Phrenic Nerve Injury: An Underrecognized and Potentially Preventable Complication of Pulmonary Vein Isolation Using a Wide-Area Circumferential Ablation Approach

SANG YONG JI, M.D., JANE DEWIRE, B.A., BERNADETTE BARCELON, R.T., BINU PHILIPS, M.D., JOHN CATANZARO, M.D., SAMAN NAZARIAN, M.D., Ph.D., ALAN CHENG, M.D., DAVID SPRAGG, M.D., HARIKRISHNA TANDRI, M.D., SANDEEP BANSAL, M.D., M.P.H., HIROSHI ASHIKAGA, M.D., Ph.D., JACK RICKARD, M.D., ARAVINDAN KOLANDAIVELU, M.D., SUNIL SINHA, M.D., JOSEPH E. MARINE, M.D., HUGH CALKINS, M.D., and RONALD BERGER, M.D., Ph.D.

From the Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Phrenic Nerve Injury. Introduction: Phrenic nerve injury (PNI) is a well-known, although uncommon, complication of pulmonary vein isolation (PVI) using radiofrequency energy. Currently, there is no consensus about how to avoid or minimize this injury. The purpose of this study was to determine how often the phrenic nerve, as identified using a high-output pacing, lies along the ablation trajectory of a wide-area circumferential lesion set. We also sought to determine if PVI can be achieved without phrenic nerve injury by modifying the ablation lesion set so as to avoid those areas where phrenic nerve capture (PNC) is observed.

Methods and Results: We prospectively enrolled 100 consecutive patients (age 61.7 ± 9.2 years old, 75 men) who underwent RF PVI using a wide-area circumferential ablation approach. A high-output (20 mA at 2 milliseconds) endocardial pacing protocol was performed around the right pulmonary veins and the carina where a usual ablation lesion set would be made. A total of 30% of patients had PNC and required modification of ablation lines. In the group of patients with PNC, the carina was the most common site of capture (85%) followed by anterior right superior pulmonary vein (RSPV) (70%) and anterior right inferior pulmonary vein (RIPV) (30%). A total of 25% of PNC group had capture in all 3 (RSPV, RIPV, and carina) regions. There was no difference in the clinical characteristics between the groups with and without PNC. RF PVI caused no PNI in either group.

Conclusion: High output pacing around the right pulmonary veins and the carina reveals that the phrenic nerve lies along a wide-area circumferential ablation trajectory in 30% of patients. Modification of ablation lines to avoid these sites may prevent phrenic nerve injury during RF PVI. (J Cardiovasc Electrophysiol, Vol. 24, pp. 1086-1091, October 2013)

atrial fibrillation, phrenic nerve capture, phrenic nerve injury, pulmonary vein isolation, radiofrequency ablation, wide-area circumferential ablation

Introduction

Phrenic nerve injury (PNI) is a well-recognized complication of atrial fibrillation (AF) ablation using the cryoballoon system with a published incidence ranging from 8% to 11%.1,2 Because of the potential for PNI, it is now standard practice to pace the right phrenic nerve from the superior vena cava during cryoballoon ablation of the right-sided pulmonary veins and to terminate cryoablation if any change in diaphragmatic capture is observed.1,2 In contrast to cryoballoon ablation, radiofrequency (RF) ablation, especially delivered with wide-area circumferential ablation (WACA) strategy, very rarely causes phrenic nerve injury. When PNI is observed, it is often associated with concomitant isolation of the SVC or RF ablation with a segmental ostial ablation in the right-sided pulmonary veins. The reported incidence of PNI ranges from 0.17% to 0.48% in RF pulmonary vein isolation (PVI) using different approaches.6-8 Consistent with the extremely low incidence of PNI, the 2012 HRS Consensus Document on AF ablation does not recommend specific measures to prevent this complication.9

Our study was motivated by the experience of 3 patients who developed phrenic nerve injury after RF PVI using the WACA approach at our institution between December 2006 and August 2012 (Fig. 1). Although each of these patients recovered fully, PNI resulted in diminished quality of life until recovery occurred. As a result of these clinical experiences, we designed this study to develop a new approach to WACA that might prevent this complication in the future. The goal of this study was to evaluate the incidence of phrenic nerve capture (PNC) using high-output pacing along the trajectory that we typically ablate using the WACA approach. If PNC was seen, we modified our ablation line to prevent
the application of RF energy in the proximity of the phrenic nerve.

