P=0.029).

**Mortality on follow-up**

Twenty-five patients (27%) died during follow-up with a median time to death of 442 days (IQR 245-655), 17 (19%) of cardiac causes. Patients with LVEF>30% had better prognosis with cardiac mortality of 10% compared to 35% for patients with LVEF≤30% over the follow-up period (HR 0.21: CI 95% 0.08-0.58; P=0.003). VT recurrence (HR 2.46: CI 95% 0.93-6.51; P=0.070) and inducibility after ablation (HR 0.8: CI 95% 0.31-2.10; P=0.647) were not associated with cardiac mortality for the entire population. The most frequent cause of death was terminal heart failure (n=15, 60%), in particular for patients with severely depressed LV function (n=9, 75%). In 3 patients death was of arrhythmic/presumed arrhythmic origin (one 80 year-old...
patient with 45% LVEF and complete acute success without ICD died unwitnessed while sleeping, 2 patients with severely depressed LVEF (26 and 19%) died due to an electrical storm that was not targeted by ablation). Seven of 13 patients (54%) with EF>30% died from non-cardiac causes compared to 1 of 12 with LVEF≤30% (P=0.073).

**VT recurrence and cardiac mortality according to LV function, VT inducibility and clinical presentation**

During follow-up, the combined endpoint of VT recurrence or cardiac death occurred in 24 of 59 patients with LVEF>30% (41%; 34% had VT recurrence and 10% cardiac death) compared to 20 of 31 patients with LVEF≤30% (65%; 48% had VT recurrence and 38% cardiac death).

Patients with a LVEF>30% had a higher probability of survival free from VT recurrence and cardiac death compared to those with LVEF≤30% (81% (CI 95%, 71-91) vs 61% (CI 95%, 43-79) at 6 months, and 80% (CI 95%, 70-90) vs 42% (CI 95%, 33-51) at 1 year follow-up, P=0.001) (Figure 5A).

Survival free from VT recurrence and cardiac death was also higher for patients who were rendered non-inducible compared to patients who remained inducible after ablation (81% (CI 95%, 69-93) vs 77% (CI 95%, 65-89) at 6 months and 68% (CI 95%, 54-82) vs 57% (CI 95%, 43-71) at 1 year follow-up: P=0.007) (Figure 5B).

In the subgroup of patients with LVEF>30%, survival free from VT recurrence and cardiac death at one year follow-up was 90% (CI 95%, 71-100) for non-inducible patients compared to 65% (CI 95% 47-83) for those who remained inducible for any VT after ablation (P=0.015) (Figure 6). This was mainly due to a higher incidence of VT recurrence in inducible patients. In fact, the probability of VT recurrence was higher in those who remained inducible after ablation (HR 4.26: CI 95% 1.54-11.78; P=0.005) whereas no significant difference was
found in the incidence of cardiac death (HR 1.23: CI 95% 0.26-6.28; P=0.774). A higher number of induced VTs (HR 1.55 per additional VT induced: CI 95% 1.23-1.88; P<0.0001) was associated with VT recurrence in these patients with LVEF>30% whereas ablation after the first documented VT episode was associated with lower VT recurrence (HR 0.25: CI 95% 0.08-0.74; P=0.012). No patient with LVEF>30% and who was rendered non-inducible by ablation after the first symptomatic VT episode had VT recurrence or died of a cardiac cause during the first year of follow-up.

On the contrary, patients with LVEF≤30% had a poor prognosis that was independent from the acute outcome of the procedure. At 1 year follow up, the cumulative incidence of VT free survival from cardiac death was 31% (CI 95% 0-60%) for non-inducible patients compared to 39% (CI 95% 27-52) for those who remained inducible after ablation (P= 0.842). Non-inducibility was neither associated with VT recurrence (HR 2.7: CI 95% 0.78-9.69; P=0.121) nor with cardiac mortality (HR 0.31: CI 95% 0.09-1.11; P=0.073) in this subgroup of patients. There was a non significant trend to a higher number of inducible VTs in patients who experienced VT recurrence (HR 1.19 per additional VT induced: CI 95% 0.99-1.42; P=0.054). Ablation after the first VT episode was not associated with lower VT recurrence in these patients (HR 0.39: CI 95% 0.00-35.63; P=0.352).

