Clinical Experience With a Novel Electromyographic Approach to Preventing Phrenic Nerve Injury During Cryoballoon Ablation in Atrial Fibrillation

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Background—Phrenic nerve palsy remains the most frequent complication associated with cryoballoon-based pulmonary vein (PV) isolation. We sought to characterize our experience using a novel monitoring technique for the prevention of phrenic nerve palsy.

Methods and Results—Two hundred consecutive cryoballoon-based PV isolation procedures between October 2010 and October 2013 were studied. In addition to standard abdominal palpation during right phrenic nerve pacing from the superior vena cava, all patients underwent diaphragmatic electromyographic monitoring using surface electrodes. Cryoablation was terminated on any perceived reduction in diaphragmatic motion or a 30% decrease in the compound motor action potential (CMAP). During right-sided ablation, a ≥30% reduction in CMAP amplitude occurred in 49 patients (24.5%). Diaphragmatic motion decreased in 30 of 49 patients and was preceded by a 30% reduction in CMAP amplitude in all. In 82% of cases, this reduction in CMAP amplitude occurred during right superior PV isolation. The baseline CMAP amplitude was 946.5±699.2 mV and decreased by 13.8±13.8% at the end of application. This decrease was more marked in the 33 PVs with a reduction in diaphragmatic motion than in those without (40.9±15.3% versus 11.3±10.5%; P<0.001). In 3 cases, phrenic nerve palsy persisted beyond the end of the procedure, with all cases recovering within 6 months. Despite the shortened application all veins were isolated. At repeat procedure the right-sided PVs reconnected less frequently than the left-sided PVs in those with phrenic nerve palsy.

Conclusions—Electromyographic phrenic nerve monitoring using the surface CMAP is reliable, easy to perform, and offers an early warning to impending phrenic nerve injury. (Circ Arrhythm Electrophysiol. 2014;7:605-611.)

Key Words: atrial fibrillation ■ catheter ablation ■ cryosurgery

The creation of circumferential lesions to electrically isolate pulmonary veins (PVs) by means of a cryoballoon catheter has emerged as an effective alternative approach to conventional point-by-point radiofrequency ablation in patients with atrial fibrillation (AF).1–3 Phrenic nerve palsy (PNP) with hemidiaphragmatic paralysis is the most frequently observed complication with cryoballoon ablation, occurring in ≈6% of clinical procedures (range, 3%–11%).2,4,5 The most commonly used preventative measure is the use of continuous abdominal palpation during phrenic nerve pacing from a catheter placed in the superior vena cava cranial to the right-sided PVs. However, despite early interruption of ablation with the perceived onset of less vigorous diaphragmatic contractions, PNP continues to be observed. Although alternative monitoring techniques, such as continuous diaphragmatic visualization and auditory monitoring of diaphragmatic contraction have been proposed, the use of diaphragmatic electromyography represents a potentially more sensitive technique for detecting early changes to the phrenic nerve.4,6 During phrenic nerve pacing a reliable diaphragmatic signal (the diaphragmatic compound motor action potential [CMAP]) can be easily recorded using surface electrodes, providing valuable information about phrenic nerve function. In a recent preclinical studies, we demonstrated that a 30% reduction in diaphragmatic CMAP amplitude presaged impending hemidiaphragmatic paralysis by ≥30 seconds.4,6 Herein, we characterize our clinical experience using diaphragmatic electromyographic monitoring for the prevention of PNP.

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Methods

Study Population
A cohort study was conducted on consecutive patients with highly symptomatic paroxysmal or persistent AF refractory to antarrhythmic drugs referred for cryoballoon-based PV isolation (PVI) between October 2010 and October 2013. It has been our approach to treat patients with persistent AF with PVI alone as the first ablation procedure. After providing written informed consent, all patients underwent routine preprocedure cardiac imaging (echocardiography, computed tomography, and MRI) to assess left atrial and PV anatomy. No patient was excluded on the basis of anatomical considerations. The study was approved by the local institutional review board.

Pulmonary Isolation Procedure
All patients were required to have received effective anticoagulation with oral vitamin K antagonists (international normalized ratio of 2–3) or dabigatran for ≥1 month and undergo transesophageal echocardiography to rule-out left atrial thrombus before ablation. All procedures were performed under conscious sedation using boluses of remifentanil and a continuous infusion of propofol. Via central venous access a 6-French deflectable decapolar catheter was inserted in the coronary sinus, a 5-French quadripolar catheter was positioned in the cranial superior vena cava, and a 9-French 9-MHz intracardiac echocardiography catheter was placed in the right atrium. Left atrial access was preferentially obtained via single transeptal puncture (or a patent foramen ovale) under intracardiac echocardiography and fluoroscopic guidance. After transeptal access, intravenous heparin was administered as a bolus (100 IU/kg) with continuous infusion to maintain an activated clotting time >300 seconds. Thereafter, the standard transeptal sheath was exchanged for a 15-French FlexCath (Medtronic CryoCath LP, Pointe-Claire, Canada) steerable sheath, through which a first- or second-generation 23- or 28-mm cryoballoon was advanced into the left atrium (Table I in the Data Supplement).