Methods

Patient Population

We prospectively enrolled 100 consecutive RF PVI patients who gave written consent for our atrial fibrillation research study that was approved by the Johns Hopkins Institutional Review Board. Patients with drug refractory paroxysmal and persistent AF were enrolled.

Ablation Procedure and the Pacing Protocol

Patients underwent RF PVI using a 3-D electroanatomic mapping system, irrigated 4-mm-tip catheter, and integrated ablation system (ThermoCool, Biosense Webster Inc., Diamond Bar, CA, USA) under general anesthesia. PVI with WACA approach was started with the left pulmonary veins, during which neuromuscular blockade was stopped. After confirmation of reversal of neuromuscular blockade with intraprocedure electromyography, high-output (20 mA at 2 milliseconds, EPS320 Micropace EP Inc., Santa Ana, CA, USA) endocardial pacing was performed with the ablation catheter to look for PNC around the wide-area circumferential trajectory for the right superior and inferior pulmonary veins. Pacing was also performed in the carina between the right superior and inferior PVs. If PNC was demonstrated along the anticipated wide-area circumferential ablation line trajectory or between the PVs, a marker dot was placed at that site in the electroanatomic map. The resulting locus of marker dots was used to indicate the course of the phrenic nerve. If PNC was identified along the anticipated wide-area circumferential ablation line trajectory, the lesion set was modified either toward the atrial side or closer to the vein, depending on the location of PNC and operator’s preference. During RF PVI, 30–35 W was delivered at each site along the ablation line.

Data Collection and Assessment of Phrenic Nerve Injury

Clinical characteristics recorded for each patient included age, sex, race, type of AF, body mass index, comorbidities, left ventricular systolic function, renal function, left atrial dimensions, and time spent during the pacing protocol. Left atrial dimension was measured based on preacquired cardiac MRI or CT image. The anteroposterior axis (X) was measured from the center of the posterior wall to the mitral valve plane, the horizontal axis (Y) was measured between the left carina and the right carina and the height (Z) was measured from the center of the left atrial floor to the center of the roof. Occurrence of phrenic nerve injury was assessed with fluoroscopy during the procedure and during physical exam prior to discharge.

Statistical Analysis

Continuous variables were reported as mean ± standard deviation and group differences determined by a 2-sample t-test (2-sided with a P ≤ 0.05 considered statistically significant). Categorical variables were summarized as percentages.

Results

Patient Characteristics

The study population consisted of 100 patients who underwent RF PVI from September 2012 to March 2013 by 10 different attending electrophysiologists at our institution and agreed to participate in our AF ablation registry (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>N or Mean (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.7 (±9.2)</td>
</tr>
<tr>
<td>Male</td>
<td>75</td>
</tr>
<tr>
<td>Caucasian</td>
<td>87</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>52</td>
</tr>
<tr>
<td>BMI</td>
<td>29.7 (±7.5)</td>
</tr>
<tr>
<td>HTN</td>
<td>12</td>
</tr>
<tr>
<td>EF (%)</td>
<td>51.5 (±10)</td>
</tr>
<tr>
<td>Pre-Cr (mg/dL)</td>
<td>1.1 (±0.2)</td>
</tr>
<tr>
<td>Post-Cr (mg/dL)</td>
<td>1.0 (±0.2)</td>
</tr>
<tr>
<td>LA_X (mm)</td>
<td>52.2 (±13.7)</td>
</tr>
<tr>
<td>LA_Y (mm)</td>
<td>57.3 (±10.6)</td>
</tr>
<tr>
<td>LA_Z (mm)</td>
<td>55.8 (±13.7)</td>
</tr>
<tr>
<td>Pacing protocol (minutes)</td>
<td>2.5 (±1.8)</td>
</tr>
</tbody>
</table>

*Plus-minus values are means ±SD.
The age of the study group was 61.7 ± 9.2 year. A total of 75% were men, 87% were Caucasian, and 52% of the patients had paroxysmal AF. Body mass index was 29.7 ± 7.5. Twelve percent of patients had diabetes mellitus and 56% had hypertension. The left ventricular ejection fraction was 51.5 ± 10%. The anteroposterior left atrial dimension was 52.2 ± 13.7 mm, while the horizontal and vertical (height) left atrial dimensions were 57.3 ± 10.6 mm and 53.8 ± 13.7 mm, respectively. Total time spent in pacing protocol was 2.5 ± 1.8 minutes. No differences were observed in the clinical characteristics of patients who did versus those who did not demonstrate PNC (Table 2).

