



REVIEW

Phrenic Nerve Injury During Ablation of Atrial Fibrillation: Mechanisms, Clinical Features, Prognosis, and Prevention Methods

Xinmeng Liu, MD^{1,2}, Rong Lin, MD³, Xiaodong Peng, MD^{1,2}, Xuesi Wang, MD^{1,2}, Yukun Li, MD^{1,2}, Fanchao Meng, MD^{1,2}, Yanfei Ruan, MD^{1,2} and Nian Liu, MD^{1,2}

¹Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

²National Clinical Research Center for Cardiovascular Diseases, Beijing, China

³North China Medical & Health Group Xingtai General Hospital, Xingtai, China

Received: 4 March 2023; Revised: 1 June 2023; Accepted: 20 June 2023

Abstract

Atrial fibrillation ablation procedures have become a focus of research among electrophysiologists, with the aim of increasing success rates while minimizing complications. One major concern is phrenic nerve injury (PNI). Despite advancements in ablation strategies, equipment, and monitoring methods, the incidence of PNI during these procedures remains substantial, particularly during cryoballoon ablation, which has a reported PNI incidence of 3.5%. This review examines recent studies, to provide a comprehensive overview of PNI mechanisms, clinical features, prognosis, and methods for prevention during ablation.

Keywords: phrenic nerve injury; atrial fibrillation; catheter ablation

Introduction

Atrial fibrillation (AF) ablation is a widely accepted therapeutic option for patients with symptomatic and drug-resistant AF. However, this procedure can lead to complications that may adversely affect patient prognosis, such as esophageal injury and pulmonary vein stenosis. One major complication warranting attention is phrenic nerve injury (PNI), because its incidence has not decreased despite advances in ablation techniques, equipment, and monitoring methods [1]. This comprehensive

review is aimed at providing detailed insights into PNI during AF ablation procedures, including its underlying mechanisms, clinical presentation, PNI characteristics, prognostic differences among different ablation modalities, and available prevention and treatment methods.

Anatomy of the Phrenic Nerve

The phrenic nerve, a branch of the cervical plexus, originates from the anterior branch of cervical nerves 3–5. It descends along the anterior scalene muscle and enters the thoracic cavity through the superior thoracic orifice between the subclavian arteries and veins.

Correspondence: Nian Liu and Yanfei Ruan,

E-mail: liunian1973@hotmail.com; ruanyanfei@hotmail.com

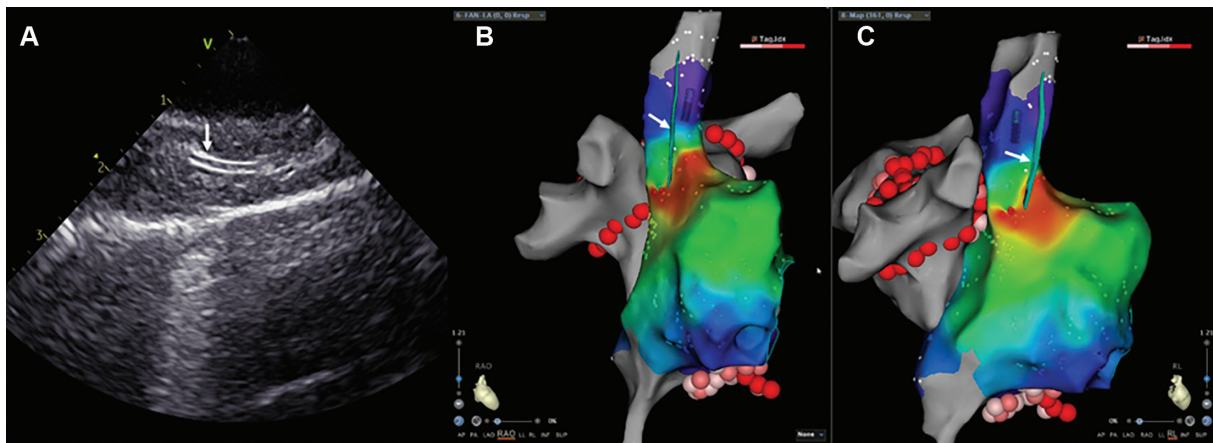


Figure 1 ICE Image of the RPN and 3D Activation Map.

The RPN is observed as a thin, round structure with a straw-like appearance, that is hypoechoic in the central region and hyperchoic in the periphery between the mediastinal pleura and the SVC (Figure 1A). The anatomical distance from the RPN to the sinus node and the RSPV is quite small in the 3D activation map of the RA and SVC in the right anterior oblique (Figure 1B) and right lateral (Figure 1C) views. The arrow indicates the RPN.

The right phrenic nerve (RPN) travels along the right innominate vein, superior vena cava (SVC), and right atrium before reaching the diaphragm. Autopsies have indicated that the RPN is anatomically closely associated with the SVC and the right superior pulmonary vein (RSPV): the distance between the RPN and SVC is only $0.3 \text{ mm} \pm 0.5 \text{ mm}$, and that between the RPN and RSPV is $2.2 \text{ mm} \pm 0.4 \text{ mm}$ [2]. Our recent study has confirmed this close relationship among the SVC, RSPV, and RPN in vivo, through integrated intracardiac echocardiography (ICE) images of the RPN and electroanatomical images of the SVC (Figure 1). That study provided the first in vivo examination of the distances between the RPN and SVC (minimum $1.0 \pm 0.4 \text{ mm}$) and RSPV (minimum $14.1 \pm 7.3 \text{ mm}$). Because of this anatomical proximity, the RPN is at high risk of injury during catheter ablation procedures aimed at isolating the SVC or ablating the RSPV [3, 4].