**Discussion**

The present study is the first to evaluate the influence of individual patient characteristics -in particular LV function- on the predictive value of non-inducibility for VT recurrence and cardiac mortality in the population currently referred for VT ablation after MI.

The predictive value of non-inducibility for VT recurrence and cardiac mortality was
influenced by the baseline LVEF. At one year follow-up, only 10% of the patients with
moderately depressed LV function that were rendered non-inducible by ablation experienced VT recurrence or died from a cardiac cause compared to 35% of patients in whom non-inducibility was not achieved. Furthermore, patients with LVEF>30% that were referred after the first documented episode of symptomatic VT and became non-inducible by ablation had an excellent prognosis. No patient with these characteristics had VT recurrence or died from a cardiac cause during the first year of follow-up. On the contrary, patients with severely depressed LV function had a poor prognosis that was independent from the acute result of the procedure or the VT clinical presentation, mainly driven by heart failure related death. In fact, more than 50% of the patients with LVEF<30% experienced VT recurrence and/or cardiac death during the first year of follow-up.

Prior reports
A recent meta-analysis including 928 post-MI patients from 8 observational studies showed that lack of inducibility of any VT after ablation was associated with lower VT/VF recurrence and all-cause mortality during follow up, and therefore proposes non-inducibility as a reasonable endpoint for the procedure.\textsuperscript{5} This meta-analysis included however an unselected pool of patients that were referred for ablation over more than 20 years (1991-2011) and did not correct for individual patient characteristics that may per se influence outcome.

The recommendations and strategies of post-MI VT ablation have changed over time. In line with clinical guidelines, the majority of patients initially included in studies had an advanced disease, with poor LV function, symptomatic heart failure and multiple VT episodes despite amiodarone.\textsuperscript{1-5,7,13} Since the publication of the last expert consensus, more patients with moderately depressed LV function after the first documented VT episode are referred for
Ablation. In this regard, our study is more representative of the current practice, since it includes only patients treated after 2008, frequently referred after the first documented VT episode (31%) with a high prevalence of moderately depressed LV function (65%). The basal cardiac function and the stage of the arrhythmic disease may impact both the outcome and the appropriate endpoint of the ablation procedure for an individual patient.

Ablation late in the therapeutic course of disease

It has been shown that, in post-MI patients, the predictive value of PES to predict ventricular arrhythmic events depends on the basal cardiac function. In the MUST trial, the cause of death of inducible patients with LVEF>30% was arrhythmic in 61% of the cases. On the contrary, no difference in the incidence of arrhythmic death was observed between inducible and non-inducible patients with LVEF<30%. In line with these results, in our study, non-inducibility was not associated with lower VT recurrence and cardiac mortality in patients with severely depressed LV function. This finding might be explained by two factors. First, not all VTs have a fixed reentrant mechanism and, in particular, in patients with advanced cardiac remodeling and heart failure, other focal arrhythmic mechanisms not so accurate reproducible by PES and not so easily approachable by our current ablation techniques may play an important role. Secondary, in patients with poor LV function and end stage heart failure, a high competing risk of non-arrhythmic cardiac death is present. In fact, the most prevalent cause of death in this population was terminal heart failure (75% of the cases).

Ablation early in the therapeutic course of disease

The evidence that supports the benefit of an early intervention in patients with post-MI VT is based on two recent randomized trials. However, in the VTACH trial, only patients with LVEF>30% had a significant higher survival free from VT/VF after ablation. According to
these results, in our study, 20% of the patients with moderately depressed LV function had VT recurrence or died from a cardiac cause during the first year of follow-up compared to 58% of patients with severely depressed LV function in spite of a similar rate of acute procedural success.