### PNC and Modification of Ablation Lesion Set

Thirty patients (30%) demonstrated PNC along the wide-area circumferential ablation line trajectory. In Figure 2, in 4 representative patients with PNC, the sites of capture were marked with blue dots on the electroanatomical maps. Once capture was observed in a particular patient, efforts were made to track the areas of phrenic nerve capture even if they extended past our anticipated wide area lesion set. All patients who demonstrated PNC (30 out of 100) along the anticipated trajectory of the wide-area circumferential lesion set had their right side ablation line modified to avoid this area (Fig. 2). Once the region of PNC was identified, depending on the location of the capture and the operator’s preference, the ablation line was modified to be either closer to the pulmonary vein (Fig. 2A) or on the atrial side of the PNC region (Fig. 2B, 2C, and 2D). Although all patients with PNC had successful adjustment of the ablation line, the carina ablation line was deferred in 20% of these patients who demonstrated capture due to its proximity to the PNC site.

### Distribution of PNC

Figure 3 shows the distribution of sites of PNC that were observed. The anterior aspect of the right carina was the most common site that demonstrated PNC (85% of the patients with PNC). The second most common site (observed in 70% of patients with PNC) was along the anterior RSPV ostium. The third most common site of PNC (observed in 30% of PNC+ patients) was along the anterior RIPV ostium. In 25% of PNC+ patients, all 3 regions showed PNC.

### Paroxysmal vs Persistent Atrial Fibrillation and PNC

In this study, 52% of the patients had paroxysmal AF. Eleven patients in PNC+ group (n = 30) had additional left atrial lines such as roof line, floor line, posterior upper and lower lines, and mitral isthmus line. Among these, 7 had persistent or longstanding persistent atrial fibrillation while 4 had paroxysmal atrial fibrillation. On the other hand, 22 patients in the PNC− group (n = 70) had additional left atrial lines such as roof line, floor line, posterior upper and lower lines, and mitral isthmus line. Among these, 14 had persistent or longstanding persistent atrial fibrillation, while 8 had paroxysmal atrial fibrillation. None of these additional lines were in the proximity to the PNC site.

### Phrenic Nerve Injury

No clinically apparent PNI occurred in either PNC+ or PNC− group.

### Discussion

#### Main Findings

We found that approximately 30% of patients undergoing AF ablation demonstrate PNC along the trajectory typically encompassed using a WACA approach. We report no PNI when the ablation line area was altered to avoid sites of PNC.

#### Clinical Characteristics

In our cohort, there were no specific clinical characteristics that predicted the incidence of PNC. In particular, PNC was not associated with the eccentric dilation of the left atrium, type of AF, or LVEF. Although intuitively, the more eccentric atrial dilation one has, the more unusual anatomic relationship could be expected between the right phrenic nerve and the right-sided pulmonary vein antra, shown in Table 2, none of the 3-dimensional axes was related to finding PNC (P = 0.81–0.93).

#### PNI During AF Ablation

Several earlier studies have reported PNI in RF PVI cases. Cappato et al. reported 0.17% of PNI incidence in their worldwide survey on catheter ablation for AF between 2003 and 2006. In their series, 20,825 catheter ablations were performed on 16,309 patients and there was no standardization of the type of lesion set. Sacher et al. reported 0.48% incidence of PNI in 3,755 consecutive patients who underwent AF ablation at 5 centers in Europe and the United States between 1997 and 2004. Different ablation strategies were used in their series, including focal ablation or segmental PVI, especially during the early phase of the study (1997–2000), WACA, and additional lines in the left atrium and SVC. Of the 18 patients who had PNI, only 3 had the WACA approach while the rest had PVI with or without additional left atrial linear lines and superior vena cava (SVC) disconnection. The authors suggested that variable anatomy was the probable cause of this complication rather than excessive RF delivery, as total RF application did not differ significantly among patients.