The left phrenic nerve (LPN) travels anterolaterally to the aortic arch and pulmonary trunk, then descends along the fibrous pericardium surface, between the mediastinal pleura of the left lung and the lateral surface of the left ventricle. A study by Sánchez-Quintana et al. on 22 human cadavers has revealed three routes that the LPN can take through the left heart: the (1) anterior route, (2) lateral route, and (3) inferior lateral route [5]. That study has indicated that 59% of LPNs follow a lateral course, whereas 23% follow an inferior path, and the LPNs

are closely associated with the left atrial appendage in both paths. This finding is consistent with those from clinical studies linking left-sided PNI to the isolation of the left atrial appendage.

Overall, the anatomical connections of the RPN to the RSPV and SVC, and of the LPN to the left atrial appendage are closely associated with the risk of PNI in multiple AF ablation procedures.

Symptoms and Categories of PNI

PNI is usually associated with ablation procedures performed on the SVC, RSPV, and left auricle. PNI is more frequently observed in the RPN than the LPN [6, 7]. The symptoms of PNI are highly variable, ranging from asymptomatic diaphragmatic elevation in mild cases to a need for mechanical ventilation in severe cases. Typical symptoms and signs include dyspnea (particularly in the supine position), chest pain, hiccups, abdominal breathing, and tachypnea. On the basis of the stage of injury to the phrenic nerve, PNI can be divided into three categories, as shown in Table 1 [8].

Characteristics of PNI in Different Ablation Procedures

The incidence and outcomes of PNI differ among ablation procedures, and cryoablation is associated with a higher PNI incidence than other methods.

Table 1 The Three Types of PNI and their Characteristics.

PNI type	Characteristics
Impending PNI	More than 30% decrease in CMAP of the phrenic nerve without a decrease in diaphragmatic movement
Transient PNI	Progressive decrease in diaphragmatic movement, as confirmed by X-ray fluoroscopy or manual palpation, which can recover before the end of the procedure
Persistent PNI	Long-lasting injury evident on postoperative radiography and persisting after the procedure

Table 2 summarizes the characteristics of PNI in different ablation procedures.

Cryoballoon Ablation

The PNI during cryoballoon ablation (CBA) varies among cryoballoon generations. The first-generation cryoballoon had limitations that were improved in the second generation. The second-generation cryoballoon has a larger and more evenly spaced freezing zone on the distal hemisphere, thereby improving procedural outcomes such as isolation success rates, and decreasing the mean procedure time and fluoroscopy time. However, the second-generation cryoballoon is associated with a higher PNI rate than the first-generation cryoballoon, a known CBA complication [9–11]. The incidence of PNI with the second-generation cryoballoon has been reported to be in the range of 3.5%–11.2% in initial studies, but as operators became more

experienced with the device, and early detection of PNI improved, the incidence of PNI decreased to approximately 4.2%–6.2% [12–15].

The third-generation cryoballoon has a shorter distal tip length (8 mm) and closer proximal placement of the spiral mapping catheter within the muscular sleeve of the pulmonary vein, thereby improving the visualization of real-time recordings in the pulmonary veins [16]. A study by Aryana et al. has indicated no difference in persistent PNI between the third- and second-generation balloons [17]. The fourth-generation cryoballoon extends the third-generation design and uses the same spaced freezing zone as the second-generation. Although the median procedure time and average freeze duration for fourth-generation balloon pulmonary vein isolation are significantly shorter than those for second-generation balloons, no statistically significant difference in PNI has been observed between generations [18, 19].

Table 2 Characteristics of PNI in Different Ablation Types.

	Incidence	Outcome	Prevention
Cryoballoon ablation	4.2%–6.2%	<ul style="list-style-type: none"> • Most (97%) PNI recovered within 12 months. 	<ul style="list-style-type: none"> • Acquiring the high-risk predictors of PNI • Monitor phrenic nerve function • Avoid deep seating of the cryoballoon to the RSPV • Minimize cryoablation duration
Laser ballooning	1.5%	<ul style="list-style-type: none"> • Similar recovery rates from persistent PNI were observed at 6 months with CBA, but a much lower recovery rate was observed at 6–12 months with CBA. 	<ul style="list-style-type: none"> • Acquiring the high-risk predictors of PNI • Monitor phrenic nerve function
Radiofrequency ablation	0.11%–0.48%	<ul style="list-style-type: none"> • Most patients (66%) showed complete recovery, whereas 17% showed partial recovery. 	<ul style="list-style-type: none"> • Acquiring the high-risk predictors of PNI • Monitor phrenic nerve function
Thoracoscopic atrial fibrillation ablation	1.25%	<ul style="list-style-type: none"> • A total of 28.6% of patients did not recover from PNI after thoracoscopic ablation. 	<ul style="list-style-type: none"> • Acquiring the high-risk predictors of PNI • Monitor phrenic nerve function
Pulsed field ablation	Not clear	<ul style="list-style-type: none"> • No evidence of PNI has been found in animal studies. • Large sample data are lacking. 	Not clear

