Results of Cryoenergy and Radiofrequency-Based Catheter Ablation for Treating Ventricular Arrhythmias Arising From the Papillary Muscles of the Left Ventricle, Guided by Intracardiac Echocardiography and Image Integration

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Background—Catheter radiofrequency ablation of ventricular arrhythmias (VAs) arising from the left ventricle’s papillary muscles has been associated with inconsistent results. The use of cryoenergy versus radiofrequency has not been compared yet. This study compares outcomes and complications of catheter ablation of VA from the papillary muscles of the left ventricle with either cryoenergy or radiofrequency.

Methods and Results—Twenty-one patients (40±12 years old; 47% males; median ejection fraction 59±7.3%) with drug refractory premature ventricular contractions or ventricular tachycardia underwent catheter cryoablation or radiofrequency ablation. VAs were localized using 3-dimensional mapping, multidetector computed tomography, and intracardiac echocardiography, with arrhythmia foci being mapped at either the anterolateral papillary muscle or posteromedial papillary muscles of the left ventricle. Focal ablation was performed using an 8-mm cryoaulation catheter or a 4-mm open-irrigated radiofrequency catheter, via transmitral approach. Acute success rate was 100% for cryoenergy (n=12) and 78% for radiofrequency (n=9; P=0.08). Catheter stability was achieved in all patients (100%) treated with cryoenergy, and only in 2 (25%) patients treated with radiofrequency (P=0.001). Incidence of multiple VA morphologies was observed in 7 patients treated with radiofrequency (77.7%), whereas none was observed in those treated with cryoenergy (P=0.001). VA recurrence at 6 months follow-up was 0% for cryoablation and 44% for radiofrequency (P=0.03).

Conclusions—Cryoablation was associated with higher success rates and lower recurrence rates than radiofrequency catheter ablation, better catheter stability, and lesser incidence of polymorphic arrhythmias. (Circ Arrhythm Electrophysiol. 2016;9:e003874. DOI: 10.1161/CIRCEP.115.003874.)

Key Words: catheter ablation ■ echocardiography ■ incidence ■ papillary muscles ■ ventricular tachycardia
WHAT IS KNOWN

- Papillary muscle–related arrhythmias represent a major clinical and therapeutic challenge.
- This kind of arrhythmia has been found to initiate ventricular fibrillation or polymorphic ventricular tachycardia.
- Recent publications associated radiofrequency ablation with low success rates, high recurrence, long procedure times and the necessity to deliver large amounts of radiofrequency energy.

WHAT THE STUDY ADDS

- This study compares the efficacy of cryoenergy during radiofrequency, as an alternate energy source for catheter ablation of papillary muscles–related arrhythmias.

all subjects gave written informed consent. Patients who developed multiple VA morphologies during follow-up were excluded from this study. Some patients included in prior publications were not eligible for inclusion due to VAs from multiple sites, not limited to the PMs. Neither was related to the ablation procedure. One operator treated the first 12 patients with cryoenergy, and a different operator treated the following 9 patients, using radiofrequency energy. The reason why energy sources were sequentially selected was because of operator preferences. Procedural outcomes such as catheter stability, incidence of multiple VAs morphologies during energy delivery, acute success rate, and long-term recurrence rate were compared between those patients treated with cryoenergy and those with radiofrequency. Each patient gave written informed consent, and all antiarrhythmic drugs were discontinued for at least 5 half-lives before the study.

All patients underwent electrophysiological study and catheter ablation. Catheter ablation was performed under conscious sedation. For mapping and pacing, standard multicatheter electrodes were placed in the coronary sinus (CS). His bundle region, and RV apex through the right femoral vein. Arrhythmia induction was attempted by programmed electric stimulation from the RV apex, RV outflow tract, and CS, with 1, 2, and 3 extrastimuli introduced after an 8-beat drive train, if necessary, with the addition of an isoproterenol infusion. Intravenous heparin was administered to maintain an activated clotting time of ≥300 s.

