Role of Alternative Interventional Procedures When Endo- and Epicardial Catheter Ablation Attempts for Ventricular Arrhythmias Fail

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Background—Ventricular tachycardia (VT) refractory to antiarrhythmic drugs and standard percutaneous catheter ablation techniques portends a poor prognosis. We characterized the reasons for ablation failure and describe alternative interventional procedures in this high-risk group.

Methods and Results—Sixty-seven patients with VT refractory to 4±2 antiarrhythmic drugs and 2±1 previous endocardial/epicardial catheter ablation attempts underwent transcoronary ethanol ablation, surgical epicardial window (Epi-window), or surgical cryoablation (OR-Cryo; age, 62±11 years; VT storm in 52%). Failure of endo/epicardial ablation attempts was because of VT of intramural origin (35 patients), nonendocardial origin with prohibitive epicardial access because of pericardial adhesions (16), and anatomic barriers to ablation (8). In 8 patients, VT was of nonendocardial origin with a coexisting condition also requiring cardiac surgery. Transcoronary ethanol ablation alone was attempted in 37 patients, OR-Cryo alone in 21 patients, and a combination of transcoronary ethanol ablation and OR-Cryo (5 patients), or transcoronary ethanol ablation and Epi-window (4 patients), in the remainder. Overall, alternative interventional procedures abolished ≥1 inducible VT and terminated storm in 69% and 74% of patients, respectively, although 25% of patients had at least 1 complication. By 6 months post procedures, there was a significant reduction in defibrillator shocks (from a median of 8 per month to 1; P<0.001) and antiarrhythmic drug requirement although 55% of patients had at least 1 VT recurrence, and mortality was 17%.

Conclusions—A collaborative strategy of alternative interventional procedures offers the possibility of achieving arrhythmia control in high-risk patients with VT that is otherwise uncontrollable with antiarrhythmic drugs and standard percutaneous catheter ablation techniques. (Circ Arrhythm Electrophysiol. 2015;8:606-615. DOI: 10.1161/CIRCEP.114.002522.)

Key Words: catheter ablation ■ surgery ■ tachycardia, ventricular

Catheter ablation is an effective treatment for drug-refractory ventricular arrhythmias. However, in some patients, endocardial combined with epicardial catheter ablation (when warranted) remains ineffective in providing arrhythmia control. The management of such patients presents a significant challenge as they face a poor prognosis from recurrent arrhythmia, heart failure, cardiogenic shock, which often presages increased mortality in follow up. Transcoronary ethanol ablation (TCEA), surgical cryoablation in the operating room (OR-Cryo), or percutaneous catheter ablation facilitated by a surgically created epicardial window (Epi-window) are often described as treatments of last resort in such patients. However in the contemporary era, the experience with these techniques is limited, and their outcomes are not fully defined. Because catheter ablation of VT continues to be increasingly used, patients with more complex disease substrates and comorbidities are being referred. Thus, a detailed understanding of the reasons for failure, available alternative interventions, and their outcomes is critical in facilitating timely and appropriate referral to a multidisciplinary team of interventional cardiologists, electrophysiologists, and cardiac surgeons.

Therefore, the purpose of this study was to characterize reasons for ablation failure and describe the approach and outcomes of a collaborative strategy of alternative interventional approaches in a high-risk group of patients who had ventricular
arrhythmias uncontrollable with antiarrhythmic drugs (AADs) and standard percutaneous catheter ablation techniques.

**Methods**

Patients in whom ≥1 attempt at percutaneous catheter ablation via the endocardial and epicardial approach (when warranted) had failed, and continued to have symptomatic, drug-refractory ventricular tachycardia (VT) or premature ventricular contractions, and were referred for alternative interventional approaches (TCEA, OR-Cryo, or percutaneous catheter ablation facilitated by a surgically created epicardial window) have been described. However, experience is limited, and outcomes with these approaches have not been defined.

**WHAT THE STUDY ADDS**

- Failure of endo/epicardial percutaneous catheter ablation attempts may be because of ventricular arrhythmias of intramural origin or nonendocardial origin with prohibitive epicardial access caused by pericardial adhesions or anatomic barriers to ablation or nonendocardial origin with need for a coexisting condition for cardiac surgery.
- Alternative interventional procedures, such as transcoronary ethanol ablation, OR-Cryo, or surgically created epicardial window, allow the possibility of achieving arrhythmia control in patients with ventricular tachycardia otherwise uncontrollable with antiarrhythmic drugs and standard percutaneous catheter ablation techniques. It is particularly effective in abolishment of ventricular tachycardia storm.
- Recurrences and mortality are high, underscoring the need for better treatment strategies.

**WHAT IS KNOWN**

- Patients with ventricular arrhythmias refractory to antiarrhythmic drugs and percutaneous endocardial and epicardial catheter ablation face a poor prognosis. Management of such patients is challenging.
- Several last resort alternative interventional approaches, such as transcoronary ethanol ablation, surgical cryoablation in the operating room (OR-Cryo), or percutaneous catheter ablation facilitated by a surgically created epicardial window have been described. However, experience is limited, and outcomes with these approaches have not been defined.

**Mapping and Ablation**

Percutaneous endo/epicardial mapping and ablation were performed as described previously (detailed in Methods in the Data Supplement). Briefly, programmed ventricular stimulation was performed, and the morphologies of the induced VTs were noted and compared with the documented VT. Sustained monomorphic VT was defined as continuous VT for ≥30 s or one that required an intervention for termination (cardioversion, pacing, or ablation).

We defined spontaneous VT as any inducible VT with an identical 12-lead ECG morphology and rate (within 20 ms) to a VT that the patient presented before ablation. If 12-lead ECGs of the presenting VT were not available before ablation, the rate cutoff and intracardiac electrogram characteristics from the implanted cardioverter defibrillator (ICD) were used. Undocumented VTs were defined as inducible VTs that did not have an identical rate (>20 ms difference), 12-lead ECG morphology or ICD-derived electrogram characteristics to the VT that the patient had presented before ablation.

Substrate mapping was performed with particular focus on the scar region facilitated by an irrigated catheter, and the CARTO electroanatomic mapping system (Biosense Webster, Diamond Bar, CA). Areas of low-voltage (<1.5 mV), dense (≤0.5 mV), and electrically unexcitable scar were identified (Methods in the Data Supplement). Late potentials in the scar were tagged. Pace mapping was performed; areas of long stimulus to QRS (S-QRS) delays (>40 ms) and where pace mapping matched QRS morphology of an induced VT were tagged. If hemodynamically tolerated, VT was reinduced and activation/entrainment mapping was performed. If not tolerated, it was terminated with radiofrequency ablation, burst pacing, or cardioversion and substrate mapping performed. Ablation-targeted presumptive channels exited within the low-voltage area including regions of long S-QRS delays (Methods in the Data Supplement). Radiofrequency ablation was delivered with an irrigated catheter (ThermoCool or ThermoCool SF; Biosense Webster) at a power of 25 to 50 W targeting an impedance drop of 10 to 20 ohms. Applications were repeated at target areas until they were rendered electrically unexcitable with unipolar pacing at 10 milliamperes at 2-ms pulse width.

Epicardial mapping was performed using the percutaneous approach if VT was suspected to be of epicardial origin or if endocardial ablation failed to terminate VT. Coronary angiography was performed before epicardial ablation to avoid coronary injury; high output pacing was also performed to avoid ablation in close proximity to the phrenic nerve.

Arrhythmia origins deep to the endocardium were defined as those for which ablation failed to abolish VT, despite the location being at the endocardial site closest to the VT based on entrainment mapping, or showing earliest endocardial activation relative to the QRS onset with focal spread away from that site, or the best pace-mapping response. Intramural circuits were defined as those deep to the endocardium and epicardium, and, in the case of intraseptal circuits, those deep to both right and left sides of the interventricular septum or on either the endo nor epicardium for nonseptal sites; or without epicardial mapping when mapping and QRS morphology were consistent with septal rather than epicardial circuits. Evidence for intramural scar was sought from cardiac magnetic resonance imaging (MRI) when available, and for the later cases, from inspection of unipolar voltage maps based on previously validated criteria.