Patients with LVEF>30% that were rendered non-inducible by ablation had a good prognosis since only 10% experienced VT recurrence or cardiac death one year after ablation. In line with a recent publication, if these patients where referred for ablation after the first documented VT episode the outcome was excellent.\textsuperscript{16} No patient fulfilling these criteria had events during the first year of follow-up, further supporting an early ablation in this patient population. Inducibility of any VT after ablation seems to be therefore a good predictor of VT recurrence in patients with moderately depressed LV function and non-inducibility might be a sufficient endpoint for the ablation procedure in these patients.

Patients with LVEF>30% in whom non-inducibility was not achieved had a worse prognosis mainly related to a higher VT recurrence rate. If non-inducibility is not achieved, analyzing and understanding the reasons for ablation failure is mandatory, to select the appropriate next step for each individual patient (eventually epicardial).\textsuperscript{17} The clinical significance of non-clinical VTs, in particular fast and non-reproducible inducible VTs, remains still unclear. Prior studies, based on the analysis of ICD recordings, suggested that the cause of recurrence in patients with non-complete acute success were non-clinical VTs that were either not targeted or not successfully abolished during ablation.\textsuperscript{1,2} In the present study, in 82% of patients with partial success and VT recurrence on follow-up VTCL was at least 30ms longer than remaining VTs, suggesting that these VTs were not the cause of recurrence. VT recurrence might be related to lesion healing but may also be due to new reentry circuits and inducibility of
non-clinical fast VTs might just indicate a more complex arrhythmic substrate. These findings support the need for additional ablation endpoints based on substrate mapping and the development of new ablation tools able to perform deeper and long-lasting lesions for patients with moderately depressed LV function in whom non-inducibility is not achieved.

**Limitations**

This study is limited by its observational nature. The reported acute and long-term outcomes after ablation come from a high-volume referral center and may therefore not apply for smaller less experienced centers. The anti-arrhythmic regimen after ablation was left at the discretion of the referral physician and this might have influenced the outcome of some patients. The number of patients with severely depressed LV function that were referred for ablation after the first episode of symptomatic VT was small limiting its power to determine if this factor was associated with better outcome. To discern between remaining VTs after ablation and recurrent VTs on follow-up, only the CL of the VTs was taken into account. Routine analysis of ICD-stored VT EG morphology was not performed.

**Conclusion**

Patients with prior MI and moderately depressed LV function that are rendered non-inducible by ablation, in particular if they are referred after the first episode of symptomatic VT have an excellent prognosis. Therefore in this population an early intervention aiming non-inducibility seems to be appropriate. On the contrary, patients with severely depressed LV function have a poor prognosis that is independent of the acute outcome of the procedure and is mainly driven by heart failure related death. In this subgroup of patients, a more conservative approach, prioritizing symptoms relief, patient comfort and safety might be preferable.
Conflict of Interest Disclosures: None

References:


Table 1: Baseline characteristics of the patients according to left ventricular ejection fraction