Imaging

A 2-dimensional ICE probe (ViewFlex, St. Jude Medical Inc) was positioned toward the RV outflow tract and RV inflow tract to visualize the different LV structures, as shown in Figure 1.

To specify VAs origin and catheter position, 3 segments were attributed to each PM: the apex, at the point of insertion of the chords (distal third of the PM); the body (middle portion of the PM); and the base, at the LV wall insertion. The base of the PM is a wide area. We considered the proximal third of the PM as base, which was in continuity with the LV inferior wall. Catheter position, contact, and stability were assessed through this method. Catheter stability was defined as the absence of back and forth movement of the catheter during energy delivery at the effective lesion site. Energy application was either stable (if the catheter show adherence in the myocardium-electrode interface) or unstable and was continuously assessed by ICE.

Multidetector computed tomography (MDCT) was performed with a 64-detector Philips Brilliance (Phillips Medical Systems) <15 days before catheter ablation. No ionic contrast material was used (Optiray 350 mg/mL) and scanning was performed with a collimated slice thickness of 0.9 mm. Prospective electrocardiographic gating at 75% of the R–R interval was performed to eliminate cardiac motion artifacts and reduce radiation dose.

The cardiac MDCT image was then integrated into the mapping system (Figure 2). This was achieved by performing the 3-dimensional reconstruction of the MDCT images (segmentation) and then aligning the 3-dimensional MDCT images with the NavX system (registration). Fiducial point pairs were created on the NavX system, by an operator identifying and selecting anatomic locations by ICE imaging. The fiducial points were then matched on the MDCT model to the same anatomic area. Matching of the fiducial points created on the NavX system was systematically confirmed by ICE, during shell construction.

Mapping and Ablation

Activation and pace mapping were performed in all cases, and the VA electrogram to QRS (EGM-QRS) interval was measured systematically. Electroanatomic 3-dimensional LV anatomic shells and activation maps (EnSite Velocity, St. Jude Medical Inc) of the LV were obtained in all cases (Figure 3). Activation points were collected using a decapolar catheter. No voltage maps were performed. Pace mapping was performed at a pacing cycle of 600 ms and stimulus amplitude of 1 mA greater than the late diastolic threshold, using a multipolar catheter. We used 2 different pace mapping criteria: (1) paced QRS match of ≥11 of 12 leads and (2) a pace-mapping score determined from the R/S ratio and fine notch of the QRS in the 12-lead ECG as previously reported (perfect pace mapping=24 points). Notching was defined as a high-frequency component of either the upstroke or the downstroke of the QRS in all 12 leads, to calculate the pace-mapping score.

Cryoablation

Cryoenergy was delivered at myocardial sites exhibiting the earliest bipolar activity or local unipolar QS pattern or at a ParkinJet network with an early activity preceding the QRS onset for ≥25 ms during the VA (Figure 3) at pace-mapping areas exhibiting QRS match of ≥11 of 12 or a pace-mapping score of ≥20. If pace mapping showed a QRS match of ≥11 of 12 and a score of ≤20 because of discrepancies in fine notch matching, cryoenergy was delivered anyway. Focal ablation was performed with a 9 Fr/8-mm cryoablation catheter (Freezer MAX 3, Medtronic, Inc, Minneapolis, MN) through a transseptal and transmural approach. Transseptal access was obtained by performing a transseptal puncture with a Brockenbrough needle, using standard 8.5 Fr SLD (St. Jude Medical Inc) sheaths. The SLD sheath was then exchanged for a 15 Fr steerable sheath (Flex Cath Advance, Medtronic, Inc, Minneapolis, MN) to help direct the cryocatheter. Special attention was given to catheter manipulation inside the LV to avoid damage to the chords because the cryocatheter is stiffer than the radiofrequency catheter. This was continuously assessed by ICE. When a reduction in the incidence of VT or PVCs was observed, cryoenergy was delivered for ≤240 s with 2 freeze–thaw–freeze cycles; otherwise, cryoenergy delivery was terminated, and the catheter was repositioned.