PNI is more commonly reported with balloon technology-based PVI than with RF PVI. Currently, cryoballoon PVI is
the most common technique that uses a balloon platform. The mechanism of PNI during cryoballoon PVI is thought to be related to the distortion of the left atrial and pulmonary vein ostial anatomy, which may reduce the distance between the balloon surface and phrenic nerve. The degree of anatomic distortion may be amplified when the device is pushed into the PV to minimize peri-balloon leak.\textsuperscript{1,2} PNI is also associated with the use of a smaller size balloon, which allows more distal advancement of the balloon toward the phrenic nerve.\textsuperscript{1}

In contrast to the clinical studies that describe the mechanism of PNI in cryoballoon PVI, there are only a handful of case reports and retrospective studies concerning PNI in RF PVI. Our manuscript describes the first prospective clinical study designed to avoid PNI in patients undergoing RF PVI using a WACA approach. Therefore, it appears that PNI is a rare, but potentially preventable complication of radiofrequency AF ablation using a WACA approach.

**Pacing Protocol and Ablation Modification**

Previous studies have shown that the course of the right phrenic nerve can be identified with high-output pacing within the SVC in conjunction with 3-dimensional (3D) electroanatomic mapping. In prior reports, 10 V at 2.9 milliseconds was used for the endocardial pacing protocol for the 3D reconstruction of the course of the phrenic nerve and this was validated with different imaging modalities.\textsuperscript{4,10,11,13,14} Assuming a pacing impedance of 500 $\Omega$, we chose an equivalent output of 20 mA at 2 milliseconds pulse width. As the goal of our study was to prevent PNI, we preferred to have higher sensitivity at the expense of probably lower specificity. Therefore, rather than 5 or 10 mA, we chose to pace with higher output that matches the previously validated range (10 V at 2.9 milliseconds).

In our study of a 100 patient cohort undergoing standard RF PVI, we found that the course of the right phrenic nerve near the right pulmonary veins could be identified with
The distribution of PNC in the region of the right-sided pulmonary veins. Among 100 patients who had the pacing protocol, 30% of patients had PNC. The anterior aspect of carina was the most common place with PNC (85% of the patients with PNC) while this was seen in 70% at the anterior aspect of the RSPV and 30% in RIPV. In 25% of PNC patients, anterior aspect of all 3 regions showed PNC. 119 × 113 mm.

function in up to 88% of the cases. More importantly, transient PNI was followed by permanent injury in each energy delivery after 20–280 seconds of additional energy delivery with higher temperature. Our ablation strategy involves moving the ablation catheter every 30–60 seconds. Furthermore, we do not employ deflectable sheaths, which are known to increase catheter contact and also lesion size. We suspect that the low incidence of phrenic nerve injury reflects, at least in part, these aspects of our ablation strategy.

Limitations

Our study, while prospective, was not randomized and so we cannot conclude that the PNC technique described is entirely responsible for the absence of PNI seen in the prospective cohort. Given the low incidence of PNI, our study is not sufficiently powered to detect clinically significant difference.

Conclusion and Clinical Implications

The results of this study demonstrate that PNI may occur during a WACA approach to AF ablation. This observation, together with our finding that capture of the phrenic nerve along a WACA ablation line trajectory can be observed in 30% of patients undergoing AF ablation, is of potential clinical importance in ongoing efforts to reduce complications of AF ablation, even if very rare. Furthermore, our findings on the distribution of PNC are also relevant to PVI using a cryoballoon, as they call into question the commonly held belief that the use of a larger balloon to stay outside the veins inherently avoids PNI and help to explain why phrenic nerve pacing during cryoballoon ablation is recommended even when larger balloon sizes that stay well outside the tubular portion of the pulmonary veins are used. Based on our clinical experience and the results of this study, we now routinely perform high-output pacing along the WACA lesion trajectory, and modify our ablation set to avoid areas of phrenic nerve capture.

References


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