The choice of the balloon diameter was determined by the left atrial and pulmonary venous anatomy observed on the preprocedural MRI or computed tomographic scan. However, whenever possible, the larger diameter cryoballoon was preferred. Before ablation a circular mapping catheter was placed sequentially within each of the 4 PV antra to record baseline electric activity (pulmonary vein potentials). Early in our experience, we advanced a variable decapolar circular mapping catheter (Lasso, Biosense-Webster, Diamond Bar, CA) through a second more posteriorly located transeptal puncture. Since 2011, the technique was modified to perform a single transeptal puncture with pulmonary vein potentials assessed by means of a small caliber 15- or 20-mm diameter circular mapping catheter (Achieve; Medtronic; Minneapolis, MN) introduced into the central lumen of the cryoballoon catheter. Thereafter, the guidewire or Achieve catheter was advanced distally into the PV to optimize support during cryoballoon positioning. The cryoballoon was inflated within the left atrium under fluoroscopic guidance and advanced to the PV ostium. Where possible the Achieve catheter was then repositioned as proximal to the PV ostium as possible, without compromising the degree of pulmonary venous occlusion. Occlusion was assessed by distal contrast injection and evaluated according to a standard semiquantitative scale from 1 (negligible occlusion with immediate rapid outflow from the PV) to 4 (total occlusion with complete contrast retention). For each vein, cryotherapy was applied for a maximum of 240 seconds, with a maximum of 1 bonus application after the attainment of PVI. In the absence of a clinical rationale to provide a bonus lesion (such as a late time to isolation or a relatively warm ablation temperature), it was our preference to proceed with no bonus lesions. The end point of the procedure was complete isolation of all PVs, as assessed by entrance and exit block.

Diaphragmatic Stimulation and CMAP Monitoring
Before ablation of right-sided PVs, a standard 5-French quadripolar catheter was placed in the superior vena cava cranial to the right superior PV (RSPV) to pace the right phrenic nerve from the distal electrode pair (5–20 mA at 0.5–2.0 ms pulse width at a cycle length of 1000 ms). In addition to direct abdominal palpation to monitor right hemidiaphragmatic excursion, diaphragmatic electromyographic monitoring was systematically performed. Per our previously described methodology, 2 standard surface electrodes were positioned on the right hemithorax to record a right diaphragmatic CMAP; the first 5 cm above the xiphoid process and the second 16 cm away along the right costal margin (Figure 1). These electrodes were connected to a central computerized electrophysiology workstation (EP Med Systems, St Jude Medical, or Prucka recording system, GE Healthcare) where bipolar electromyography signals were amplified and band-pass filtered between 1 and 50 Hz.

Before engagement of the RSPV with the cryoballoon, a phrenic capture threshold was determined and the baseline CMAP amplitude recorded. Superior vena cava catheter positioning was optimized during right phrenic nerve pacing to obtain the highest amplitude diaphragmatic CMAP signals (second component after excluding the stimulation artifact; Figures 2 and 3). Thereafter a reverification of phrenic pacing threshold and CMAP amplitude was performed after ensuring adequacy of PV occlusion (because the PV ostial geometry and relationship with the phrenic nerve can be altered by balloon inflation). During ablation, diaphragmatic CMAP signals were continuously displayed and analyzed in real time (in addition to being recorded on a hard disk and stored on an optical drive). Ablation was terminated on any perceived reduction in the strength of diaphragmatic contraction or a 30% reduction in the maximal diaphragmatic CMAP amplitude from baseline (Figure 4).

Phrenic nerve impairment was defined as a loss of diaphragmatic movement despite pacing the phrenic nerve at twice the capture threshold. Transient dysfunction was defined as a recovery of phrenic nerve function by the conclusion of the index ablation procedure.

Figure 1. Configuration of surface electrodes to record the surface hemidiaphragmatic compound motor action potential (CMAP). The first standard surface electrode was positioned 5 cm above the xiphoid with the second surface electrode positioned 16 cm along the right costal margin (A). These were connected via standard ECG cables to the pin box of the EP recording system (B). Adapted from Franceschi et al. with permission of the publisher. Copyright © 2011, Heart Rhythm Society. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
Persistent PNP was defined as phrenic nerve dysfunction that persisted beyond the conclusion of the procedure.

