How Close Are the Phrenic Nerves to Cardiac Structures? Implications for Cardiac Interventionalists

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Phrenic Nerves and Cardiac Structures. ***Background:*** **Phrenic nerve injury is a recognized complication following cardiac intervention or surgery. With increasing use of transcatheter procedures to treat drug-refractory arrhythmias, clarification of the spatial relationships between the phrenic nerves and important cardiac structures is essential to reduce risks.**

Methods and Results: **We examined by gross dissection the courses of the right and left phrenic nerves in 19 cadavers. Measurements were made of the minimal and maximal distances of the nerves to the superior caval vein, superior cavoatrial junction, right pulmonary veins, and coronary veins. Histologic studies were carried out on tissues from six cavaders. Tracing the course of the right phrenic nerve revealed its close proximity to the superior caval vein (minimum 0.3 ± 0.5 mm) and the right superior pulmonary vein (minimum 2.1 ± 0.4 mm). The anterior wall of the right superior pulmonary vein was <2 mm from the right phrenic nerve in 32% of specimens. The left phrenic nerve passed over the obtuse cardiac margin and the left obtuse marginal vein and artery in 79% of specimens. In the remaining specimens, its course was anterosuperior, passing over the main stem of the left coronary artery or the anterior descending artery and great cardiac vein.**

Conclusions: **The right phrenic nerve is at risk when ablations are carried out in the superior caval vein and the right superior pulmonary vein. The left phrenic nerve is vulnerable during lead implantation into the great cardiac and left obtuse marginal veins.** *(J Cardiovasc Electrophysiol, Vol. 16, pp. 309-313, March 2005)*

ablation, atrium, catheter ablation, sinoatrial node

Introduction

Phrenic nerve injury after cardiac intervention or surgery is a well-recognized complication. Its reported incidence following electrophysiologic or radiologic techniques is estimated at between 2.5% and 24%.[1-4] Albeit uncommon, injury to the phrenic nerve resulting in permanent paralysis of the diaphragm is an unwelcome complication. Specifically, there are reports of injury to the right phrenic nerve following catheter ablation for inappropriate sinus tachycardia[5] and for electrical isolation of the right pulmonary veins and/or at circumferential ablation around their orifices using radiofrequency or cryoablation[6-8] to treat atrial fibrillation. Damage to the left phrenic nerve has been reported in a patient following radiofrequency ablation for Wolff–Parkinson–White syndrome.[9] Additionally, recent advances in lead technology and surgical approach, such as cardiac resynchronization therapy (CTR) with the left ventricular lead placed in a tributary of the coronary sinus and left ventricular steroid epicardial leads or both atrial and ventricular leads, have demonstrated occurrence of left phrenic nerve dysfunction when used in adults or children.[1,2,10-13]

The purpose of this study was to determine by careful morphological dissection and histological sections the course of the right and left phrenic nerves and their relationship to cardiac structures so as to provide detailed anatomical background essential to interventionists who carry out ablation procedures or implantations of pacing leads.

Materials and Methods

Nineteen human cadavers, nine from the Department of Anatomy, University of Extremadura and ten from the Department of Anatomy, University of Graz (Austria) formed the study group. There were 11 male and 8 female cadavers with an average age of 70 (range 54–83) years. They were without obvious signs of thoracic pathology or prior surgery and none of the 19 patients had a history of atrial arrhythmia. The cadavers from Graz were embalmed by Thiel's method[14,15] and the cadavers from Badajoz (Extremadura, Spain) were fixed in 10% formalin and preserved in 30% ethanol. The right and left anterolateral walls of the thorax and the right and left pleural cavity were opened and the both were reflected from the mediastinal pleura. The right and left phrenic nerves were easily visible through the mediastinal

We acknowledge funding support of grant SAF2004-06864 from Ministerio de Educación y Ciencia, Spain (DS-Q, JAC, and VC), Red de Enfermedades Cardiovasculares, RECAVA, Spain (JAC and JF), and Royal Brompton and Harefield Hospital Charitable Fund (SYH).