The incidence of PNI resulting from CBA of the pulmonary veins for the treatment of AF can vary according to several factors. One such factor is the type of pulmonary vein isolation: a higher incidence of PNI is observed in right superior pulmonary vein isolation (RSPVI) than right inferior pulmonary vein isolation (RIPVI). The incidence of PNI during RSPVI and RIPVI has been reported to be 5.5% and 0.7%, respectively, in 2018 by Miyazaki et al., and to be 3.9% and 1.8%, respectively, in 2021 by Tokuda et al. [8, 20]. The higher PNI incidence for RSPVI can be explained anatomically, because the phrenic nerve was found to be closer to the RSPV than the RIPV in an autopsy study ($2.1 \text{ mm} \pm 0.4 \text{ mm}$ and $7.8 \text{ mm} \pm 1.2 \text{ mm}$, respectively). In addition, no significant difference in recovery time from PNI has been observed between patients undergoing RSPVI versus RIPVI.

Most cases of PNI recover within a year after ablation, but persistent PNI can occur in 0.3%–0.6% of patients. In 2022, Heeger et al. reported that 97% of PNI cases recover within 12 months, 98.7% of patients recover from PNI, and only 0.3% have persistent symptoms. The authors have established a YETI score using five significant predictors to predict a patient's probability of recovery from PNI within 12 months: age, low temperature at the time of PNI, use of a bonus freezing protocol, use of a double-stop technique at the time of PNI, and CMAP amplitude loss $>30\%$ [15].

The following steps can be taken to avoid PNI during CBA:

1. Avoiding deep seating of the cryoballoon to the RSPV: During ablation, avoiding deep seating of the cryoballoon to the RSPV is essential, because the phrenic nerve travels anteriorly in the distal right pulmonary vein, and deeper placement increases the risk of PNI [21].
2. Minimizing cryoablation duration: Marleen et al. have reported that the incidence of PNI in patients with short, moderate, and long CBA times is 1.7%, 6.5%, and 6.8%, respectively ($P < 0.001$), thus suggesting that shortening the cryoablation duration can decrease the incidence of PNI [22]. The study has also indicated that cryoablation times shorter than 2 minutes affect success rate for the left pulmonary vein isolation but not the right pulmonary vein isolation during

CBA. Therefore, prolonging the cryoballoon application duration to improve efficacy rates for the pulmonary vein on the right side is not recommended. Instead, a tailored approach with shorter ablation times might maintain similar efficacy rates while decreasing complications.

Laser Balloon Ablation

Laser balloon ablation (LBA) is a technique in which laser energy is concentrated to create lesions in the heart, similarly to radiofrequency ablation (RFA). A study by Tohoku et al. has reported a lower incidence of PNI with LBA than CBA, with probabilities of 1.5% and 4.2%, respectively [23]. However, the study found no significant difference in the incidence of persistent PNI between groups. The difference in energy transfer and lesion formation between techniques is believed to contribute to the higher incidence of PNI in CBA. CBA delivers cryogenic energy directly to the endocardial tissue in contact, thus resulting in homogeneous lesion formation. The catheter-pushing maneuver performed during CBA decreases the distance between the balloon surface and the phrenic nerve, thereby increasing the risk of PNI. In contrast, LBA creates linear lesions under endoscopic guidance and has the advantage of visual guidance, thus allowing the operator to adjust the depth of the energy titration point. These differences in ablation technique may lead to more frequent PNP in patients undergoing CBA. If PNI does occur in LBA, it tends to be persistent, and a long time may be necessary to recover, because of several factors. First, cryoballoon requires a certain time phase, typically 180–240 seconds, to reach a minimum temperature plateau and achieve lesion formation, during which the procedure can be terminated if signs of PNI are detected. In contrast, energy transfer during LBA can be achieved locally within 20 seconds, and the tissue temperature can be maintained for more than 10 seconds after the ablation. The phrenic nerve has been shown to recover its function when the tissue temperature returns to normal. However, PNI under LBA than in cryoballoon may be more difficult to recover from, because of the lower temperature difference between the tissue and blood in LBA.

Radiofrequency Ablation

In RFA for atrial fibrillation, the incidence of PNI has been reported to range from 0.11% to 0.48% [24]. The incidence of PNI in RFA is generally lower than that in CBA. Maltoni et al., in 2018, found a significantly lower incidence of PNI in RFA than in CBA (risk ratio 5.43, 95%); however, radiofrequency ablation is associated with a higher incidence of other cardiovascular complications, such as pericardial effusion and cardiac tamponade. No significant difference between RFA and CBA has been observed regarding atrial fibrillation recurrence [25]. However, the incidence of transient PNI is lower with RFA than CBA. Nonetheless, no significant difference between techniques has been reported in the case of permanent PNI [26].

Regarding PNI recovery, most patients (66%) who experience PNI during RFA achieve complete recovery, whereas 17% achieve partial recovery. Real-time monitoring of phrenic nerve function (e.g., fluoroscopic diaphragmatic movements, palpation of diaphragmatic movements or recording of CMAP) is used during RFA to minimize the risk of PNI. If PNI is detected during the procedure, RFA should be immediately stopped.

