Ablation for atrial fibrillation

Subclavian vein pacing and venous pressure waveform measurement for phrenic nerve monitoring during cryoballoon ablation of atrial fibrillation

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Keywords
Cryoballoon • Atrial fibrillation • Phrenic nerve palsy

Introduction

Persistent phrenic nerve palsy is the most common complication of balloon cryoablation for atrial fibrillation (AF), occurring in ~5% of cases.1 It is also known to complicate ~0.5% of cases of radiofrequency (RF) ablation for AF.2 Although most cases resolve within 1 year, the condition can be disabling. We have recently described a technique for the prevention of the persistent phrenic nerve palsy during balloon cryoablation for AF.3 This technique relies on reliable phrenic nerve stimulation and early identification of developing nerve dysfunction. Although phrenic nerve stimulation is an established technique, widely used in both RF and balloon-based AF ablation, little data exist regarding how to best monitor phrenic nerve function.

The right phrenic nerve is most susceptible to damage during ablation of AF but left phrenic nerve palsy has also been reported4,5. The incidence of left phrenic nerve palsy remains unknown because left phrenic nerve monitoring is not routinely performed and cases may be asymptomatic or unrecognized. The left phrenic nerve may also be at risk during epicardial ventricular tachycardia ablation.

Phrenic nerve monitoring usually relies on subjective single-operator assessment of diaphragmatic movement, which undergoes
Subclavian vein pacing and VPW measurement for phrenic nerve monitoring

What’s new
- Left subclavian vein pacing is a novel technique which allows left phrenic nerve monitoring during cryoballoon and radiofrequency ablation for atrial fibrillation and epicardial ventricular tachycardia ablation.
- Right phrenic nerve stimulation by right subclavian vein pacing is superior to lateral superior vena cava pacing in terms of lower pacing thresholds.
- Phrenic nerve monitoring by use of the venous pressure waveform allows for reproducible, multi-observer assessment and documentation of the response to phrenic pacing.
- Pacing the phrenic nerves with a submaximal stimulus may improve the sensitivity of monitoring.

Methods

Study population
The approach to the general cryoablation procedure has been described in detail previously. Incremental stepwise observations were made in 100 consecutive patients undergoing balloon cryoablation. The first 50 patients underwent monitoring of the left phrenic nerve in addition to the standard procedure. Patients 51–75 underwent left phrenic nerve monitoring and additional comparative assessment of right subclavian vein thresholds and SVC thresholds. Patients 76–100 underwent left phrenic nerve monitoring, right subclavian vein and SVC pacing assessment, and additional venous pressure waveform (VPW) measurement. The three types of assessment were considered not to interact with each other, and are presented individually.

Monitoring the left phrenic nerve during balloon cryoablation
In 100 consecutive patients, following transeptal puncture and prior to cryoablation, the quad polar His bundle recording catheter (CRD, St Jude Medical) was relocated to the left subclavian vein, posterior to the left medial clavicular head using the postero-anterior fluoroscopic projection. High output pacing was delivered to a widely spaced bipole (poles 1 and 4 at 25 mA at 700 ms cycle length) (Micropace EPS 320 cardiac stimulator). The pacing current was then gradually decreased with the operator continuously assessing diaphragmatic motion by a hand placed on the abdomen. The capture threshold was defined as the minimum current that was able to produce detectable diaphragmatic motion through the entire respiratory cycle. Cryoablation of the left-sided pulmonary veins (Arctic Front Advance, Medtronic) was performed during continuous left phrenic nerve pacing.

Comparing right subclavian pacing with superior vena cava pacing
Fifty consecutive patients undergoing balloon cryoablation for AF were assessed. Prior to cryoablation of the right-sided pulmonary veins, the His bundle recording catheter was relocated to the SVC, directed laterally. High output pacing to the widely spaced bipole as described previously was delivered. The pacing current was then gradually decreased with the operator continuously assessing diaphragmatic motion by a hand placed on the abdomen, and the capture threshold recorded. The pacing catheter was rotated by ±90° to assess for lower capture thresholds in the close vicinity, and also to assess for catheter stability. The pacing catheter was then relocated to the right subclavian vein, and the capture threshold reassessed in the same manner. During cryoablation the subclavian vein position was used for phrenic nerve monitoring.

