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Tracing The Right Phrenic Nerve – A Systematic Review and Meta-Analysis

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Abstract

Background:The Right phrenic nerve (RPN) is vulnerable to injury during the isolation of the right pulmonary veins (RPV). The study aimed to provide a comprehensive meta-analysis of the overall prevalence of right phrenic nerve injury (RPNI), its course and its association with the superior and inferior pulmonary veins.

Methods: Through December 2017, a database search was performed on PubMed, Science Direct, EMBASE, SciELO, and Web of Science. The references were also extensively searched in the included articles.

Results: Detection of the RPN may vary according to the identification method. It ranges from 100% in postmortem studies, 93% in intraoperative, to 57.88% in computer tomography (CT) imaging. Based on the included studies (n-507), the distance from the right superior pulmonary vein (RSPV) ostium to the RPN was 12.48mm (±6.21). In postmortem studies, the distance was 6.92mm (±3.94); in pre or intraoperative techniques, 13.32mm (±5.96) if noninvasive, 13.97mm (±7.8) if invasive. Distances ranged from 0–42.6 mm. For the right inferior pulmonary vein (RIPV) (n-125) the mean distance was 16.53mm (±8.92) with distances from 0.4 – 68mm. The risk of RPNI with distance-included studies was 12.46% (47 RPNI in 377 cases). In the meta-analysis, the distance from the RSPV to the RPN that was associated with an increased risk of RPNI was 7.36mm.

Conclusion: RPNI is a relatively rare complication. A firm understanding of its course, relation to the PV ostium, and detection are vital for preventing future injuries and complications.

Introduction

Catheter ablation has become a first-line treatment for the prevention of recurrences of paroxysmal atrial fibrillation after discovering myocardial sleeves activity responsible for arrhythmia, [1] and is the treatment gold standard since 2012 [2]. Unfortunately, the anatomy of right-sided pulmonary veins (RPV) and its close relation to the right phrenic nerve (RPN) makes it susceptible to injury during pulmonary vein isolation (PVI), which was initially reported in 2004 [3]. Previously, right phrenic nerve injuries (RPNI) during PVI RF ablations were a rare complication, estimated around 0.48% [4] while the first significant cryoballoon (CB) observation from 2008 shown a risk level of 7.5% [5] even reaching as high as 24.4%[6] in 2014. That is why a RPNI was called "another Achilles' heelfor AF ablation" [7]. Phrenic nerve injury may be transient or persistent. Transient, where the RPNI resolves at the end of the procedure, whereas a persistent injury persist beyond the procedure [8]. The injury is most commonly transient, and all the clinical symptoms do not occur after postprocedural hospital discharge. In recent publications, the longest period for phrenic nerve paralysis (PNP) recovery was 314 days, while the average time to recovery was 3-6months [9,5]. Through the years of practice and CB generations, various techniques were undertaken to decrease the risk of RPNI. From compound motor action potential (CMAP) in 2011 [11], to immediate balloon deflation (IBD) proposed by Gosh in 2013, temperature controlled application proved by Mugnai and Kuhne [12, 13], the pull back technique proposed by Okshige 2018 [33] to anatomical assessment of the left atrium and adjacent structures[14].Larger RPV dimensions, early branching patterns originating from the main ostium, and shorter distances from RPV to SVC are associated with RPNI both at right superior pulmonary vein (RSPV) and right inferior pulmonary vein (RIPV) [14]. For cryoballon ablation(CBA), the RSPV – RPN distance measured from the ostium was found to have the most accurate correlation in predicting RPNI.Schmidt pointed out in 2008 that the general recommendation for a minimum distance of the phrenic nerve to the RSPV ostium cannot be provided [22].Horton et al.[21] suggested that a PN location within 10 mm of the RSPV poses a higher risk of RPNI when using a balloon-based ablation system. Canpolat [20] demonstrated that after their analysis estimate, the incidence of RPNI was increased when the distance of the RSPV ostium–RPA distance

Key Words

RPN, RPNI, PNP, Pulmonary vein ablation

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was 8.0 mm or less.

The RPN, associated with a bundle of pericardiacophrenic vessels, descends along the anterolateral surface of the SVC, after which it turns posteriorly approaching the superior cavoatrial junction and continues in close proximity to the RPV before reaching the diaphragm [15].

