Elimination of Local Abnormal Ventricular Activities: A New End Point for Substrate Modification in Patients with Scar-Related Ventricular Tachycardia

Running title: Jaïs et al.; A new end point for VT ablation

Pierre Jaïs, MD1; Philippe Maury, MD2; Paul Khairy, MD, PhD3; Frédéric Sacher, MD1; Isabelle Nault, MD, FRCPC4; Yuki Komatsu, MD1; Mélèze Hocini, MD1; Andrei Forclaz, MD1; Amir S. Jadidi, MD1; Ruksen Weerasooriya, MBBS1; Ashok Shah, MD1; Nicolas Derval, MD1; Hubert Cochet, MD1; Sebastien Knecht, MD1; Shinsuke Miyazaki, MD1; Nick Linton, MEng MRCP; Lena Rivard, MD6; Matthew Wright, MBBS, PhD1; Steven Wilton, MD1; Daniel Scherr, MD1; Patrizio Pascale, MD1; Laurent Roten, MD1; Michala Pederson MD1; Pierre Bordachar, MD1; François Laurent, MD1; Steven J. Kim, MEng5; Philippe Ritter, MD1; Jacques Clementy, MD1; Michel Haïssaguerre, MD1

1CHU Bordeaux, Bordeaux, France; 2CHU Toulouse, Toulouse, France; 3Montreal Heart Institute, Montreal, Canada; 4Institut Universitaire de Cardiologie et de pneumologie de Québec (IUCPQ) Québec, Canada; 5St. Jude Medical, Inc., St. Paul, MN

Correspondence:
Pierre Jaïs, MD
Hôpital Haut-Lévêque
Avenue de Magellan
33604 Bordeaux-Pessac, France
Tel: 33.5.57.65.64.71
Fax: 33.5. 57 65 65 09
E-mail: pierre.jais@chu-bordeaux.fr

Abstract:

**Background** - Catheter ablation of ventricular tachycardia (VT) is effective and particularly useful in patients with frequent defibrillator interventions. Various substrate modification techniques have been described for unmappable or hemodynamically intolerable VT. Non-inducibility is the most frequently used endpoint but is associated with significant limitations such that the optimal endpoint remains unclear. We hypothesized that elimination of local abnormal ventricular activities (LAVA) during sinus rhythm or ventricular pacing would be a useful and effective endpoint for substrate-based VT ablation. As an adjunct to this strategy, we used a new high density mapping catheter and frequently employed epicardial mapping.

**Methods and Results** - Seventy patients (67±11 y, 7 female) with VT and structurally abnormal ventricle(s) were prospectively enrolled. Conventional mapping was performed in sinus rhythm in all while a high density Pentaray™ mapping catheter was used in the endocardium (n=35) and epicardially. LAVA were recorded in 67 patients [95.7%, 95% confidence interval (CI; 89.2%, 98.9%)]. Catheter ablation was performed targeting LAVA using an irrigated-tip catheter placed endocardially via a transeptal or retrograde aortic approach or epicardially via the sub-xiphoid approach. LAVA were successfully abolished or dissociated in 47 of 67 patients [70.1%, 95% CI (58.7%, 80.1%)]. In multivariate analysis, LAVA elimination was independently associated with a reduction in recurrent VT or death [hazard ratio 0.49, 95% CI (0.26, 0.95), P=0.035] during long-term follow-up (median 22 months).

**Conclusions** - LAVA can be identified in most patients with scar-related VT. Elimination of LAVA is feasible and safe and associated with superior survival free from recurrent VT.

**Key words:** ablation; epicardial; mapping; ventricular tachycardia; End Point
Introduction
Catheter ablation of ventricular tachycardia (VT) in the setting of structural heart disease is challenging. Current ablation strategies often rely on the ability to identify a re-entrant circuit and target a critical isthmus using activation and entrainment mapping\textsuperscript{1-5}. A reliably inducible, well-tolerated and single monomorphic VT is ideal but, unfortunately, not the rule. Factors such as non-inducibility or poor hemodynamic tolerance may render the VT unmappable. In such situations, various ablation strategies such as 3-dimensionally guided substrate mapping and pacemapping have been described\textsuperscript{6-12}. While “late potentials” were recently proposed as ablation targets, the impact of ablation and correlations with clinical outcomes have not been reported\textsuperscript{13}. In addition, the proposed approach relied solely on non-inducibility as an endpoint, which has important caveats: reproducibility is limited, it does not consistently predict long-term outcomes, and the significance of inducing non-clinical VT(s) remains uncertain.

We hypothesized that elimination of local abnormal ventricular activities (LAVA) recorded during sinus rhythm or ventricular pacing would be feasible as an endpoint for VT ablation; and that complete elimination of LAVA would lead to a reduction in arrhythmia-free survival.

Material and Methods
Study population
From January 2006 to January 2010, 70 consecutive patients undergoing VT ablation at 2 centers were prospectively enrolled after providing written informed consent. Inclusion criteria consisted of: 1) documented episodes of repetitive sustained VT, resistant to anti-arrhythmic drug therapy and requiring external cardioversion or implantable cardioverter-defibrillator (ICD)
antitachycardia pacing or shocks; 2) structural heart disease with ischemic or non-ischemic dilated cardiomyopathy. Patients were excluded if ventricular arrhythmias were attributable to an acute or reversible cause. Patients with repetitive premature ventricular contractions or non-sustained VT in the absence of sustained VT were also excluded.

**Preprocedural Preparation**

All patients underwent an imaging study to assess ventricular function and identify areas of ventricular scar. In patients without an ICD, magnetic resonance imaging was the preferred imaging modality. In others, an echocardiogram was performed. Barring extreme rhythm instability, all antiarrhythmic drugs but amiodarone were discontinued for a period of at least 5 half-lives.