Thoracoscopic Atrial Fibrillation Ablation

A study examining the safety and effectiveness of a combined thoracoscopic endocardial epicardial technique for treating AF has found no cases of PNI in a group of 78 consecutive patients treated with this method between 2009 and 2012. This lack of PNI risk may be attributable to the protective measures taken by surgeons during the procedure. For instance, surgeons are cautious to maintain a distance of at least 2.5–3 cm from the phrenic nerve when opening the pericardium, thereby minimizing the occurrence of PNI after surgery [27, 28]. However, these findings must be confirmed by further larger studies. According to the Netherlands Heart Registration data from 9549 atrial fibrillation ablations in 2022, the incidence of PNI was lowest in patients treated with conventional RF (0.07%) and higher in those treated with cryoballoons (1.41%) and thoracoscopic ablation (1.25%). PNI during thoracoscopic ablation is also associated

with manipulating ablation and endoscopic tools or blunt trauma caused by traction of the pericardial cradles [29]. All patients treated with RF recovered PNI within 180 days, whereas only 41.9% of cryoballoon patients and 42.9% of patients undergoing thoracoscopic ablation recovered within 180 days. No recovery from PNI was observed in 28.6% of patients after thoracoscopic ablation and 32.3% of patients after cryoballoon procedures.

Pulsed Field Ablation

Pulsed field ablation (PFA) is a new ablation method that uses pulsed electric fields instead of thermal energy for energy delivery. PFA uses subsecond electric fields to create microscopic pores in cell membranes, in a process known as electroporation. Cardiomyocytes have low thresholds to these fields and consequently are more sensitive than other cell types. This myocardial sensitivity in PFA may help minimize collateral damage to non-target tissues, such as the esophagus, blood vessels, and nerves. Animal studies have shown no evidence of accidental PNI with pulsed ablation. Results from three clinical trials on 121 patients with persistent atrial fibrillation (IMPULSE, PEFCAT, and PEFCAT II) have found no indication of esophageal injury or phrenic neuropathy after ablation [30]. However, Pansera et al. have reported three cases of transient PNI during pulmonary vein isolation with PFA [31]. The PNI lasted less than 1 minute, and all cases were spontaneous and showed complete recovery. The authors have suggested that the transient nerve dysfunction might have been caused by hyperpolarization of the nerve or the effects of irreversible electroporation on the motoric endplate. Although the results of PFA show good efficacy and safety, they do not demonstrate the superiority of PFA over other techniques. Further large-scale prospective studies are needed to directly compare the differences between PFA and other methods.

Prevention of PNI

Phrenic Nerve Imaging by Computed Tomography

Computed tomography (CT) imaging of the phrenic nerve has been shown to be useful in predicting PNI

before an operation. Matsumoto et al. first demonstrated that the phrenic nerve and its relationship to cardiac anatomy can be visualized with 64-slice CT [32]. They have suggested that such imaging may help avoid PNI before surgery. Ichihara et al. have reported that a distance of 12.4 mm between the RSPV ostium and right peri-cardiophrenic bundles is the optimal cutoff to prevent RPN injury [33]. Strökeret et al. have found that an RSPV-left atrial angle greater than 141° and an RSPV area larger than 275 mm^2 also predict PNI [34]. Miyazaki et al. have determined that the optimal threshold values for coronal and horizontal RSPV diameters to predict PNI are 18.2 mm and 16.3 mm, respectively [20]. Maj et al. have reported that a carina width of 8.5 mm is the optimal cutoff point for predicting PNI during both right-sided pulmonary vein applications [35].

Despite the ability to predict PNI with these metrics, CT imaging is not currently used in clinical settings, because of concerns over increased radiation exposure and lower detection rates (LPN: 74%–86.8%; RPN: 47%–51.2%) [32, 36]. A summary of the anatomical predictors of PNI in CT and their sensitivities and specificities is provided in Table 3.

Fluoroscopy and Palpation of the Diaphragm

PNI can be diagnosed during phrenic nerve pacing by continuous or intermittent fluoroscopy of the right hemidiaphragm. This method is used to observe diminished diaphragmatic excursions and is considered accurate, but it exposes both operators and patients to radiation. To minimize radiation exposure, the more commonly used method is palpation of the intensity of the diaphragmatic excursion below the rib cage. Reduced contractile

movements of the diaphragm may indicate PNI. Although this method is simple and widely used, it can be influenced by respiratory factors. Both fluoroscopy and palpation are considered gold standards for detecting PNI. However, these methods were not the first methods used for this purpose.

Diaphragmatic Compound Motor Action Potential

Diaphragmatic compound motor action potential (CMAP) is a valuable tool for early detection of PNI. To record CMAP, two EKG electrodes are placed 5 cm above the xiphoid and along the right rib margin. CMAP amplitude is measured from peak to peak when the phrenic nerve is captured, and is compared with the baseline. A 35% decrease in CMAP amplitude predicts and prevents PNI [37]. On average, palpable PNI occurs 59 seconds after the decrease in CMAP amplitude, thus highlighting the early identification capability of this method. CMAP amplitude also predicts PNI recovery time: a cutoff value of 0.20 mV indicates recovery after 2 days, with a sensitivity of 57.1% and specificity of 100% [19]. However, PNI can occur in 0.6% of cases without a decrease in CMAP amplitude [7]. Another method to prevent PNI uses a quadripolar catheter in the right hepatic vein to record diaphragmatic CMAP amplitude during phrenic nerve pacing. This method eliminates the variation caused by respiratory movements and surface electrode habituation, particularly in patients with CMAP amplitudes below 0.2 mV. A $\geq 30\%$ decrease in CMAP amplitude from baseline indicates PNI. Therefore, recording of CMAP amplitude with body surface electrodes and monitoring with a hepatic vein quadripolar catheter can help prevent PNI.