Focusing on the anatomical relation of the RPN in CBA, it is essential to obtain accurate anatomical data on the course of the nerve. The aim of the analysis was to provide a comprehensive and evidence-based assessment of the RPN distance from RSPV and RIPV. We also aimed to investigate the course-related consequences and its association for RPNI.

Methods

Search strategy

Through September 2018, searchers were performed on MEDLINE, EMBASE, Google Scholar, and Cochrane Database in order to identify eligible articles for the meta-analysis. This review was performed as per the Preferred Reporting Items for Systematic Reviews and meta-analysis guidelines. The exhaustive search strategy employed for databases is presented in Table 1. No date limits or language restrictions were applied. The references in the included articles were also extensively searched. The risk of bias and quality assessment scores were both performed based on previously validated tools.

Criteria for study selection

Eligible studies for meta-analysis [for RPNI] were included under certain conditions such as: reported clear, data was easy to extract for further analysis, studies were postmortemcadaveric, electrophysiological, 3D modeling or imaging studies. The exclusion criteria included: case studies, case reports, conference abstracts and letters to the editor; incomplete and unclear data, studies on animals, or not related to electrophysiology procedures. For systematic review, anatomical, clinical, and radiological reports ware taken. We used them to show all possible discrepancies in tracing and measuring the distance of the right phrenic nerve. For identification of RPA in imaging studies, RPPA was taken into consideration – table 1 with a possibility of vessel detection. All studies were independently evaluated for inclusion by two reviewers (MK and MM). Any disparities arising during the assessment were resolved by a consensus among all the reviewers, after consulting with the authors of the original study, if possible.

Data extraction

Data were independently extracted from the included articles by two independent reviewers (MK and MM). These data included the ability to identify the right phrenic nerve RPPA, distance from PV ostium to the RPN, or the RPPA, amount of RPNI and correlation between distance and risk of RPNI. The primary outcome was to estimate the mean distance between right-sided PV ostium and RPN. Secondary outcomes such as the possibility of visualization RPN and risk of RPNI were also noted when data were available. In the event of data inconsistencies, the reviewers did not use the study in meta-analysis.

Statistical analysis

Statistical analysis was performed by experienced statisticians using

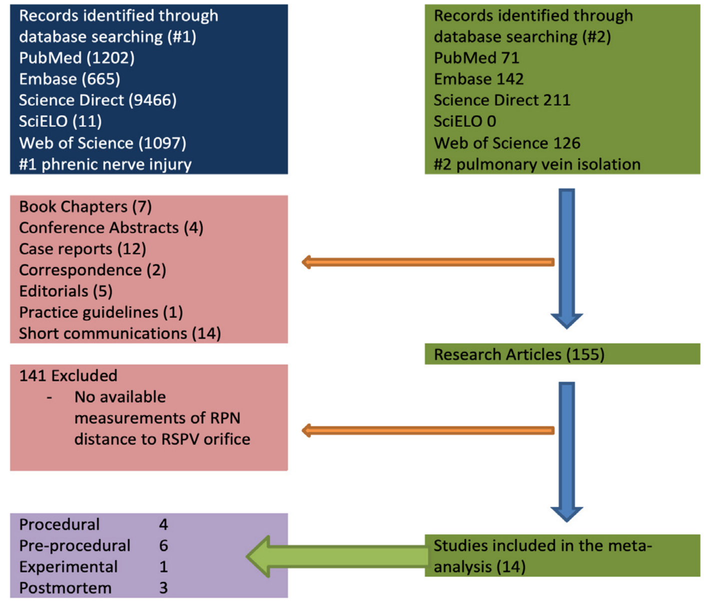

Figure 1: Flowchart of study search, eligibility, assessment, and inclusion

Statistica 13 software (StatSoft). Continuous variables are expressed as mean ±SD or median range, as appropriate. 95% Confidence intervals for individual groups, and the whole was measured. For a subset of studies with analyzable and comparable data, the results were synthesized quantitatively by performing random-effects model meta-analyses to compute absolute net changes in continuous variables (i.e., RPN – RPV ostium) and pooled OR for binary variables (i.e., RPNI versus RPN noninjured). All pooled estimates were displayed with a 95% CI. The existence of heterogeneity among effect sizes of individual studies was assessed using the Q test and the T2 index, with a value of 95% or higher indicating medium-to-high heterogeneity. To explore sources of heterogeneity, we performed subgroup meta-analyses according to RPNI – RPV ostium's and study typesetting (postmortem, intraoperative, or imaging). Sensitivity analysis, Egger's Test, and Rosenthal's N - the "Fail-safe" test ware used.