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Manuscript received 11 November 2004; Revised manuscript received 17 December 2004; Accepted for publication 27 December 2004.

doi: 10.1046/j.1540-8167.2005.40759.x

pleura. The latter was then cut to expose the nerve completely. Both the superior and inferior right pulmonary veins were also exposed and measurements taken without separating the right phrenic nerve from the pericardium. Using a pair of calipers, we measured the maximal and minimal distances (in millimeters) between right phrenic nerve and right anterolateral wall of the superior caval vein (SCV), between the nerve and the superior cavoatrial junction, and between the nerve and the anterior walls of the superior and inferior pulmonary veins. In addition, the left phrenic nerve and the coronary vessels with their major branches related to the left phrenic nerve were carefully dissected in nine cadavers. The maximal and minimal distances between left phrenic nerve and great cardiac vein (GCV) or coronary sinus and left obtuse marginal vein (LOMV) were measured. We excised tissue blocks containing the full thicknesses of the right pulmonary veins and left atrial wall and part of SCV, fibrous pericardium, and right phrenic nerve from six cadavers. From each cadaver, three blocks of approximately 5-mm thickness were dehydrated in a graded series of ethanol, embedded in paraffin, and serially sectioned at 10 μm in a transverse plane for histological examination. Deparaffinized sister sections were stained with Masson's trichrome technique, and with van Gieson stain.

Statistical Study

Data are expressed as mean ± standard deviation. Quantitative data were compared using an unpaired *t*-test. Correlations between quantitative variables were performed by standard linear regression studies. P values less than 0.05 were considered significant.

Results

In the thorax, the right phrenic nerve is covered by the mediastinal pleura. It descends almost vertically first along the right brachiocephalic vein and continues along the right anterolateral surface of the SCV (Fig. 1). The nerve is only separated by pericardium at the anterolateral junction between the SCV and the right atrium (RA). It can be followed inferiorly along the pericardium overlying the right aspect of the right atrial wall (Fig. 1). From here it passes in front of the root of the lung, where its passage becomes partially embedded in between the fibrous pericardium and the mediastinal pleura until it reaches the diaphragm. Branches from the nerve then spread to the upper surface of the diaphragm while the main trunk passes through the diaphragm along the inferior caval vein (ICV) to the undersurface of the diaphragm. Histologic examination of the transverse sections revealed the close anatomic relationship between the course of the right phrenic nerve and SCV and the right superior pulmonary vein (RSPV) with the right superior cavoatrial junction at the pulmonary hilum (Fig. 2). In all cases, variable amounts of fatty and connective tissue were encountered around the site where the phrenic nerves coursed along the fibrous pericardium. In terms of proximity to cardiac structures relevant to ablationists, the right phrenic nerve is close to the SCV superiorly (Table 1) and adjacent to the lateral border of the entrance of the ICV to the RA inferiorly (Fig. 2A). While the right phrenic nerve is immediately adjacent to the anterolateral wall of the SCV, it veers posteriorly as it approaches the superior cavoatrial junction (Table 1). More inferiorly, it passes close to the junction of the left atrium to the RSPV (Table 1) (Fig. 2B,C). In six specimens (32%), the anterior wall of the RSPV is <2 mm from the phrenic nerve. All specimens examined by histology revealed a sleeve of myocardium surrounded by the proximal portion of the RSPV. Measured from the venoatrial junction, the maximal extension of this vein ranged from 7 to 14 mm (mean 9.3 ± 1.5 mm). The thickness of sleeve ranged from 0.2 to 1.6 mm with the thicker portions at the venoatrial junction. In contrast, the right inferior pulmonary venous junction was at least a mean of 7 mm away from the nerve (Table 1). Myocardial sleeves were found in four specimens and they ranged from 2 to 7 mm (mean 4.3 ± 1.2 mm) in length. The thickness of the sleeves ranged from 0.1 to 1 mm.