Radiofrequency Ablation

Radiofrequency energy was delivered using the same criteria previously described. Focal ablation was performed with a 4-mm open-irrigated radiofrequency ablation catheter (Therapy Cool, St. Jude Medical Inc) through a transseptal or transaortic approach. When a reduction in the incidence of VT or PVCs was observed radiofrequency energy was delivered for ≤200 s, with 2 posterior 45-s consolidation lesions at the same area; otherwise, radiofrequency delivery was terminated, and the catheter was repositioned.

The end point of catheter ablation was the elimination and nonducibility of VAs during isoproterenol infusion (2–10 μg/min) and burst pacing from the RV to a cycle length as short as 300 ms. Procedural acute success was defined as abolition of inducible or spontaneous VA.

ECG Analysis

Twelve-lead ECGs during the VAs and pace mapping were recorded digitally at a sweep speed of 100 to 200 mm/s in all patients for...
offline analysis. The QRS duration and axis, notching, and R to S (R/S) transition in precordial leads were measured with electronic calipers (EP-WorkMate 4.2 System, St. Jude Medical, Inc) by 2 experienced investigators blinded to the site of the origin. If there were discrepancies between those results, they were adjudicated by a third investigator.

Follow-Up
All patients were monitored continuously for 24 hours after the ablation procedure. Electrocardiography and echocardiography were performed before discharge in all patients. Follow-up information was obtained from direct evaluation in the arrhythmia clinic. Patients underwent 24-hour Holter monitoring and baseline electrocardiography before and 1, 3, and 6 months after the procedure. Arrhythmia burden was assessed before and after catheter ablation. All patients who reported symptoms underwent Holter monitoring to document the cause of symptoms. Successful long-term catheter ablation was defined as a significant reduction or absence of the clinical arrhythmia at 1, 3, and 6 months follow-up. Significant reduction of the clinical arrhythmia was defined as Holter burden reduction of the clinical VA by ≥50% when compared with Holter recordings before catheter ablation. No antiarrhythmic drugs were continued after catheter ablation unless VA recurrence occurred. All patients underwent echocardiography with color Doppler at discharge and 30 days after the ablation to evaluate the mitral valve, specially the degree of mitral regurgitation.

Statistical Analysis
Continuous data are expressed as mean±SD, and categorical data are presented as absolute values and percentages. Statistical analysis was performed using the Rank-sum test for non-normally distributed variables, and categorical variables were compared using the χ² test. Kaplan–Meier curves were generated, and the comparison among the 2 groups was performed using the Log-rank test. Data analysis was executed with the SSPS software version 20. For all tests, a P value of ≤0.05 was considered statistically significant.

Results

Patient Characteristics
Twenty-one (21) patients underwent PM VAs catheter ablation. The median age was 40±12 years old and 47% were males. The LV ejection fraction median was 59±7.3%. Five patients (23.8%) presented mitral valve prolapse, 2 of them with severe regurgitation. One patient presented a dilated
cardiomyopathy. Only 3 patients exhibited VAs at the ALPM and were all treated with cryoenergy. Twelve patients were treated with cryoenergy and 9 with radiofrequency. The population baseline characteristics are summed up in Table 1.

### Procedural Outcomes

Termination of the arrhythmia was observed in 19 patients without further inducibility. There were no intraoperative complications.

Patients treated with cryoenergy (n=12) showed a 100% acute success rate, whereas those treated with radiofrequency (n=9) presented a 78% success rate ($P=0.08$). Two patients from the radiofrequency group were treated with cryoablation because of unsuccessful radiofrequency ablation, after this study was concluded. Both were successfully ablated, and no VA recurrence was observed. These 2 patients were not considered for analysis in the cryoablation group.