Results

Study Identification

Figure 1 presents an overview of the flow of studies in the meta-analysis. Through database searching, 12441 initial articles were identified. An additional 550 articles were identified from reference searching. After removing duplicates and primary screening, 155 articles were assessed by full text for eligibility in the meta-analysis. Of

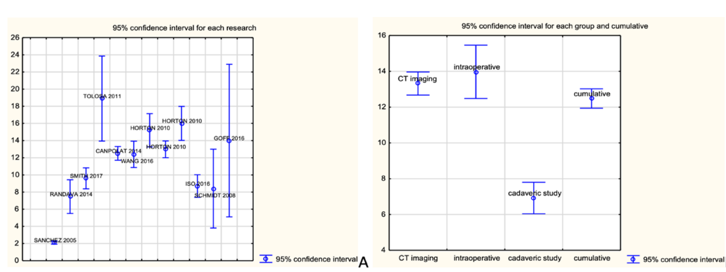

Figure 2A&2B: Graphical presentation of the RPN distance from the RSPV ostium in the 95% confidence interval A – among individual publications B – among different groups of publications (1 – CT; 2 – Intraoperative; 3 – postmortem)

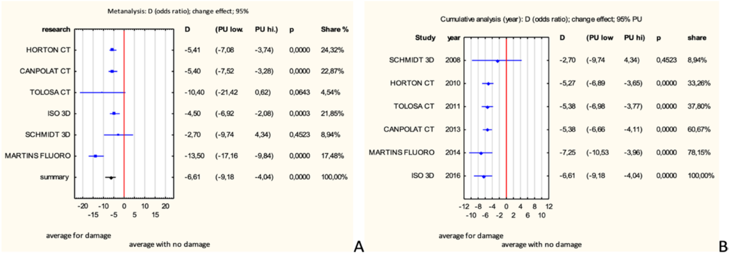

Figure 3A&3B: Forest plot for the risk of injury RPN and the distance relationship; D = average for damage - average with no damage; B - Forest plot of cumulative effect over the years of publications; D = average for damage - average with no damage

these, 14 were deemed eligible and included, while 141 were excluded for not reporting extractable RPN-RPV distance rates.

Characteristics of included studies

The characteristics of the included studies in the meta-analysis are listed in table 1, along with the reported RPN or RPPA identification. A total of 14 selected studies from 13 research publications (n=850; identified RPN -621,) 6 CT imaging (Matsumoto 2007, Horton 2010, Nieto-Tolosa 2011, Canpolat 2014, Wang 2016, Ozawa 2018) 3 postmortem/cadaveric (Sanchez 2005, Randhava 2014, Smith 2017), 5 procedural 3D/cadaveric (Goff 2016), 1 pacing (Horton 2010), 2 3D/pacing (Schmidt 2008, Iso 2016), 1 pacing/fluoroscopy were included (Martins 2010).

RPN/RPPB Detection capability

The detection of the RPN may vary according to the identification method used. In postmortem studies, tracing the RPN was always accurate (100%); in invasive methods/intraoperative, it was almost always detectable (93%). Noninvasive methods of tracing RPPB are not as efficient as invasive or postmortemtechniques, with only 57.88% (20-100%) of detection.

Mean distance of right phrenic nerve

From all included studies (n-507), the distance from RSPV ostium to RPN was 12.48mm, (±6,21) nevertheless, the distance varies according to the method used. In postmortem studies, the mean distance is significantly shorter (6.92mm) than in pre or intraoperative techniques (13.32mm noninvasive, 13.97mm invasive) figure2A,B. The minimal measured distance from RSPV was 0mm – meaning the RPN was directly attached to the veno-atrial junction while the longest measurement was 42.6mm (table 2). There were significantly fewer amounts of measurements that were identified for RIPV. From the included studies (n-125), the mean distance between the RIPV ostium and RPN was 16.53mm (±8.92) with distances from 0.4 – 68mm (table 3).

Risk of Phrenic nerve injury with distance included studies

Combining accessible data of the number of RPNI with distance included studies, we estimated that the amount of incidence was 12.46% (47 RPNI in 377 cases). The highest risk was in Martins research – 19.7% [6], the lowest in Canpolat – 2.75% [20].