In the nine hearts that were dissected to reveal the left phrenic nerve, we traced its vertical descent behind the left brachiocephalic vein. It continues closely over the aortic arch, pulmonary trunk, and the pericardium over the left atrial appendage (Fig. 3A,B). From there, it passes along the pericardium overlying the left ventricle (LV). In front of the root of the left lung, the left phrenic nerve is located between the fibrous pericardium that covers the anterolateral face of the LV and the mediastinal pleura, and it takes an oblique passage downward to reach the diaphragm behind the tip of the LV (Fig. 3). In six of the specimens (67%), the nerve was separated from the fibrous pericardium by variable amounts of adipose tissue. The relationships of the nerve to the left heart structures depended on whether it descended along a path related to the anterior surface of the LV or passed leftward

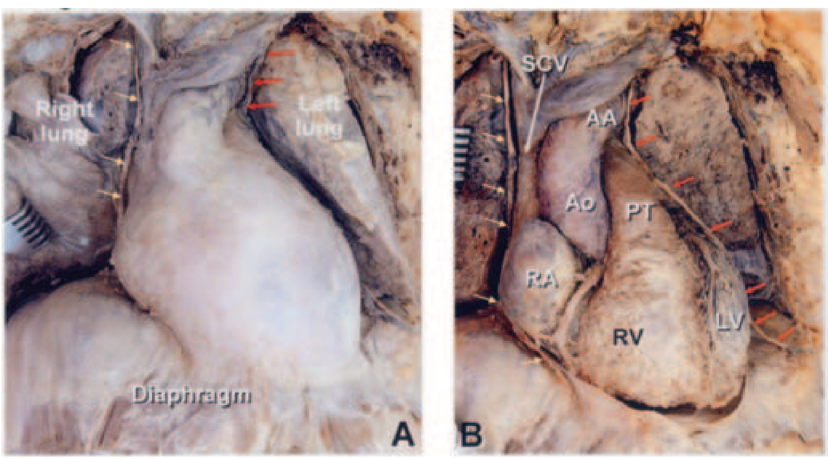

Figure 1. *A: Dissection of the thorax of a cavader shows the heart enclosed within the fibrous pericardial sac and the right and left phrenic nerves (yellow and red arrows respectively). B: The courses of the right nerve (yellow arrows) and left nerve (red arrows) are clearly visible after partial removal of the fibrous pericardium and lungs. The right phrenic nerve can be seen emerging alongside the right brachiocephalic vein and has a course that descends along the pericardium more or less parallel to the superior caval vein (SCV) to the undersurface of the diaphragm. The left phrenic nerve emerges beside the left brachiocephalic vein, and descends on the pericardium anterior and lateral to the aortic arch (AA), alongside the distal part of pulmonary trunk (PT), left atrial appendage and lateral wall of left ventricle to penetrate the left part of the diaphragm. Ao = aorta; LV = left ventricle; RA = right atrium; RV = right ventricle.*