**LV access and Electrophysiological Study**

The electrophysiological study and ablation were conducted with post absorptive conscious sedation using 1) midazolam, 0.02 mg/kg prior to femoral puncture; 2) morphine sulphate, 0.1 to 0.2 mg/kg, and 3) supplementary analgesia (sufentanil, 0.05 to 0.15 μg) under supervision of an anaesthesiologist for the pericardial approach. Non-invasive or intra-arterial blood pressure monitoring and digital pulse oximetry were performed continuously. ICD therapies were inactivated.

Vascular sheaths were inserted into the right femoral vein (2 to 3), right femoral artery (1), and/or subxiphoid area (1 or 2) under local anaesthesia (bupivacaine). A steerable quadripolar or decapolar catheter (2-5-2mm, Xtrem, ELA medical, Montrouge, France) was positioned in the right ventricular apex or coronary sinus. The left ventricle (LV) was accessed by transeptal (BRK needle, St. Jude Medical, USA) and/or retrograde routes with or without pericardial access for additional epicardial mapping. The mode of access to the LV was at the
operator’s discretion. However, in the absence of contraindications, dual or triple accesses were encouraged. Upon attaining LV access, a 50 U/kg heparin bolus was administered intravenously and repeated as necessary to target an activated clotting time >250 seconds.

**Pericardial approach**

Pericardial access was obtained if a previous endocardial procedure had failed, if an epicardial substrate was suspected (based on VT morphology on surface ECG and the nature of the underlying heart disease)\(^14\), and if endocardial mapping did not reveal LAVA or if endocardial ablation did not result in LAVA elimination. The pericardial approach, as described by Sosa et al\(^15\), was modified to access the pericardial space through an anterior puncture, as it was considered safer than the conventional inferior puncture. The pericardial puncture was guided by a 90° left lateral fluoroscopic projection (Figure 1)\(^16\). To facilitate subsequent pericardial punctures, 50 to 100 mL of air was instilled into the pericardial space, and aspirated thereafter\(^17\). A standard steerable sheath (Agilis, St Jude, USA) was used to provide catheter stability and manoeuvrability.

**Mapping**

Surface electrocardiograms (ECGs) and bipolar intracardiac electrograms were continuously monitored on LabSystem Pro (Bard Electrophysiology, Lowell, MA, USA). Signals were sampled at 1 kHz and filtered at 0.1-50 Hz for surface ECGs and 30-250 Hz for intracardiac signals, displayed at an amplification of 0.1 mV/cm.

VT induction was attempted at baseline using: 1) programmed ventricular stimulation from two right ventricular sites (outflow tract and apex), at two drive trains (400 and 600 ms), with up to 3 extrastimuli decremented to ventricular refractoriness or 250 ms, whichever was higher; and 2) incremental burst pacing up to 200 ms. If hemodynamically stable VT was
induced, it was mapped to identify the site of earliest ventricular activation and abnormal
presystolic ventricular potentials, if any. Tachycardia was then terminated by overdrive pacing.
Detailed LV endocardial and epicardial mapping was performed using the roving ablation
(Thermocool or Navistar, Biosense Webster, USA) and/or a high-density mapping catheter
(Pentaray, Biosense Webster) to identify and localize LAVA. Concealed entrainment was used
whenever possible and appropriate. Use of 3D-electroanatomic mapping systems was at the
operator’s discretion.

Ventricular mapping was undertaken to identify and localize regions displaying LAVA
and to characterize healthy and scarred areas by conventional voltage criteria. Thereafter,
substrate mapping focused on abnormal myocardium and bordering zones based on: 1) low
voltage areas with 3D mapping or identified scar from prior cardiac imaging, 2) the VT
morphology on surface ECG, and 3) scar information obtained from previous mapping
procedures, whenever available.

**Definition of Local Abnormal Ventricular Activities**

LAVA were defined as: 1) sharp high frequency ventricular potentials possibly of low amplitude,
2) distinct from the far field ventricular electrogram, 3) occurring anytime during or after the far
field ventricular electrogram in sinus rhythm or before the far field ventricular electrogram
during VT, 4) that sometimes displayed fractionation, double or multiple components separated
by very low amplitude signals or an isoelectric interval, and 5) were poorly coupled to the rest of
the myocardium as demonstrated by the manoeuvres detailed below. These high frequency sharp
signals were considered indicative of local electrical activity arising from pathological tissue\textsuperscript{18-20}. Examples are shown in **Figure 2**.

To confirm the nature of LAVA and distinguish them from far field ventricular
electrograms in the presence of ambiguity, different manoeuvres were used. Programmed ventricular stimulation was performed from the RV apex or sites in closer proximity to LAVA. LAVA were observed to progressively split further away from the far field ventricular electrogram following an earlier extrastimulus (S2), which sometimes resulted in conduction block (i.e., absence of LAVA at a site where LAVA was previously recorded after ensuring due catheter stability and contact, Figure 3). Local ectopics (Figure 4A) or local pacing with decremental output was also employed (Figure 4B). Loss of capture of the far field component was marked by a distinct change in the stimulus to QRS delay and QRS morphology (Figure 4B). Pacing endocardially while simultaneously recording on the corresponding epicardial surface allowed documentation of intramyocardial conduction time. Substantial delay in intramyocardial conduction was caused by poor coupling between the LAVA generating myocardial bundles and remaining myocardium (Figure 5).

LAVA were characterized by measuring the signal amplitude and local delay with reference to the far field ventricular electrogram and end of the QRS complex on surface ECG. The amplitude and duration of far field ventricular electrograms were also recorded. Measurements were undertaken offline by 2 observers using electronic and manual callipers.

**Catheter Ablation**

As a general rule, for all patients in whom LAVA were observed, ablation of LAVA in sinus rhythm was encouraged, with complete LAVA elimination targeted as the procedural outcome. In patients in whom at least one VT was inducible and well tolerated (i.e., 11 during the first intervention; 3 during subsequent interventions), ablation was guided by conventional entrainment mapping criteria to identify the critical isthmus\(^5\). Following restoration of sinus rhythm, further mapping and ablation was undertaken to completely eliminate LAVA (Figure 6).
When VT was not inducible or poorly tolerated, ablation was conducted in sinus rhythm with the same endpoint.