Postablation Follow-Up and Outcomes
All patients were discharged home within 24 hours after the procedure. After the procedure, patients continued anti-coagulation with dabigatran or warfarin (to maintain an international normalized ratio of 2–3) for a minimum of 3 months. Antiarrhythmic medications (sotalol, propafenone, flecainide, or dofetilide) were usually discontinued at the time of the index ablation procedure but were occasionally continued for a maximum of 3 months post ablation at operator discretion. Patients were followed up at 1, 3, 6, and 12 months post ablation. In the case of phrenic nerve dysfunction a chest radiograph was performed at baseline (the day after the procedure) and every 3 months until resolution. No patient was lost to follow-up and all completed the required outpatient visits and monitoring.

Statistical Analysis
Continuous variables are summarized by their mean±SD and categorical variables by frequencies and percentages. Associations between procedural variables (predictors) and phrenic nerve impairment were assessed by simple and multivariable logistic regression analyses that adjusted for the non-independent data structure (ie, patient-effect) using generalized estimating equation–modified multinomial logistic regression analyses. To select the best subset of predictors, a step-wise variable selection approach was used. A similar approach using generalized estimating equations was performed at baseline (the day after the procedure) and every 3 months post ablation. A P value of <0.05 was considered statistically significant. All models were also validated using appropriate diagnostic methodology. All analyses were performed using SAS Software Version 9.3 (SAS Institute Inc, Cary, NC). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree with the written article.

Results
Baseline Characteristics
A total of 183 consecutive patients (59±10 years; 74% men) underwent a total of 200 cryoballoon-based PVI procedures for paroxysmal (90%) or persistent (10%) AF between October 2010 and October 2013. Baseline characteristics are presented in Table I in the Data Supplement. AF was diagnosed an average of 6.1±4.9 years before the intervention. Twenty-six patients (14%) had a CHADS Score ≥2 (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke.). The left atrial diameter averaged 37.7±8.5 mm and the left ventricular ejection fraction was 59.7±6.2%. Fifty-nine (30%) procedures were for recurrent AF after a prior AF ablation intervention (index radiofrequency ablation in 59% and cryoballoon ablation in 41%).

Cryoballoon Ablation
A total of 741 PVs were identified and targeted for ablation, including 18 right middle PVs. Left and right common PVs were treated as separate segmental branches. Eighty-four previously isolated PVs were not targeted for ablation (12 right superior, 25 right inferior, 6 right middle, 5 left superior, and 36 left inferior PVs). Procedural parameters are summarized in Tables I and II in the Data Supplement. A 28-mm diameter cryoballoon was used in 136 (68%) patients (54 Arctic Front and 82 Arctic Front Advance, Medtronic CryoCath LP). An additional focal cryocatheter (Freezor max 8 mm, Medtronic CryoCath LP) was required in 8 (4.0%) patients for touch-up to achieve PVI (1 right superior, 2 right inferior, 4 left superior, 5 left inferior, 5/8 during redo procedures). The procedure duration (groin puncture to sheath removal) was 227.9±78.6 minutes, with a fluoroscopy time of 47.4±20.4 minutes. An average of 6.9±2.9 cryoballoon applications (including bonus lesions) were performed per patient (total cryoablation time per patient of 24.9±11.2 minutes). Real-time PV electrograms were observed for only 20.3% of cryoapplications because of a distal Achieve position. In those where we observed real-time PVI the mean time to isolation was 48.6 seconds.

The procedural end point of complete isolation of all targeted PVs was achieved in all procedures. Excluding PNP (discussed separately below) a total of 10 complications were observed in 9 patients, including 1 tamponade requiring drainage, a transient ischemic event, and 8 local groin complications (5 hematomas and 3 arteriovenous fistulas).

Phrenic Nerve Function and Ablation of Right-Sided PVs
Relevant to phrenic nerve function, a total of 381 right-sided PVs were targeted for ablation (Table II in the Data Supplement). The average PV size was 16.1±3.9×19.6±4.4 (ovality index of 0.83±0.12). The 28-mm cryoballoon was used alone in 234 PVs (Arctic Front in 81; Arctic Front Advance in 153), the 23-mm cryoballoon in 142 PVs (Arctic Front in 85; Arctic Front Advance in 57), and both balloons in 5 PVs (Arctic Front in 3; Arctic Front Advance in 2). An average of 1.5±0.9 lesions were delivered for
each right-sided vein (cumulative ablation time of 321.3±206.3 seconds). Real-time PVI was observed in only 1 case with CMAP decrease. In this case the time to isolation was short (19 seconds).

Before ablation, a reliable CMAP signal could be recorded in all. Baseline CMAP amplitude was 946.5±609.2 μV. At end ablation the CMAP amplitude decreased by an average of 13.8±13.8% (Table). This decrease was more marked in the 33 patients with clinical phrenic nerve injury (palpably decreased diaphragmatic motion; 40.9±15.3% versus 11.3±10.5% in those without diminished hemidiaphragmatic contractility; *P*<0.0001). In all cases, a 30% reduction in CMAP amplitude preceded clinical phrenic nerve impairment. In an additional 18 cases, a 30% decrease in phrenic CMAP was observed without clinical phrenic nerve impairment.