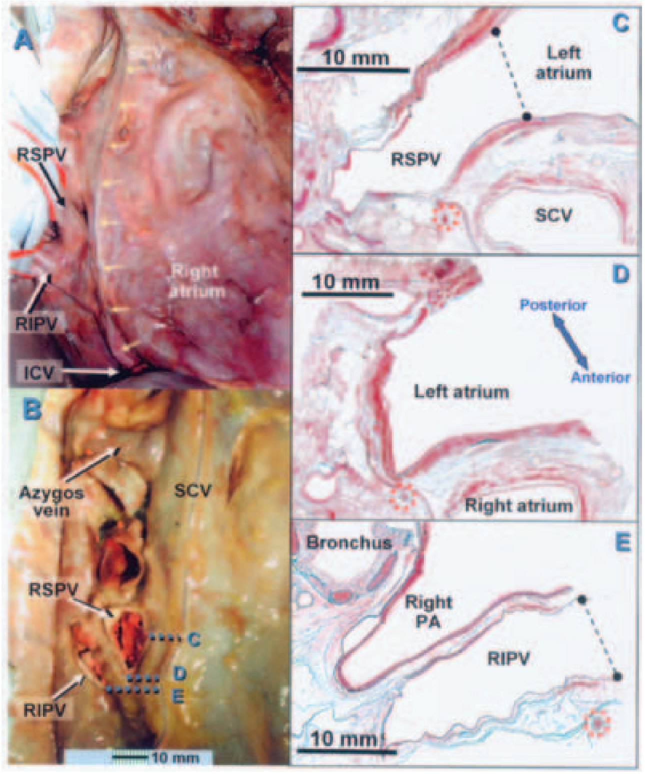

Figure 2. *A: The right pulmonary veins are visible from this anterior view by deflecting the right atrial wall leftward. The course of right phrenic nerve indicated by yellow arrows is closely related to the superior cavoatrial junction and the orifices of the right pulmonary veins. B: Dissection of the right lateral view of the pulmonary pedicle of a specimen embalmed by Thiel's method. In the upper part of the pedicle is the main bronchus, underneath the PA and lower part the pulmonary veins. The dotted lines correspond to the transverse histological sections in the right hand panels. Levels C and E are at minimal distances between the nerve and the anterior walls of the pulmonary veins. C, D, E: Histological sections through the RSPV, the intervenous left atrium, and the inferior pulmonary vein respectively. The right phrenic nerve (surrounded by dots) is adherent to the fibrous pericardium (thin red/green line). The broken lines indicate the pulmonary venous orifices. Note the myocardial sleeve (red) on the outer side of the RSPV. ICV = inferior caval vein; PA = pulmonary artery; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SCV = superior caval vein. (Masson's trichrome stain.)*

along a course related to the obtuse margin of the LV. In seven specimens (79%), the nerve passed along the obtuse margin and was close to the lateral vein or LOMV and left marginal artery (Fig. 3A,B,C). When the course was related to the anterior aspect of the LV (two specimens, 21%) the nerve passed close to the main stem of the left coronary artery or its superior interventricular branch (left anterior descending coronary artery) and the GCV (anterior interventricular vein) (Fig. 3D,E,F). The minimal and maximal distances across the fibrous pericardium between the left phrenic nerve and GCV and LOMV are presented in Table 2. In three of the seven specimens (43%) the lateral vein or LOMV was <3 mm from the left phrenic nerve.

Discussion

Details of the spatial relationship of the course of the phrenic nerves with emphasis on proximity to cardiac structures that are relevant to transcatheter intervention are not readily available in textbooks. Improvements in imaging techniques can allow cardiac interventionists a better perspective of spatial relationships, but these tools are not available in every center. As transcatheter procedures are used increasingly to treat patients with drug-refractory arrhythmias, an understanding of anatomical relationships potentially can help avoid some adverse events.

TABLE 1

Distances in Millimeters (with Range) between the Right Phrenic Nerve and the Anterolateral Wall of the Superior Caval Vein (SCV), Junction between SCV and Right Atrium (SCV-AJ), Right Superior Pulmonary Vein (RSPV), and Right Inferior Pulmonary Vein (RIPV)

	Right Phrenic Nerve (mm)	
	Minimal (Range)	Maximal (Range)
SCV	0.3 ± 0.5 (0–0.9)	1.3 ± 0.5 (1–2.3)
SCV-AJ	5.8 ± 1.1 (3.2–7.5)	7.6 ± 1.2 (6.2–10.5)
RSPV	2.1 ± 0.4 (1.5–2.5)	3.2 ± 0.9 (1.5–4.5)
RIPV	7.8 ± 1.2 (6–10)	12.3 ± 1.4 (10–15.5)

Superior Caval Vein, Cavoatrial Junction, and Sinus Node

The present study demonstrates the course of the right phrenic nerve *in situ* and highlights its proximity to the SCV and the right upper pulmonary vein. Both these regions are relevant to catheter ablation. The SCV and junction between the right SCV and the RA is targeted for modifying the sinus node in patients with inappropriate sinus tachycardia, reentrant sinus tachycardia, and arrhythmogenic foci for atrial fibrillation.[16-19] Our recent study on the sinus node demonstrated the location and extent of nodal tissues.[20] In some cases, we observed ramifications from the sinus node ascending into the muscular sleeves of the SCV. If these extensions are targeted by the ablative catheter, it is reasonable to assume that risk to the right phrenic nerve will be particularly high. For one reason, the nerve courses directly over this area. For another, the venous wall, even with its muscular sleeve, is thinner than the atrial wall that is reinforced by the thickness of the terminal crest. In the normal cadavers we found the transmural thickness of the venous wall at the venoatrial junction to be a minimum of 1.8 ± 0.7 mm (range 1.2–3.2) and a maximum of 3.2 ± 0.8 mm (range 2.3–5.3). When ablating from within the atrial chamber, usually the body of the sinus node is "protected" by the thickness of the crest, whereas the nodal "head" can be more vulnerable due to its more superior location relative to the crest.[20] A recent report described a combined epicardial–endocardial approach to ablation in a case of inappropriate sinus tachycardia.[21] The operators used an 8-mm tip catheter in unipolar mode on both surfaces. The authors reported no complications with the procedure. It may be that the positioning of the catheter on the epicardium directed the heating effect of radiofrequency toward the cardiac surface and away from the phrenic nerve. Alternatively, the variable amounts of fatty connective tissue encountered in all specimens around the phrenic nerve along the fibrous pericardium may also protect the nerve from damage.