Phrenic nerve monitoring using the venous pressure waveform
During balloon cryoablation procedures, venous access was gained from the left and right femoral veins. In 25 consecutive patients, a pressure line flushed with saline was connected to the side arm of a left femoral venous sheath. Venous sheaths used were either a 6F sheath containing a 5F quad polar catheter (CRD, St Jude Medical) or a 12F ‘Triport’ sheath containing a 7F coronary sinus catheter (CSM, St Jude Medical) and a 5F quadrapolar catheter. The venous line was connected to a standard pressure transducer of the type routinely used during cardiac catheterization. This allowed the VPW to be displayed and recorded (Prucka/ Cardiolab, GE Medical). During left- and right-sided phrenic nerve pacing, the operator assessed the strength of diaphragmatic contraction by manual palpation of the abdomen. The operator could also observe the transduced VPW. Peak-to-peak amplitudes from the VPW were measured at the initiation of pacing at each ablation, and also from the end of each ablation, and continuously recorded. Minor variation of the VPW amplitude was present due to phase of respiratory cycle, so waveforms from the mid-cycle were assessed. As VPW monitoring is a novel technique, with no data to support its clinical use, the primary monitoring of phrenic nerve function during cryoablation was by manual palpation.

Statistical methods
Data are presented as means and standard deviations (SD) for normally distributed continuous variables, and medians with inter-quartile ranges (IQRs) for non-normally distributed data. Comparisons were made using the independent groups, paired group Student’s t-test or Mann–Whitney U test as appropriate. A P-value < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using Prism 4 (Graphpad).

Results
Monitoring the left phrenic nerve during balloon cryoablation
One hundred consecutive patients undergoing balloon cryoablation for AF were assessed. Left phrenic nerve capture was achieved in 96 patients.
of 100, with obstruction due to pacemaker/defibrillator leads being responsible for inability to advance the pacing catheter to the location of the phrenic nerve in two patients, and inability to pass the catheter into the left subclavian vein in two patients. The optimal stimulation site was posterior to the proximal head of the clavicle (Figure 1). The median capture threshold was 2.5 mA (IQR 1.4–3.5). Pacing at outputs near threshold demonstrated a graded response rather than an all-or-nothing phenomenon, with diaphragmatic movement becoming progressively stronger until maximal movement was attained. Pacing more laterally resulted in upper limb movement due to brachial plexus stimulation. The distribution of capture thresholds is shown in Figure 2. No patient developed significant weakening of diaphragmatic contraction, suggesting that (i) there was no significant left phrenic nerve dysfunction due to cryoablation, and (ii) that the capture threshold was stable over time.

**Pacing from the right subclavian vein vs. the superior vena cava**

In 50 consecutive patients, capture thresholds were obtained from the SVC and the right subclavian vein. The median threshold was lower at the subclavian vein than the SVC (1.8 mA IQR 1.4–3.3 vs. 6 mA IQR 3.4–8.0, $P < 0.001$). The optimal pacing site was posterior to the proximal head of the clavicle (Figure 3). Pacing more distally resulted in upper limb movement due to brachial plexus stimulation. The distribution of capture thresholds is shown in Figure 4. As with left subclavian pacing, pacing at both right-sided sites demonstrated a graded response to pacing rather than an all-or-nothing phenomenon.

**Phrenic nerve monitoring using the venous pressure waveform**

In 25 consecutive patients, discrete pressure waveforms were obtained during cryoablation from the first two ablations to each of the left superior, left inferior, right inferior, and right superior pulmonary veins, resulting in data for 200 individual ablations (all cases...
28 mm Arctic Front Advance, Medtronic). Variations in measured peak-to-peak amplitude correlated well with subjective palpation. The peak-to-peak amplitudes generated by stimulating the right phrenic nerve was greater than with left phrenic nerve stimulation (7.0 ± 0.34 vs. 5.2 ± 0.26 mmHg, \( P = 0.0001 \)). Amplitudes recorded at the start of cryoablation were higher than those recorded at the end of cryoablation (5.9 ± 0.2 vs. 5.0 ± 0.1 mmHg, \( P < 0.0001 \)). Amplitude recordings from the start and end of cryoablation are presented in Table 1.