**Approach to Alternative Interventional Approaches**

If endocardial mapping was unsuccessful, alternative interventional procedures were considered encompassing 1 or a combination of TCEA, Epi-Window, or OR-Cryo. TCEA was performed if (1) septal intramural origin was confirmed with biventricular mapping (±MRI) and ablation on both sides of the septum had failed; (2) nonseptal intramural circuits were confirmed with endo/epicardial mapping (±MRI), and ablation on either side had been unsuccessful; (3) origin deep to the endocardium was suspected, but epicardial...
Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
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</tr>
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<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>62±11</td>
</tr>
<tr>
<td>Male sex</td>
<td>52 (78)</td>
</tr>
<tr>
<td>NYHA class ≥3</td>
<td>17 (25)</td>
</tr>
<tr>
<td>LVEF, mean±SD, y</td>
<td>32±14</td>
</tr>
<tr>
<td>LVDD, mean±SD, mm</td>
<td>62±10</td>
</tr>
</tbody>
</table>

Cause of heart disease
- Ischemic: 32 (48)
- Nonischemic: 32 (48)
- Idiopathic dilated: 20
- Other*: 12
- No structural heart disease: 3 (4)
- ICD: 63 (94)
- Previous cardiac surgery: 25 (37)
- No of previous failed VT ablations, n, median (range): 2 (1–10)
- Endocardial+epicardial mapping/ablation alone: 24
- Endocardial mapping/ablation alone: 43
- No epicardial access†: 26
- Septal or outflow tract intramural origin: 13
- Clinical instability‡: 1
- Need for other cardiac surgery: 3
- No of previously failed AAD, n, median (range): 4 (1–7)
- No of AADs at time of alternative interventional procedure, n, median (range): 3 (1–5)
- No of patients taking drugs at time of interventional procedure
  - Amiodarone: 50 (76)
  - Lidocaine: 21 (32)
  - Mexilitine: 27 (41)
  - Quinidine: 11 (17)
  - Sotalol: 11 (17)
  - Other β blocker: 54 (82)
  - Dofetilide: 6 (9)
  - Combination therapy: 61 (92)
- Procedural indication
  - SMVT: 63 (94)§
  - NSVT/PVCs: 4 (6)§

All categorical values are stated as absolute number (%). AADs indicates antiarrhythmic drugs; ICD, implanted cardioverter defibrillator; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic diameter; NSVT, nonsustained VT; NYHA, New York Heart Association; PVC, premature ventricular contractions; and SMVT, sustained monomorphic VT.

*Detailed in Methods in the Data Supplement.
†Previous cardiac surgery (23; dense adhesions 3).
‡Clinical instability post endocardial ablation (1, PVC-triggered ventricular fibrillation storm requiring multiple shocks).
§VT storm in 35 patients (52%) for at least one of their procedures.

access failed or was felt to be prohibited by previous cardiac surgery or likely pericardial adhesions. An Epi-window was considered if VT originated deep to the endocardium in the infero-posterior LV and percutaneous epicardial access was not felt to be an option as noted above, and if TCEA targeting this region either could not be performed or was unsuccessful. OR-Cryo was considered initially for VT deep to the endocardium when there was need for other cardiac surgery. It was also a fallback option if TCEA or Epi-window either could not be performed or was unsuccessful. Further attempts at percutaneous endo/pericardial catheter ablation were performed after alternative interventional procedures if clinically indicated for ventricular arrhythmias uncontrollable with AADs. Progression from a less invasive (eg, TCEA) to a more invasive (eg, OR-Cryo) alternative interventional procedure occurred if ventricular arrhythmias were uncontrollable with AADs after the previous procedure or if a particular alternative intervention was considered unsuitable for the treatment of the arrhythmia.

Transcorynary Ethanol Ablation
The details of TCEA procedure have been described previously (Methods in the Data Supplement). Briefly, the procedure involved an electrophysiologist and an interventional cardiologist experienced in TCEA. VT inducibility was confirmed, the putative target region identified using previous 3-dimensional electroanatomic maps and VT terminated with pacing or cardioversion. Selective coronary angiography identified arterial branches supplying the target region that were sufficiently distal without collateral flow to avoid unnecessary ventricular damage. The artery was engaged with an angioplasty wire and a balloon deployed at its ostium. VT was then reinduced, and iced saline injected through the central lumen in an attempt to terminate VT with balloon inflation. If VT terminated with iced saline infusion or after blood flow occlusion, or was no longer inducible with these maneuvers, ethanol injection was then performed. Vessel occlusion was verified with contrast injection after guidewire removal. Programmed ventricular stimulation was then repeated. Other coronary branches were targeted if the VT continued, was modified, or remained inducible.

OR-Cryo and Surgical Epicardial Window
Surgical ablation in the operating room was performed under direct vision using a cryoablation probe (majority of cases; CryoCath, Montreal, Canada) or radiofrequency ablation (1 case; COBRA RF device; Atticture, West Chester, OH). When epicardial access was not possible because of previous cardiac surgery or adhesions, and VT origin from the inferior/posterior LV was suspected, a subxiphoid surgical window was attempted in the electrophysiology laboratory, as described previously, by a cardiac surgeon and under general anesthesia (Methods in the Data Supplement).

Outcomes and Follow-Up
Outcomes reported were as follows: abolishment of at least 1 inducible VT (either spontaneous or undocumented), complete success (noninducibility of any VT spontaneous and undocumented), partial success (abolishment of at least 1 spontaneous VT), and failure (residual inducibility of spontaneous VT). Other outcomes reported were termination of VT storm, procedure-related complications, 30-day mortality, VT recurrence, and overall survival in follow-up. The number of ICD shocks and number of AADs used for arrhythmia control in the 6 months after the final alternative interventional procedure were compared with 1 month before. Follow-up included review of records of all hospital and outpatient clinic visits and discussion with referring cardiologists and primary care physicians. The National Social Security Death Index was searched for mortality information.

Statistical Analysis
The Statistical Package for the Social Sciences for Windows (IBM SPSS, release 22; Armonk, NY) was used for analysis (Methods in the Data Supplement). Continuous variables were expressed as mean±SD (normally distributed) or median with interquartile ranges (Q25–Q75; if not normally distributed). Paired sample t test was used when comparing AAD drug use and shock burden before and after alternative interventional procedures. VT recurrence and overall survival were estimated by using the Kaplan–Meier procedure and log-rank χ2 test and a 95% confidence interval (CI) also provided, where applicable. Cox-regression models were used to
derive independent predictors of mortality (Methods in the Data Supplement). Graphs were constructed using GraphPad Prism (version 6; La Jolla, CA). A 2-tailed P value <0.05 was considered statistically significant.

**Results**

**Procedural Characteristics**

Eighty alternative interventional procedures were attempted in 67 patients over a median of 20 days (Q25–Q75, 6–35 days). This included 50 TCEA, 26 OR-Cryo, and 4 Epi-window cases. TCEA alone was attempted in 37 patients, OR-Cryo alone in 21 patients, the remaining 9 patients required a combination of TCEA and OR-Cryo (5 patients), or TCEA and Epi-window (4 patients). Median follow-up duration was 30 months (Q25–Q75, 7–53 months) after the first alternative interventional procedure.

**Reasons for Failure and Approaches Used**

Failures of percutaneous catheter ablation was attributed to VT of (1) intramural origin (35 patients); (2) nonendocardial origin (epicardial or intramural) with prohibitive epicardial access because of previous cardiac surgery or pericardial adhesions (16 patients); (3) anatomic barriers to ablation (8 patients); and (4) nonendocardial origin with the need for cardiac surgery for a coexisting condition (8 patients; Figure 1; Results in the Data Supplement; illustrative cases in Figures in the Data Supplement).

**Transcoronary Alcohol Ablation**

Fifty TCEA procedures were attempted in 46 patients (single procedure, 42 patients; 2 procedures, 4 patients) targeting VTs of intramural origin (32 patients) or nonendocardial origin with prohibitive epicardial access (14 patients; Table 2). Target sites were septal (31 patients), nonseptal (11 patients; inferior 9, anterior 1, lateral LV 1 patient, respectively), aortomitral continuity (3 patients), and right ventricular outflow tract (RVOT; 1 patient; Table 2). Two patients had previous OR-Cryo (1) and Epi-window (1). TCEA could not be performed in 8 of 46 patients (17%) who then underwent repeat RF catheter ablation (3), OR-Cryo (1), a surgical Epi-window (1), or were managed with AADs (3 patients; Table 2; Results in the Data Supplement). Of the 41 procedures in 38 patients in whom TCEA was performed, ethanol was injected down 48 arteries (mean, 1.2±0.4 vessels per patient; range, 1–2; mean dose of 2.6±1.2 mL; Figure 2).}

A median of 3 VTs (Q25–Q75, 2–4) were inducible per procedure before TCEA. TCEA abolished at least 1 inducible VT in 71% (27/38 patients) and terminated VT storm in 70% (16/23 patients). Of patients with VT storm recurrence, previously ineffective AADs became effective in 4 patients;