Catheter stability was achieved in all patients treated with cryoenergy and only in 2 patients treated with radiofrequency ($P=0.001$). Incidence of multiple VA morphologies was observed in 7 patients treated with radiofrequency (77.7%), whereas none was observed in those treated with cryoenergy ($P=0.001$), as shown in Table 2. All patients included in this study had single VA morphology before catheter ablation. Multiple VA morphologies were only observed during catheter ablation and related to radiofrequency delivery.

Pace mapping showed a pace-mapping score average of 21 for radiofrequency and 22 for cryoablation. Only 1 patient in the cryoablation group and 1 patient in the radiofrequency group presented a score of <22 points. The PMPM had higher prevalence of clinical arrhythmias (85.7% PMPM VAs versus 14.3% ALPM VAs). Only 3 patients had PVCs originating at the ALPM. The PM base was the most frequent site of origin of VAs (Table 3). In the cryoablation group, VAs originating from the base of the PM were observed in 6 patients, the apex in 3 patients, and the body in 3 patients. In the radiofrequency group, VAs originating from the base of the PM were observed in 6 patients, and 3 patients showed VAs from the body. Pace mapping showed ≥11 of 12 match in all treated PMs at the site of effective lesion. Purkinje potentials (PP) were observed in 13 (62%) patients, mainly in VAs with origin at the base of the PM (base 100% versus body 16 versus apex 0%). Total fluoroscopy time was 11±3 minutes, and total procedure time was 129±17 minutes. Although the cryocatheter is stiffer and unidirectional, manipulation did not represent a problem while using a steerable sheath, and no significant manipulation inconveniences were observed during the procedures. All anatomic locations were equally targeted with either the cryocatheter or the radiofrequency catheter.

### Follow-Up Outcomes

Median follow-up was 360 days (interquartile range, 116–365) for cryoablation and 87 days (interquartile range, 65–148) for radiofrequency. No evidence of postprocedure complications assessed by cardiac ultrasound was observed. There was no increase in the incidence of mitral valve regurgitation, or an increase of MR severity after ablation, using either method.

None of the patient treated with cryoablation showed VA recurrence during follow-up (recurrence rate of 0%). One patient from the cryoablation group showed a 50% VA Holter burden reduction, from 40% to 19%, during the first month. After 6 months, Holter burden was <5% and the patient remained asymptomatic, without the use of antiarrhythmic drugs. Four patients (44%) presented VA recurrence during follow-up in the radiofrequency group ($P=0.03$). VA Holter burden was decreased from 20±15% to 2.8±5% in the cryoablation group and from 21±12% to 11±8% in the radiofrequency group. Figure 4 shows the free from VAs survival curves.

### ECG Analysis

Mean QRS duration was 138±6 ms. VAs with RSr pattern were the most frequent (57% versus 43%). The rSR pattern...
was more frequent at the ALPM. VAs with early R/S transition at V3 or V4 were more frequently seen at the base of PMPM (76%). Electrocardiographic characteristics are summed up in Table 3.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RF (n=9)</th>
<th>CRYO (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean</td>
<td>40.0±10.6</td>
<td>41.4±14.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Male</td>
<td>4 (44.4%)</td>
<td>6 (50%)</td>
<td>0.8</td>
</tr>
<tr>
<td>LVEF</td>
<td>59.9±9.5</td>
<td>58.1±5.1</td>
<td>0.08</td>
</tr>
<tr>
<td>SHD</td>
<td>3 (33.3%)</td>
<td>4 (33.3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>VT</td>
<td>2 (22.2%)</td>
<td>3 (25.0%)</td>
<td>0.04</td>
</tr>
<tr>
<td>NSVT</td>
<td>1 (11.1%)</td>
<td>7 (58.3%)</td>
<td></td>
</tr>
<tr>
<td>PVC</td>
<td>6 (66.7%)</td>
<td>2 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>AADs Pre</td>
<td>1 (11.1%)</td>
<td>3 (25%)</td>
<td>0.4</td>
</tr>
<tr>
<td>AADs Post</td>
<td>1 (11.1%)</td>
<td>0</td>
<td>0.4</td>
</tr>
</tbody>
</table>

AAD Pre indicates use of antiarrhythmic drugs prior ablation; AAD Post, use of antiarrhythmic drugs after ablation; CRYO, cryoablation; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; RF, radiofrequency; SHD, structural heart disease; VT, ventricular tachycardia.