Ablation was performed with a 3.5 mm externally irrigated-tip catheter. Radiofrequency energy with a power of 25 to 50 W was delivered at all sites displaying LAVA. If a definite sequence of activation of LAVA was clearly discerned on the Pentaray catheter, the earliest signals were targeted first (Figure 6B and C). If both epicardial and endocardial LAVA were observed, ablation was performed initially on the endocardial side to abolish the potentials transmurally, with subsequent epicardial ablation if required (Figure 6B and C). Four types of responses to catheter ablation of LAVA were predefined: no effect, delay, abolition, or dissociation. Complete elimination was defined as abolition or dissociation at all LAVA sites, whereas partial elimination was defined as abolition or dissociation at some but not all LAVA sites. For epicardial ablation in the pericardial space, the procedure was terminated if 15 minutes of RF energy delivery failed to eliminate LAVA in the region of interest. No time limit was imposed for RF ablation on the endocardial surface, which remained at the operator’s discretion.

After ablation, the ventricle was remapped. Additional substrate ablation was performed if residual LAVA were identified or if VT remained inducible. Remapping and inducibility testing were avoided in unstable patients to limit procedural duration in the interest of patient-safety. In addition to complete elimination of LAVA, non-inducibility was also considered a procedural endpoint in patients with previously inducible VT.

**Post-procedural Care**

Venous and arterial sheaths were immediately withdrawn. Pericardial sheaths were retracted after confirming a dry pericardial aspirate. ICD therapies were reprogrammed with active VT and ventricular fibrillation zones. Patients were monitored at least 48h in-hospital. Pre-
and ventricular fibrillation zones. Patients were monitored at least 48h in-hospital. Pre-
procedural anti-arrhythmic drugs were continued unless contraindicated or not tolerated.

Follow-up

Patients were followed at 1, 3, 6 and 12 months for the first year and every 6 months thereafter.
ICDs were interrogated at each visit and arrhythmia logs retrieved. A detailed history, Holter
monitoring, and ECG were performed in symptomatic patients without ICDs. An
echocardiogram was conducted at 6 or 12 months to reassess ventricular function. Patients with
relapse(s) were offered repeat ablation on a case-by-case basis. The primary endpoint was a
composite of death or recurrent VT. Qualifying arrhythmias included any
electrocardiographically documented VT, whether detected by ICDs, 12-lead ECGs, Holter
monitors, or rhythm strips, irrespective of morphology or rate.

Statistical analysis

Continuous variables are summarized by mean±standard deviation or median and interquartile
range (25th, 75th percentile) depending on normality of distribution, as assessed by normal
probability and quartile plots. Categorical variables are represented by frequencies and
percentages. Two-group comparisons between clinical (Table 1), LAVA (Table 2), and
procedural (Table 3) characteristics in patients with and without LAVA elimination were
performed using independent Student t-tests, Wilcoxon rank-sum tests, or Fisher’s exact tests,
where appropriate. However, since multiple VTs may have been induced in a given patient,
generalized estimating equations (GEE) were used to compare VT cycle lengths by specifying an
identity link and exchangeable correlation structure. The LV ejection fraction prior to ablation
and at the last follow-up visit was compared using a paired Student t-test. Factors associated
with LAVA elimination were assessed in univariate logistic regression models. Since no such
factor was identified, multivariate logistic regression was not performed. Freedom from recurrent VT or all-cause death was plotted using the Kaplan-Meier method in patients with and without LAVA elimination, and compared by the log rank statistic. Time 0 was defined as time of initial VT ablation. Cox proportional hazard models were used to assess predictors of recurrent VT or death in patients with LAVA identified during the index procedure. Proportional-hazards assumptions were verified by assessing time-dependent covariates (with time modelled linearly and logarithmically) and by plotting Schoenfeld residuals supplemented by testing for non-zero slopes. Baseline imbalances in patients with and without LAVA elimination and variables significant at the 0.2 level in univariate analyses were considered in an automated stepwise multivariate Cox regression model (entry 0.05; removal 0.10). Candidate variables included all clinical, LAVA, and procedural characteristics listed in Tables 1 to 3. Agreement between LAVA elimination and non-inducibility as procedural outcomes was assessed by the kappa statistic and summarized as percent overall, positive, and negative agreement. P-values <0.05 were considered statistically significant. Statistical testing was performed using SAS software Version 9.2 (SAS Institute, Cary, NC).

Results

Study population

During the study period, 133 patients underwent VT ablation. Fifty-seven patients were excluded due to following non-qualifying diagnoses: arrhythmogenic right ventricular cardiomyopathy (N=20), idiopathic VT (N=22), congenital heart disease (N=8), valvular heart disease (N=3), hypertrophic cardiomyopathy (N=1), and catecholaminergic VT (N=1). An
additional 6 patients declined consent. The study population consists of the remaining 70 patients. Baseline characteristics are summarized in Table 1.

LV Access

A retrograde approach was used in 61 (87%) and a transseptal approach in 32 (46%) patients. Percutaneous epicardial access was obtained in 21 (31%) patients, 15 of whom had a prior myocardial infarction and 6 of whom had non-ischemic dilated cardiomyopathy. One patient underwent concomitant epicardial ablation (without endocardial ablation) during open-chest surgery.

LAVA mapping and characteristics

LAVA, the primary target of ablation, were found in 67 of 70 patients [95.7%, 95% confidence interval (CI; 89.2%, 98.9%)] during the initial ablation procedure. In patients with three-dimensional electroanatomic mapping, LAVA occupied 39±32 of the 245±174 cm² of the LV surface (16%). Endocardial and epicardial LAVA were present in 63/70 (90%) and 17/21 (81%) patients, respectively. LAVA were observed epicardially in 4 of the 7 patients with no endocardial LAVA, while the remaining 3 patients had no identified LAVA.

