Novel Electromyographic Monitoring Technique for Prevention of Right Phrenic Nerve Palsy during Cryoballoon Ablation

Running title: Franceschi et al.; Phrenic nerve palsy prevention and cryoballoon

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Abstract

**Background** - Right phrenic nerve palsy (PNP) is the most frequent complication of cryoballoon (CB) ablation. Diaphragmatic electromyography (EMG) can predict PNP with a comfortable safety margin. Our goal was to evaluate the feasibility, efficacy and safety of EMG-guided phrenic nerve (PN) monitoring using a novel hepatic vein approach for prevention of PNP.

**Methods and Results** - This study includes 57 patients (47 males) indicated for CB ablation for treatment of atrial fibrillation. During right superior pulmonary vein ablation, the PN was paced at 60 bpm and diaphragmatic compound motor action potential (CMAP) amplitude was recorded via a quadripolar catheter positioned in a subdiaphragmatic hepatic vein. If a 30% drop in CMAP amplitude was observed, ablation was discontinued with forced deflation. Reliable recording of CMAP prior to ablation was feasible in 50/57 patients (88%). In 7 patients (12%), stable PN pacing could not be achieved. In 44/50 patients, CMAP amplitude remained constant during cryoapplication. The mean value of CMAP amplitude was 639.7±240.5 μV; mean variation was 13±4.3%. In 6/50 patients (12%) including 5 treated with a 23 mm CB and one with a 28 mm CB, the 30% reduction cutoff was reached and cryoablation was discontinued. Recovery of CMAP amplitude after discontinuing cryoablation took less than 60 seconds in all cases. No PNP or complication related to PN monitoring occurred.

**Conclusions** - Recording of diaphragmatic CMAP using a catheter positioned in a sub-diaphragmatic hepatic vein seems feasible during CB ablation. EMG-guided PN monitoring seems safe and potentially helpful for prevention of PNP.

**Key words:** atrial fibrillation, catheter ablation, complication, cryoballoon, phrenic nerve
Introduction

Over the past decade, catheter ablation has emerged as a therapeutic option in patients with paroxysmal atrial fibrillation. Balloon-based ablation tools capable of electrical isolation of pulmonary veins (PV) in a single application have been developed and shown to be safe and effective in clinical studies\(^1\)\(^2\). The most frequent complication of cryoballoon (CB) PV isolation procedures is right phrenic nerve injury. This occurs in 6-7% of patients despite preventive measures that generally consist of monitoring abdominal contraction by palpation during phrenic nerve pacing and discontinuing ablation if a decrease in contraction strength is noted\(^1\).

Our group has been investigating a more objective technique using diaphragmatic electromyography (EMG) to monitor phrenic nerve function\(^3\). A preliminary study in dogs showed that diaphragmatic compound motor action potentials (CMAP) could be recorded during phrenic nerve pacing and that a 30% reduction in CMAP amplitude was predictive of impending hemi-diaphragmatic paralysis with a wide safety margin. Based on these findings, we hypothesized that phrenic nerve palsy (PNP) could be prevented by discontinuing cryoablation when a 30% reduction in CMAP was observed. In our animal study, diaphragmatic CMAP recording was performed using an esophageal catheter thus requiring complete apnea during CB ablation to obtain stable CMAP amplitude. Since 4 minutes apnea is an unacceptable option in clinical practice, an alternative approach using surface abdominal electrodes\(^4\) was tried but proved to have three major drawbacks. First, a major pacing artifact limited recording to a small terminal segment of the CMAP. Second CMAP amplitude showed variations of 30% with respiratory movements\(^5\), i.e., the exact value of the cut-off for discontinuing cryoablation observed in the animal study. Third, placement of electrodes for effective recording was challenging, particularly in obese patients\(^3\).
The purpose of this report is to describe a novel approach using a multipolar catheter positioned in a sub-diaphragmatic hepatic vein to record phrenic CMAP amplitude as a basis for EMG-guided PN monitoring. The twofold aim of this clinical study was to assess the feasibility of the new approach and evaluate the safety and efficacy of the technique for prevention of right PNP during CB procedures.