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**Figure 1.** Reasons for failure of prior catheter ablation attempts, site of origin of ventricular arrhythmias, and alternative interventional approaches used. *One patient in this group had 1 previous attempt at epicardial mapping, after which adhesions developed and repeat epicardial access could not be obtained. †Epicardial fat prohibiting ablation in right ventricular (RV) free wall in 2 patients and inferior left ventricular (LV) in 1 patient. All anatomic segments refer to the LV unless otherwise stated. A indicates anterior; AIV, anterior interventricular vein; AMC, aortomitral continuity; Ap, apical; ApI, apical inferior; ApS, apical septum; ApIS, apical inferoseptum; BAS, basal anteroseptum; Bl, basal inferior; BIS, basal inferoseptum; BS, basal septum; CS, coronary sinus; Diag, diagonal branch; Endo, endocardial; Epi, epicardial; Epi-W, surgically created epicardial; LAD, left anterior descending; LCx, left circumflex; LVOT, left ventricular outflow tract; MAS, mid anteroseptum; MI, mid inferior; OR, surgical cryoablation; OT, outflow tract; RVOT, right ventricular outflow tract; and TCEA, transcoronary ethanol ablation.
1 patient required OR-Cryo for abolishment of VT storm and the remaining 2 patients were considered unsuitable for any further interventions because of extensive comorbidities and died during the same hospitalization.

Complete success, partial success, and failure were achieved in 37%, 29%, and 18% of patients, respectively; in 16% of patients, reinduction was not performed to avoid aggravating hemodynamic distress (Figure 3A). Management subsequent to TCEA is expanded in Results in the Data Supplement. Of note, of 15 patients undergoing repeat procedures, all but 1 patient had VT origin from the same region; however, VT morphology had been altered suggesting a significant TCEA effect.

Complications occurred in 12 of 38 patients (32%), the majority of which were anticipated AV block from TCEA of a basal septal coronary branch (Table 2; Figure 3B). Procedure-related death occurred in 1 patient (2.6%) who died of multiorgan failure caused by cholesterol embolization syndrome. Death within 30 days occurred in 5 of 38 patients (13%; Table 2; Figure 3B) predominantly because of failure to control incessant VT in whom further procedures were not performed because of their fragile clinical state.

There was no significant change in LV function post TCEA (pre versus post LV ejection fraction of 31±14%, respectively; difference of 0.2%, 95% CI, 1.2% to 1.6%; P=0.76). LV function was also preserved in the subset of patients in whom >1 vessel was targeted (pre versus post LV ejection fraction of 21±4% versus 19±6%, respectively; difference of 2.2%; 95% CI, −4.5% to 8.9%; P=0.41); this is difficult to interpret, however, in the setting of recurrent VT episodes.

When examining patients who underwent TCEA alone, VT recurrence at 6 and 12 months were 74% (95% CI, 61%–87%) and 82% (95% CI, 71%–95%), respectively (median time to recurrence 17 days). There was no significant difference in VT recurrence between septal and nonseptal targets (at 6 months, 75% versus 69%, respectively; P=0.82). In patients who underwent TCEA alone, there was a significant reduction in burden of ICD shocks (median, 6 to 3; P=0.001), and number of AAD required for arrhythmia control when comparing 1-month pre to 6 months post TCEA procedure (median, 3 to 2; P=0.04; Table 2.

### Table 2. Procedural Characteristics According to Type of Alternative Interventional Procedure

<table>
<thead>
<tr>
<th>Procedure attempted</th>
<th>TCEA</th>
<th>OR-Cryo</th>
<th>Epi-Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure performed</td>
<td>38 patients</td>
<td>26 patients</td>
<td>4 patients</td>
</tr>
<tr>
<td>Indication (no. of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intramural VT origin</td>
<td>32</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Nonendocardial VT origin with prohibitive epicardial access</td>
<td>14</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Need for other cardiac surgery</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Anatomic barriers to ablation</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Target sites (no. of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal</td>
<td>31</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nonseptal (inferior 9, anterior 1, and lateral 1)</td>
<td>19</td>
<td>4 (apical inferior 1, basal inferior 2, and apical RV 1)</td>
<td></td>
</tr>
<tr>
<td>Aortomitral continuity</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Outflow tract</td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Complications</td>
<td>12/38 patients (32%)</td>
<td>5/26 (19%)</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>Complication type</td>
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<tr>
<td>AVB alone (6)</td>
<td>MV endocarditis (1)</td>
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</tr>
<tr>
<td>AVB + stroke (1)</td>
<td>Fatal intraoperative pulmonary embolus (1)</td>
<td></td>
<td></td>
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<tr>
<td>Increased ventricular pacing requirement (1)</td>
<td>Transient right coronary artery occlusion (1)</td>
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<td>Contrast nephropathy (1)</td>
<td>Phrenic nerve injury (1)</td>
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<tr>
<td>Cholesterol embolization (1)</td>
<td>Symptomatic left anterior descending coronary artery stenosis (1)</td>
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<tr>
<td>Hypotension requiring IABP (1)</td>
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<tr>
<td>Coronary vasospasm (1)</td>
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<tr>
<td>Procedure-related mortality</td>
<td>1/38 patients (2.6%) (multiorgan failure caused by cholesterol embolization)</td>
<td>2/26 patients (8%; fatal intraoperative pulmonary embolus 1; mitral valve endocarditis 1)</td>
<td>0/4 patients (0%)</td>
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<tr>
<td>30-d mortality</td>
<td>5/38 patients (13%; multiorgan failure caused by cholesterol embolization syndrome: 1; refractory heart failure and incessant VT: 4)</td>
<td>As above</td>
<td>0/4 patients (0%)</td>
</tr>
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</table>

Epi-Window indicates surgical epicardial window; IABP, intra-aortic balloon pump; MV, mitral valve; OR-Cryo, surgical cryoablation; RV, right ventricle; TCEA, transcoronary ethanol ablation; and VT, ventricular tachycardia.
Figure 3C). Six- and 12-month mortality were 21% (95% CI, 9% to 34%), and 27% (95% CI, 0% to 71%), respectively.

OR-Cryo

Twenty-six patients underwent OR-Cryo targeting VTs of intramural origin (5 patients), nonendocardial origin with prohibitive epicardial access (5 patients), nonendocardial origin with need for other cardiac surgery (8 patients), and anatomic barriers prohibiting catheter ablation (8 patients; Figure 1). Four patients had previous TCEA attempts of whom 1 patient had no suitable targets and 3 patients had VT recurrence after TCEA. OR-Cryo targets were nonseptal (19 patients), septal (1), and outflow tracts (6; Figure 4; Results in the Data Supplement; details of cardiac surgery shown in Table I in the Data Supplement).

A median 1 VT (Q25–Q75, 1–6) per procedure was inducible. OR-Cryo abolished at least 1 inducible VT in 69% (18/26 patients) and terminated VT storm in 80% (8/10 patients). In 2 patients in whom VT storm was not abolished after OR-Cryo, previously ineffective, AADs became effective (Results in the Data Supplement).

Figure 2. Coronary targets for Transcoronary ethanol ablation. CB indicates conus branch; Circ, left circumflex coronary artery; D1, first diagonal branch; LAD, left anterior descending coronary artery; LCx, left circumflex; main LCA, left main coronary artery; OM, obtuse marginal branch; PD, posterior descending branch; PL, posterolateral branch; and RCA-right coronary artery. Reprinted from Austen et al17 with permission of the publisher. Copyright © 1975, American Heart Association, Inc.

Figure 3. A, Acute outcomes, (B) complications/30-day mortality, and (C) arrhythmia burden/antiarrhythmic drug use pre (leftward bars) vs post procedure (rightward bars). AADs indicates antiarrhythmic drugs; Epi-window, surgically created epicardial window; ICD, implanted cardioverter defibrillator; OR-Cryo, surgical cryoablation; and TCEA, transcoronary ethanol ablation. *To avoid hemodynamic stress.
Complete success, partial success, and failure occurred in 65%, 4%, and 8% of patients, respectively; in 24% of patients, reinduction was not performed to avoid aggravating hemodynamic distress (Figure 3A). Complications occurred in 5 of 26 patients (19%), procedural and 30-day mortality occurred in 2 of 26 patients (8%), one who died of a fatal intraoperative pulmonary embolus and another who died of prosthetic mitral valve endocarditis (Table 2; Figure 3B; Results in the Data Supplement).