Characteristics of the LAVA signals are summarized in Table 2. The LAVA amplitude was significantly higher when recorded from the epicardium [median 0.37 (0.20, 0.60) mV] compared to the endocardium [median 0.11 (0.08, 0.22) mV, P=0.002]. At sites where LAVA were recorded, the median amplitude and duration of the far field endocardial ventricular electrogram were 0.20 (0.10, 0.50) mV and 60 (50, 83) ms, respectively. Normal amplitude (>1.5 mV) was found in only 2 patients. The median delay between the far field ventricular electrogram and LAVA was 80 (60, 110) ms and the median delay between the end of QRS on the surface ECG and onset of LAVA was 0 (0, 40) ms. LAVA occurred before the end of the
QRS in 13 of 63 (21%) patients (negative delay). No specific LAVA characteristic predicted the ability to achieve complete LAVA elimination.

**Ablation**

The Pentaray catheter was used to map the endocardium in 35 patients and in all epicardial procedures. In addition, standard entrainment and electroanatomic mapping were each performed in 11 patients, with both mapping modalities in 3 patients. LAVA was eliminated in 47 of 67 patients [70.1%, 95% CI (58.7%, 80.1%)] patients, with signals abolished in 40 (60%) and dissociated in 7 (10%). No baseline clinical characteristic, including age, ejection fraction, and type of cardiomyopathy was predictive of LAVA elimination. Interestingly, in 5 cases, endocardial ablation could abolish potentials recorded from the epicardium as well (Figure 6 B).

As noted in Table 3, procedural and fluoroscopy times were similar in patients with and without complete LAVA elimination. However, a significantly longer radiofrequency (RF) energy delivery time was observed in cases where all LAVA were successfully ablated. In addition, LAVA elimination was more frequently achieved when a transseptal approach was used and when VT was inducible. There was little agreement between non-inducibility of VT and LAVA elimination as procedural endpoints (kappa statistic 0.038±0.097, P=0.70). Overall percent agreement was 54.0% [95% CI (41.7%, 65.7%)], with a positive percent agreement of 30.0% [95% CI (14.6%, 52.2%)] and negative percent agreement of 65.1% [95% CI (50.1%, 77.6%)].

**Adverse events**

Adverse events potentially related to the procedure occurred in 6 patients [8.6%, 95% CI (3.5%, 16.6%)], 4 of 47 (9%) with and 2 of 20 (10%) without LAVA elimination. Complications in patients with LAVA elimination included atrial fibrillation requiring anticoagulation with late development of tamponade, and prolonged pericardial bleeding after epicardial ablation. Both
were managed conservatively. In addition 2 patients died within 24 hours of the procedure; one due to a low flow state and another from low flow and arrhythmia recurrence. Complications in patients without LAVA elimination consisted of right ventricular perforation requiring surgical repair and tamponade during endocardial ablation managed conservatively.

**Follow-up**

Patients were followed for a median of 22 (14, 27) months from the initial ablation procedure. The combined endpoint of VT recurrence or death occurred in 39 patients [55.7%, 95% CI (44.0%, 66.8%)], with recurrent VT in 32 (46%) and death in 13 (19%). The combined endpoint occurred in 21 of 47 (45%) patients with LAVA elimination, with recurrent VT in 15 (32%) and death in 9 (19%). In contrast, the combined endpoint occurred in 16 of 20 (80%) patients without LAVA elimination, with recurrent VT in 15 (75%) and death in 4 (20%). None of the 3 patients without LAVA identified at the index procedure died during follow-up. However, 2 experienced recurrent VT at 6 and 9.5 months. Overall, 6 patients who died experienced recurrent VT prior to their demise. Three patients died during the first 24 hours of an ablation procedure, two after the initial intervention (as mentioned above) and a third with ischemic heart disease and an ejection fraction of 20% developed pulseless electrical activity during reintervention. Two patients died of heart failure, at 10 days and 6 months. One patient without an ICD died suddenly at 5 weeks and another at 30 months from VT storm. Six others died from non-cardiac causes unrelated to the procedure from 20 days to 40 months post-intervention. One patient with VT relapse underwent heart transplantation 5 months after the procedure.

In univariate Cox regression analyses, elimination of LAVA was the only factor significantly associated with a reduction in recurrent VT or death [hazard ratio 0.48, 95% CI (0.25, 0.92), P=0.027]. Non-inducibility (P=0.11) and ischemic versus non-ischemic heart
disease (P = 0.29) were not predictive of VT-free survival. Event-free survival curves are portrayed in Figure 7. Elimination of LAVA remained significantly associated with a reduction in VT or death in the multivariate regression analysis that controlled for baseline imbalances (e.g., age, type of heart disease, and RF ablation time) between patients with and without complete LAVA elimination [hazard ratio 0.49, 95% CI (0.26, 0.95), P = 0.035].

**Repeat ablation**

A redo procedure was performed in 14 patients, 6 of whom had LAVA successfully eliminated during the first intervention and 8 of whom had persistent LAVA. LAVA had recovered in 5 of the 6 patients with initial LAVA elimination and were successfully re-eliminated. The sixth patient had reintervention for symptomatic premature ventricular beats from the left ventricular outflow tract, with no relationship to the index procedure. In the 8 patients with initially persisting LAVA, repeat ablation eliminated LAVA in 4 and failed in the other 4. At last follow-up, 62.7% of patients remained free of VT recurrence after the last ablation procedure. The left ventricular ejection at the last follow-up visit was not significantly different from baseline (P = 0.34).

**Discussion**

**Main Findings**

This study describes a new approach for substrate modification in scar-related VT, targeting LAVA and aiming at either isolating or dissociating these electrically surviving myocardial fibers amidst the scar areas. It also emphasizes the advantage of using a high density mapping catheter and the benefit of a concomitant epicardial approach. The main findings are: 1) LAVA are observed in the majority of patients with ischemic or dilated cardiomyopathy; 2) LAVA can
be eliminated or dissociated by catheter ablation in sinus rhythm; 3) Ablation of LAVA appears reasonably safe; 4) LAVA elimination is a clear procedural endpoint; 5) Complete elimination of LAVA is associated with a superior clinical outcome.

