Anatomic evaluation of the left phrenic nerve relevant to epicardial and endocardial catheter ablation: Implications for phrenic nerve injury

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BACKGROUND/OBJECTIVE The purpose of this study was to clarify the spatial relationship between the left phrenic nerve (LPN) and key cardiac structures in order to minimize the risk of phrenic nerve injury during interventions.

METHODS The course and relationship of the LPN to various cardiac structures were examined by gross dissection and histologic sections of 22 human cadavers.

RESULTS The nerve descended on the fibrous pericardium along one of three courses: over the anterior surface of the left ventricle (18%), over the lateral margin of the left ventricle (59%), and in a posteroinferior direction (23%). The endocardium of the roof of the left atrial appendage was <4 mm from the LPN in 2 (9%) specimens. The nerve passed <2.5 mm from the epicardium of the apex of the left atrial appendage in 7 (31%) specimens. Regardless of the position of the nerve in relation to the high left ventricular wall, the nerve was <3 mm from the epicardial surface in 8 (36%) specimens and passed <6 mm from the epicardium of the right ventricular outflow tract in 2 (9%) specimens.

CONCLUSION During electrophysiologic interventions, the LPN is especially at risk when procedures are performed in the vicinity of the left atrial appendage and high left ventricular wall.

KEYWORDS Anatomy; Ablation; Atrial tachycardia; Atrial appendage; Ventricular tachycardia

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Introduction

Anatomic and electroanatomic reconstruction studies have shown a close relationship between the right phrenic nerve and its proximity to the superior vena cava and the right superior pulmonary vein.[1,2] In addition, the proximity of the left phrenic nerve (LPN) to the left atrial appendage (LAA) has been well established.[1,3] A multicenter study showed that of almost 4,000 patients who underwent atrial fibrillation ablation, 18 patients sustained phrenic nerve injury.[4] It is well recognized that focal atrial tachycardia may arise from any part of the atrial myocardial region, and the LAA is one of the major sites.[5] The risk of inducing LPN injury is a known complication of atrial ablation when transmural lesions are created inside or around the roof of the orifice of the LAA.[4] Reports have described original techniques for preventing LPN injury during epicardial catheter ablation at the LAA and high lateral left ventricular wall given the close contact of the LPN with these structures.[6,7] Independent of the type of ablation (endocardial/epicardial), catheter (4 mm, 8 mm, irrigated tip, balloon), or energy source (radiofrequency, ultrasound, cryothermia, and laser) used, the risk of LPN injury exists. For a better understanding of the anatomic relationship of the LPN to various cardiac structures, we extended our previous work[1] to provide more detailed information on the course of the LPN relative to the LAA, the high left ventricular wall, and right ventricular outflow tract, from both the endocardial and epicardial aspects.

Materials and methods

After local institutional ethics approval was obtained, 22 human cadavers (14 male and 8 female; average age 64 years, range 52–78 years) from the Department of Anatomy, University of Extremadura (Badajoz, Spain) were studied. All did not have signs of cardiac surgery or a history of atrial arrhythmia. Ten cadavers were dissected, and the

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other 12 used for histologic sections. Anterior thoracotomy was performed to reveal the mediastinal pleura and the fibrous pericardium. The left lung was partially removed to visualize the great arteries (aorta and pulmonary trunk) and the LPN, which was accompanied by the pericardiophrenic vein and artery in the fibrous pericardium. Once the left pulmonary hilum was exposed and the LPN dissected, calipers were used to measure the minimal distances between the LPN and the endocardium and epicardium of the roof of the mouth of the LAA, between the nerve and the endocardium and epicardium of the apex of the atrial appendage, between the nerve and the epicardium of the high left ventricular wall, and between the nerve and the right ventricular outflow tract if it coursed over the tract. Tissue blocks were excised from 12 specimens. The blocks contained the LPN and the full thicknesses of at least the LAA and lateral region of the left atrium, fibrous pericardium, ascending aorta, high left ventricular wall, and part of the right ventricular outflow tract. From each specimen, four blocks approximately 5 mm thick were sectioned in transverse (six specimens) and frontal (six specimens) planes. The blocks were processed and serially sectioned at 12 μm for histologic examination. Sister sections were stained with Masson trichrome technique and van Gieson stain. On the histologic sections the same minimal distances as those obtained using the calipers were measured using an image analysis program (SigmaScanPro 5.0, Jandel Scientific, San Rafael, CA, USA) so that the data could be correlated with macroscopic dissections.