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<th>All (n=91)</th>
<th>EF &gt; 30% (n=59)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67 ± 10</td>
<td>69 ± 8</td>
<td>64 ± 13</td>
<td>P=0.048</td>
</tr>
<tr>
<td>Male sex</td>
<td>82 (90%)</td>
<td>53 (90%)</td>
<td>29 (91%)</td>
<td>P=1.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (45%)</td>
<td>30 (51%)</td>
<td>11 (34%)</td>
<td>P=0.186</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (14%)</td>
<td>8 (14%)</td>
<td>5 (16%)</td>
<td>P=0.764</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>32 (35%)</td>
<td>23 (39%)</td>
<td>9 (28%)</td>
<td>P=0.362</td>
</tr>
<tr>
<td>History of Stroke/TIA</td>
<td>8 (9%)</td>
<td>6 (10%)</td>
<td>2 (6%)</td>
<td>P=0.708</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>28 (31%)</td>
<td>13 (22%)</td>
<td>15 (47%)</td>
<td>P=0.018</td>
</tr>
<tr>
<td>History of renal failure</td>
<td>29 (32%)</td>
<td>15 (25%)</td>
<td>14 (45%)</td>
<td>P=0.063</td>
</tr>
<tr>
<td>Prior admissions for heart failure</td>
<td>40 (44%)</td>
<td>17 (29%)</td>
<td>23 (72%)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>34 (37%)</td>
<td>17 (29%)</td>
<td>17 (53%)</td>
<td>P=0.026</td>
</tr>
<tr>
<td>MI acute reperfusion</td>
<td>15 (16%)</td>
<td>10 (17%)</td>
<td>5 (16%)</td>
<td>P=1.000</td>
</tr>
<tr>
<td>Time since MI, y</td>
<td>19 ± 9</td>
<td>20 ± 9</td>
<td>18 ± 7</td>
<td>P=0.441</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>37 (41%)</td>
<td>25 (42%)</td>
<td>12 (38%)</td>
<td>P=0.823</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>36 (39%)</td>
<td>23 (39%)</td>
<td>13 (41%)</td>
<td>P=1.000</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>34±12</td>
<td>41 ± 7</td>
<td>20 ± 5</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>ICD before ablation</td>
<td>57 (63%)</td>
<td>30 (51%)</td>
<td>27 (84%)</td>
<td>P=0.002</td>
</tr>
<tr>
<td>Prior VT ablation</td>
<td>10 (11%)</td>
<td>3 (5%)</td>
<td>7 (22%)</td>
<td>P=0.030</td>
</tr>
<tr>
<td>Clinical VT mean CL, ms</td>
<td>382±84</td>
<td>353 ± 77</td>
<td>438 ± 69</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Medication at admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>81 (89%)</td>
<td>53 (90%)</td>
<td>28 (88%)</td>
<td>P=0.737</td>
</tr>
<tr>
<td>Antialdosteronnic</td>
<td>31 (34%)</td>
<td>20 (34%)</td>
<td>11 (34%)</td>
<td>P=1.000</td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
<td>76 (84%)</td>
<td>51 (86%)</td>
<td>25 (78%)</td>
<td>P=0.378</td>
</tr>
<tr>
<td>Betablockers</td>
<td>69 (76%)</td>
<td>43 (73%)</td>
<td>26 (81%)</td>
<td>P=0.448</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>39 (43%)</td>
<td>21 (36%)</td>
<td>18 (56%)</td>
<td>P=0.076</td>
</tr>
<tr>
<td>VT clinical presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrical storm</td>
<td>15 (17%)</td>
<td>8 (14%)</td>
<td>7 (22%)</td>
<td>P=0.378</td>
</tr>
<tr>
<td>Incessant VT</td>
<td>14 (15%)</td>
<td>7 (12%)</td>
<td>7 (22%)</td>
<td>P=0.234</td>
</tr>
<tr>
<td>ICD therapies</td>
<td>24 (26%)</td>
<td>13 (22%)</td>
<td>11 (34%)</td>
<td>P=0.221</td>
</tr>
<tr>
<td>Below ICD detection</td>
<td>10 (11%)</td>
<td>6 (10%)</td>
<td>4 (13%)</td>
<td>P=0.737</td>
</tr>
<tr>
<td>First episode</td>
<td>28 (31%)</td>
<td>25 (42%)</td>
<td>3 (9%)</td>
<td>P=0.001</td>
</tr>
</tbody>
</table>

TIA indicates transitory ischemic attack; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LV, left ventricular; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia; CL, cycle length; ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.
Table 2: Electrophysiological and procedural characteristics according to left ventricular ejection fraction