Material and Methods

Study Design

From June 2011 to August 2012, a total of 57 consecutive patients indicated for CB PV isolation at our center were included after providing informed consent. The selection criteria for CBPV isolation were symptomatic paroxysmal or persistent (less than 6 months) AF that was refractory to at least one anti-arrhythmic drug. The day before CB ablation, all patients underwent two-dimensional transesophageal echocardiography to rule out thrombi in the left atrial appendage as well as trans-thoracic examination with determination of left atrial dimensions and assessment of left ventricular and valvular function. Pre-procedural evaluation also included computed tomography scan to map left atrial anatomy. Patients with left atrial thrombus, severe uncontrolled heart failure, and left atrial dimensions ≥50 mm were not included in the study.

CB ablation procedure

All procedures were performed under conscious sedation. Briefly, a quadripolar catheter Josephson curve (St Jude Medical, Minnetonka, MN, USA) was positioned on the His bundle and a deflectable hexapolar catheter (Xtrem catheter, Sorin Group) was positioned in the coronary sinus via femoral access. These two catheters were used as landmarks for transseptal puncture to allow placement of a steerable 15 Fr sheath (Flexcath, Medtronic) in the left atrium (LA). Following transseptal puncture, an intravenous unfractionated heparin bolus (100 IU/kg)
was administered. Before introducing the balloon catheter in the sheath, a 20 mm-diameter Achieve catheter (Achieve mapping catheter, Medtronic) was inserted in the lumen of the cryoballoon. Then a 23 or 28 mm cryoballoon (Arctic Front©, Medtronic CryoCath LP) was advanced through the sheath into the LA using the Achieve catheter as a guidewire. Choice of balloon diameter was based on LA and PV dimensions measured on pre-procedural computed tomography scans. Before ablation, the Achieve catheter was positioned in the venous ostium to record baseline electrical activity. Then, the CB was wedged in the ostium and occlusion was tested with contrast agent. When the operator considered that PV occlusion was sufficient, cryoapplication was started. The duration of each cryoapplication was 240 seconds. After each cryoapplication, PV isolation was assessed with the Achieve catheter. If necessary, PV isolation was completed with an irrigated radiofrequency catheter. After a waiting period of 20 minutes following the last cryoapplication, PV isolation was re-evaluated to detect early recovery of LA–PV conduction.

**Phrenic Nerve Monitoring**

Phrenic nerve monitoring was performed during right superior pulmonary vein (RSPV) cryoapplication. The deflectable hexapolar catheter was moved to the SVC to pace the right PN (10V; 2.9ms at 60/min). Particular attention was paid to ensure stable pacing. Pacing was performed with the distal pair of electrodes. The quadripolar catheter (4 mm electrodes spaced 10 mm apart) was moved to a right-sided sub-diaphragmatic hepatic vein and connected to the central computerized electrophysiology workstation (Prucka CardioLab, General Electric). Bipolar EMG signals were recorded between the electrodes proximal and distal to the quadripolar catheter so as to create the maximal inter-electrode space. Using this technique, EMG recording covered a large part of the right hemi-diaphragm. Signals were amplified and
band-pass filtered between 5 Hz and 150 Hz. During each RSPV cryoapplication, EMG signals were continuously recorded on a hard disk and stored on an optical drive. During right PN pacing prior to cryoapplication, the position of the quadipolar catheter in the hepatic vein was optimized to obtain the highest diaphragmatic CMAP signal amplitude (if possible > 300μV). The abdomen was continuously palpated during cryoapplication.