Decrease in venous pressure amplitude of 30% or more occurred in 26 of 200 ablation cycles (13%). In only six ablation cycles was diminution of diaphragmatic motion apparent by palpation (operator not blinded to VPW). In three of six cases, the decrease in motion by palpation was judged to be either so slow in onset, or small in magnitude that it did not warrant interruption of therapy, and ablation was completed without phrenic nerve palsy. Three patients developed loss of palpable diaphragmatic contraction due to transient phrenic nerve palsy. All were successfully treated with immediate balloon deflation (IBD). In each case, normal phrenic nerve function recovered prior to the end of the case. Figure 5 shows the displayed VPW from one of the cases.

During the three episodes of phrenic nerve dysfunction, we reassessed capture thresholds while there was persisting diaphragmatic weakness, without altering the catheter position. In each case, the initially low capture threshold (mean 1.5 mA) rose significantly (mean 13 mA). During the recovery phase, phrenic nerve capture thresholds returned to their baseline values.

When considering only ablation of the right-sided pulmonary veins, which account for nearly all previously reported phrenic nerve injury (and 100 VPW measurements from 25 patients in this study), a reduction of the VPW amplitude by 50% was seen to precede a palpable decrease in diaphragmatic motion in all patients who developed transient phrenic nerve palsy. Reduction in VPW amplitude by 50% preceded the ablation stop command (decided by traditional palpation monitoring) by a mean of 28 s. This suggests that if cryoablation had been halted at a VPW reduction of 50%, of the 100 right-sided ablations, each of the 3 ablations that would have developed phrenic nerve palsy would have to be terminated early (sensitivity for predicting PNP 100%), and 3 additional ablations that did not develop phrenic nerve palsy would have been terminated early (specificity 50%).

**Discussion**

Phrenic nerve palsy remains a significant complication of both cryoballoon and RF ablation for AF ablation. We present four novel findings to improve the efficacy of phrenic nerve monitoring during cryoballoon ablation for AF:

1. Left phrenic nerve pacing at the subclavian vein is easily achievable in the majority of cases, with no significant increase in procedural time, cost, or risk.
2. Right phrenic nerve stimulation by right subclavian vein pacing is superior to lateral SVC pacing in terms of lower pacing thresholds.
3. Phrenic nerve monitoring by use of the VPW allows for reproducible, multi-observer assessment and documentation of the physical response to phrenic pacing. The technique uses inexpensive, easily available equipment which can be used with all catheter lab systems, without hardware modification.
4. Pacing the phrenic nerves with a submaximal stimulus may improve the sensitivity of monitoring.

These findings are relevant for both cryoablation and RF procedures for AF, as phrenic nerve palsy is a well-recognized complication of both approaches.

**Table 1 Venous pressure amplitudes recorded for cryoablation at each pulmonary vein**

<table>
<thead>
<tr>
<th></th>
<th>LSPV1</th>
<th>LSPV2</th>
<th>LIPV1</th>
<th>LIPV2</th>
<th>RSPV1</th>
<th>RSPV2</th>
<th>RIPV1</th>
<th>RIPV2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start amplitude</td>
<td>5.4 (1.5)</td>
<td>5.7 (1.7)</td>
<td>5.6 (1.6)</td>
<td>5.4 (1.6)</td>
<td>6.6 (2.4)</td>
<td>6.7 (2.4)</td>
<td>7.0 (2.4)</td>
<td>7.0 (2.1)</td>
</tr>
<tr>
<td>End amplitude</td>
<td>4.8 (1.5)</td>
<td>5.3 (1.6)</td>
<td>5.5 (1.6)</td>
<td>5.2 (1.5)</td>
<td>5.2 (1.9)</td>
<td>5.1 (2.0)</td>
<td>5.7 (2.1)</td>
<td>5.3 (2.1)</td>
</tr>
<tr>
<td>% Change</td>
<td>-11.1</td>
<td>-9.0</td>
<td>-0.8</td>
<td>-4.2</td>
<td>-27.9</td>
<td>-31.3</td>
<td>-22.6</td>
<td>-31.0</td>
</tr>
<tr>
<td>( P )</td>
<td>0.006</td>
<td>0.009</td>
<td>0.04</td>
<td>0.08</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table showing the mean peak-to-peak measured amplitudes (mmHg) for the venous pressure wave generated during first and second ablations at the different pulmonary veins (\( n = 25 \) for each group).