On the other hand, the mean of minimal distances of the anterior wall of the superior venoatrial junction to the right phrenic nerve suggests that ablating in this area in the majority of patients will not endanger the nerve. But, this supposition does not take into account the type and mode of energy

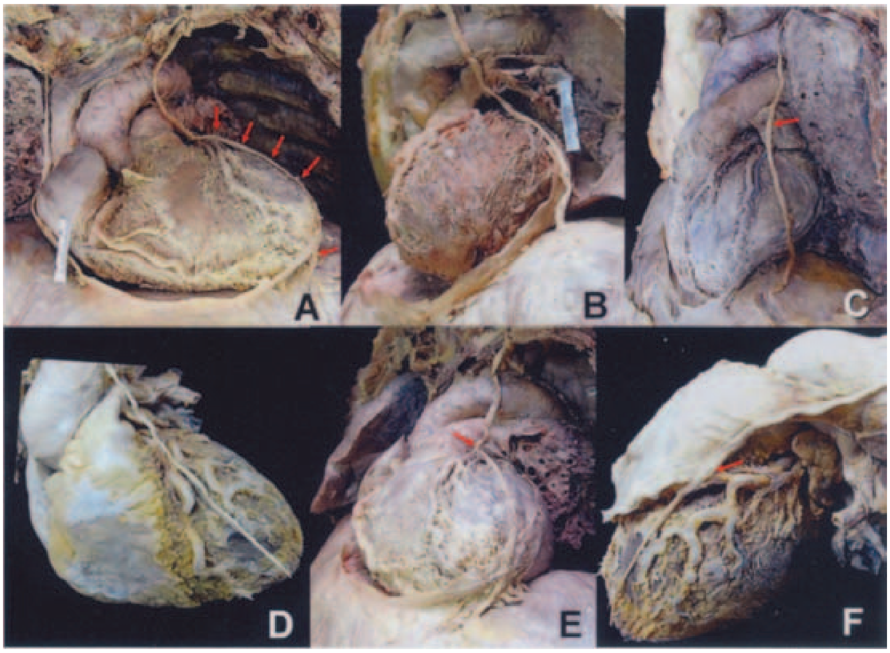

Figure 3. *A: Dissection of the frontal view of the heart after removal of fibrous pericardium and left lung showing the arrangement of the phrenic nerves. Note the left phrenic nerve sweeping over the left heart border. B: This tilted left anterior oblique view shows the left phrenic nerve passing alongside the obtuse margin of the heart. C: Left lateral view after removal of the fibrous pericardium and part of the left lung shows the course of the left phrenic nerve running over the tip of the left atrial appendage and close to the left marginal artery and the lateral or left obtuse marginal vein. D: Anterior view of an isolated heart specimen following removal of the pericardium. The left phrenic nerve courses over the sternocostal surface. E: Left anterior oblique view shows the relationship of the left phrenic nerve to the anterior descending coronary artery and the interventricular or GCV. F: Left lateral view of the heart shows left phrenic nerve passing over the anterior descending artery to course close to a diagonal artery.*

deployed. Injury to the phrenic nerve following cardiac surgery is well recognized. Topical cardiac cooling is thought to be a major cause, suggesting the nerve axon is either susceptible to low temperatures or a prolonged period of cooling[22,23] with implications for using cryothermia, especially in the epicardial approach. Furthermore, it is worth noting that an experimental study comparing linear lesions produced by radiofrequency current ablation using bipolar two catheter technique with unipolar application on the porcine RA reported paresis of the right diaphragm in 9 out of a total of 12 pigs.[24] In the human clinical setting, transient phrenic nerve paresis has been observed during cryoablation of RSPV in 2% of patients.[7]