When examining patients who underwent OR-Cryo alone, VT recurrence at 6 and 12 months was 43% (95% CI, 22% to 63%) and 49% (95% CI, 27% to 70%), respectively (median time to recurrence, 20 months). When comparing 1 month pre to 6 months post OR-Cryo procedure, there was a significant reduction in the burden of ICD shocks (median, 8 to 0; P=0.009), and number of AAD required for arrhythmia control (median, 3 to 2; P=0.001; Figure 3C). Six- and 12-month mortality was 12% (95% CI, 0% to 25%) and 17% (95% CI, 2% to 32%), respectively. Six patients underwent repeat procedures for VT recurrence (Results in the Data Supplement).

Epi-Window in the Electrophysiology Laboratory
Four patients underwent surgical Epi-window targeting VTs of nonendocardial origin (Table 2). Three had previous cardiac surgery and 1 had attempted percutaneous epicardial access hampered by dense adhesions (1). Ablation regions were located in the inferior LV (apical 1 and basal 2) or apical right ventricular (1). Three patients had undergone previous TCEA (absent targets 1, failed TCEA 2; Results in the Data Supplement). A median of 2 VTs (Q25–Q75, 1–4) were inducible. Epi-window abolished at least 1 inducible VT in all patients. Complete success was achieved in 3 of 4 patients (75%) and partial success in 1 patient (25%). No complications or procedure-related deaths occurred (Table 2; Figure 3B).

VT recurred in 3 patients (75%); 1 underwent repeat radiofrequency ablation, whereas VT control was achievable with AADs in the other 2 patients (Results in the Data Supplement). When comparing 1 month pre to 6 months post Epi-window procedure, there was a trend toward reduction in ICD shocks (median, 5.5 to 0.5; P=0.17) and a significant reduction in number of AAD required for arrhythmia control (median, 3 to 2; Figure 3C).

Outcomes After All Alternative Interventional Procedures
When all interventional procedures were considered together, at least 1 inducible VT was abolished in 69% (45/67 patients) and VT storm was abolished in 74% (26/35 patients). Complete success, partial success, and failure were achieved in 48%, 19%, and 15% of patients, respectively; in 18% of

Figure 4. Surgical cryoablation targets. *One patient had 3 sites targeted in the same procedure—inferobasal free wall right ventricle (RV), septal right ventricle right ventricular outflow tract (RVOT), inferobasal septal left ventricle (LV). AIV indicates anterior interventricular vein; AV, aortic valve; CS, coronary sinus; Dx, diagonal; GCV, great cardiac vein; IVS, interventricular septum; LA, left atrium; LAD, left anterior descending; LCA, left coronary artery; LCC, left coronary cusp; LCx, left circumflex; LVOT, left ventricular outflow tract; MCV, middle cardiac vein; MV, mitral valve; OM, obtuse marginal; PA, pulmonary artery; PDA, posterior descending artery; PM, papillary muscle; RA, right atrium; RAA, right atrial appendage; RCA, right coronary artery; RCC, right coronary cusp; RV, right ventricle; RVOT, right ventricular outflow tract; and TV, tricuspid valve. Reprinted from Das and Zipes18 with permission of the publisher. Copyright © 2012, Elsevier, Inc.
patients, reinduction test was not performed to avoid aggravating hemodynamic distress (Figure 3A). Overall complication rate was 25%; procedural and 30-day mortality were 4% and 10%, respectively (Table 2; Figure 3B).

VT recurrence at 6 and 12 months was 55% (95% CI, 43% to 68%) and 67% (95% CI, 55% to 79%), respectively, while on a median of 2 AADs (Q25–Q75, 2–3). At 6 months after the final alternative interventional procedure, AAD requirement was significantly lower than 1 month before (pre: median, 3; Q25–Q75, 2–3 versus post: median, 2; Q25–Q75, 2–3; P<0.001; Figure 3C). Only 1 patient had arrhythmia-free survival without AAD. The burden of ICD shocks reduced from a median of 8 shocks (Q25–Q75, 4–17) in the 1 month before a median of 1 shock (Q25–Q75, 0–4) at 6 months after the final alternative interventional procedure (P<0.001; Figure 3C).

Six and 12-month mortality were 17% (95% CI, 8% to 26%) and 22% (95% CI, 12% to 32%), respectively. Failure to terminate VT storm after all available alternative interventional procedures was associated with high 12 mortality (48±18%). Complete procedural success (VT noninducibility) was associated with a significantly lower 12-month mortality (6%) compared with those who were inducible for any VT or not tested (36%; P=0.01). Complete procedural success was also an independent predictor of survival in a multivariable model accounting for clinical and procedural factors (hazard ratio, 0.35; 95% CI, 0.14 to 0.9; P=0.03; univariable analysis in Table II in the Data Supplement).

Discussion

Catheter ablation plays an important role in the management of ventricular arrhythmias in patients with structural heart disease.1 Ablation reduces the burden of ICD shocks, which are otherwise associated with poor quality of life and increased mortality.1,19 Successful ablation can be life saving in VT storm1,3 and can reverse premature ventricular contraction–induced cardiomyopathy.1 Patients with drug-refractory VT in whom exhaustive efforts using standard percutaneous catheter ablation techniques have also failed carry a poor prognosis from uncontrollable VT, progressive heart failure and high mortality in follow-up.3,20 Indeed, failed ablation portends a ≈4- to 6-fold higher odds of death3 with 1 study showing that the majority of patients (79%) who died within 6 months of an ablation procedure had failed ablation and experienced recurrent VT.20 In such patients, alternative interventional procedures are often described as treatment of last resort; however, experience with these techniques and an appreciation of their outcomes in the contemporary era remains limited.4,5

In this study, we outlined the reasons for failure, describe available alternative interventional procedures, which may be used within the collaborative framework of electrophysiologists, interventional cardiologists, and cardiac surgeons to improve outcome in a high-risk group of patients. The study is contextually important as the utilization of catheter ablation for the management of VT increases and with it, patients with more complex disease substrate and comorbidities are referred.8
We found that failure of endocardial or epicardial catheter ablation is often because of deep intramural circuits, anatomic obstacles to ablation, or prohibitive pericardial access because of adhesions when epicardial or intramural circuits are suspected that can be overcome with adjunctive interventional approaches encompassing TCEA, Epi-window, or OR-Cryo. In some patients, when epicardial or intramural circuits are suspected, one may forego an aggressive epicardial approach if cardiac surgery is required for a coexisting condition especially as the site of origin can be successfully targeted during surgery.

The collaborative approach to alternative interventional procedures was used to treat a population of patients who were acutely ill with frequent ICD shocks (median, 7) or VT storm (approximately one half of the patients), failed multiple previous ablation attempts (median, 2), and were exposed to the toxicity of multiple AAD (92% on combination therapy), including amiodarone (approximately three fourth of patients). This strategy offered the possibility of achieving or improving VT control with a significant reduction in the burden of ICD shocks and AAD use post procedure. Importantly, VT storm was abolished in approximately three fourth of patients. Indeed, the approach resulted in comparable rates of noninducibility of VT (48% in our study versus 41%–49%20,21), VT-free survival (45% at 6 months in our study versus 46%–53%20,21), and reduction in burden of ICD shocks, to that reported in some previous series using standard percutaneous catheter ablation techniques alone, despite a potentially higher risk group of patients in our study. Furthermore, procedural mortality (4% in our study versus 3%20,21) and overall mortality (22% at 12 months versus 18%–25%20,21) were also comparable. As an organized, sequential approach to the use of these alternative interventional procedures, we propose a stepwise decision tree by which these procedures may be used (Figure 5). It is critical to note that other interventional approaches, while not used in the present study because of lack of availability or concern about surgical risk, remain feasible alternatives when standard catheter ablation techniques and AADs fail to control ventricular arrhythmias. Techniques, such as bipolar ablation,22 renal denervation,23 and left or bilateral cardiac sympathetic denervation,24 have been shown to control VT storm and reduce burden of arrhythmia in follow-up.25

In the present study, failure to terminate VT storm was associated with a 48% mortality rate by 12 months, highlighting the high-risk group in this series, and underscoring the need for better treatment options. Finally, noninducibility of any VT, when achievable with a strategy of alternative interventional procedures was associated with markedly improved survival, consistent with previous studies using conventional techniques in potentially lower risk patients compared with the present population.26

Limitations
The effectiveness of different interventional approaches could not be directly compared because of heterogeneities in patient factors, disease substrate, site of origin, and the patients’ fragile clinical state. Other interventional approaches, as mentioned previously, were not used. It is feasible that these approaches may have improved outcomes further, which needs to be investigated prospectively.

Conclusions
The use of alternative interventional procedures, such as TCEA, OR-Cryo, or Epi-Window (in combination, if necessary), within a collaborative framework of electrophysiologists, interventional cardiologists, and cardiac surgeons offers the possibility of achieving arrhythmia control in patients with VT otherwise uncontrollable with AADs and standard percutaneous catheter ablation techniques. The approach is especially effective in the abolishment of VT storm.