**Significance of LAVA**

Residual electrical activity persisting within scar areas has been previously reported. This phenomenon has been studied in animal preparations, particularly in myocardial infarction models. Surviving cells surrounded by fibrosis were poorly coupled to the rest of the myocardium and were demonstrated to be responsible for the critically slow conduction needed for re-entry. Unhomogeneous scars and/or heterogeneous necrosis, as seen in ischemic and dilated cardiomyopathy, therefore provide an ideal substrate for VT. In humans, many investigators have reported such abnormal electrical potentials, using such terms as “delayed”, “isolated”, or “late”. However, prior descriptions of electrical characteristics were limited, with no data on amplitude and timing in relation to the QRS or to local or far-field ventricular signals. In addition, the precise distinction between the origin of the near versus far-field signal had not been described.

Involvement of this abnormal electrical activity in VT circuits has previously been demonstrated by activation and entrainment mapping. One group of investigators who proposed targeting it during VT ablation did not report elimination or dissociation of this abnormal activity. Moreover, no data on the impact of catheter ablation targeting LAVA were reported and LAVA elimination was never assessed as an endpoint to define procedural success. Instead, non-inducibility was regarded as the acute procedural endpoint. The only report describing a similar strategy included a small number of patients with arrhythmogenic right ventricular cardiomyopathy. The authors reported that LAVA elimination was associated with a
significantly better outcome. Interestingly, a similar observation was noted in our study wherein the population consisted of patients with ischemic and non-ischemic dilated cardiomyopathy.

**LAVA elimination defining acute procedural success**

Most strategies for VT ablation aim at rendering VT non-inducible, but this endpoint has several disadvantages. In some patients, VT cannot be induced despite clinical documentation. At the other end of the spectrum, several VTs of different morphologies can be induced in some.

Whereas all clinical VTs should be eliminated, the strategy for VTs never observed clinically but induced after ablation is less clear. Ablation can modify VT circuits and exits without abolishing the ability to sustain ventricular arrhythmia and non-clinical VTs may represent genuine circuits and, therefore, the substrate for relapse. In addition, a non-clinical VT that might have never been documented could become clinical after the procedure. Nevertheless, targeting non-clinical VTs may lead to excessive ablation.

The strategy of complete LAVA elimination overcomes some of these limitations of inducibility as the procedural endpoint. One advantage is that VT is neither required for mapping and ablation nor for the evaluation of efficacy. This approach is associated with substantially improved comfort for the patient and physician, does not require complex invasive techniques such as hemodynamic support, and allows for online monitoring of the impact of ablation on the arrhythmogenic substrate. It does not necessarily rely on 3-dimensional mapping systems, entrainment mapping, or pace mapping.

Complete elimination of LAVA was confirmed in 70.1% of patients in whom they had been documented. Interestingly, procedures associated with LAVA elimination had significantly longer RF ablation times. While it may be possible that more extensive ablation could improve procedural outcomes independent of LAVA, the superior survival free from recurrent VT in
patients with complete LAVA elimination was independent of RF ablation time. These results, therefore, suggest that this strategy more thoroughly addresses the arrhythmogenic substrate and carries the potential to improve long-term results.

High density mapping and pericardial approach

An additional novel feature of this study is its use of the Pentaray catheter in the pericardial space to provide high-density maps of a large region. The splines of the catheter are soft and do not produce a substantial amount of mechanical ectopies. The catheter was stable within the pericardium and provided clean (noise-free) electrical signals. During endocardial catheter ablation at sites facing the epicardial splines, very few or no artifactual interferences were observed, enabling careful monitoring of transmural response to ablation. Alternative multielectrode catheters such as basket or balloon arrays are of interest but cannot be positioned within the pericardial space and may restrict catheter manipulation within the ventricular cavity. Moreover, the signals may be influenced or altered by catheter to catheter contact during endocardial mapping.

Safety

The systematic use of an anterior (superficial) approach to access the pericardium instead of a conventional inferior approach likely contributed to the reasonable procedural safety in patients with an epicardial approach. In particular, it may explain the absence of abdominal complications during pericardial puncture.

Clinical follow-up

Elimination of LAVA was associated with a significant reduction in VT recurrence or death. Our definition of long-term success was strict, since it considered all-cause death or any arrhythmia relapse as a failure, whereas others have relied on outcomes limited to clinical VT or
a reduction in arrhythmia burden. Moreover, while some have reported freedom from VT after ablation in the 75 to 100% range, direct comparisons are obscured by the shorter follow-up (7, 8 months), fewer number of patients (20 or less), and inclusion limited to patients with ischemic heart disease. Our observed event-free survival rate (Figure 7) is consistent with other large multicenter series reporting success rates of 51 to 53% in ischemic heart disease. Acutely, a 51% success rate has been reported in non-ischemic substrates.

**Study Limitations**

We consider that targeting beyond the so-called clinical VT to attain complete LAVA elimination offers a more complete modification of the VT substrate compared to the usual endpoint of non-inducibility. However, since the study was observational in nature, it remains possible that patients in whom LAVA could be eliminated may have had VT that was more amenable to ablation in general and may, therefore, have had superior outcomes regardless. Our promising results provide the grounds for pursuing a randomized clinical trial to definitely assess whether the LAVA elimination strategy improves outcomes. It should also be noted that, in a minority of patients, entrainment and electroanatomic mapping were also performed. The study was not designed to determine the optimal density of maps, nor the role of adjunctive mapping techniques, in targeting and eliminating LAVA. We recognize that a potential disadvantage of this strategy could be greater tissue destruction than required to achieve clinical success. However, the post ablation LV ejection fraction remained unchanged in our study, suggesting that the ablation of surviving cells in scar areas was not deleterious.