Risk of phrenic nerve injury – distance relation

In the meta-analysis, a decreased distance between the RSPV ostium - RPNI, was directly associated with an increased risk of RPNI. The average distance was shorter by 6.61mm from the massed average of the invasive group (figure 3A). Measuring the distance from the RSPV ostium to RPN, the damage distance was 7.36mm. Data from Horton 2010 [21], Canpolat 2014 [20], and ISO 2016 [23] had the most significant impact on the study while Nieto-Tolosa 2011 [18] did not – because of the small sample. Additional results - The variance of the effect size (T2) and the significance level (Wi) in individual studies used to calculate the sampling error are presented in Appendix Table 1. In the cumulative variance the Nieto- Tolosa CT study brings the most additional variability (burden) – see appendix.

The cumulative analysis was performed relative to the year in which the study was conducted – figure 3B. It shows how the cumulative effect and its estimation changed over time after upcoming publications. We can see that the initial insignificant cumulative effect changed to a significant effect after attaching the Horton 2010 publication. The results are presented below as a forest plot Figure 3B, a table in an appendix (table 2 appendix).

Heterogeneity and sensitivity analysis

The study determines how significant the differences between the effects obtained in individual publications have an impact on the total effect of meta-analysis. The result that was calculated was p = 0.0014. The estimated value of real variance T2, and the corresponding 95% confidence interval are 6.3592 (1.606; 17.149). Real variance accounts for around 75% (coefficient I2) of the total volatility. This means that the research is highly heterogeneous. This confirms the correctness of the decision to build a model with a variable effect. This is confirmed by the following graphs of L'Abbegi and Galbraith. – see appendix Figure 1 appendix and Figure 2 appendix.

We also wanted to compare data of the injured phrenic nerves between various methods – figure 4A. We found three main methods of tracing the right phrenic nerve – pacing (blue; Tolosa, Horton, Canpolat) 3D – (green; Schmidt, ISO) and fluoroscopic evaluation (red Martins). Each method was presented in a forest plot below. We see that pacing and 3D systems are similar in detecting the presence of the RPN, while Martins 2014 significantly differs because of a different method used.

The different method used by Martins was significantly highlighted in sensitivity analysis – figure 4B, when individual tests were turned off. The cumulative effect and limits of the confidence interval for the

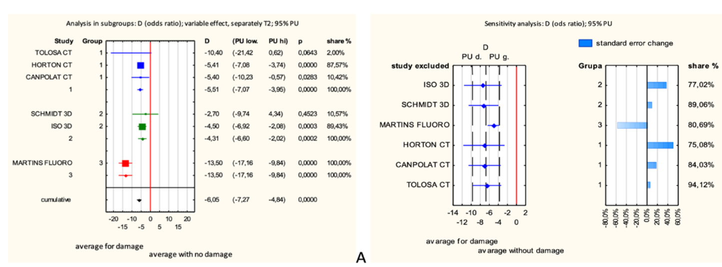

Figure 4A&4B: Sensitivity analysis in various methods of tracing RPN, B. Sensitivity analysis for each publication

Table 1: Table of included studies

	Study	Country	Type	n (detection)	N (RPN)	% of visualisation
1	WANG 2016 [16]	China	CT – RPPA	62	121	51,20%
2	MATSUMOTO 2007 [17]	USA/ Japan	CT – RPPA	50	106	47%
3	NIETO-TOLOSA 2011 [18]	Spain	CT – RPPA	10	55	20%
4	OZAWA 2018 [19]	Japan	CT – RPPV	18	56	30%
5	CANPOLAT 2014 [20]	Turkey	CT – RPPV	145	162	89,50%
6a	HORTON 2010 [21]	USA	CT – RPPV	71	71	100%
6b	HORTON 2010 [21]*	USA	CT – RPPV	37	37	100%
6c	HORTON 2010 [21]	USA	Pacing	71	71	100%
7	SCHMIDT 2008 [22]	Germany	3D/ pacing RSPV	7	18	39%
8	ISO 2016 [23]	Japan	3D/ pacing RSPV	20	20	100%
9	GOFF 2016 [24]	USA	3D/PM	7	10	70%
11	MARTINS 2014 [6]	France	FLUORO/ P-svc	81	81	100%
12	SMITH 2017 [25]	USA	Cadaveric	30	30	100%
13	SANCHEZ 2005 [15]	Spain	Cadaveric	19	19	100%
14	RANDHAVA 2014 [26]	India	Cadaveric	30	30	100%
	Summary			658	887	74%
	Study	Country	Type	n (detection)	N (RPN)	% of visualization
	Overall			658	887	74%
1	CT imaging		CT – RPPV	393	679	57,88%
2	Intraoperative		3D/ pacing RSPV	186	200	93%
3	Postmortem		Cadaveric	79	79	100%