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References


Role of Alternative Intervenitional Procedures When Endo- and Epicardial Catheter Ablation Attempts for Ventricular Arrhythmias Fail


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Supplemental Material
Supplemental Methods

1. Endocardial and Epicardial Mapping and Ablation

(a) Setup: Procedures were performed under either conscious sedation or general anesthesia as described previously. Using femoral venous access multipolar electrode catheters were positioned in the right ventricular (RV) apex and the His bundle region. Arterial access was obtained for hemodynamic monitoring and to facilitate retrograde aortic access to the left ventricle (LV) when necessary. When available, intracardiac echocardiography was used for image integration into an electroanatomic mapping system (CARTO, Biosense Webster, Diamond Bar, CA, USA), to confirm catheter-tissue contact and assess for complications. Bipolar electrograms were band-pass filtered from 30 to 500 Hertz (Hz) and digitally recorded along with a 12-lead surface EKG using the Cardiolab electrophysiology system (General Electric Healthcare, Buckinghamshire, UK). In the electroanatomic mapping system bipolar electrograms were high pass filtered at 20 to 30 Hz and low pass filtered at 400 Hz.

(b) Protocol of programmed ventricular stimulation: Programmed ventricular stimulation was performed with up to 3 extrastimuli scanned to refractoriness or a minimum coupling interval of 180 milliseconds (ms), applied following a basic drive of 600 ms and then 400 ms from 2 RV sites; burst pacing was also employed if ventricular tachycardia (VT) was not inducible with programmed extrastimulation.
(c) **Pacing settings:** Pace and entrainment mapping were performed using unipolar pacing from the distal electrode with an initial current strength of 10 milliAmps (mA) and a pulse width of 2 ms.³

(d) **Catheters used:** Substrate mapping was performed using a 4-millimetre (mm) or 3.5-mm-tip catheter (NaviStar, NaviStar ThermoCool or ThermoCool SF; Biosense Webster, Diamond Bar, CA, USA) and the CARTO electroanatomic mapping system (Biosense Webster, Diamond Bar, CA, USA).

(e) **Voltage mapping definitions:** Areas of low voltage (<1.5 millivolts [mV]), and dense scar (≤0.5mV) were identified.⁴ Electrically unexcitable scar was defined and tagged as sites where the pacing threshold exceeded 10 mA with 2-ms pulse width.³

(f) **Ablation strategy:** Late potentials in the scar were tagged. Pace-mapping was performed and areas of long stimulus-to-QRS delays (> 40 ms) and where pace-mapping matched QRS morphology of an induced VT were tagged. After identification of scar regions, the catheter was positioned at a site where pace mapping resembled the clinical or inducible VT and/or where stimulus-QRS delay was >40 ms indicative of slowed conduction. VT was then initiated with programmed stimulation and entrainment maneuvers attempted immediately. If this suggested a putative isthmus site and ablation was commenced immediately; otherwise continued in VT if it was hemodynamically tolerated. If the induced VT was hemodynamically unstable, it was terminated with RF ablation, rapid pacing, or
cardioversion and further mapping was then performed during sinus or paced rhythm. Ablation targeted presumptive channels and exits within the low-voltage area. When these sites were adjacent to a valve annulus or region of electrically unexcitable scar, ablation lesions were extended to the unexcitable area with the intention of transecting reentry circuit paths. If no low-voltage area was identified, ablation was attempted at the likely exit region identified as sites with presystolic electrograms during VT or where pace mapping resembled the VT QRS. Post ablation, programmed ventricular stimulation was repeated to confirm arrhythmia non-inducibility.

2. Transcoronary Ethanol Ablation

The details of transcoronary ethanol ablation (TCEA) procedure have been described previously. Selective coronary angiography was performed with an activated clotting time >250 seconds achieved with systemic heparanization. The target coronary artery ostium was selectively engaged using an angioplasty wire. An over-the-wire balloon sized to be slightly larger than the angiographic diameter of the target was deployed in the ostium of the target branch vessel. VT was then re-induced, and with the balloon fully inflated, iced saline (2–3 milliliters [mL]) was injected through the central lumen in an attempt to terminate VT. Alcohol injection was performed only if VT terminated during iced saline infusion in the vessel, or if VT that had been inducible before subselective cannulation of the vessel was no longer inducible when blood flow was interrupted in the vessel. Once an appropriate target site had been identified, 1 mL of sterile absolute ethanol was injected with the
balloon inflated for 10 minutes. After deflation of the balloon, contrast was injected to assess target vessel patency. If perfusion was present, a second 1 mL of additional ethanol was infused, and the balloon inflation was maintained for 10 minutes after that infusion. During ethanol injection, the balloon was fully inflated to prevent backwash of ethanol into other coronary vessels, and occlusion was verified using contrast injection after guidewire removal. If the VT continued, another branch was targeted. This could be repeated up to a maximum of 5 mL of ethanol in one artery.

After TCEA, programmed ventricular stimulation was repeat, as described previously. If the targeted VT remained inducible, an adjacent vessel supplying the target region was assessed using the same method.  

3. Surgical Epicardial Window

A 3-inch vertical incision was made in the midline epigastrium as described previously. The abdominal fascia was opened in the linea alba, directed toward the left of the xiphoid process superiorly. The pericardium was exposed and opened horizontally, parallel to the diaphragmatic reflection. The pericardiotomy was extended to the patient’s left to improve visualization of the ventricles. Blunt dissection of adhesions was performed to fully expose the diaphragmatic and posterior epicardium. An 8 French (Fr) sheath was then inserted into the pericardial space. Through the sheath, a 7Fr mapping and a 4-millimeter (mm) tip ablation catheter was inserted into the pericardial space.  

Expanded Statistical Methods
The Statistical Package for the Social Sciences for Windows (IBM SPSS, release 22, Armonk, New York, USA) was used for analysis. Continuous variables were expressed as mean ± standard deviation if normally distributed; median and interquartile range 25%-75% (Q25-Q75) were used if the data was clearly skewed. Where normal distribution was not present, log transformation of the raw values was performed to meet the assumption of homogeneity of variance. Raw mean values were compared using the Student t–test if normally distributed. In the absence of normal distribution, log-transformed mean values were used. Paired sample t-test was used when compared shock burden in the 1 month prior versus 6 moths post alternative interventional procedures using raw or log transformed values, where appropriate. Similarly, antiarrhythmic drug use in the 1 month prior versus 6 moths post alternative interventional procedures were compared using the paired sample t-test using raw or log transformed values, where appropriate. To test for associations between categorical variables, chi-square tests or Fisher’s exact test were used. Recurrence of VT and overall survival were estimated by using the Kaplan-Meier procedure and log-rank χ2 test. Multivariable Cox Regression analysis was used to determine predictors of mortality. Clinically relevant baseline and procedural characteristics were tested for a univariate association designated as a categorical or continuous variable, where relevant (Supplemental Table 2). Those characteristics with a univariable P<0.2 were entered in the final multivariable model in a “stepwise backward: likelihood ratio” fashion to determine independent predictors of mortality. A two-tailed P value <0.05 was considered statistically significant.
**Supplemental Results**

1. **Expanded Baseline characteristics:** The predominant ventricular arrhythmia was sustained monomorphic VT in 63/67 patients (94%) but 4 patients had incessant premature ventricular contracts (PVCs, Table 1, main file). Two of these patients had mean PVC burden of 28±11% with a decline in left ventricular ejection fraction (LVEF) from 63±3% to 33±18%; one patient had recurrent PVC-triggered ventricular fibrillation (VF) storm and one patient had incessant, highly symptomatic PVCs/non-sustained VT, unresponsive to anti-arrhythmic drugs (AADs). Twenty four patients had failed prior endo and epicardial mapping/ablation; 43 patients had endocardial mapping alone (Table 1, main file).

2. **Causes of non-ischemic cardiomyopathy (from Table in manuscript file):**
Hypertrophic (2 patients), lamin A/C (1 patient) and adriamycin-induced (1 patient) cardiomyopathy; valvular or congenital heart disease (8 patients) including aortic stenosis (1 patient), aortic regurgitation (1 patient), mitral regurgitation (1 patient), aortic stenosis and mitral regurgitation (1 patient), post aortic valve replacement (1 patient), post mitral valve replacement (1 patient), post combined aortic and mitral valve surgery (1 patient), and post ventricular septal defect repair (1 patient).