Table 3 Anatomical Predictors of PNI in CT.

Indicator	Cutoff point	Sensitivity	Specificity
Distance between the RSPV ostium and right peri-cardiophrenic bundles	12.4 mm	96.6%	88.9%
RSPV-left atrial angle	141°	91%	85%
RSPV area	275 mm^2	88%	85%
Coronal RSPV diameters	18.2 mm	73.3%	60.0%
Horizontal RSPV diameters	16.3 mm	46.7%	78.1%
Carina width	8.5 mm	87.3%	75.0%

Intracardiac Echocardiography

ICE allows for continuous visualization of the motion of the liver and its capsule, and provides additional indirect imaging of the contraction of the diaphragm during phrenic nerve pacing. By placing the ICE transducer at the diaphragm level and directing it toward the liver, decreased liver motion can be observed, according to decreased diaphragmatic motion after phrenic nerve stimulation (PNI) [38]. ICE conveniently enables continuous, direct visualization of the diaphragm without fluoroscopy, thus substantially decreasing radiation exposure to patients and operators. Our recent study has demonstrated that ICE can visualize the RPN in 92% of patients [4]. The nerve appears as a straw-like structure running through the space between the superior vena cava and the mediastinal pleura (Figure 1). Thus, ICE provides a new way to observe the phrenic nerve in real time during atrial fibrillation ablation. In that study, SVC isolation was performed with the guidance of ICE, and no cases of PNI were found. However, further controlled clinical studies are needed to determine the superiority of ICE for mapping and visualizing the phrenic nerve compared with pacing techniques or CMAP.

Fetal Heart Rate Monitoring

To detect changes in the pitch of diaphragmatic contractions, an external Doppler fetal heart monitor is positioned on the right side of the costal margin. This monitor uses the Doppler effect to create an acoustic representation of the diaphragmatic contractions. As the strength of the diaphragmatic contraction decreases during phrenic nerve pacing, a noticeable change in tone can be detected. The fetal heart monitor can provide auditory signals for physicians and healthcare personnel conducting PNI assessment [39].

Modified Neonatal Blood Pressure Cuff

A modified neonatal blood pressure cuff consisting of a water-filled neonatal cuff attached to the right costal margin via a Velcro band on the chest and connected to a pressure transducer, is used to assess diaphragmatic contractility. The cuff is placed on the abdominal surface to record the pressure

signal generated by the diaphragm's contraction. MacVeigh et al. have found that the amplitude of the diaphragmatic pressure signal varies with the amplitude of the pacing stimulus during phrenic nerve pacing [40]. As the pacing stimulus amplitude decreases, the pressure signal amplitude decreases gradually. A strong correlation exists between the strength of diaphragmatic contraction, as assessed by X-ray fluoroscopy, abdominal palpation, and diaphragmatic pressure signals. This approach has the advantage of decreasing exposure to radiation and the need for operator assistance, and it is also a method for monitoring phrenic nerve function.

Femoral Vein Pressure Waveform

During the balloon cryoablation procedure, venous access is obtained from the left and right femoral veins. A saline-flushed pressure tube is connected to the left femoral vein sheath, and is followed by a standard pressure transducer, thus enabling the vein pressure waveform (VPW) to be displayed and recorded. The peak-to-peak amplitude of the VPW is measured at the start and end of each ablation pacing of the phrenic nerve. Ghosh et al. have observed a 50% decrease in the baseline peak-to-peak venous waveform amplitude after withdrawal of radiofrequency ablation. This method identifies phrenic nerve injury an average of 28 seconds earlier than conventional palpation methods [41]. The application of the VPW provides more effective assessment of phrenic nerve function than the standard technique of diaphragm palpation. Its equipment is affordable and readily available, thereby allowing for repeatable, multi-observer evaluation of phrenic nerve function and monitoring of left-sided phrenic nerve function. However, the proposed 50% decrease in VPW amplitude as a threshold for identifying impending PNI is based on retrospective observational data and requires further validation in prospective clinical use.

In conclusion, the various techniques used to prevent PNI each have strengths and weaknesses, and most experts recommend using a combination of at least two methods to decrease the incidence of PNI. Although traditional methods such as fluoroscopy and diaphragmatic palpation are commonly used, they have limitations, such as substantial radiation exposure and a lack of early PNI detection. Newer

techniques, such as ICE, show promise in preventing PNI, but further research with larger sample sizes is needed to validate their effectiveness. Table 4 summarizes the various methods and their advantages and disadvantages.

Treatment of PNI

Continuous positive pressure ventilation and surgical intervention (diaphragm plication or diaphragm pacing) are recommended for patients with severe and persistent phrenic nerve injury causing respiratory distress. However, continuous mechanical ventilation until phrenic nerve function is restored may carry a risk of complications, such as lung infection; moreover, the likelihood of recovery of diaphragmatic function in the early postoperative period is low. Surgical intervention decreases the associated complications and hospital lengths of stay. However, the timing of surgery remains controversial, and these surgical treatments have varying efficacy and may not be appropriate for all patients. In some cases, physical therapy can help improve the strength and function of the diaphragm, mainly if the injury is mild or early. Therapists can work with patients to help them regain their breathing through exercises targeting the diaphragm. Patients with PNI must work closely with their healthcare

providers to develop a treatment plan that addresses their needs and goals. Treatments may involve a combination of medical and surgical treatments and lifestyle modifications, such as changes to the diet and exercise routine, to help improve breathing and overall health. The PNI treatment modalities and their corresponding indications, advantages and disadvantages are shown in Table 5.