**Conclusions**

Local abnormal ventricular potentials are identifiable in most patients with scar related VT.
Pending detailed mapping, catheter ablation can be used to eliminate them in sinus rhythm with a reasonable safety profile and distinctly clear end point. This comprehensive substrate modification strategy is associated with superior survival free from recurrent VT.

**Funding Sources:** This study was supported by a grant from Fondation Leducq (09 CVD 03)

**Conflict of Interest Disclosures:** Dr Jais, Haissaguerre, Hocini and Sacher have received lecture fees from Biosense Webster and St Jude Medical for less than 10,000 annual USD.

**References:**


19. de Bakker JM, van Capelle FJ, Janse MJ, van Hemel NM, Hauer RN, Defauw JJ, Vermeulen FE, Bakker de Wekker PF. Macroreentry in the infarcted human heart: the mechanism of


Table 1. Baseline clinical characteristics in all patients and according to whether or not local abnormal ventricular activities (LAVA) were completely eliminated.

<table>
<thead>
<tr>
<th></th>
<th>All Patients N=70</th>
<th>LAVA eliminated N=47</th>
<th>LAVA not eliminated N=20</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67±11</td>
<td>66±12</td>
<td>68±9</td>
<td>0.66</td>
</tr>
<tr>
<td>Male gender, N (%)</td>
<td>63 (90)</td>
<td>41 (87)</td>
<td>19 (95)</td>
<td>0.67</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>31 (44)</td>
<td>22 (47)</td>
<td>7 (35)</td>
<td>0.41</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>18 (26)</td>
<td>12 (26)</td>
<td>6 (30)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypercholesterolemia, N (%)</td>
<td>40 (57)</td>
<td>30 (64)</td>
<td>9 (45)</td>
<td>0.59</td>
</tr>
<tr>
<td>Active smoking, N (%)</td>
<td>32 (46)</td>
<td>24 (51)</td>
<td>8 (40)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

*Comparisons between patients with and without complete LAVA elimination

<table>
<thead>
<tr>
<th>Type of heart disease, N (%)</th>
<th>All Patients N=70</th>
<th>LAVA eliminated N=47</th>
<th>LAVA not eliminated N=20</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>56 (80)</td>
<td>40 (85)</td>
<td>14 (70)</td>
<td>0.19</td>
</tr>
<tr>
<td>Non-ischemic</td>
<td>14 (20)</td>
<td>7 (15)</td>
<td>6 (30)</td>
<td>0.77</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator, N (%)</td>
<td>53 (76)</td>
<td>37 (79)</td>
<td>14 (70)</td>
<td>0.53</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy, N (%)</td>
<td>13 (19)</td>
<td>8 (17)</td>
<td>4 (20)</td>
<td>0.74</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>35±10</td>
<td>34±10</td>
<td>37±11</td>
<td>0.28</td>
</tr>
<tr>
<td>Amiodarone, N (%)</td>
<td>42 (60)</td>
<td>28 (60)</td>
<td>13 (65)</td>
<td>0.79</td>
</tr>
<tr>
<td>Beta-blockers, N (%)</td>
<td>56 (80)</td>
<td>40 (85)</td>
<td>14 (70)</td>
<td>0.16</td>
</tr>
<tr>
<td>Number of procedures per patient†</td>
<td>1 (1, 1)</td>
<td>1 (1, 1)</td>
<td>1 (1, 2)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

LAVA denotes local abnormal ventricular activities
*Comparisons between patients with and without complete LAVA elimination
†Non-normally distributed variables are summarized as median and interquartile range (25th, 75th percentile)

Table 2. Characteristics of local abnormal ventricular activities (LAVA) during the initial intervention in all patients and according to whether or not LAVA were completely eliminated.

<table>
<thead>
<tr>
<th></th>
<th>All Patients N=70</th>
<th>LAVA eliminated N=47</th>
<th>LAVA not eliminated N=20</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAVA endocardial amplitude, mV</td>
<td>0.11</td>
<td>0.12</td>
<td>0.14</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>(0.08, 0.22)</td>
<td>(0.08, 0.21)</td>
<td>(0.10, 0.29)</td>
<td></td>
</tr>
<tr>
<td>LAVA epicardial amplitude, mV</td>
<td>0.37</td>
<td>0.39</td>
<td>0.22</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>(0.20, 0.60)</td>
<td>(0.20, 0.70)</td>
<td>(0.18, 0.50)</td>
<td></td>
</tr>
<tr>
<td>Far-field ventricular endocardial amplitude, mV</td>
<td>0.20</td>
<td>0.18</td>
<td>0.25</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>(0.10, 0.50)</td>
<td>(0.10, 0.60)</td>
<td>(0.10, 0.43)</td>
<td></td>
</tr>
<tr>
<td>Duration of far-field ventricular signal, ms</td>
<td>60</td>
<td>61</td>
<td>60</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>(50, 83)</td>
<td>(50, 80)</td>
<td>(50, 108)</td>
<td></td>
</tr>
<tr>
<td>Endocardial far-field V to LAVA delay, ms</td>
<td>80</td>
<td>90</td>
<td>70</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>(60, 110)</td>
<td>(70, 115)</td>
<td>(55, 100)</td>
<td></td>
</tr>
<tr>
<td>Endocardial QRS to LAVA delay, ms</td>
<td>0</td>
<td>20</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>(0, 40)</td>
<td>(0, 40)</td>
<td>(0, 40)</td>
<td></td>
</tr>
</tbody>
</table>