Statistical analysis

Results of quantitative measurements are expressed as mean ± SD and range.

Results

The LPN is the most important branch of the left cervical plexus. It originates mainly from the fourth cervical nerve but also receives contributions from the third and fifth cervical spinal nerves, descending along the neck anterior to the scalenus muscles and proximal part of the left subclavian artery. Inside the chest it runs dorsal to the left brachiocephalic vein, anterolateral to the aortic arch and pulmonary trunk where it runs on the surface of the fibrous pericardium to course between the mediastinal pleura of the left lung and the lateral surface of the left ventricle. In the lung hilum, the nerve passes anterior to the left superior and inferior pulmonary veins. It terminates at the diaphragm behind the tip of the left ventricle. The nerve and its accompanying pericardiophrenic artery and vein form the pericardiophrenic neurovascular bundle, which is surrounded by a fat pad of variable thickness (0.1–1.2 mm) adherent to the pericardium. The mean thickness of the fibrous pericardium measured on histology was 0.5 ± 0.1 mm (range 0.2–1 mm). In all 22 cases, the relationships of the nerve to left heart structures depended on which of the following three courses the nerve took as it descended toward the cardiac apex: (1) along a course related to the anterior surface of the heart (anterior course); (2) passed leftward along a course related to the apex of the LAA and obtuse margin of the left ventricle (lateral course); or (3) passed posteriorly to the inferior ("posterior") surface of the left ventricle (inferior course; Figure 1).

In 4 (18%) specimens, the LPN took an anterior course and was related to the anterior interventricular groove, high part of the right ventricular outflow tract, anterior part of high left ventricular wall, and left main coronary artery or great cardiac vein (Figures 1 and 2). When the course of the nerve was lateral, it descended close to the tip of the LAA and obliquely along the obtuse margin of the left ventricle (13 specimens [59%]; Figures 1, 3A, and 3B) to be related to the epicardium of the high left ventricular wall. In 5 (23%) specimens (Figures 1, 3C, and 3D), the nerve had an inferior course. It passed posteriorly and inferiorly, with a close relationship to the roof of the mouth of the LAA and

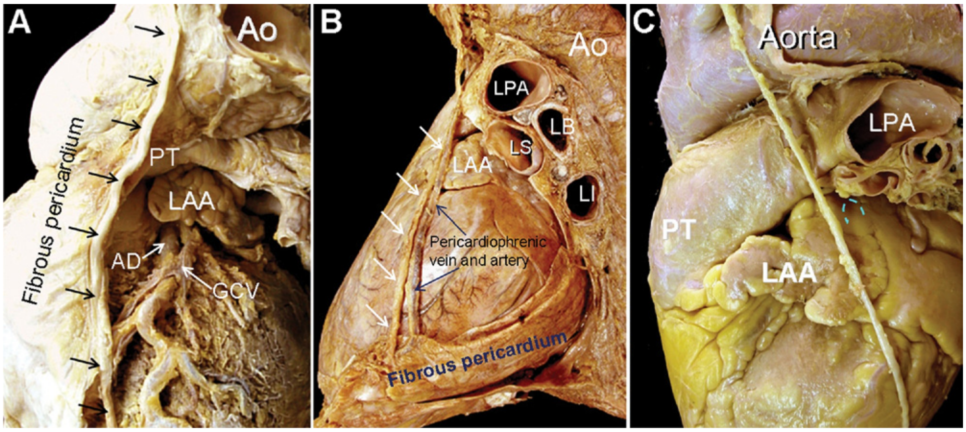

Figure 1 Anatomic relationship between left phrenic nerve (LPN) and heart. The LPN *(arrows)* descends lateral to the aortic arch, alongside the distal part of the pulmonary trunk. From there, it takes one of three courses: anterior **(A),** lateral **(B),** or inferior **(C),** to penetrate the left part of the diaphragm close to the apex of the left ventricle. At the location shown in **C,** the nerve has a close relationship with the roof of the mouth of the left atrial appendage *(broken line).* AD = anterior descending coronary artery; Ao = aorta; GCV = great cardiac vein; LAA = left atrial appendage; LB = left bronchus; LI = left inferior pulmonary vein; LPA = left pulmonary artery; LS = left superior pulmonary vein; PT = pulmonary trunk.