If phrenic CMAP amplitude remained stable, i.e., varied less than 30% in relation to baseline phrenic CMAP amplitude, the duration of cryoapplication was 240 seconds with the possibility of performing a second cryoapplication at the operator’s discretion. If the 30% reduction cut-off considered as predictive of phrenic nerve palsy was reached, RSPV cryoapplication was discontinued using the “forced deflation” emergency maneuver. In this case, fluoroscopy was performed to assess diaphragm motion with forced respiratory movement.

In the post-procedural analysis, phrenic CMAP amplitudes were measured from the start of each RSPV cryoapplication. Each measurement involved averaging of 4 consecutive phrenic CMAP amplitude values. If cryoapplication was discontinued due to a 30% drop in phrenic CMAP, phrenic CMAP recording was continued for 60 seconds thereafter.

**Post-procedural management**

All patients were discharged the day after ablation. Two-dimensional transthoracic echocardiography and chest X-ray were performed in all cases to rule out post-procedural pericardial effusion and phrenic nerve palsy. Low-molecular-weight heparin was started the same day following ablation. Oral anti-coagulation was started the day following the procedure. Patients were dismissed on both oral anti-coagulation and low-molecular-weight heparin. When the target INR of 2–3 was reached low-molecular-weight heparin was discontinued and oral anti-coagulation was administered alone for 3 months after the procedure. Anti-arrhythmic therapy
was administered for 3 months following the procedure and then discontinued if AF did not recur.

Follow-up

In patients in whom cryoapplication was discontinued due to a 30% reduction in CMAP amplitude, clinical examination and 24-hours Holter monitoring were performed at 3, 6, and 9 months following ablation. Documented episodes of AF lasting ≥30 s were considered as recurrences. No blanking period was considered.

Study Endpoints

The main study endpoint was to assess the feasibility and safety of phrenic nerve monitoring based on CMAP amplitude measured using a multipolar catheter in a sub-diaphragmatic hepatic vein during cryoballoon procedure. The secondary endpoint was to evaluate the efficacy of this monitoring technique for prevention of phrenic nerve palsy.

Statistical Analysis

Data are presented as mean ± standard deviation for continuous variables and as counts (%) for categorical ones. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patients and procedures

Patient and procedure characteristics are summarized in table 1. Acute PV isolation was obtained in all patients. In 3 patients, a radiofrequency catheter was used to complete PV isolation. Three acute complications occurred, i.e., groin hematoma in 2 cases and pericardial effusion not requiring pericardocentesis in 1. The mean size of the RSPV was 21±4 x 17±3 mm.
Baseline phrenic CMAP recording with catheter in hepatic vein

In 7 patients (12%), steady baseline phrenic CMAP amplitude could not be obtained because the pacing catheter could not be positioned properly at the PN level in the SVC. As a result, large variations in CMAP amplitude occurred and EMG-guided phrenic nerve monitoring was impossible.

In the remaining 50 patients (88%), a steady baseline diaphragmatic CMAP was obtained (mean, 639.7±240.5 μV). CMAPs amplitude remained stable after the catheter was placed in a hepatic vein. When positioning was too proximal, respiratory movement caused strong amplitude variations (figure 1). In that case, the catheter was moved to a more distal position. The phrenic CMAP signal appeared as a sharp stable potential with a minimal pacing artifact (figure 2).

Cryoballoon ablation with EMG-guided phrenic nerve monitoring

Patients with <30% reduction in CMAP amplitude (figure 3)

In 44 of the 50 patients (88%) in whom EMG-guided phrenic nerve monitoring was performed, the variation in CMAP amplitude was <30% reduction throughout the 240-second RSPV cryoapplication. In this group, the mean value of maximal CMAP amplitude variation recorded during cryoapplication was 13±4.3% (extremes, +5.5±3.4% and -7.5±3.4%). In all patients, abdominal palpation demonstrated stable diaphragmatic contraction. Next-day chest X-ray showed no right PNP.