3. **Reasons for Failure and Approaches Employed**
   
   (a) **Intramural Circuits:** In the 35 patients with VTs of intramural origin, 26 patients had septal origin, 3 patients had non-septal LV origin (basal lateral 2; apical inferior 1), 3 patients had outflow tract origin (left ventricular outflow tract [LVOT] 2, right
ventricular outflow tract [RVOT] 1) and 3 patients had aorto-mitral continuity (AMC) origin of VT (Figure 2, main file). Sites of septal origin were basal septum (13 patients), basal anteroseptum (2 patients), basal inferoseptum (1 patient), mid anteroseptum (2 patients), apical septum (4 patients) and apical inferoseptum (4 patients).

In patients with proven intramural origin of VTs, all 26 patients with septal circuits were treated with TCEA (illustrative example in Supplemental Figure 1, also refer to Figure 2 main file for summary of approaches). Non-septal circuits in the basolateral (2 patients) and apical inferior LV (1 patient) were treated with TCEA (1 patient) or surgical cryoablation (OR-cryo, 2 patients; one following failed TCEA). Outflow tract and aorto-mitral continuity (AMC) circuits were treated with TCEA (3 patients) or OR-cryo (3 patients; one following failed TCEA).

(b) Non-endocardial origin with no possible epicardial access: In 16 patients with non-endocardial origin with no possible epicardial access, site of origin was septal in 5 patients (basal 3, apical inferoseptal 2), non-septal in 10 patients (anterior wall 1, basal, mid and apical inferior walls in 4, 3 and 1 patient, respectively) and RVOT in 1 patient (Figure 2, main file).

In patients with non-endocardial origin with prohibitive epicardial access septal circuits (5 patients) were predominantly targeted with TCEA (4 patients), but required Epi-window in 1 patients to target the apical inferior septum after failing a TCEA procedure (Figure 2, main file). Patients with non-septal sites (10) were treated with OR-cryo (5 patients), Epi-window (3 patients) and TCEA (3 patients). Illustrative
cases are shown in Supplemental Figures 2, 3 in Supplemental Figures and Figure 3 in main file). Figure 2 in the main file summarizes these approaches.

(c) Anatomic barriers to ablation: In 4 patients, the site of origin was in close proximity to the coronary branches prohibiting safe ablation. These included anterolateral LV below the anterior branch of the ramus intermedius coronary artery (1), at the junction of the left anterior descending and left circumflex (2 patients), and below the first diagonal (1 patient). In 4 patients, the site of origin could not be adequately targeted due to inability to maneuver the ablation catheter to the anterior interventricular vein (1 patient), prominent epicardial fat prohibiting successful ablation over the lateral and inferior RV free wall (1 patient) and the inferior LV (1 patient). In one patient prominent RV trabeculations prevented adequate abolishment of PVC-triggered VF storm with endocardial catheter ablation prompting an emergent open chest surgical approach (Figure 2, main file). All patients in this group underwent OR-Cryo. Illustrative cases are shown in Supplemental Figure 4 and 5.

(d) Suspected non-endocardial origin with need for other cardiac surgery: In 8 patients, the origin of arrhythmia was suspected to be non-endocardial (septal 1 patient, non-septal 5 patients, LVOT origin 2 patients, respectively) with anticipated need for cardiac surgery for another condition. The type of arrhythmia, mapping approach and targeted region are detailed in Supplemental Table 1 and shown in Figure 5 in the manuscript.
In further detail, one patient with septal VT had coronary artery bypass grafting, LV aneurysm resection with endoventricular patch repair and mitral valve replacement 13 days prior, who develop incessant VT seven days post-operatively concurrent with the development of mitral valve bacterial endocarditis. Endocardial mapping showed likely origin from the LV apical septum with RV apical entrainment consistent with an outer loop. LV access was not obtained due to recent surgery; thus attempts at terminating the VT from the RV apical septum were made, but were unsuccessful. Thus the patient underwent redo mitral valve surgery and repeat LV aneurysm reconstruction with extended endocardial resection.

Two patients had arrhythmia origin from the intramural LVOT and failed endocardial catheter ablation; both patients had moderate-severe aortic regurgitation necessitating valve replacement (one patient also requiring coronary artery bypass grafting [CABG] and ascending aortic root repair). Cryoablation of the LVOT was performed concurrently in both these patients.

Five patients had non-septal site of origin included 2 patients with arrhythmia origin from inferior epicardial LV with need for concurrent mitral and aortic valve replacement (1) and CABG (1). One patient had multiple VT circuits from the inferobasal free wall RV, septal RVOT and inferobasal septal LV who underwent cryoablation to these regions concurrently with CABG, mitral and tricuspid valve repair and left atrial appendage resection. One patient had VT from the anterior wall and failed endocardial catheter ablation had concurrent severe chronic ischemic cardiomyopathy and refractory heart failure who was previously listed for left ventricular assist device implantation (LVAD) and thus underwent concurrent
endocardial and epicardial cryoablation of extensive anterior wall scar and LVAD insertion. Lastly, one patient had an LV apical scar failed endocardial catheter ablation and needed concurrent CABG and LV apical aneurysm repair.

4. Transcoronary alcohol ablation

(a) Reasons for which TCEA could not be performed and subsequent approach employed: TCEA could not be performed in 8 of 46 patients (17%) due to absence of sufficiently sized coronary artery perfusing the target region (3 patients), presence of multiple collaterals deeming TCEA unsafe (2 patients), lack of effect of cold saline injection in the target vessel on the VA (2 patients) and non-inducibility of VT at baseline (1 patient; Figure 3, main file). The patient who was non-inducible at tie of TCEA underwent empiric substrate modification to the scar region. Of the 8 patients in whom TCEA was attempted but not performed, 3 underwent subsequent RFA, 1 underwent OR-cryo, 1 underwent epicardial ablation via an Epi-window and 3 were managed with anti-arrhythmic drugs.

(b) Coronary targets for TCEA: Coronary targets were branches of the left main/left anterior descending (54%), left circumflex (21%), branches to the LV from the right coronary artery (25%; Figure 4 main file). In total, 77% of the arteries targeted septal intramural circuits, 23% targeted non-septal intramural circuits (inferior wall 6 patients, lateral wall 1 patient, anterior wall 1 patient, AMC 3 patients).
(c) **Complications:** Complications occurring in 12 patients included complete AV block (7), contrast nephropathy (1), cholesterol embolization in 1 (who died subsequently), stroke (1, then developed complete AVB), transient hypotension (1, who required short period of intraaortic balloon counterpulsation support and died later), and coronary vasospasm (1 patient). In one patient, there was progressive increase in right ventricular pacing requirement from 27% to 65%. No instances of coronary artery dissection, perforation, inadvertent alcohol extravasation into major coronary branches occurred.

(d) **Cause of death:** Five patients who died within 30 days of the TCEA procedure were due to multi-organ failure due to cholesterol embolization syndrome (1 patients), refractory HF and incessant VT (4 patients). In these patients, TCEA had not abolished “spontaneous” VT in 2 patients, modified “spontaneous” VT in 1 patient, abolished “spontaneous” but “non-spontaneous” VTs remained inducible in 1 patients and 1 patient was non-inducible for any VT.

(e) **Management subsequent to TCEA:** Of the 38 patients in whom TCEA was attempted, 31 patients had VT recurrence. Fifteen patients with VT recurrence underwent repeat procedures (12 of 15 patients within 6 months of the first TCEA procedure; three procedures were performed 18 months, 3 years and 4 years later, respectively) and 16 patients were managed with AADs. Amongst patients who underwent repeat procedures, repeat TCEA was performed in 3 patients (1 patient subsequently underwent RFA, and 1 patient underwent surgical epicardial window
creation), 7 patients underwent repeat RFA, 3 patients underwent OR-cryo (1 patients undergoing a subsequent RFA) and 2 patients underwent surgical epicardial window creation (Figure 4, manuscript file).

During repeat TCEA, the same vessel (posterior descending coronary artery) was targeted in one patient as it had recannulized; in the remaining patients, TCEA targeted other vessels supplying the VT origin (first, then second septal in 1 patient; third, then the second obtuse marginal coronary artery in the other patient). Of 15 patients who underwent repeated electrophysiological study for recurrent VT after TCEA, VT originated from the same region as was targeted at the prior TCEA in all but 1 patient. In all patients, the recurrent VT had a different QRS morphology than observed at the first TCEA, suggesting that the substrate had been modified.

5. OR-Cryo

(a) Prior mapping/ablation attempts: Ten patients had failed prior endo and epicardial mapping/ablation; 8 patients had prior cardiac surgery, 2 patients had pericardial adhesions prohibiting epicardial access; 4 patients had prior TCEA attempts of whom 1 patient had no suitable targets and 3 patients had failed TCEA.