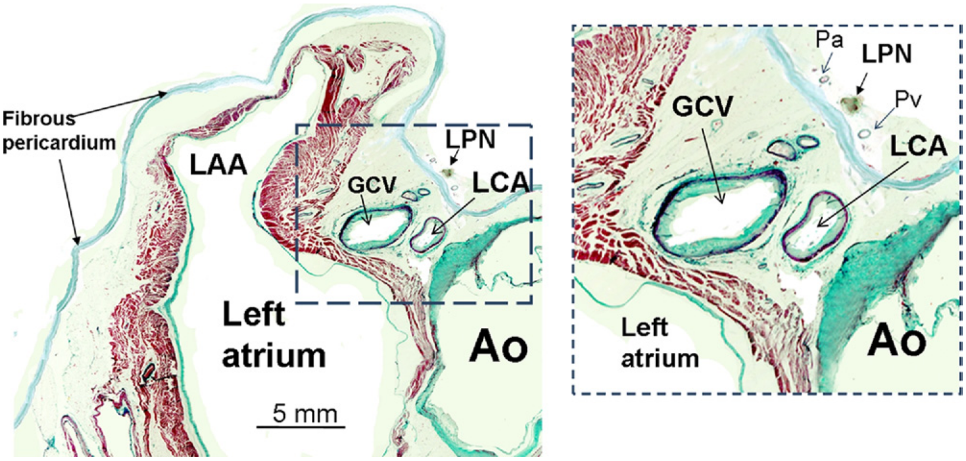

Figure 2 Histologic section in transverse plane stained with Masson trichrome technique, with a magnification of the location of the left phrenic nerve (LPN) in its anterior course. The LPN is adherent to the fibrous pericardium related to the high anterior left ventricular wall, left main coronary artery, and great cardiac vein. Ao = aorta; GCV = great cardiac vein; LAA = left atrial appendage; LCA = left main coronary artery; Pa = pericardiophrenic artery; Pv = pericardiophrenic vein.

to the epicardium of the high inferolateral left ventricular wall and inferior left ventricular vein. Along this course, its descent in the left hilum was anterior to the pulmonary veins, especially the superior vein where the minimal distance was 9.3 ± 2.5 mm. The minimal distances (and ranges) between the LPN and cardiac structures are listed in Table 1.

Discussion

LPN injury

Among cardiovascular surgeons, phrenic nerve injury is a known complication of myocardial hypothermia due to ice slush during cardioplegic arrest. Recovery has been observed in 90% of cases.[8] LPN stimulation also is a well-recognized complication after cardiac resynchronization