Patients with ≥30% reduction in CMAP amplitude (figure 4 and 5)

In 6 patients (12%), variation in CMAP amplitude reached the 30% threshold during the RSPV cryoapplication. Cryoballoon size was 23-mm in 5 patients and 28 mm in 1. Subjective assessment by palpation did not detect any change in contraction strength in any of these patients. The reduction threshold was reached at 72, 81, 88, 105, 136 and 140 seconds (mean,
104±28 seconds). Upon recognizing the 30% reduction in CMAP amplitude, the operator discontinued cryoapplication by performing the “forced deflation” emergency maneuver. In all cases, CMAP amplitude continued to decrease moderately for several seconds after “forced deflation” and then progressively returned to baseline within 60 seconds. In all cases, RSPV isolation was achieved despite truncated cryoapplication. The mean reduction of CMAP amplitude at the time of “forced deflation” was 33±4% as compared to baseline. Diaphragmatic movement based on fluoroscopic evaluation after cryoapplication and at the end of the procedure was normal. Next-day chest X-ray showed no right PNP.

**Safety**

No adverse event related to PN monitoring was observed during or after the procedure. Positioning of the catheter in the hepatic vein was painless. The “forced deflation” emergency maneuver caused no untoward effect.

**Follow-up**

The mean follow-up in the 6 patients in whom cryoapplication was discontinued was 198±92 days. Two patients had documented AF recurrences. One patient did not undergo a redo procedure. In the other patient, redo was carried out 7 months after the first procedure. Redo consisted of radiofrequency isolation of the common trunk of left-sided PV. The right-sided veins were not reconnected. In this patient, during the first cryoballoon procedure only one RSVP application was performed, discontinued by forced deflation at 136 seconds. The patient is currently free from AF with a follow-up of 3 months after redo. The remaining 4 patients in whom cryoapplication was discontinued were recurrence-free at the time of the last follow-up examination.
Discussion

Cryoballoon catheter ablation is effective for PV isolation. The most frequent complication is right PNP. This clinical study describes a novel EMG-guided phrenic nerve monitoring technique to prevent this complication. The four most important findings are as follows. First, diaphragmatic EMG using a catheter positioned in a hepatic vein provides stable reliable CMAP amplitude recording during CB ablation in most patients. Second, using this technique no case of PNP occurred in a series of 50 CB procedures (2/3 with the 23mm CB) including six in which RSVP cryoapplication was discontinued using the “forced deflation” maneuver due to a >30% drop in CMAP amplitude. Third, no complication occurred in relation to monitoring. Fourth, the main technical problem was failure to achieve stable phrenic nerve pacing in 12% of cases.

Advantages of hepatic vein for diaphragmatic EMG recording

None of the three approaches proposed for diaphragmatic EMG recording, i.e., surface electrodes, esophageal electrodes, and direct needle is suitable for monitoring during cryoballoon catheter ablation. Due to its invasive nature, direct needle recording is unsuitable for EP procedures. Recording with esophageal electrodes is a non-invasive option, but the amplitude of recorded values can vary 2 to 3 fold in function of the distance between the electrodes and the diaphragmatic muscle that fluctuates with respiratory movement. Stable baseline recording values can be obtained with esophageal electrodes by inducing apnea as in our preclinical trial in dogs, but this is unacceptable in clinical use. The third approach, i.e., electrodes placed on the surface of the abdomen has three major drawbacks. The first is that surface electrodes are subject to 30% CMAP amplitude variation with respiratory movements, i.e., the exact threshold for discontinuation of cryoapplication to prevent PNP. The second is that effective placement of surface electrodes can be a challenge, especially in obese patients. The third is that, in our
experience, use of surface electrodes was associated with a large pacing artifact that masked all but a small terminal segment of the phrenic CMAP. The most likely causes for this artifact are the short distance from the pacing catheter in the SVC to the surface electrodes and phrenic nerve pacing at high amplitude and duration.