<table>
<thead>
<tr>
<th></th>
<th>All (n=91)</th>
<th>EF &gt; 30% (n=59)</th>
<th>EF ≤ 30% (n=32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inducible before ablation</td>
<td>85 (93%)</td>
<td>54 (92%)</td>
<td>31 (97%)</td>
<td>P=0.419</td>
</tr>
<tr>
<td>Number of Induced VTs</td>
<td>3.6 ± 2.5</td>
<td>2.8 ± 2.0</td>
<td>5.0 ± 2.9</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Induced VT max CL, ms</td>
<td>418 ± 116</td>
<td>367 ± 86</td>
<td>507 ± 108</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Induced VT mean CL, ms</td>
<td>355 ± 87</td>
<td>323 ± 63</td>
<td>409 ± 97</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Induced VT min CL, ms</td>
<td>295 ± 79</td>
<td>282 ± 61</td>
<td>319 ± 101</td>
<td>P=0.036</td>
</tr>
<tr>
<td>HD unstable VT inducible</td>
<td>64 (70%)</td>
<td>39 (72%)</td>
<td>25 (81%)</td>
<td>P=0.443</td>
</tr>
<tr>
<td>LBBB VT inducible</td>
<td>55 (60%)</td>
<td>30 (51%)</td>
<td>25 (78%)</td>
<td>P=0.033</td>
</tr>
<tr>
<td>Epicardial mapping</td>
<td>7 (8%)</td>
<td>4 (7%)</td>
<td>3 (9%)</td>
<td>P=0.236</td>
</tr>
<tr>
<td>Complete success</td>
<td>43 (47%)</td>
<td>30 (51%)</td>
<td>13 (41%)</td>
<td>P=0.386</td>
</tr>
<tr>
<td>Partial success</td>
<td>44 (49%)</td>
<td>25 (42%)</td>
<td>19 (59%)</td>
<td>P=0.132</td>
</tr>
<tr>
<td>Remaining VT mean CL, ms</td>
<td>279 ± 59</td>
<td>275 ± 59</td>
<td>286 ± 59</td>
<td>P=0.531</td>
</tr>
<tr>
<td>Procedural duration, min</td>
<td>207 ± 92</td>
<td>202 ± 80</td>
<td>216 ± 113</td>
<td>P=0.516</td>
</tr>
<tr>
<td>Fluoroscopic time, min</td>
<td>38 ± 23</td>
<td>36 ± 21</td>
<td>41 ± 25</td>
<td>P=0.434</td>
</tr>
<tr>
<td>ICD after ablation</td>
<td>77 (85%)</td>
<td>47 (80%)</td>
<td>30 (94%)</td>
<td>P=0.126</td>
</tr>
<tr>
<td>Amiodarone post-ablation</td>
<td>44 (48%)</td>
<td>22 (37%)</td>
<td>22 (54%)</td>
<td>P=0.005</td>
</tr>
</tbody>
</table>

VT indicates ventricular tachycardia; CL, cycle length; LBBB, left bundle branch block; ICD, implantable cardioverter defibrillator.

Figure Legends:

Figure 1: Predictors of inducibility after ablation

MI indicates myocardial infarction; LVEF, left ventricular ejection fraction; AAD, antiarrhythmic drugs; VT, ventricular tachycardia, CL, cycle length; LBBB, left bundle branch block; Min, minimum; Max, maximum.
Figure 2: A: One-year ventricular tachycardia (VT) burden before (blue lines) and after ablation (red lines) of 77 patients with follow-up longer than 1 year. The number of VT episodes is truncated at 100. B: One-year shock burden before (blue lines) and after ablation (red lines) in patients with prior ICD and follow-up longer than 1 year. The number of shocks is truncated at 10. Q1-Q3 indicates interquartile range.

Figure 3: One-year ventricular tachycardia (VT) burden before (blue lines) and after ablation (red lines) in patients with LVEF>30% (Panel A) and LVEF≤30% (Panel B). The number of VT episodes is truncated at 100.

Figure 4: The cycle length of the spontaneous ventricular tachycardia (VT), slowest remaining VT after ablation and recurrent VT from 28 patients with partial success and VT recurrence on follow-up are plotted.