(b) Intra-operative inducibility of VT: Intraoperatively, VT could either not be induced was not induced to avoid aggravating the patient’s hemodynamic state in 11 of 26 patients (42%) who underwent substrate-guided cryoablation based on the previous electrophysiology study/ablation procedure; the remaining underwent
activation, pace mapping, substrate-guided or a combined approach (Supplemental Table 1).

(c) Post OR-Cryo ablation testing and subsequent management: Of the 20 patients who underwent post-ablation testing, 17 of 20 patients (85%) were non-inducible; 6 patients did not undergo repeat testing to avoid aggravating the patient’s hemodynamic state. Of the 11 patients who did not undergo pre-ablation induction, 5 patients underwent post ablation testing and were non-inducible; 6 patients were not tested post ablation.

Of the 15 patients who were inducible for VAs pre-ablation, 12 patients (80%) become non-inducible and 3 patients still had inducible clinical VT. OR-Cryo abolished VT storm in 8 of 10 patients (80%); previously ineffective AADs became effective in 2 patients with VT storm recurrence.

Three patients who remained inducible were subsequently managed with AADs (1 patient), or repeat endocardial ablation (2 patients). Of these 3 patients, 1 patient had likely mid-myocardial inferior LV wall substrate as no early sites of activation or fractionated were seen with epicardial mapping; VT was subsequently manageable with prior ineffective AADs. In the second patient had PVC origin was likely midmyocardial underneath the great cardiac vein (GCV)/anterior interventricular vein (AIV) junction as repeated cryoablation in this area would transiently suppress them only to return during rewarming. The patient subsequently underwent an endocardial radiofrequency ablation (RFA) where long duration RF application in the endocardial LVOT below the left coronary cusp
corresponding to the site of earliest epicardial activation at the GCV/AIV junction resulted in PVC abolishment. In the third patient, who was undergoing epicardial cryoablation of basolateral/posterior LV when acute thrombosis of the right coronary artery (RCA) developed as a result of nearby cryoablation prompting procedure termination and urgent coronary angiography; abciximab administration resulted in complete resolution. This patient did well for 3 years when VT recurred prompting subsequent RFA for VTs originating from the same region, albeit of different morphology, suggesting some effect of prior cryoablation.

**(d) Complications:** Complications occurred in 5 patients including mitral valve endocarditis leading to death (1), fatal intra-operative pulmonary embolus (1), transient RCA that resolved with abciximab (1), phrenic nerve injury (1) and symptomatic left anterior descending artery stenosis 3 months post cryoablation near its location (1). Two patients died (8%) died within 30 days of the procedure due to the aforementioned reasons.

**(e) Repeat procedures after OR-Cryo:** Six patients underwent repeat procedures for arrhythmia recurrence at a mean of 8±12 months (median 3 [IQR25-75%: 0-16 months]) post surgical cryoablation; 4 patients underwent endocardial RFA and 1 patients underwent TCEA. New VT had developed from the original scar in 2 patients, new VTs from new regions of scar had developed in 1 patient who had a developed a progressive dilated cardiomyopathy. Two patients had recrudescence of similar clinical VT due to presumed mid-myocardial site of origin, requiring TCEA (1
patient) and endocardial RFA (1 patient) to achieve arrhythmia control. In 1 patient, clinical PVC recurred and was successfully ablated from the LVOT beneath the left coronary cusp, as previously mentioned.

6. Epi-window

(a) Repeat procedures after Epi-window: The patient undergoing a repeat procedure had non-spontaneous VT inducible at the end of the Epi-window procedure arising from epicardial region not accessible due to adhesions. In this patient, TCEA was attempted but failed as extensive collaterals supplied the target region deeming TCEA unsafe. Endocardial RFA was performed, however VT termination was achieved only after long duration of ablation at the inferolateral LV apex and mid inferior LV suggesting an intramural circuit.
Supplemental References


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<td>Endo LVOT Likely intramural in LVOT at LCC-RCC junction</td>
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<td>LV apex, apical one-third of the anterior wall and inferior wall, and apical one-half of the septum and inferior wall, need for redo cardiac surgery</td>
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<td>LVOT</td>
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<td>GCV/AIV junction, close proximity to the LAD and LCX</td>
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<td>GCV/AIV junction, close proximity to the LAD and LCX</td>
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<th>Endo</th>
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<th>Intramural at RCC/LCC junction and aortic annulus</th>
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<td>Endo</td>
<td>LVOT</td>
<td>Intramural at RCC/LCC junction and aortic annulus</td>
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**Abbreviations:**

Mapping Approach: S=Substrate Guided, A=Activation mapping guided, C= combined substrate and activation mapping guided, An=non-inducible, hence based on anatomical guidance by findings of catheter ablation, P=Pace mapping.

Incision: M-median sternotomy, A-anterior thoractomy, L-lateral thoractomy

AIV- anterior interventricular vein, AMC- aorto-mitral continuity, AR- aortic regurgitation, AVR- aortic valve replacement, CABG- coronary artery bypass grafting, CAD- coronary artery disease, DCM- dilated cardiomyopathy, GCV- great cardiac vein, HD- heart disease, LAA- left atrial appendage, LAD- left anterior descending coronary artery, LCC- left coronary cusp, LCX- left circumflex coronary artery, LV- left ventricle, LVAD- left ventricular assist device, LVOT- left ventricular outflow tract, MV- mitral valve, NICM- non-ischemic cardiomyopathy, OM- obtuse marginal, PVC- premature ventricular contraction, RCC- right coronary cusp, RF- radiofrequency, RV- right ventricle, RVOT- right ventricular outflow tract, SHD- structural heart disease, TCEA- transcoronary ethanol ablation, TV- tricuspid valve, VF- ventricular fibrillation, VT-ventricular tachycardia.
### Supplemental Table 2

<table>
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<th>Variable</th>
<th>Univariable Hazard ratio (95% confidence interval)</th>
<th>P value</th>
<th>Multivariable Hazard ratio (95% confidence interval)</th>
<th>P value</th>
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<td>Age</td>
<td>1.06 (1.02-1.1)</td>
<td>0.007</td>
<td>1.04 (0.997-1.092)</td>
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<tr>
<td>Male gender</td>
<td>1.05 (0.4-2.81)</td>
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<td>NYHA class ≥3</td>
<td>1.9 (0.85-4.28)</td>
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<td>LVEF (each 1% increase)</td>
<td>0.97 (0.93-0.99)</td>
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<td>LVDD (each 1% increase)</td>
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<td>1.04 (0.99-1.1)</td>
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<td>Ischemic compared to non-ischemic cardiomyopathy</td>
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<td>Number of previously failed ablations</td>
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<td>Number of previously failed AADs</td>
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<td>Number of current AADs</td>
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<td>Number of VT episodes in the preceding month</td>
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<td>VT storm</td>
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<td>Number of VTs induced</td>
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<td>VT origin (compared to septal origin)</td>
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<td>- non-septal</td>
<td>0.38 (0.15-0.97)</td>
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<td>- LVOT</td>
<td>0.84 (0.19-3.7)</td>
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<td>- AMC</td>
<td>1.2 (0.15-9.36)</td>
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<td>- RVOT</td>
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<td>- intramural origin</td>
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<td>- Non-endocardial origin with need for other cardiac surgery</td>
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(compared to those who were inducible for any VT or not tested) 0.36 (0.16-0.83) 0.02 0.35 (0.14-0.9) 0.03
Any complication or not 0.96 (0.4-2.3) 0.92

**Abbreviations:**
AADs- anti-arrhythmic drugs, AMC- aorto-mitral continuity, LVEF- left ventricular ejection fraction, LVIDD- left ventricular internal diastolic diameter, LVOT- left ventricular outflow tract, NYHA- New York Heart Association, RVOT- right ventricular outflow tract, VT- ventricular tachycardia.
Supplemental Figure Legends

Supplemental Figure 1: Example of a patient with ventricular tachycardia (VT) originating from an intramural site of origin treated with transcoronary ethanol ablation (TCEA). 60 year old man with non-ischemic cardiomyopathy (ejection fraction [EF] 30%) with sustained monomorphic VT from the region of the aortic annulus and aorto-mitral continuity (VT1-4, A). This region had small area of endocardial bipolar voltage (B, arrow), normal epicardial bipolar voltage (C, arrow) and abnormal unipolar voltage suggesting intramural scar (D, arrow). Endocardial radiofrequency ablation (RF) was performed from the aortic annulus leftwards along the mitral annulus resulting in slowing of VT cycle length (CL) but not termination (B-D). Coronary angiography identified a small ramus branch as a target for ethanol injection (E, arrow showing balloon inflation in the vessel); rendering “spontaneous” VTs non-inducible.