Data presented as mean (SD). \( P \)-value for paired Student’s t-test between start and end amplitudes.

LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein.
We have recently reported that IBD at the first sign of impending phrenic nerve dysfunction may completely avoid persistent phrenic nerve palsy. However, the use of rapid warming may result in less durable pulmonary vein isolation since rapid warming is the most potent predictor of late pulmonary vein reconnection. Even earlier detection of impending phrenic nerve dysfunction might prevent the need for IBD and rapid warming, preserving the efficacy of the ablation lesion.

Damage to the left phrenic nerve during balloon cryoablation is rare. This is due to relatively anterior course on the left side compared with the right phrenic nerve. Our data primarily confirm the utility of the left subclavian vein pacing site for left phrenic nerve monitoring during cryoablation, with left diaphragmatic stimulation being possible with no significant increase in procedural time, risk, or cost. While we did not detect phrenic nerve dysfunction during our initial 100 cases constituting the study group, we did detect a left phrenic nerve palsy at case 134. This was treated successfully by IBD. Although rare, unmonitored left phrenic nerve palsy may be particularly severe, as cryoablation would have been completed and cold exposure for the nerve, more prolonged.

Right phrenic nerve palsy remains the most common complication of balloon cryoablation. Superior vena cava pacing is recommended for monitoring the right phrenic nerve, and has also been successful in avoiding phrenic nerve damage during RF ablation. However, reliable capture of the phrenic nerve requires that the stimulus is constantly delivered above the capture threshold. Lower baseline capture thresholds and higher catheter stability are likely to avoid erroneous loss of diaphragmatic response, aiding rapid recognition of phrenic nerve palsy due to ablation. Our observations support the use of pacing at the right subclavian vein as having superior thresholds measurements.

Reproducible and recordable assessment of phrenic nerve function during balloon cryoablation is rarely employed. Our data (Table 1) demonstrate that diaphragmatic contraction strength (measured by VPW amplitude) is significantly weaker following ablation at each pulmonary vein, and as expected this is more pronounced for the right-sided veins than the left-sided veins. This is frequently not detectible by manual palpation, and once it is detected, overt phrenic nerve palsy commonly follows. This suggests that an objective assessment of phrenic nerve function is desirable, and is likely to be more sensitive than manual palpation, which appears to be an inherently insensitive method of monitoring.

The method described in this report uses simple equipment that is universally available at little cost, and displays a reproducible measurement that can be observed by multiple personnel during ablation, and has replaced intermittent fluoroscopy as our adjunct to manual palpation during cryoablation.

Objective measurement of diaphragmatic response to pacing the right phrenic nerve was proposed by Franceschi et al. by measuring the compound motor action potential (CMAP). This method uses ECG leads placed along the costal margin to detect the electrical activity produced by diaphragmatic stimulation. A fall in the CMAP magnitude of 30% was able to predict the onset of phrenic nerve palsy. While this method is attractive in its overall aim and described implementation (on the EP Workmate system), it requires either hardware cable modification and differing filtering on other hardware platforms which can result in excessive noise. Also, the trace shows both the diaphragmatic electrogram and the surface QRS on the same
recording which impedes rapid assessment (see signal labelled thoracic in Figure 5). An alternative to modifying the hardware cabling is to move the position of any two limb lead electrodes to the costal margin. However, this would result in an altered ECG appearance during the electrophysiological procedure. Furthermore, monitoring of CMAP recordings only allows monitoring of the right phrenic nerve, whereas the VPW allows monitoring of both phrenic nerves without alteration of any settings or hardware. The method described by Franceschi measures the electrical response of the diaphragm, whereas the method described in this report displays a mechanical measure of diaphragmatic output.