On average, a 30% reduction in CMAP amplitude occurred 119.6±51.0 seconds after initiation of cryoablation. In all cases, the targeted PV was already successfully electrically isolated. The majority of phrenic nerve impairments were observed during ablation of the RSPV (42/51 PVs with electromyographic phrenic impairment and 28/33 PVs with clinical phrenic impairment). The 23-mm cryoballoon was used in 25 of 51 (49%) PVs with associated electromyographic phrenic impairment and 20 of 33 (61%) with clinical phrenic impairment (whereas this balloon size was used in 121/330 [37%] and 127/348 [36%] without electromyography or clinical phrenic nerve injury, respectively; both *P*<0.05). The second-generation cryoballoon was used in 20 of 51 (39%) PVs with associated electromyographic phrenic impairment and 14 of 33 (42%) with clinical phrenic impairment (whereas this balloon size was used in 192/330 [58%] and 198/348 [57%] without electromyography or clinical phrenic nerve injury, respectively).

Use of the second-generation cryoballoon catheter (*P*=0.0182), PV height (*P*=0.0372), the nadir ablation temperature (*P*=0.0001), and the targeted PV (right superior versus inferior PV; *P*=0.0001) were all significant predictors of electromyographic or clinical phrenic nerve impairment in simple generalized estimating equation–modified logistic regression models. In generalized estimating equation–modified multivariable logistic regression analyses, targeting right superior versus inferior PVs was associated with a 6.5-fold higher odds of developing electromyographic or clinical phrenic nerve impairment (*P*<0.0001). The lowest quartile for nadir ablation temperature (ie, ≤−62.0°C) was associated with 4.56-fold increased risk when compared with the highest quartile (ie, >−45°C). There was no association between electromyographic or clinical phrenic nerve impairment and the use of the 23-mm cryoballoon, primary versus redo procedures, the degree of PV occlusion, PV dimensions (height, width, or ovality), body mass index, or sex.

In cases where a reduction in hemidiaphragmatic motion was observed, 90.6% (30/33) were transient, with the majority (23/33) recovering within 5 minutes (mean time to recovery, 29.0±12.4 seconds). The remaining 6 of 33 transient palsies recovered within 30 minutes, with only 3 of 33 cases of PNP persisting beyond the end of the ablation procedure. All of these persistent phrenic nerve palsies were asymptomatic and recovered by 6 months of follow-up.

### Repeat Procedures

Of the 49 patients where a 30% reduction in CMAP amplitude was observed, 9 underwent repeat ablation for arrhythmia recurrence. In 7 cases, phrenic nerve impairment had occurred while ablating the RSPV (5 clinical PNP and 2 isolated 30% CMAP reductions) and in 2 cases occurred during isolation of the right inferior PV (both isolated 30% CMAP reductions). Of those with recurrence undergoing repeat procedures, only 3 of the 25 were done with the second-generation balloon, accounting for 6 reconnected PVs (versus 52 in the 22 patients treated with the first-generation balloon; 2.5 PVs per patient; *P*=0.37).
Table. Patient and Procedure Characteristics Associated With Electromyographic Phrenic Nerve Impairment or Clinical PNP