Abbreviations: br- branch, endo- endocardial, epi- epicardial.

Supplemental Figure 2: Example of a patient with VT of non-endocardial origin (epicardial or intramural) with prohibitive epicardial access due to prior cardiac surgery who was treated with surgical cryoablation. 74 year old man with a prior inferior myocardial infarct, coronary artery bypass grafting (CABG), ischemic cardiomyopathy (left ventricular ejection fraction 15-20%) who presented with VT storm. A number of inferior wall VTs were inducible with apical and basal exits from the septal and lateral aspects of the scar (VT 1-5, A). Endocardial substrate mapping showed a dense network of late potentials within a large inferior wall endocardial
scar extending from the base to the apex (B). Sites of capture would exhibit long stimulus to QRS delays of > 80 ms with pace maps that matched the induced VT morphologies with >10/12 match. Despite extensive endocardial RF, VT remained inducible and recurred after 2 endocardial catheter ablation procedures. An attempt at TCEA showed no suitable targets. Due to the refractory nature of the VT, prior cardiac surgery, lack of TCEA targets, and a large inferior wall scar which may not be completely accessible by Epicardial window alone, he was referred for complete surgical cryoablation. During surgery, the inferoposterior left ventricle was exposed, where myocardial scarring was visible. A multipolar electrode was used for mapping, and cryoprobe was used for ablation (D, E). When in sinus rhythm, areas of late potentials within the scar were identified (F,G). Programmed ventricular stimulation induced the clinical VT with presystolic activation located in the mid ventricular region of the scar. A line of cryoablation lesions were placed through the scar resulting in termination of VT (H) resulting in non-inducibility at the end of the procedure and late potential abolishment (G).

Abbreviations: A- atrial, EGMs- electrograms, LP- late potentials, PM- pace maps, V- ventricular.

**Supplemental Figure 3:** Example of a patient with VT of suspected non-endocardial origin (epicardial or intramural) with prohibitive epicardial access due pericardial adhesions from epicardial defibrillator patches who was treated with TCEA. 64 year old man with ischemic cardiomyopathy (EF 25-30%) with a large anterior wall myocardial infarct 40 years prior and previous epicardial defibrillation patches who presented with VT storm. Four morphologies of VT were inducible with septal,
lateral, basal and apical exits (A) out of a large anterior wall scar (B). Extensive substrate modification was performed, however VT-1 recurred 3 days later, prompting an attempt at TCEA. Cardiac catheterization showed an occluded left anterior descending coronary (LAD) at the ostium. A conus branch supplied a large and tortuous collateral to the proximal LAD just beyond the point of LAD occlusion (C). The collateral was wired with an angioplasty wire and a 1.5 mm balloon advanced to the distal LAD (D). The balloon was inflated and vessel occluded followed by ethanol injection resulting in complete vessel occlusion. Programmed ventricular stimulation still induced a slow VT; additional alcohol ablation was performed more proximally but still distal to the first septal branch resulting in occlusion of the LAD beyond the first septal branch (E). No further VT was inducible; the patient has not had recurrent VT after 7 months’ follow up.

Abbreviations: AP-antero-posterior, Endo-endocardial, Epi-Epicardial, LAD-left anterior descending, LAO-left anterior oblique, RAO-right anterior oblique.

Supplemental Figure 4: 78 year old man with a history of ischemic cardiomyopathy (ejection fraction 25%), prior bypass surgery who presented with VT storm had 6 inducible VTs (A) related to a large inferior wall scar extending from the septum to the lateral mitral annulus with a large border zone near the base (B). Endocardial RF substrate-based abolished all VTs except VT-6 (cycle length of 520 ms) that terminated after a long duration of radiofrequency ablation (>30 seconds) at the mid inferoseptal aspect of the scar preceded by cycle length slowing with intra-procedural recurrence shortly thereafter suggesting an non-endocardial origin.
Angiography showed that the scar was supplied by the native PD via a saphenous vein graft (SVG) to the RCA (arrows, C and D). An interventional wire was passed down this vessel and its distal tip made an active pacing lead in unipolar configuration utilizing the His-indifferent electrode. In the distal branch (arrow, D), a good pace map with stimulus to QRS delay was noted (E). The upper and lower branch of the vessel were selected, and TCEA successfully performed resulting in vessel occlusion. The patient had recurrence of a new VT similar to VT-6, a few days later due to targeted branch recanalization. Repeat TCEA was performed, however a similar VT recurred again. Given prior history of bypass grafting, two failed TCEA procedures with no further coronary targets, and an inferior wall scar, a surgical epicardial window was created. A large area of low voltage at the interventricular septum from the apex to the mid RV was noted (F). Pace mapping from the apex produced a near perfect pace match to the VT that had recurred clinically; furthermore pacing from this site induced the VT. RF ablation terminated the VT (G). Ablation was continued from the apex to the basal RV (F); the patient was non-inducible at the end of the procedure, on subsequent non-invasive programmed stimulation.

Abbreviations: ABL- ablation, Endo- endocardial, Epi- Epicardial, LAO- left anterior oblique, PDA- posterior descending coronary artery, PM- pace map, RV- right ventricular.

Supplemental Figure 5: Example of a patient in whom epicardial ablation was hampered by prominent epicardial fat prohibiting effective ablation who underwent surgical cryoablation. A 59 year old man with non-ischemic cardiomyopathy (EF 45-
50%) presenting with recurrent sustained monomorphic VT had 4 VTs inducible (VT1-4, A). Substrate mapping showed normal endocardial bipolar right ventricular (RV) voltage (not shown). Epicardial mapping (B) showed extensive RV free wall scar extending from base to apex. Substrate modification was performed on 2 occasions, however VT recurred. Mapping in the operating room revealed prominent epicardial fat that hindered myocardial lesion formation. Epicardial fat was divided and dissected down to the myocardial surface parallel to the acute marginal branch of the right coronary artery with dissection carried out all the way to the tricuspid annulus. Cryoablation lesions were delivered to the basal segment of the RV 2 cm above the acute margin rendering the VT non-inducible.

*Abbreviations:* RV-right ventricle

**Supplemental Figure 6:** Example of a patient in whom endocardial catheter ablation failed to treat premature ventricular contraction (PVC)-triggered recurred ventricular fibrillation (VF) storm due to prominent RV trabeculations who subsequently underwent surgical cryoablation. A 57 year old female with an implantable defibrillator due to a prior history of idiopathic VF arrest in the setting of normal left and right ventricular function (normal MRI, no inherited arrhythmia syndromes identified). She presented with recurrent monomorphic PVC-triggered VF storm. The PVC had a left bundle, left superior axis (A). During endocardial mapping, closely-coupled PVCs would frequently trigger VF requiring 30 external shocks for cardioversion. RV voltage was normal (not shown). Activation and pace mapping showed Purkinje potentials preceding the PVCs, good pace maps and early activation
in the RV free wall (B). However a far-field, slurred potential was seen even earlier, suggesting possible intramural or epicardial origin. PVCs were abolished with endocardial catheter ablation only to recur within 24 hours causing PVC-triggered VF storm requiring multiple shocks and anti-arrhythmic drug infusions (C). The patient was taken emergently to the OR due to her fragile condition. No visible endocardial lesion was seen suggesting that the catheter may have been lodged in between trabeculations. A total of 2.5 cm diameter endocardial and epicardial cryo-applications were delivered to the mid RV free wall. The patient has not had any PVCs at 3 years’ follow up.

Abbreviations: RV-right ventricle
Supplemental Figure 1:

(A) 1 2 3 4

I
II
III
avR
avL
avF
V1
V2
V3
V4
V5
V6

(B) Endo Bipolar
(C) Epi Bipolar

(D) Endo Unipolar

(E) Ramus Br.
Supplemental Figure 2:
Supplemental Figure 3:


(B) 3D endocardial bipolar maps showing different perspectives:
- RAO: Right Anterior Oblique
- AP: Anterior
- LAO: Left Anterior Oblique
Supplemental Figure 4:

(A) 1 2 3 4 5 6

I
II
III
avR
avL
avF
V1
V2
V3
V4
V5
V6

(B) Endo bipolar LV

Endo bipolar LV
Supplemental Figure 5:

(A) ECG leads I, II, III, avR, avL, avF, V1, V2, V3, V4, V5, V6

(B) RV Epicardial Bipolar
Supplemental Figure 6:

(A) 

(B) RV Activation map

(C)