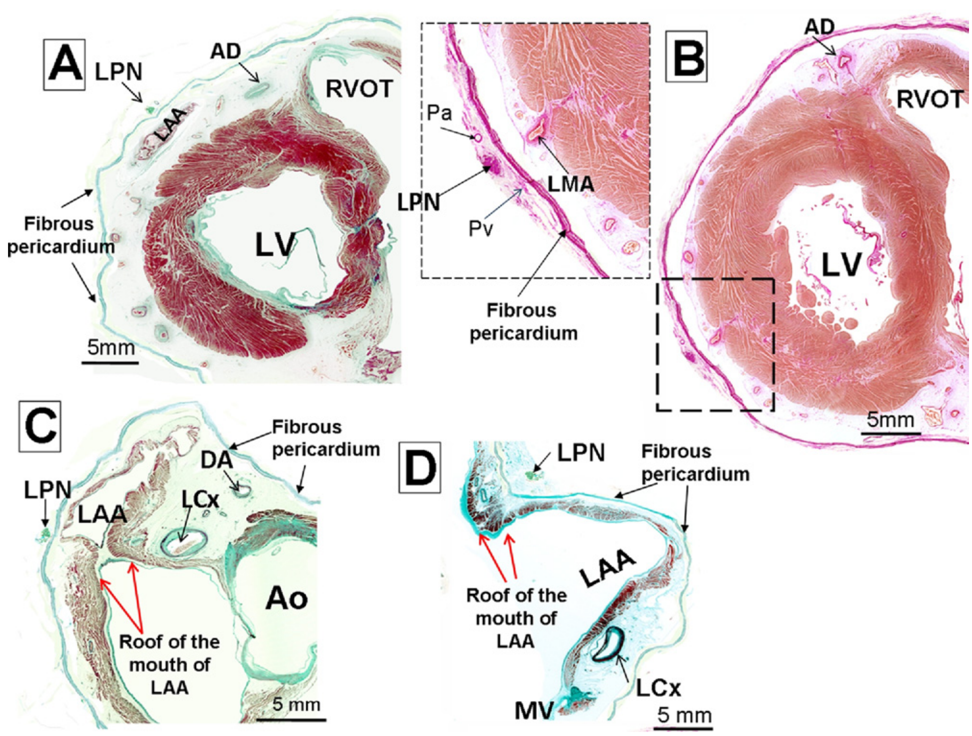

Figure 3 **A, B:** Histologic sections in transverse plane from two hearts showing the lateral course of the left phrenic nerve (LPN) in relation to the tip of the left atrial appendage (LAA) **(A)** and left marginal artery (LMA) **(B)**. **C, D:** Histologic sections in transverse **(C)** and frontal **(D)** planes showing the LPN in relation to the roof of the mouth of the left atrial appendage when the LPN takes an inferior course. AD = anterior descending coronary artery; Ao = aorta; DA = Anterior descending coronary artery; LCx = left circumflex artery; LV = left ventricle; MV = mitral valve; Pa = pericardiophrenic artery; Pv = pericardiophrenic vein; RVOT = right ventricular outflow tract.

Table 1 Minimal distance from anterior, lateral, and inferior courses of the left phrenic nerve to various cardiac structures

	Minimal distance and range (mm)	
	Endocardium	Epicardium
LPN-RLAA (anterior course)	8.5 ± 1.5 (range 5.5–12.5)	5 ±1 (range 2.5–7.5)
LPN-RLAA (lateral course)	7.3 ± 1.5 (range 4.5–10.5)	4 ± 1 (range 2.5–5.5)
LPN-RLAA (inferior course)	5.5 ± 1.5 (range 3.5–7.5)	3 ± 1 (range 1.5–5.5)
LPN-ALAA (anterior course)	7 ± 1.5 (range 3.5–9.5)	4.5 ± 1.5 (range 2–6)
LPN-ALAA (lateral course)	5 ± 1.5 (range 2.5–7.5)	2.5 ± 1 (range 1.5–4.5)
LPN-ALAA (inferior course)	6 ± 1.5 (range 3.5–8.5)	3.5 ± 1 (range 2–5)
LPN-RVOT (anterior course)	10.5 ± 2 (range 7–13)	6 ± 1.5 (range 5–8)
LPN-HLVW (anterior course)	—	3.5 ± 0.5 (range 2.5–5.5)
LPN-HLVW (lateral course)	—	2.3 ± 0.5 (range 1.5–5)
LPN-HLVW (inferior course)	—	2 ± 0.5 (range 1.5–4.5)

ALAA = apex of left atrial appendage; HLVW = high left ventricular wall; LPN = left phrenic nerve; RLAA = roof of left atrial appendage; RVOT = right ventricular outflow tract.

therapy using left ventricular veins.[9,10] Although the variable thickness of the fat pad around the pericardiophrenic neurovascular bundle and the fibrous pericardium may provide some protection when intervening in the pericardial space, the distances from some cardiac structures still are relatively small. For example, the LPN passed <3 mm from the left marginal vein in 43% of postmortem heart specimens studied previously.[1] In patients with nonischemic cardiomyopathy and ventricular tachycardia, a common target area is the lateral left ventricular wall. A report by Fan et al[11] mapped the LPN close to this area, thus highlighting the importance of identifying its course prior to carrying out epicardial ablations.

We previously described two patterns of distribution of the LPN where it either descended along a path related to the anterior surface of the left ventricle or passed leftward along a course related to the obtuse margin of the left ventricle.[1] On closer examination, the second pattern had two variants depending on whether the nerve coursed to the lateral margin of the left ventricle or, less commonly, veered more posterolaterally and inferiorly over the surface of the left ventricle (Figures 1B and 1C). Notably, the first report of occurrence of LPN injury during catheter ablation concerned a patient who had undergone ablation of a left posterolateral accessory pathway.[12]

LPN and epicardial or endocardial roof of the mouth of the LAA

The LAA is one of the major sources of focal atrial tachycardias.[5] In an article describing 50 foci of atrial tachycardias originating from the left atrium, 13 were at the base of the LAA.[13] However, LPN injury can occur during radiofrequency delivery at the proximal roof of the appendage, as reported in two patients.[4] In 23% of our specimens, the LPN coursed over the roof of the neck of the appendage.