Figure 5: Ventricular tachycardia free survival from cardiac death according to left ventricular ejection fraction (panel A) and inducibility after ablation (panel B)

Figure 6: Ventricular tachycardia free survival from cardiac death according to left ventricular ejection fraction and inducibility after ablation
<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 years↑</td>
<td>0.92 (0.62 - 1.38)</td>
<td>0.689</td>
</tr>
<tr>
<td>Male gender</td>
<td>4.47 (0.88 - 22.85)</td>
<td>0.072</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>1.98 (0.79 - 4.96)</td>
<td>0.145</td>
</tr>
<tr>
<td>Heart failure hospitalizations</td>
<td>1.69 (0.73 - 3.90)</td>
<td>0.221</td>
</tr>
<tr>
<td>Number of MI</td>
<td>1.83 (0.64 - 5.23)</td>
<td>0.262</td>
</tr>
<tr>
<td>Acute reperfusion</td>
<td>1.42 (0.46 - 4.39)</td>
<td>0.539</td>
</tr>
<tr>
<td>Inferior MI</td>
<td>1.44 (0.61 - 3.38)</td>
<td>0.402</td>
</tr>
<tr>
<td>Age of MI, per 5 years↑</td>
<td>0.87 (0.66 - 1.15)</td>
<td>0.334</td>
</tr>
<tr>
<td>LVEF &gt; 30%</td>
<td>0.66 (0.28 - 1.58)</td>
<td>0.352</td>
</tr>
<tr>
<td>Number of failed AADs</td>
<td>1.53 (0.86 - 2.70)</td>
<td>0.278</td>
</tr>
<tr>
<td>Amiodarone preablation</td>
<td>1.11 (0.48 - 2.55)</td>
<td>0.808</td>
</tr>
<tr>
<td>First episode of VT</td>
<td>0.46 (0.18 - 1.13)</td>
<td>0.089</td>
</tr>
<tr>
<td>Electrical storm</td>
<td>0.75 (0.25 - 2.27)</td>
<td>0.423</td>
</tr>
<tr>
<td>Incessant VT</td>
<td>0.44 (0.14 - 1.43)</td>
<td>0.173</td>
</tr>
<tr>
<td>Number of clinical VTs</td>
<td>0.78 (0.45 - 1.34)</td>
<td>0.361</td>
</tr>
<tr>
<td>Mean CL of clinical VTs, per 50ms↑</td>
<td>1.15 (0.89 - 1.48)</td>
<td>0.286</td>
</tr>
<tr>
<td>Number of induced VTs</td>
<td>1.42 (1.15 - 1.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>Induction of hemodynamically unstable VT</td>
<td>6.55 (2.11 - 20.32)</td>
<td>0.001</td>
</tr>
<tr>
<td>Induction of LBBB VT</td>
<td>2.29 (0.92 - 5.67)</td>
<td>0.074</td>
</tr>
<tr>
<td>Min CL of induced VTs, per 50ms ↓</td>
<td>2.79 (1.66 - 4.72)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Max CL of induced VTs, per 50ms ↓</td>
<td>0.92 (0.77 - 1.12)</td>
<td>0.439</td>
</tr>
</tbody>
</table>
A

Median 3
(Q1-Q3 2-12)

Median 0
(Q1-Q3 0-0)

p<0.0001

VT burden
1-year pre-ablation

100 80 60 40 20 0

VT burden
1-year post-ablation

B

Median 6
(Q1-Q3 3-16)

Median 0
(Q1-Q3 0-5)

p=0.046

VT burden
1-year pre-ablation

100 80 60 40 20 0

VT burden
1-year post-ablation
VT cycle lengths

- Presentation
- Remaining
- Recurrence

p = 0.155

p < 0.0001

p < 0.0001
Re-Assessing Non-Inducibility as Ablation Endpoint of Post-Infarction Ventricular Tachycardia: The Impact of Left Ventricular Function

Marta de Riva, Sebastiaan R.D. Piers, Gijs F.L. Kapel, Masaya Watanabe, Jeroen Venlet, Serge A. Trines, Martin J. Schalij and Katja Zeppenfeld

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