LAVA denotes local abnormal ventricular activities; V, ventricular
*Comparisons between patients with and without complete LAVA elimination
Table 3. Procedural characteristics in all patients and according to whether or not local abnormal ventricular activities (LAVA) were completely eliminated.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Patients N=70</th>
<th>LAVA eliminated N=47</th>
<th>LAVA not eliminated N=20</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transseptal access, N (%)</td>
<td>32 (46)</td>
<td>26 (55)</td>
<td>4 (20)</td>
<td>0.013</td>
</tr>
<tr>
<td>Epicardial access, N %)</td>
<td>21 (30)</td>
<td>17 (36)</td>
<td>4 (20)</td>
<td>0.11</td>
</tr>
<tr>
<td>Inducibility of VT at baseline, N (%)</td>
<td>49 (70)</td>
<td>31 (66)</td>
<td>17 (85)</td>
<td>0.012</td>
</tr>
<tr>
<td>Number of VT morphologies induced†</td>
<td>2 (1, 3)</td>
<td>1 (1, 3)</td>
<td>2 (1, 3)</td>
<td>0.27</td>
</tr>
<tr>
<td>Cycle length of mapped VTs, ms</td>
<td>400 (322, 450)†</td>
<td>400 (328, 460)†</td>
<td>400 (318, 440)†</td>
<td>0.23†</td>
</tr>
<tr>
<td>Entrainment mapping, N (%)</td>
<td>11 (16)</td>
<td>7 (15)</td>
<td>4 (20)</td>
<td>0.72</td>
</tr>
<tr>
<td>Electroanatomic mapping, N (%)</td>
<td>11 (16)</td>
<td>8 (17)</td>
<td>3 (15)</td>
<td>1.00</td>
</tr>
<tr>
<td>LAVA in sinus rhythm, N (%)</td>
<td>67 (96)</td>
<td>47 (100)</td>
<td>20 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>LAVA in VT, N (%)</td>
<td>36 (51)</td>
<td>25 (53)</td>
<td>10 (50)</td>
<td>1.00</td>
</tr>
<tr>
<td>Endocardial LAVA, N (%)</td>
<td>63 (90)</td>
<td>42 (89)</td>
<td>20 (100)</td>
<td>0.55</td>
</tr>
<tr>
<td>Epicardial LAVA, N (%)</td>
<td>17 of 21 (81)†</td>
<td>13 of 17 (76)†</td>
<td>4 of 4 (100)†</td>
<td>1.00</td>
</tr>
<tr>
<td>VT inducibility after ablation, N (%)</td>
<td>21 (30)</td>
<td>15 (32)</td>
<td>6 (30)</td>
<td>0.78</td>
</tr>
<tr>
<td>Radiofrequency ablation time, min</td>
<td>23±11</td>
<td>26±11</td>
<td>18±9</td>
<td>0.007</td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>42±20</td>
<td>44±19</td>
<td>36±21</td>
<td>0.14</td>
</tr>
<tr>
<td>Total procedural duration, min</td>
<td>148±73</td>
<td>186±78</td>
<td>155±57</td>
<td>0.092</td>
</tr>
</tbody>
</table>

LAVA denotes local abnormal ventricular activities; VT, ventricular tachycardia
*Comparisons between patients with and without complete LAVA elimination
†Non-normally distributed variables are summarized by the median value and interquartile range (25th, 75th percentile)
‡P-value derived from a generalized estimating equations (GEE) analysis that adjusts for multiple observations in the same patient
¶The denominator reflects the number of patients with epicardial access

Figure Legends:

Figure 1. Lateral fluoroscopic projection showing the subxiphoid pericardial puncture using Tuohy needle. The course of the needle in the substernal space is almost tangential to the posterior border of the sternum. It penetrates the parietal layer of the pericardium anteriorly as visualized from the contrast staining the anterior pericardium. Intrapericardial entry is confirmed with contrast trickling into the pericardial space (arrows). The guide wire is then inserted.

Figure 2. Electrogram recordings from different patients to show various characteristics of LAVA (arrows). Panel 1: The potential representing LAVA is fused with the terminal portion of
the far-field ventricular signal making it difficult to identify LAVA as a separate signal. **Panel 2:** LAVA potential occurs just after and with a slightly higher frequency than the far-field ventricular potential. LAVA in panels 1 and 2 occur within the QRS complex. **Panel 3:** LAVA is a double component potential which closely follows the far-field ventricular signal. The early component is a high frequency potential which is almost fused with the preceding far-field ventricular potential. It occurs within the terminal portion of the QRS complex. Another low amplitude signal follows an isoelectric interval and represents the late component of LAVA which occurs after the QRS complex. **Panel 4:** LAVA are represented by pluricomponent signals without isoelectric interval. These signals can be visualized distinctly from the preceding far filed ventricular signal. **Panel 5:** Double component LAVA signal. While the early component is recorded just after the QRS complex, the late component is recorded after the inscription of T wave on surface ECG.

**Figure 3.** Role of LAVA in the induction of VT and influence of radiofrequency energy on LAVA. **Pre-RF energy delivery. Panel A:** At first sight, the local ventricular electrogram during baseline paced rhythm looks simple. However, in the terminal portion of this simple-looking signal, a very high frequency component (LAVA) can be identified. **Panel B:** Programed electrical stimulation from the right ventricle unmasks the LAVA potential by increasing the delay from the far-field signal. The delay observed during RV pacing suggests poor coupling of the muscle bundle generating the LAVA signal. The delay is maximal with S3 which is not only associated with a change in the polarity of LAVA but also with the induction of VT. **Post-RF energy delivery. Panel C:** After delivery of radiofrequency energy, there is a remarkable delay (cf. panel A) between the far-field ventricular signal and LAVA during...
baseline paced rhythm. **Panel D:** Repeat programmed electrical stimulation from the right ventricle results in absence of LAVA signals following the far-field ventricular potential during S2 and S3 (empty arrows). Absence of LAVA is associated with an inability to induce the VT. Although ablation has rendered VT non-inducible, further RF energy application is indicated to completely eliminate the LAVA.