Conclusion

PNI is a well-known complication of ablation procedures, and the incidence of PNI varies among ablation procedures. The cause of PNI is often associated with the phrenic nerve anatomy.

Symptoms of PNI exhibit a wide range of variability, ranging from mild cases with asymptomatic diaphragmatic elevation to severe cases requiring mechanical ventilation. Despite the differences in ablation procedures and the incidence of PNI, most cases of PNI recover [29]. Early detection of PNI is crucial for avoiding injury and facilitating early repair of the PNI [42–44]. Many techniques have been used to prevent PNI during the procedure, such as fluoroscopy or visualizing the diaphragm with X-rays. However, these methods have drawbacks such as exposure to radiation and the influence of respiratory changes. The ICE technique, a relatively

Table 4 Methods of Preventing PNI and their Advantages and Disadvantages.

Method	Advantages	Disadvantages
Computed tomography	<ul style="list-style-type: none"> • Localization of the phrenic nerve • Prediction of the risk of PNI with different indicators 	<ul style="list-style-type: none"> • Radiation exposure • Low detection rate
Fluoroscopy and palpation of the diaphragm	<ul style="list-style-type: none"> • Effective observation of diaphragmatic movements 	<ul style="list-style-type: none"> • Fluoroscopy: radiation exposure for the patient and operator • No early prediction of PNI
Diaphragmatic compound motor action potential	<ul style="list-style-type: none"> • Early prediction of PNI • Prediction of the length of PNI recovery time 	<ul style="list-style-type: none"> • Influenced by respiratory changes or anesthetic drugs • Need for accurate baseline amplitude
Intracardiac echocardiography	<ul style="list-style-type: none"> • Visualization of the RPN in real time • High detection rate • Minimal radiation exposure 	<ul style="list-style-type: none"> • Additional venous access required • Validation in large samples required
Fetal heart rate monitor	<ul style="list-style-type: none"> • Potential early prediction of PNI • Minimal radiation exposure 	<ul style="list-style-type: none"> • Difficulty in recording for obese patients • Validation in large samples required
Modified neonatal blood pressure cuff	<ul style="list-style-type: none"> • No radiation exposure 	<ul style="list-style-type: none"> • Special blood pressure cuff required • Validation in large samples required
Femoral vein pressure waveform	<ul style="list-style-type: none"> • No radiation exposure • Potential early prediction of PNI 	<ul style="list-style-type: none"> • Validation in large samples required

Table 5 PNI Treatment Modalities and their Corresponding Indications, Advantages, and Disadvantages.

Treatment	Indication	Advantages	Disadvantages
Physical therapy	• Impending or transient PNI	• Easy and simple operation	• Efficacy not demonstrated in large populations
Continuation of mechanical ventilation	• Respiratory insufficiency	• No other surgical intervention required	• Risk of complications such as pulmonary infections
Surgical intervention	• Confirmed diaphragmatic paralysis and respiratory insufficiency	• Diminished risk of pulmonary infection • Shortened hospital stay • Extubation soon after the procedure	• Inability to determine discharge time • Controversial timing of surgery • Varying efficacy of these surgical treatments • May not be appropriate for all patients

new approach, has been explored for preventing PNI injury and offers an advantage of real-time monitoring of RPN function. However, similarly to fetal heart rate monitors, modified neonatal blood pressure cuffs, and VPW techniques, its application is currently restricted. Large-scale studies are required to ascertain the efficacy of preventing PNI in the future. Treatments vary according to the degree of PNI, and include continuous physical therapy, positive pressure ventilation, and surgical intervention.

Data Availability Statement

Data availability is not applicable to this article, because no new data were created or analyzed in this study.

Conflict of Interest

The authors declare no conflicts of interest.

Ethics Statement

Not applicable.

Author Contributions

All authors jointly developed the research idea. Ximeng Liu drafted the initial manuscript, and the other authors contributed edits and enhancements to the final version. All authors actively participated in the article's development and unanimously approved the submitted version.

Funding or Acknowledgments

This work received support from the National Science Foundation of China through grant Nos. 81870244, 82170318, and 81770318, as well as from the Beijing Municipal Science and Technology Commission (Z181100001718174).

REFERENCES

1. Abugattas JP, de Asmundis C, Iacopino S, Salghetti F, Takarada K, Coutiño HE, et al. Phrenic nerve injury during right inferior pulmonary vein ablation with the second-generation cryoballoon: clinical, procedural, and anatomical characteristics. *Europace* 2018;20(10): 1–8.
2. Sánchez-Quintana D, Cabrera JA, Climent V, Farré J, Weiglein A, Ho SY, et al. How close are the phrenic nerves to cardiac structures? Implications for cardiac interventionalists. *J Cardiovasc Electrophysiol* 2005;16(3):309–13.
3. Liu X, Lin R, Peng X, Wang X, Li Y, Liu X, et al. Visualization and mapping of the right phrenic nerve by intracardiac echocardiography during atrial fibrillation ablation. *EP Eur* 2023;25:1352–60.
4. Smith NM, Segars L, Kauffman T, Olinger AB. Using anatomical landmark to avoid phrenic nerve injury during balloon-based procedures in atrial fibrillation patients. *Surg Radiol Anat* 2017;39(12):1369–75.
5. Sánchez-Quintana D, Ho SY, Climent V, Murillo M, Cabrera JA. Anatomic evaluation of the left phrenic nerve relevant to epicardial and endocardial catheter ablation:

- implications for phrenic nerve injury. *Heart Rhythm* 2009;6(6):764–8.
6. Sacher F, Monahan KH, Thomas SP, Davidson N, Adragao P, Sanders P, et al. Phrenic nerve injury after atrial fibrillation catheter ablation: characterization and outcome in a multicenter study. *J Am Coll Cardiol* 2006;47(12):2498–503.
 7. Bai R, Patel D, Di Biase L, Fahmy TS, Kozeluhova M, Prasad S, et al. Phrenic nerve injury after catheter ablation: should we worry about this complication? *J Cardiovasc Electrophysiol* 2006;17(9):944–8.
 8. Tokuda M, Yamashita S, Sato H, Oseto H, Ikewaki H, Yokoyama M, et al. Long-term course of phrenic nerve injury after cryoballoon ablation of atrial fibrillation. *Sci Rep* 2021;11(1):6226.
 9. Liu J, Kaufmann J, Kriatselis C, Fleck E, Gerds-Li JH. Second generation of cryoballoons can improve efficiency of cryoablation for atrial fibrillation. *Pacing Clin Electrophysiol* 2015;38(1):129–35.
 10. Giovanni GD, Wauters K, Chierchia GB, Sieira J, Levinstein M, Conte G, et al. One-year follow-up after single procedure Cryoballoon ablation: a comparison between the first and second generation balloon. *J Cardiovasc Electrophysiol* 2014;25(8):834–9.
 11. Aytemir K, Gurses KM, Yalcin MU, Kocyigit D, Dural M, Evranos B, et al. Safety and efficacy outcomes in patients undergoing pulmonary vein isolation with second-generation cryoballoon†. *Europace* 2015;17(3):379–87.
 12. Guiot A, Savouré A, Godin B, Anselme F. Collateral nervous damages after cryoballoon pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2012;23(4):346–51.
 13. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol* 2013;61(16):1713–23.
 14. Metzner A, Rausch P, Lemes C, Reissmann B, Bardyszewski A, Tilz R, et al. The incidence of phrenic nerve injury during pulmonary vein isolation using the second-generation 28 mm cryoballoon. *J Cardiovasc Electrophysiol* 2014;25(5):466–70.
 15. Heeger CH, Sohns C, Pott A, Metzner A, Inaba O, Straube F, et al. Phrenic nerve injury during cryoballoon-based pulmonary vein isolation: results of the worldwide YETI registry. *Circ Arrhythm Electrophysiol* 2022;15(1):e010516.
 16. Pott A, Petscher K, Messemer M, Rottbauer W, Dahme T. Increased rate of observed real-time pulmonary vein isolation with third-generation short-tip cryoballoon. *J Interv Card Electrophysiol* 2016;47(3):333–9.
 17. Aryana A, Kowalski M, O'Neill PG, Koo CH, Lim HW, Khan A, et al. Catheter ablation using the third-generation cryoballoon provides an enhanced ability to assess time to pulmonary vein isolation facilitating the ablation strategy: Short- and long-term results of a multicenter study. *Heart Rhythm* 2016;13(12):2306–13.
 18. Wissner E. Ablation of atrial fibrillation using the fourth-generation cryoballoon Arctic Front Advance PRO. *Future Cardiol* 2021;17(1):81–7.
 19. Miyazaki S, Hasegawa K, Mukai M, Aoyama D, Nodera M, Shiomi Y, et al. The advantages and disadvantages of the novel fourth-generation cryoballoon as compared to the second-generation cryoballoon in the current short freeze strategy. *J Interv Card Electrophysiol* 2022;63(1):143–52.
 20. Miyazaki S, Kajiyama T, Watanabe T, Hada M, Yamao K, Kusa S, et al. Characteristics of phrenic nerve injury during pulmonary vein isolation using a 28-mm second-generation cryoballoon and short freeze strategy. *J Am Heart Assoc* 2018;7(7):e008249.
 21. Kulkarni N, Su W, Wu R. How to prevent, detect and manage complications caused by cryoballoon ablation of atrial fibrillation. *Arrhythm Electrophysiol Rev* 2018;7(1):18–23.
 22. Molenaar MMD, Timmermans CC, Hesselink T, Scholten MF, Ter Bekke RMA, Luermans JGLM, et al. Shorter cryoballoon applications times do effect efficacy but result in less phrenic nerve injury: results of the randomized 123 study. *Pacing Clin Electrophysiol* 2019;42(5):508–14.
 23. Tohoku S, Chen S, Last J, Bordignon S, Bologna F, Trolese L, et al. Phrenic nerve injury in atrial fibrillation ablation using balloon catheters: incidence, characteristics, and clinical recovery course. *J Cardiovasc Electrophysiol* 2020;31(8):1932–41.
 24. Bohnen M, Weber R, Minners J, Eichenlaub M, Jadidi A, Müller-Edenborn B, et al. 3D mapping of phrenic nerve course for radiofrequency pulmonary vein isolation. *J Cardiovasc Electrophysiol* 2023;34(1):90–8.
 25. Maltoni S, Negro A, Camerlingo MD, Pecoraro V, Sassone B, Biffi M, et al. Comparison of cryoballoon and radiofrequency ablation techniques for atrial fibrillation: a meta-analysis. *J Cardiovasc Med (Hagerstown)* 2018;19(12):725–38.
 26. Fortuni F, Casula M, Sanzo A, Angelini F, Cornara S, Somaschini A, et al. Meta-analysis comparing cryoballoon versus radiofrequency as first ablation procedure for atrial fibrillation. *Am J Cardiol* 2020;125(8):1170–9.
 27. Pison L, Gelsomino S, Lucà F, Parise O, Maessen JG, Crijns HJGM, et al. Effectiveness and safety of simultaneous hybrid thoracoscopic and endocardial catheter ablation of lone atrial fibrillation. *Ann Cardiothorac Surg* 2014;3(1):38.
 28. Pison L, La Meir M, van Opstal J, Blaauw Y, Maessen J, Crijns HJ. Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. *J Am Coll Cardiol* 2012;60(1):54–61.
 29. Mol D, Renskers L, Balt JC, Bhagwandien RE, Blaauw Y, van Driel VJHM, et al. Persistent phrenic nerve palsy after atrial fibrillation ablation: Follow-up data from The Netherlands Heart Registration. *J Cardiovasc Electrophysiol* 2022;33(3):559–64.