<table>
<thead>
<tr>
<th></th>
<th>Clinical PNP</th>
<th>CMAP Decrease Without PNP</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>59±9</td>
<td>60±7</td>
<td>59±10</td>
</tr>
<tr>
<td>Body mass index (mean±SD)</td>
<td>28±4</td>
<td>28±4</td>
<td>28±6</td>
</tr>
<tr>
<td>Targeted vein: RSPV/RIPV/RMPV</td>
<td>28/5/0</td>
<td>14/2/2</td>
<td>146/168/16</td>
</tr>
<tr>
<td>Second-generation balloon used, n (%)*</td>
<td>14 (42%)</td>
<td>6 (33%)</td>
<td>191 (58%)</td>
</tr>
<tr>
<td>23-mm balloon used, n (%)†</td>
<td>20 (61%)</td>
<td>6 (33%)</td>
<td>121 (37%)</td>
</tr>
<tr>
<td>PV ovality (PV height/PV width, mm; mean±SD)</td>
<td>0.8±1.0</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
</tr>
<tr>
<td>PV dimensions: height×width, mm (mean±SD)</td>
<td>17±4×20±4</td>
<td>18±5×21±5</td>
<td>16±4×20±4</td>
</tr>
<tr>
<td>No. of applications (mean±SD)</td>
<td>1.3±0.9</td>
<td>1.3±0.6</td>
<td>1.6±1.0</td>
</tr>
<tr>
<td>Grade 3 or 4 occlusion, %</td>
<td>96.9%</td>
<td>94.4%</td>
<td>93.6%</td>
</tr>
<tr>
<td>Total cryoablation time, s (mean±SD)</td>
<td>194±200</td>
<td>178±121</td>
<td>342±203</td>
</tr>
<tr>
<td>Acute isolation: isolated/targeted, %</td>
<td>33/33</td>
<td>18/18</td>
<td>329/330</td>
</tr>
<tr>
<td>CMAP and diaphragmatic weakness</td>
<td>(100.0%)</td>
<td>(100.0%)</td>
<td>(99.7%)</td>
</tr>
<tr>
<td>Time to 30% reduction in CMAP amplitude, s (mean±SD)</td>
<td>109±55</td>
<td>115±45</td>
<td>n/a</td>
</tr>
<tr>
<td>Temperature at 30% reduction in CMAP amplitude, °C (mean±SD)</td>
<td>−59±9</td>
<td>−52±15</td>
<td>n/a</td>
</tr>
<tr>
<td>Acutely impaired diaphragmatic motion, n</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Persistently impaired diaphragmatic motion, n</td>
<td>3</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Permanent phrenic nerve injury (&gt;6 mo), n</td>
<td>0</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Nadir ablation temperature, °C (mean±SD)†</td>
<td>−60±9</td>
<td>−58±11</td>
<td>−52±11</td>
</tr>
</tbody>
</table>

CMAP indicates compound motor action potential; n/a, not applicable; PNP, phrenic nerve palsy; PV, pulmonary vein; RIPV, right inferior PV; RMPV, right middle PV; and RSPV, right superior PV.

*P<0.1, †P<0.05, and ‡P<0.001 in global comparisons between the 3 groups.

Discussion

Cryoballoon-based PVI is an efficacious means of achieving durable PVI. Nevertheless, phrenic nerve injury remains the most frequently observed complication, occurring in ~6% of cases (range, 3%–11%) despite the early interruption of ablation when less vigorous diaphragmatic excursion is detected by continuous abdominal palpation during phrenic nerve pacing. Within this context, our series of electromyographic monitoring has demonstrated the following: (1) diaphragmatic electromyographic monitoring is technically feasible using standard surface ECG electrodes, (2) diaphragmatic electromyographic monitoring is a reliable method to monitor phrenic nerve function during cryoablation and offers an early warning to impending phrenic nerve injury, and (3) diaphragmatic electromyography does not adversely compromise acute procedural efficacy or longer term isolation.

Diaphragmatic CMAP During Cryoballoon Ablation

In addition to abdominal palpation, alternative proposed approaches to monitoring phrenic nerve function during cryoballoon ablation for AF have included continuous diaphragmatic visualization and auditory monitoring of diaphragmatic contraction. These techniques seem most useful in confirming established phrenic nerve injury because they are altered too late in the pathophysiological process to prevent nerve damage. In contrast, real-time diaphragmatic electromyographic monitoring represents a potentially more sensitive tool for detecting early changes to phrenic nerve function. Specifically, during phrenic nerve pacing a reproducible supramaximal hemidiaphragmatic CMAP can be reliably recorded using surface electrodes, providing valuable information about phrenic nerve function.

In a recent preclinical feasibility study, we demonstrated that it is technically possible to record high-quality diaphragmatic CMAP signals during cryoballoon ablation, and that a 30% reduction in diaphragmatic CMAP amplitude reliably predicts impending hemidiaphragmatic paralysis (presaging diaphragmatic paralysis by abdominal palpation by 31±23 seconds).

At repeat procedure, in those with a 30% reduction in CMAP amplitude, an average of 2.4 PVs had reconnected, with left-sided PVs reconnecting more frequently than the right-sided PVs (2 left PVs/patient versus 0.4 right PVs/patient; 4 RSPV, 0 right inferior PV, 9 left superior, and 9 left inferior PV). In only 2 cases was a PV reconnection observed in the index PV associated with phrenic nerve injury (2/7 RSPVs, 0/2 right inferior PVs). In comparison, in patients without a change in CMAP amplitude undergoing repeat procedure for arrhythmia recurrence (N=16), an average of 2.3 PVs had reconnected, with a more balanced pattern of PV reconnection between right- and left-sided PVs (0.9 right PVs/patient versus 1.6 left PVs/patient). Of note, 10 of 16 (62.5%) RSPVs had reconnected in the group without CMAP abnormality compared with 4 of 9 (22.2%) in those where a 30% reduction in CMAP amplitude was observed (P=0.001). In all cases the reconnected PVs were successfully reisolated, without complication.
early termination of ablation, effectively limiting impending phrenic nerve injury before it becomes clinically apparent.