**Figure 4. A.** LAVA during sinus and ectopic beats in a patient with anterior myocardial infarction. **Panel A:** Surface ECG leads show one sinus beat followed by an ectopic beat. During sinus beat, complex ventricular electrogram signal shows three components labelled as 1, 2 and 3 in the order of their occurrence with fusion between the first two of them. Component 1 represents far-field ventricular signal and components 2 and 3 represent high and low frequency LAVA signals respectively. The sequence of occurrence of these components is altered during an ectopic beat. High frequency component 2 which precedes the QRS complex is followed by the far-field ventricular signal (component 1) with a marked delay between them suggestive of local conduction disturbance. Also note the change in the polarity of high frequency LAVA signal (2) between the two beats. Component 3 represents low frequency LAVA originating from another poorly coupled local muscle bundle. **Panel B:** (Top) Fluoroscopic image showing a transseptal sheath used to map the endocardial LV with an ablation catheter and a Pentaray catheter lying epicardially facing the endocardial catheter. (Bottom) During the first beat, in sinus rhythm, a far-field low amplitude potential is recorded endocardially on the ablation catheter suggestive of a scar tissue. The terminal deflection of this signal occurring at the end of the QRS complex is suspected to be LAVA. The ambiguity is resolved when the suspected LAVA potential clearly precedes the far-field ventricular signal in the two local ectopic beats following the sinus beat. A
low amplitude but high frequency LAVA potential precedes the onset of QRS (and far-field ventricular signal) by more than 100 ms, demonstrating the poor coupling of the bundle generating LAVA with the rest of the myocardium. Interestingly, the LAVA are better seen on the corresponding epicardial aspect of the ischemic scar. **B. Outcomes of pacing with progressive reduction in the current strength from the site recording LAVA endocardially in a patient with ischemic cardiomyopathy. Left:** The delay between the pacing stimulus and the QRS-onset increased from 126ms to 206ms and the QRS complex became wider when the pacing current strength was reduced from 7mA to 6mA. By reducing the output, the capture might be more limited to the muscle bundles (near field) lying amidst the scar tissue and responsible for generating the LAVA signal. Due to their poor coupling to the rest of the myocardium, the stimulus to the QRS-onset delay gets prolonged with reduction in current strength. Narrower QRS complex could be explained by wider field of capture and different route of exit of the impulse with higher current strength than otherwise. **Right:** Twelve lead ECG during pacing at progressively reducing current strength (output energy) shows change in the morphology of QRS as described above.

**Figure 5.** Intramyocardial conduction time in a patient with anterior myocardial infarction. **Left:** Pacing the endocardial site of LAVA with the ablation catheter (RF) and recording the signals from the corresponding epicardial sites using the Pentaray (splines A to E) catheter. The intramyocardial conduction time between the endocardially delivered pacing stimulus and the signal recorded on the corresponding epicardial site is 200ms. Such an exotic delay for the impulse to reach the epicardial aspect suggests the presence of poorly coupled muscle bundles surviving in the scar tissue. **Right:** Fluroscopic image showing a transseptal sheath used to map
the endocardial LV with the ablation catheter and a Pentaray catheter lying epicardially facing the endocardial catheter.

**Figure 6. A.** Endocardial and epicardial LAVA recordings in a patient with severe ischemic left ventricular dysfunction (LV ejection fraction – 26%) and scar-related VT. **Top:** Fluoroscopic image showing a transseptal sheath used to map the endocardial LV with the ablation catheter and a Pentaray catheter lying epicardially facing the endocardial catheter. **Bottom:** Panel A: LAVA is recorded on all the splines (A to E) of the Pentaray with a maximum delay of 130ms from the far-field endocardial ventricular potential in sinus rhythm. During a local endocardial ectopy, the delay on the corresponding epicardial site is remarkably increased to a maximum value of 276 ms. Panel B: During VT, the epicardial LAVA recordings cover almost the entire cycle length of the tachycardia. Panel C: Twelve lead ECG during VT. **B.** Effect of endocardial ablation on epicardially recorded LAVA in the patient described in Figure 6A. **Top:** Four fluoroscopic images in different projections (AP, LAO) showing transseptally accessed LV during endocardial ablation at different sites and a Pentaray catheter lying epicardially facing the endocardial catheter to monitor the effect of ablation on the epicardial LAVA. The absence of direct contact between both catheters allows convenient monitoring of LAVA in absence of artefacts during RF delivery shown in the corresponding panels below each image. **Bottom:** Panel A: LAVA recorded on the endocardial site is later than the latest LAVA on the epicardial site. Since endocardial LAVA earlier than the epicardial LAVA is the target site for ablation, ablation is not undertaken at the suboptimal site shown here. Panel B: Ablation catheter is moved to another site where continuous LAVA (arrows) are recorded endocardially immediately following the end of the far field ventricular potential. Such a site where endocardial LAVA
precedes the epicardial recordings is considered appropriate for endocardial ablation. **Panel C:** Ablation at the site shown in panel B is associated with changes in LAVA epicardially. Ablation is continued endocardially with an endpoint of complete abolition of LAVA. **Panel D:** Ablation results in abolition of LAVA on most of the splines of Pentaray. Dissociated LAVA can be observed on some splines. The end point is adequately reached. **C.** This electroanatomic map obtained from another patient depicts the epicardial activation in sinus rhythm in a patient with dilated cardiomyopathy. The area with latest activation appears in blue where some of the potentials are shown with LAVA. LAVA at the center show the latest activities, with predominantly superior input that would be targeted first. No LAVA were recorded endocardially in this patient. Most of the ablation was carried out epicardially.

**Figure 7.** The Kaplan-Meier curves depict freedom from recurrent ventricular tachycardia or death in patients with and without complete elimination of local abnormal ventricular activities (LAVA)
Epicardial mapping
Log Rank P=0.022

Event-free survival (%)

Time (months)

Complete elimination of LAVA
Non-complete elimination of LAVA

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Complete LAVA elimination</th>
<th>Non-complete LAVA elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk</td>
<td>47</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>
Elimination of Local Abnormal Ventricular Activities: A New End Point for Substrate Modification in Patients with Scar-Related Ventricular Tachycardia


_Circulation_. published online April 4, 2012;

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2012/04/02/CIRCULATIONAHA.111.043216

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/