30. Di Monaco A, Vitulano N, Troisi F, Quadrini F, Romanazzi I, Calvi V, et al. Pulsed field ablation to treat atrial fibrillation: a review of the literature. *J Cardiovasc Dev Dis* 2022;9(4):94.
31. Pansera F, Bordignon S, Bologna F, Tohoku S, Chen S, Urbanek L, et al. Catheter ablation induced phrenic nerve palsy by pulsed field ablation-completely impossible? A case series. *Eur Heart J Case Rep* 2022;6(9):ytac361.
32. Matsumoto Y, Krishnan S, Fowler SJ, Saremi F, Kondo T, Ahsan C, et al. Detection of phrenic nerves and their relation to cardiac anatomy using 64-slice multidetector computed tomography. *Am J Cardiol* 2007;100(1):133–7.
33. Ichihara N, Miyazaki S, Iwasawa J, Matsuda J, Taniguchi H, Nakamura H, et al. Prevalence and pre-procedural predictors associated with right phrenic nerve injury in electroanatomical map-guided, second-generation cryoballoon ablation: single large balloon and single 3-minute freeze techniques. *JACC Clin Electrophysiol* 2016;2(4):508–14.
34. Ströker E, de Asmundis C, Saitoh Y, Velagić V, Mugnai G, Irfan G, et al. using the 28-mm second-generation cryoballoon. *Heart Rhythm* 2016;13(2):342–51.
35. Maj R, Borio G, Ströker E, Sieira J, Rizzo A, Galli A, et al. Phrenic nerve palsy during right-sided pulmonary veins cryoapplications: new insights from pulmonary vein anatomy addressed by computed tomography. *J Interv Card Electrophysiol* 2021;60(1):85–92.
36. Wang YJ, Liu L, Zhang MC, Sun H, Zeng H, Yang P. Imaging of pericardiophrenic bundles using multislice spiral computed tomography for phrenic nerve anatomy. *J Cardiovasc Electrophysiol* 2016;27(8):961–71.
37. Lakhani M, Saiful F, Parikh V, Goyal N, Bekheit S, Kowalski M. Recordings of diaphragmatic electromyograms during cryoballoon ablation for atrial fibrillation accurately predict phrenic nerve injury. *Heart Rhythm* 2014;11(3):369–74.
38. Kowalski M. Prevention of phrenic nerve palsy during cryoballoon ablation for atrial fibrillation. In: Chan N-Y, editor. *The practice of catheter cryoablation for cardiac arrhythmias*. Wiley-Blackwell; 2013. pp. 67–81.
39. Parikh V, Kowalski M. Comparison of phrenic nerve injury during atrial fibrillation ablation between different modalities, pathophysiology and management. *J Atr Fibrillation* 2015;8(4):1314.
40. MacVeigh TJ, Lim HW, Friedman PL. A new "hands-free" non-fluoroscopic method for monitoring phrenic nerve function during catheter ablation. *J Innov Card Rhythm Manag* 2014;5:1517–24.
41. Ghosh J, Singarayay S, Kabunga P, McGuire MA. Subclavian vein pacing and venous pressure waveform measurement for phrenic nerve monitoring during cryoballoon ablation of atrial fibrillation. *Europace* 2015;17(6):884–90.
42. Mondésert B, Andrade JG, Khairy P, Guerra PG, Dyrda K, Macle L, et al. Clinical experience with a novel electromyographic approach to preventing phrenic nerve injury during cryoballoon ablation in atrial fibrillation. *Circ Arrhythm Electrophysiol* 2014;7(4):605–11.
43. Franceschi F, Koutbi L, Gitenay E, Hourdain J, Maille B, Trévisan L, et al. Electromyographic monitoring for prevention of phrenic nerve palsy in second-generation cryoballoon procedures. *Circ Arrhythm Electrophysiol* 2015;8(2):303–7.
44. Miyazaki S, Ichihara N, Taniguchi H, Hachiya H, Nakamura H, Usui E, et al. Evaluation of diaphragmatic electromyograms in radiofrequency ablation of atrial fibrillation: prospective study comparing different monitoring techniques. *J Cardiovasc Electrophysiol* 2015;26(3):260–5.