Right Pulmonary Veins

As the right phrenic nerve descends toward the diaphragm, it veers rightward and runs anterior to the right pulmonary veins. It is closer to the right upper veins than to the lower veins (minimal mean 2.1 ± 0.4 mm vs 7.8 ± 1.2 mm) and in six specimens (32%) the RSPV was <2 mm from the phrenic nerve. Although we have found only one report[6] of right phrenic nerve palsy following percutaneous radiofrequency ablation for atrial fibrillation, preliminary results of through-the-balloon circumferential ultrasound ablation to isolate the pulmonary veins reported one patient with right phrenic nerve paralysis following ablation in an anterior branch of the right upper pulmonary vein.[25] In the latter case, there was partial recovery of phrenic nerve function at 3-months follow-up.

TABLE 2

Distances in Millimeters (with Range) between the Left Phrenic Nerve and Great Cardiac Vein (GCV), and Left Obtuse Marginal Vein (LOMV)

	Left Phrenic Nerve (mm)	
	Minimal (Range)	**Maximal (Range)**
GCV	1.4 ± 0.3 (1–2.3)	2.5 ± 0.5 (1.5–3.5)
LOMV	3.5 ± 0.5 (2–4.3)	4.5 ± 0.7 (3.5–7.5)

Left Phrenic Nerve and Coronary Veins

Cardiac resynchronization therapy has emerged as a nonpharmacological treatment of heart failure in patients with mechanical ventricular dyssynchrony. The main goal of CTR is a restoration of the synchrony of the late activated left ventricular regions that are mostly confined to the left lateral ventricular wall, especially in dilated cardiomyopathy.[26] The most popular site that has been proposed for implanting the left ventricular pacing lead is in a tributary of the coronary sinus.[1,2,10,13] According to various authors the common veins used for implantation are the lateral vein or LOMV (34%),[1] the GCV or anterior interventricular vein (24%), and the "posterior" or middle cardiac vein (21%).[13] These studies reported detection of left phrenic nerve stimulation in 1–3% of patients during implantation.[1,2,10,13] In a recent review,[27] we showed the anatomical variability of the coronary sinus and its branches, and crossover spatial relationship with branches of coronary arteries. The present study demonstrates the course of the left phrenic nerve *in situ* and highlights its proximity to the lateral vein or LOMV and the great cardiac or anterior interventricular vein. In 43% of cases, we found the left phrenic nerve at a distance of less than 3 mm from the lateral vein, and in 21% the nerve was less then

2 mm from the GCV. Since these are the most commonly used veins, it would be prudential to look for phrenic nerve stimulation when implanting leads there. It is interesting that the European experience of transvenous left ventricular lead implantation encountered only two cases of phrenic nerve stimulation in their series of 150 patients.[10] These investigators recommend avoiding the "posterior" wall of the LV to lessen the risk of phrenic nerve stimulation. Since the attitudinally correct term for "posterior" is inferior, this recommendation is at odds with the anatomical findings presented above, and with the preference of surgeons for implanting epicardial leads on the diaphragmatic (inferior) surface of the LV. A recent surgical series reporting on placement of temporary epicardial pacing leads following open-heart surgery found five patients (28%) with left phrenic nerve stimulation when the lateral wall was used.[28] On balance, the best location for achieving most effect must be weighed up against increased risk of trauma to important cardiac and extracardiac structures.[28,29]

Conclusions

Despite the obvious limitations of using cadaveric materials for making measurements, the preparations by Thiel's method,[14,15] which is considered one of the best for preserving geometry and spatial relationships of structures should give useful guidelines to practitioners working on living patients. Arguably, enlargement of the atrial chambers, or the heart overall, could distort the courses of the phrenic nerves. However, since the phrenic nerves travel in the fibrous pericardium, the relationship with cardiac structures is likely to remain the same whether the heart is normal sized or enlarged. Our study demonstrates the close proximity of the SCV and the RSPV to the right phrenic nerve. The passage of the left phrenic nerve over the GCV or LOMV should be borne in mind when implanting leads in these veins.

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