Discussion

The ancient Egyptian Edwin Smith Papyrus, written between 3000 and 2500 B.C., refers to the use of cooling techniques to treat medical disorders. Catheter cryoablation was introduced...
Cryoblation for Papillary Muscle Arrhythmias

Table 3. Electrophysiological Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ALPM (n=3)</th>
<th>PMPM (n=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRSM</td>
<td>rSR</td>
<td>2 (66.7%)</td>
<td>7 (38.9%)</td>
</tr>
<tr>
<td></td>
<td>RSr</td>
<td>1 (33.3%)</td>
<td>11 (61.1%)</td>
</tr>
<tr>
<td>QRSD</td>
<td>133.3±2.1</td>
<td>142.2±9.2</td>
<td>0.08</td>
</tr>
<tr>
<td>QRSA</td>
<td>Inferior</td>
<td>3 (100%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Superior</td>
<td>0</td>
<td>18 (100%)</td>
</tr>
<tr>
<td></td>
<td>Notch</td>
<td>1 (33.3%)</td>
<td>8 (44.4%)</td>
</tr>
<tr>
<td>R/S</td>
<td>3</td>
<td>1 (33.3%)</td>
<td>7 (38.9%)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0</td>
<td>7 (38.9%)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2 (66.7%)</td>
<td>3 (16.7%)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1 (3.5%)</td>
<td>1 (5.5%)</td>
</tr>
<tr>
<td>PP</td>
<td>0</td>
<td>13 (72.2%)</td>
<td>0.02</td>
</tr>
<tr>
<td>VEGM–QRS</td>
<td>32.7±3.5</td>
<td>33.6±5.1</td>
<td>0.9</td>
</tr>
<tr>
<td>PMS</td>
<td>22.7±1.2</td>
<td>22.8±1.7</td>
<td>0.6</td>
</tr>
<tr>
<td>SpA</td>
<td>1 (33.3%)</td>
<td>13 (72.2%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Location</td>
<td>Apex</td>
<td>2 (66.7%)</td>
<td>1 (5.5%)</td>
</tr>
<tr>
<td></td>
<td>Base</td>
<td>0</td>
<td>12 (66.7%)</td>
</tr>
<tr>
<td></td>
<td>Body</td>
<td>1 (33.3%)</td>
<td>5 (27.8%)</td>
</tr>
</tbody>
</table>

ALPM indicates anterolateral papillary muscle; NOTCH, high-frequency component of the QRS complex; PMPM, posteromedial papillary muscle; PMS, pace-mapping score; PP, Purkinje potentials; QRSA, QRS axis; QRSD, QRS complex duration; QRSM, QRS complex morphology in V1; R/S transition, precordial lead at which the QRS becomes predominantly negative; SpA, number of patients in which the clinical arrhythmia was spontaneous during the procedure; and VEGM–QRS, time interval from the ventricular electrogram to the first QRS deflection during the clinical arrhythmia. Localization=origin of the clinical arrhythmia at the apex, body, or base of the papillary muscle.