**CMAP and Efficacy of PVI**

Importantly, the widespread adoption of electromyography-based phrenic nerve monitoring is contingent on demonstrating that procedural efficacy is not compromised by early termination of cryoballoon ablation on detection of CMAP amplitude reduction. As the phrenic nerve is an extracardiac structure, it has been postulated that its injury inherently implies lesion transmurality. However, because the temperature required to induce nonfreezing nerve injury is substantially warmer than that required to produce a permanent myocardial ablation lesion (ie, +3 to +10 versus −20 to −40°C, respectively), it may be theoretically possible to impair phrenic nerve function without effective electric isolation of the PV. Reassuringly, in this initial clinical study, the PV in question was successfully electrically isolated in all cases in which ablation was prematurely interrupted because of a reduction in CMAP amplitude. Moreover, these patients had a nonsignificantly lower rate of electric reconnection of the right PVs on repeat procedures for arrhythmia recurrence suggesting that the index ablation lesion was not only transmural but also durable.

**Practical Aspects of CMAP Measurement**

Diaphragmatic electromyographic monitoring is predicated on the ability to record a reproducible, and reliable hemidiaphragmatic CMAP. In our initial animal model, we used an esophageal approach. However, this signal was less stable and more susceptible to respiratory variation. An alternative approach that we conceived and validated in our canine model, and was subsequently used in a limited case-series, is to record CMAPs via a standard electrophysiology catheter placed in a subdiaphragmatic hepatic vein. Although this technique is feasible and provides reliable signals in the majority of cases (eg, 50/57 patients in the series of Franceschi et al), it necessitates an additional venous puncture and electrophysiology catheter, thus incurring additional cost and risk of complication.

In contrast, the use of modified chest wall surface electrodes provides several tangible advantages. First, the set up is relatively simple, using standard surface ECG electrodes connected directly into the computerized electrophysiology workstation (Figure 1). By displaying the signal in real-time phrenic nerve integrity is continuously monitored allowing termination of ablation at the earliest sign of impending phrenic nerve injury. Second, the technique is noninvasive and thus does not incur additional risk of complication or cost. Third, surface monitoring offers improved signal stability, integrity, and reproducibility compared with esophageal monitoring. Specifically, adequate CMAP recordings were reliably obtained in all 200 patients in this series. Moreover, we did not find that signal amplitude and integrity were ever compromised by anthropometric characteristics or pacing artifact.

With respect to this latter point, although we made every effort to minimize the degree of artifact by determining the phrenic pacing threshold before the onset of ablation, even in the case of high output and high pulse width we never found the surface CMAP signal to be significantly compromised (Figure 3).

Irrespective of the monitoring technique used, it is important to note that the hemidiaphragmatic CMAP is dependent on reliable phrenic capture. At times respiratory motion can alter the degree of phrenic capture, which may modify the CMAP amplitude. In this case, the reduction in CMAP amplitude is rhythmic and recovers with changes in the respiratory phase. Typically this manifests as an inspiratory decrease in CMAP amplitude with normalization at end expiration (Figure 4). This is in contrast to electromyographic phrenic injury whereby the decrease in CMAP amplitude is progressive and unrelated to respiratory phase.

Finally, the appropriate clinical response to CMAP amplitude changes is unknown. Currently it is our approach to terminate ablation with a 30% decrease in CMAP amplitude. However, we do not use a forced cryoballoon deflation. Unlike the rapid tissue rewarming that follows cessation of focal cryoablation, a considerably longer delay may be expected between termination of cryoballoon ablation and rewarming of the phrenic nerve, because the balloon temperature must reach +20°C to allow deflation. During this period, continued venous occlusion may slow the passive rewarming process, further prolonging the period of cold-induced injury. Forced deflation of the cryoballoon catheter may accelerate tissue rewarming and, potentially, reduce the extent of phrenic nerve injury. The safety of such an approach remains to be demonstrated.

**Limitations**

This study constitutes a nonrandomized analysis of consecutive patients undergoing PVI in a real-life clinical setting at a single center. The main goal of our study was to characterize our clinical experience using diaphragmatic electromyographic monitoring for the prevention of phrenic nerve monitoring. Although no direct comparison with standard monitoring techniques was performed, the incidence of persistent phrenic nerve injury in our series is substantially lower than that reported throughout the literature. Finally, although an electromyographic-guided approach seems to be associated with a marked reduction in acute and persistent hemidiaphragmatic paralysis without compromising the efficacy of ablation, randomized studies are required for confirmation.

**Conclusions**

In this first clinical study of 200 procedures assessing the novel electromyographic approach to monitoring phrenic nerve function during cryoballoon ablation for AF, early interruption of ablation on a 30% reduction in the diaphragmatic CMAP amplitude yielded favorable procedural safety outcomes. The incidence of PNP persisting beyond the end of the procedure was 1.5%. In all cases, diaphragmatic function normalized within 6 months. Moreover, prematurely interrupting ablation on the basis of a reduction in CMAP amplitude was not associated with a higher incidence of PV reconnection in the subgroup of patients with repeat procedures.