Other methods of preventing phrenic nerve palsy include fluoroscopic monitoring of diaphragmatic motion during spontaneous respiration, predicting phrenic nerve injury by observing balloon position compared with phrenic pacing catheter position, and the proximal seal technique, which uses a more atrial balloon position during ablation of the right superior pulmonary vein; however, none of these methods are completely successful in preventing phrenic nerve injury.

Monitoring venous pressure trends during ablation procedures also can provide useful haemodynamic information in patients undergoing complex ablation procedures. Patients developing cardiac tamponade demonstrate increasing venous pressures as systolic arterial pressure falls. As this value is recorded throughout the procedure, rapid assessment of the cardiac filling pressures is possible should the patient suddenly become unstable.

Phrenic nerve pacing with a sub-maximal response

We hypothesized that maximal stimulation of the diaphragm by high output pacing as typically used (20 mA, 2 ms) may impair sensitivity to detect phrenic nerve dysfunction, as a subtle decline in function is masked by other functional fibre conduction. We have noted that increasing pacing output at levels above the ‘threshold’ results in increasing diaphragmatic motion until a maximal response is achieved. This is probably due to recruitment of increasing number of nerve fibres as stimulus strength is increased, with peripheral fibres being captured at low output, and more central/insulated fibres only recruited at higher outputs.

During clinical episodes of phrenic nerve dysfunction during cryoablation, we have noted that there is a decline in diaphragmatic response, which is not discernible by palpation in the early stages, but becomes apparent once the phrenic nerve function is more markedly impaired. The time course of this decline in function can be highly variable and unpredictable, as is the recovery.

Threshold re-assessment during episodes of nerve dysfunction demonstrates that the weakening of contraction is accompanied by a significant increase in capture threshold. This suggests that if the nerve had been captured using a sub-maximal stimulus, that the same level of phrenic nerve dysfunction would have resulted in decreased diaphragmatic motion at an earlier point in the ablation cycle, hence increasing the sensitivity of the manoeuvre. The outermost fibres of the phrenic nerve, closest to the cryoballoon are initially cooled, and stop contributing to diaphragmatic motion. This is only apparent to the operator when the ratio of dysfunctional fibres: captured and functional fibres reach a particular level. This concept is displayed pictorially in Figure 6. There are a number of factors that affect the ‘noticeability’ of phrenic nerve dysfunction, including patient factors (abdominal obesity, etc.) and operator factors (hand sensitivity, level of concentration, etc.). Histopathologic microscopy of sections of canine phrenic nerve also displays the initially peripheral lesion due to cryoablation.

Limitations

Results comparing the pacing characteristics at the lateral SVC and the right subclavian vein are from a small number of patients selected to undergo cryoballoon ablation for AF. However the differences in
threshold are significantly different, both clinically and statistically. Comparing catheter stability directly was not possible in this study as we only used the subclavian vein position during cryoablation procedures. However the experience presented includes in excess of 1600 min of pacing at the subclavian vein positions in 100 different patients, without a single episode of clinically relevant catheter displacement, despite vigorously moving anatomy (the pacing electrodes are positioned further away from the rapidly moving diaphragm).

Use of VPWs allows more robust assessment of phrenic nerve function compared with the standard technique of manual palpation. The proposed use of a 50% reduction in VPW amplitude as a cut-off to identify impending phrenic nerve palsy has been retrospectively derived from observational data, and is yet to be validated in prospective clinical use.

The results presented are observational data, and in order to demonstrate clear benefit a randomized trial would need to be performed.

Conclusions

Left and right phrenic nerve stimulation can be reliably achieved by pacing at the left and right subclavian veins, respectively. Pacing the right phrenic nerve at the right subclavian vein position results in lower capture thresholds and may result in less catheter instability in clinical practice. Left phrenic nerve dysfunction due to balloon cryoablation at the left pulmonary veins is rare, and the true incidence remains unknown. The novel technique of left subclavian vein pacing will allow this to be determined. Despite the low risk of left-sided phrenic nerve damage, we recommend the routine use of left subclavian vein pacing for protection of the left phrenic nerve, with no significant increase in procedural cost or risk. Venous pressure waveform monitoring allows reproducible multi-observer assessment of phrenic nerve contraction strength, and allows detection of impending phrenic nerve palsy.

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