Cryoablation has been reported as a safe alternative for catheter ablation in idiopathic VT arising from the RV outflow tract, aortic cusps, and epicardium,19,20 Cryothermal safety profile is further from the base of the PM. This would explain why PP are rarely seen at the body or apex of the PM. Ablation at sites with excellent pace mapping can be unsuccessful,15 suggesting that the site of VA origin may be located away from the breakout site. In this study, ablation at sites with excellent pace mapping (breakout) showed high success rates. Most of these patients present multiple VT morphologies during radiofrequency ablation.15 All patients in this study presented single VA morphologies before catheter ablation. We think this was the reason why in all cases energy delivery was localized. Incidence of multiple VA morphologies was observed only during energy delivery and was only related to radiofrequency. We think this was associated to the lack of catheter stability and brushing-like movement of the catheter during radiofrequency delivery, accounting for iatrogenic polymorphic VAs, which were not targeted for ablation. This was not observed in the cryoablation group and was attributed to the adherence property of cryoenergy delivery. Patients treated with cryoablation presented single VA morphologies during cryoenergy delivery, whereas those treated with radiofrequency presented a higher incidence of multiple VA morphologies during energy delivery (0% versus 77%, P=0.001). This finding may suggest that radiofrequency could be related to a proarrhythmic effect.

Radiofrequency Energy

Catheter irrigation is often used to cool the ablation electrode such that more power can be delivered without being limited by the formation of thrombus at the catheter–tissue interface.16 A major concern during radiofrequency ablation is mitral valve dysfunction by injury or rupture of the PMs, specially when using irrigated tip ablation catheters, although this has not yet been reported. Excessive intramyocardial heating can produce steam formation and abrupt volume expansion, which may be audible as steam pops.17 Pops are capable of causing deep tissue tears, and patients with ventricular perforations are more likely to require surgical repair.18

Cryoenergy

Cryoablation has been reported as a safe alternative for catheter ablation in idiopathic VT arising from the RV outflow tract, aortic cusps, and epicardium,19,20 Cryothermal safety profile is...
attributed to the mechanism of tissue destruction.\textsuperscript{12} Histology of chronic lesions shows well-demarcated lesions with minimal tissue disruption and preserved underlying architecture.\textsuperscript{21}

Catheter stabilization during ablation at the PMs is a major consideration. Stabilization is achieved because of catheter–tissue adherence after reaching temperatures of $-80^\circ$C.

### Imaging Techniques
Cardiac multi-imaging integration is the corner stone of PM ablation. ICE represents a key element guiding the fusion process between cardiac MDCT images and electroanatomic mapping systems, allowing for live visualization. This permits navigation on a 3-dimensional model of the LV with precise detail on the PMs, chordae, and mitral valve leaflets. Catheter position, stability, lesion formation, and continuous monitoring for complications are achieved through these methods.

### Electrocardiographic Characteristics
Right bundle branch block was always present,\textsuperscript{22,23} and the most frequent QRS pattern was RsR. Superior axis VAs suggested an origin in the PMPM, whereas inferior axis was consistent with the ALPM. Early precordial R/S transition was more frequently seen in V As originating at the base of the PM.

Monomorphic ventricular PVCs originating from the PMs have been found to initiate ventricular fibrillation or polymorphic VT. Catheter ablation of PVC-triggered VF-PMVT is highly successful,\textsuperscript{24,25} although recent data show that PVCs originating in the PMs are associated with low radiofrequency ablation success rates (60%), high recurrence rate, long procedure size of sample, and a clear tendency in favor of cryoenergy over RF. Although the acute success rate with cryoablation was not statistically significant, we think this was because of the limited comparison different energy sources for catheter ablation of ventricular arrhythmias. These results should be further evaluated in prospective trials.

### Conclusions
Cryoaiblation for VAs originating at the PMs of the LV was associated with higher success rates, lower recurrence rates, better catheter stability, and less incidence of polymorphic arrhythmias. These results should be further evaluated in prospective trials.

### Acknowledgments
We acknowledge Laura Gutierrez, Juan Pablo Costabel, and Dr. Alberto Alves de Lima from the Buenos Aires Cardiovascular Institute and Dr. Felix Ayala-Parades from the Centre Hospitalaire Universitaire de Sherbrooke.

### Disclosures
None.

### References
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