**Disclosures**

Drs Dubuc, Guerra, and Andrade are consultants for Medtronic CryoCath LP. Drs Dubuc, Andrade, and Khairy have received grant support from Medtronic CryoCath LP for investigator-initiated research. Dr Roy was chairman of a clinical adjudicating events committee for a trial sponsored by Medtronic CryoCath LP. The other authors report no conflicts.
Electromyography to Prevent Phrenic Nerve Injury

Phrenic nerve injury with hemidiaphragmatic paralysis is the most frequently observed complication with cryoballoon ablation, occurring in ≈6% of clinical procedures. The most commonly used preventative measure is the use of continuous abdominal palpation during phrenic nerve pacing from a catheter placed in the superior vena cava. Despite early interruption of ablation with the perceived onset of less vigorous diaphragmatic contractions, phrenic nerve injury continues to be observed. The use of diaphragmatic electromyography represents a potentially more sensitive technique for detecting early changes to the phrenic nerve. During phrenic nerve pacing a reliable diaphragmatic signal (compound muscle action potential) can be easily recorded using surface electrodes. In preclinical studies, we demonstrated that a 30% reduction in cryoballoon ablation motor action potential amplitude reliably predicts impending hemidiaphragmatic paralysis by 31±23 seconds. Moreover, the use of this technique resulted in a significant reduction in the incidence of acute hemidiaphragmatic paralysis, persistent hemidiaphragmatic paralysis, and the histological severity of phrenic nerve injury in a randomized and blinded comparison with standard techniques. The series presented herein represents our initial clinical experience with diaphragmatic electromyographic monitoring and is the largest series to date using this technique. Confirming our preclinical studies, clinical phrenic nerve injury was universally heralded by a progressive decline in compound muscle action potential amplitude. Using an approach of early interruption of ablation on a 30% reduction in compound motor action potential amplitude, we were able to limit the extent of phrenic nerve injury (incidence of 1.5% with diaphragmatic function normalization within 6 months) with and without compromising ablation efficacy.
Clinical Experience With a Novel Electromyographic Approach to Preventing Phrenic Nerve Injury During Cryoballoon Ablation in Atrial Fibrillation

Blandine Mondésert, Jason G. Andradè, Paul Khairy, Peter G. Guerra, Azadeh Shohoudi, Katia Dyrda, Laurent Macle, Léna Rivard, Bernard Thibault, Mario Talajic, Denis Roy and Marc Dubuc

Circ Arrhythm Electrophysiol. 2014;7:605-611; originally published online July 13, 2014; doi: 10.1161/CIRCEP.113.001238

An erratum has been published regarding this article. Please see the attached page for:
http://circep.ahajournals.org/content/7/5/995.full.pdf

Data Supplement (unedited) at:
http://circep.ahajournals.org/content/suppl/2014/07/12/CIRCEP.113.001238.DC1
In the article “Clinical Experience With a Novel Electromyographic Approach to Preventing Phrenic Nerve Injury During Cryoballoon Ablation in Atrial Fibrillation” by Mondésert et al, which was published in the August 2014 issue (Circ Arrhythm Electrophysiol. 2014;7:605–611), a correction was needed.

Azadeh Shohoudi, PhD, has been added as an author.

The authors apologize for the original omission.

The online version of the article has been corrected.
**SUPPLEMENTAL MATERIALS**

**Table 1**: Patients baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients/Procedures</td>
<td>183/200</td>
</tr>
<tr>
<td>Age in years – mean±SD</td>
<td>59±10</td>
</tr>
<tr>
<td>Male – number (%)</td>
<td>135 (74%)</td>
</tr>
<tr>
<td>Hypertension – number (%)</td>
<td>73 (37%)</td>
</tr>
<tr>
<td>Diabetes – number (%)</td>
<td>20 (10%)</td>
</tr>
<tr>
<td>Body mass index in kg/m² – mean±SD</td>
<td>28±6</td>
</tr>
<tr>
<td>Paroxysmal AF – number (%)</td>
<td>179 (89.6%)</td>
</tr>
<tr>
<td>Number of repeat procedures – number (%)</td>
<td>59 (30%)</td>
</tr>
<tr>
<td>Prior RF Ablation</td>
<td>35 (59%)</td>
</tr>
<tr>
<td>Prior Cryoballoon Ablation</td>
<td>24 (41%)</td>
</tr>
<tr>
<td>CHADS₂ score – number (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>100 (55%)</td>
</tr>
<tr>
<td>1</td>
<td>57 (31%)</td>
</tr>
<tr>
<td>≥2</td>
<td>26 (14%)</td>
</tr>
<tr>
<td>Duration of atrial fibrillation in years – mean±SD</td>
<td>6±5</td>
</tr>
<tr>
<td>LV ejection fraction in % – mean±SD</td>
<td>60±6</td>
</tr>
<tr>
<td>Left atrial diameter in mm – mean±SD</td>
<td>38±8</td>
</tr>
</tbody>
</table>