Use of a nonradiofrequency source of energy seems unlikely to prevent this complication, as phrenic nerve injury has been reported with ultrasound,[4,14,15] laser,[13,15] and cryotherapy.[8,16,17] The phrenic nerve is vulnerable to heat as well as to cold. It can be injured by a variety of catheters sizes/types (standard 4 mm, 8 mm, 4-mm irrigated tip, balloon). However, the balloon or cryoballoon design appears more prone to cause phrenic nerve injury.[14,18,19] Using 64-slice multidetector computed tomography, Matsumoto et al[20] identified the LPN in 78 (74%) of 106 patients and noted that it crossed the LAA (72 [91%] patients). Our study showed that, after the LPN passed over the LAA, its relationship to the left heart structures depended on whether it descended along a path posteroinferiorly (5 [23%] specimens) or along a lateral path (13 [59%] specimens). In the first variant, the nerve passed close to the roof of the mouth of the LAA (Figures 3C and 3D) at a distance <4 mm to the endocardium and <2 mm to the epicardium in 2 (40%) of the 5 specimens. In the remaining specimens, the minimal distances between the LPN and the roof of the LAA were greater (Table 1).

LPN and epicardial or endocardial surfaces at the apex of the atrial appendage and left ventricular wall

In terms of proximity to endocardium or epicardium of the tip of the LAA, the nerve passed close by in 5 (23%) specimens where its distance to the endocardium was <4 mm, and in 7 (31%) specimens its distance to the epicardium was <2.5 mm.

Epicardial catheter ablation is increasingly important in the treatment of ventricular arrhythmias.[21] LPN injury is a recognized complication after radiofrequency delivery to the posterolateral left ventricular epicardium at the level of the mitral valve annulus.[14] Although pace mapping can identify sites close to the phrenic nerve so as to avoid ablations in its vicinity, no specific approaches to prevent phrenic nerve injury during catheter ablation have been described. The course of the LPN along the basal border of the left ventricle is variable. In 2 (9%) specimens, the nerve was located <4 mm from the high anterior left ventricular wall and left main coronary artery. In 8 (36%) specimens, the nerve was located <3 mm to the epicardium of the obtuse margin of the left ventricular wall, and in 2 (9%) specimens it was located <3 mm to the epicardium of the high inferolateral left ventricular wall and inferior left ventricular vein. Electroanatomic maps can incorporate tags at these sites to help the operator avoid the LPN.

LPN and epicardial or endocardial surfaces of the high right ventricular outflow tract

The right ventricular outflow tract is a common target for ablation of focal ventricular tachycardia.[22] Little is known about the spatial relationship between the LPN and the right ventricular outlet. Our study showed that when the LPN takes an anterior course, it likely will pass over the lateral margin of the high right ventricular outflow tract. In two of our specimens, the LPN was <6 mm from the epicardial surface.

Although not seen in the present series, the LAA can be elongated in some hearts, and its tip portion overlaps the right ventricular outlet (S.Y. Ho, unpublished data). When the LPN takes an anterior course in such cases, ablations at the tip of the appendage may place the LPN at risk for injury. On the other hand, the overlying appendage can provide some protection for the LPN when ablating inside the outflow tract region.

Study limitations

Despite the obvious limitations associated with using cadaveric material for obtaining measurements (shrinkage and change of the elastic properties of the tissues) in a small series, we believe the spatial relationships are valid because the LPN travels in the fibrous pericardium, which forms a cover that supports the nerve. We hope our observations will engender interest among other researchers for investigations in much larger series.

Conclusion

Although imaging techniques such as 64-slice multidetector computed tomography enable adequate detection of the LPN in relation to cardiac anatomy,[20] information on the distances between structures remains scarce. This study highlighted the variable courses of the LPN and showed that, in some cases, the LPN can be extremely close to cardiac structures that commonly are ablated.

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