The approach to CMAP recording described in this report is totally new and different. It presents several advantages. First, electrode location close to the diaphragm allows recording of high CMAP amplitude values. Second, the distance between the muscle and electrode does not vary during respiration since the liver moves with the diaphragm. Because this distance is stable, the CMAP amplitude variation observed during recording was low. This feature is essential since reduction of CMAP amplitude is the key to predicting and preventing PNP based on EMG-guided phrenic nerve monitoring. A third advantage of the novel method proposed here is that despite its invasive character, set-up using a simple venous femoral access and a quadripolar catheter remains easy in the EP laboratory. Another practical aspect of the technique is that recorded CMAP potentials can be displayed directly on the central computerized electrophysiology workstation. A fourth advantage is that, unlike surface recording, the pacing artifact is minimal so that CMAP potential is completely visible.

**Diaphragmatic EMG recording during cryoballoon ablation**

In our preclinical study, we identified a 30% reduction in CMAP amplitude as the cut-off value for predicting hemi-diaphragmatic paralysis with a comfortable safety margin. Based on this finding, it was hypothesized that PNP could be prevented by discontinuing cryoapplication as soon as a 30% reduction was observed.

In a subsequent report, we described the first clinical application of this prevention technique. Diaphragmatic CMAP was monitored using surface electrodes during cryoballoon
ablation of the RSPV in a 51-year-old man⁴. Cryoablation was discontinued with ‘forced deflation’ maneuver when the decrease in CMAP amplitude reached 20% reduction while the diaphragmatic excursion remained intact. A transient drop in hemi diaphragmatic motion ensued but full recovery was observed within 1 minute.

The present study is the first to describe EMG-guided phrenic nerve monitoring using an electrode placed in a hepatic vein during cryoballoon ablation. The findings support the hypothesis that PNP can be avoided by EMG-guided phrenic nerve monitoring, despite the use of 23mm CB in more than two thirds of cases.

Although CMAP recording for right PN monitoring in our study was performed only during RSPV CB application, we recommend PN monitoring for both right PVs since PNP is possible even during RIPV CB application.

**Forced deflation emergency maneuver**

In this study, “forced deflation” was performed in case of 30% reduction in CMAP amplitude. Our aim was to accelerate rewarming by allowing immediate return of convective blood flow that has been shown to limit the extent of cryolesions.⁷⁻⁸. Indeed, balloon inflation during cryoapplication results in complete occlusion of the vein and stops blood flow. Normally, when cryoapplication is stopped, deflation does not occur until balloon temperature rises to +20°. This can take a long time if balloon temperature is low. Our reasoning was that, by avoiding this delay, “forced deflation” would limit cold-induced injury and enable faster PN recovery. While the safety of this method has not been demonstrated in a large patient cohort, it is noteworthy that no complications were observed in small clinical series and animal studies.⁹⁻¹⁰.

Whether combining CMAP monitoring and forced deflation is necessary to avoid PNP is unclear and will require dedicated study.
Efficacy of pulmonary vein isolation

Patients in whom the procedure was interrupted due to the threat of right PN received a single
cryoapplication in the RSPV. Mean treatment time in these patients was only 104±28 seconds,
but that was sufficient to obtain acute PV isolation. In the patient who underwent redo 7 months
later, the RSPV was still isolated. Nevertheless, a larger cohort will be needed to compare long-
term procedural success rates in patients undergoing truncated procedures and those receiving
full treatment.

Instability of right phrenic nerve pacing

Stable PN pacing could not be achieved in a few patients. Indeed, positioning of the pacing
catheter can be challenging because the PN is a narrow structure at the posterior face of the SVC
that is a large sized vessel. CMAP amplitude depends on the total number of muscular fibers
recruited. When PN capture is unstable, CMAP amplitude varies greatly from one beat to
another. Stable CMAP amplitude is an indispensable condition for EMG-guided phrenic nerve
monitoring. It would be useful to design a dedicated catheter for PN pacing via the SVC.