**Procedural Parameters**

<table>
<thead>
<tr>
<th>Cryoballoon</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st} generation 23mm – number</td>
<td>36</td>
</tr>
<tr>
<td>1\textsuperscript{st} generation 28mm – number</td>
<td>38</td>
</tr>
<tr>
<td>1\textsuperscript{st} generation both 23 and 28mm – number</td>
<td>16</td>
</tr>
<tr>
<td>2\textsuperscript{nd} generation 23mm – number</td>
<td>28</td>
</tr>
<tr>
<td>2\textsuperscript{nd} generation 28mm – number</td>
<td>76</td>
</tr>
<tr>
<td>2\textsuperscript{nd} generation both 23 and 28mm – number</td>
<td>6</td>
</tr>
<tr>
<td>Procedure duration in minutes – mean±SD</td>
<td>228±79</td>
</tr>
<tr>
<td>Fluoroscopy time in minutes – mean±SD</td>
<td>47±20</td>
</tr>
<tr>
<td>Total number of cryoapplications per patient – mean±SD</td>
<td>7±3</td>
</tr>
<tr>
<td>Total cryoablation time per patient in minutes – mean±SD</td>
<td>25±11</td>
</tr>
</tbody>
</table>
**Table 2:** Characteristics of the right-sided pulmonary veins. Legend: CMAP - compound motor action potential; PV - pulmonary vein

<table>
<thead>
<tr>
<th>Pulmonary veins - targeted for ablation/total</th>
<th>Right Superior</th>
<th>Right Inferior</th>
<th>Right Middle</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV dimensions – mean±SD*</td>
<td>188/200</td>
<td>175/200</td>
<td>18/24</td>
</tr>
<tr>
<td>Height in mm</td>
<td>17±4</td>
<td>16±4</td>
<td>10±4</td>
</tr>
<tr>
<td>Width in mm</td>
<td>21±4</td>
<td>19±4</td>
<td>12±4</td>
</tr>
<tr>
<td>PV ovality (height/width)</td>
<td>0.8±0.1</td>
<td>0.8±0.1</td>
<td>0.9±0.1</td>
</tr>
<tr>
<td>Cryoballoon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st generation 23mm – number</td>
<td>39</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>1st generation 28mm – number</td>
<td>43</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>1st generation both 23 and 28mm – number</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2nd generation 23mm – number</td>
<td>25</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>2nd generation 28mm – number</td>
<td>78</td>
<td>69</td>
<td>6</td>
</tr>
<tr>
<td>2nd generation both 23 and 28mm – number</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Complete Occlusion – Grade 3 or above</td>
<td>179 (95%)</td>
<td>163 (93%)</td>
<td>16 (89%)</td>
</tr>
<tr>
<td>Number of applications per vein – mean±SD**</td>
<td>1.7±1.1</td>
<td>1.4±0.7</td>
<td>1.1±0.2</td>
</tr>
<tr>
<td>Total cryoablation time in seconds – mean±SD***</td>
<td>350±251</td>
<td>300±149</td>
<td>228±87</td>
</tr>
<tr>
<td>Minimum temperature reached in °C – mean±SD</td>
<td>-55±10</td>
<td>-51±12</td>
<td>-53±11</td>
</tr>
<tr>
<td>30% reduction in CMAP amplitude – number</td>
<td>42 (22%)</td>
<td>7 (4%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Clinical phrenic nerve impairment – number</td>
<td>28 (15%)</td>
<td>5 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Acute PV isolation (balloon only) – number (%)</td>
<td>187 (99.5%)</td>
<td>173 (98.9%)</td>
<td>18 (100%)</td>
</tr>
<tr>
<td>Focal cryoablation required for isolation – number</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*The comparison of veins’ height, width and ovality between the three targeted veins were conducted using a linear mixed model, adjusting for patients’ effect assuming normally distributed random errors. The means of height and ovality of RS and RI veins were significantly different from RM vein (with both P<0.0001). Similarly, the mean width of RS and RM veins were significantly different (with P<0.001) but no significant difference between RI and RM veins.

**The average numbers of application were significantly different at three different types of targeted veins. The incident rate ratios of repeated application was estimated to be 1.546 and 1.254 in RS and RI veins respectively compared to RM veins.

***The means of total cryoablation time for different targeted vein (PV) were significantly different (P<0.0001). There was no significant association between degree of complete and PV, using a GEE modified simple logistic regression which adjusts for patients’ effect.