Limitation

The main limitations of this study are the small size of the patient population and the absence of
blinding and randomization. Larger studies will be needed to confirm the findings reported here.
Long-term follow-up will be necessary to assess the efficacy in terms of AF recurrence rate after
procedures using the EMG-guided approach. Since this study as carried out using the “Artic
Front” version of the CB, another study is needed to determine if CMAP monitoring remains
effective using the new CB version “Artic Front Advance”.

Conclusion

Phrenic CMAP amplitude recording using a catheter positioned in a sub-diaphragmatic hepatic
vein seems feasible during cryoballoon procedures in most patients. It seems to be a safe and reliable method to obtain stable phrenic CMAP amplitude measurements in the EP laboratory. EMG-guided PN monitoring, with forced deflation of cryoballoon ablation upon a 30% reduction in the diaphragmatic CMAP amplitude could be helpful in preventing of hemi-diaphragmatic paralysis without compromising the success of acute pulmonary vein isolation.

**Conflict of Interest Disclosures:** Dr Frédéric Franceschi is a consultant for Medtronic Cryocath LP.

**References**


**Table 1.** Baseline patient and procedure characteristics

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<td>Male gender (n)</td>
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<tr>
<td>Hypertension (%) / ICM (%) / DCM (%)</td>
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<td>Fluoroscopy time (min)</td>
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<td>Cryoballoon applications (n)</td>
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<td>CB 23mm / 28mm / 23-28mm</td>
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</table>

ICM: ischemic cardiomyopathy; DCM: dilated cardiomyopathy; LA: left atrium; CB: cryoballoon.

**Figure Legends**

**Figure 1.** Catheter position during phrenic CMAP recording. Antero-posterior fluoroscopic view centered on the diaphragm. The cryoballoon has been inflated at the RSPV ostium and the Achieve catheter is inside the vein. The quadripolar catheter has been positioned in a sub-diaphragmatic hepatic vein to record phrenic CMAP. A hexapolar catheter has been placed in the
superior vena cava to pace the right phrenic nerve. Figure 1A shows the position of the quadripolar catheter deep inside a hepatic vein, close to the diaphragm. When properly positioned as shown, stable CMAP recording is obtained. In figure 1B, the quadripolar catheter is improperly positioned more proximally. In this location, CMAP recordings fluctuate in function of respiratory movements. The catheter must be moved to a more distal position.

**Figure 2.** Diaphragmatic compound motor action potential (CMAP). Surface ECG lead V1 and a diaphragmatic CMAP tracing recorded by a quadripolar catheter in a sub-diaphragmatic hepatic vein, with a sweep speed of 100 mm/s. The right phrenic nerve is paced and captured from within the superior vena cava at a cycle length of 1000 ms (60 bpm). Note the stability of CMAP signals with a minimal pacing artifact.

**Figure 3.** Mean amplitude of the phrenic compound motor action potential (CMAP) in patients with < 30% reduction in CMAP amplitude. Mean phrenic CMAP values during 44 cryoapplications lasting 240 seconds in the RSPV. Note the stability of CMAP amplitude.

**Figure 4.** Mean amplitude values of the phrenic compound motor action potential (CMAP) in patients with ≥ 30% reduction in CMAP amplitude. Curve centered on the time of forced deflation (T0) showing 60 seconds before and after discontinuation of cryoapplication. Note the stability of CMAP amplitude at the beginning of the curve. After discontinuation of cryoapplication, CMAP increases progressively back to the baseline value in less than 60 seconds.
Figure 5. Example of phrenic compound motor action potential (CMAP) amplitude in a patient with threatened right PN during RSPV cryoballoon (CB) ablation. When CB ablation in the RSPV is started, baseline CMAP amplitude is 472μV (T0). Amplitude displayed minimal variations during the first 60 seconds but then showed a progressive decrease to 340 μV at 72 seconds (28% decrease from baseline value). At that point, the cryoapplication was discontinued with forced deflation. After deflation, CMAP amplitude gradually returned to the baseline value within approximately 40 seconds.
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_Circ Arrhythm Electrophysiol._ published online October 10, 2013; 
_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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