CT – computer tomography, RPPA – right pericardiacophrenic artery, 3D – three dimensional, PM – postmortem, SVC – superior vena cava. *6b Horton2010 (control group of 37 patients undergoing balloon-based procedures used in Horton study [21])

overall meta-analysis are marked on this graph with vertical lines Figure 4B and data in Table 3 appendix.

Assessment of publication bias and Fail-safe number test

The funnel plot for the outcome of RPNI in the studies included in the meta-analysis was symmetric and the Egger test was not significant (P = .59), did not show the existence of susceptibility to publication bias.

The last issue examined was whether it would be necessary to further analyze the distance of the RPN over the right pulmonary veins. For which we used Rosenthal's N (the "fail-safe" number) described by Rosenthal (1979). This value determined the number of works that did not indicate an effect (e.g., a mean difference of 0) that was needed to reduce the summary effect from statistically significant to statistically insignificant. In our analysis, the number of "fail-safe" publications determined by the Rosenthal method amounted to 72. Therefore, the obtained effect could be considered stable because it will not (with a small number of works) undermine the obtained effect. Besides, the Rosenthal factor fs = 4.35 was greater than 1, which means that the probability of publishing significance is minimal. As we know (obtained), the common difference was D = -6.61. The Orwin method checked how many papers with a relative risk of -3 needed to be included to reduce the relative risk to 1.12. The obtained result was 16 research papers.

Discussion

Present results and their variability showed that methods of distance measurement of the RPN may have a significant impact on the final result. postmortem study results have a different approach - where the distance assessment is taken externally from the epicardium, differently from the non-invasive visualization where the RPP bundle is traced, and finally, the intraoperative method with endocardial stimulation. The same intraoperative methods also have high variability relative to each other, as demonstrated by statistical analysis.

RSPV

From all included studies (n-507), the distance from the right superior pulmonary vein (RSPV) ostium to the RPN was 12.48mm (±6.21). In postmortem studies, the distance was significantly shorter, ranged 6.92mm (±3.94). From imaging studies, the distance to RPPB

Table 2: RPN – RSPV distance

Publication	Type of study	N	mean	SD	Range form	Range to	(95%CI)
SANCHEZ 2005 [15]	PM	19	2.1	0.4	1.5	2.5	(1.92 – 2.28)
RANDHAVA 2014 [26]	PM	30	7.47	5.51	0	20.81	(5.50 – 9.44)
SMITH 2017 [17]	PM	28	9.6	3.3	4.3	18.8	(8.38 – 10.82)
NIETO - TOLOSA 2011 [18]	CT	10	18.9	8	3	26	(13.94 – 23.86)
CANPOLAT 2014 [20]	CT	145	12.5	4.9	5.9	25	(11.7 – 13.3)
WANG 2016 [16]	CT	62	12.39	6.18	1.72	26.44	(10.85 – 13.93)
HORTON 2010 [21]	CT	71	15.2	8.3	3	42.6	(13.27 – 17.13)
HORTON 2010 [21]	CT	37	12.99	3.02	6	21.5	(12.02 – 13.96)
HORTON 2010 [21]	P	71	16	8.5	3	42	(14.02 – 17.98)
ISO 2016 [23]	3D/P	20	8.7	3	5	11.8	(7.38 – 10.01)
SCHMIDT 2008 [22]	3D/P	7	8.4	6.2	1	17	(3.81 – 12.99)
GOFF 2016 [24]	CT/3D	7	14	12	8	20	(5.11 – 22.89)
Overall	507		12.48	6.21	0	42.6	(11.94 – 13.02)
Group 1	325		13.32	5.96	1.72	42.6	(12.67 – 13.97)
Group 2	105		13.97	7.8	1	42	(12.48 – 15.46)
Group 3	77		6.92	3.94	0	20.81	(6.04 – 7.80)

was 13.32mm (±5.96). A similar distance was found collecting intraoperative techniques - 13.97mm (±7,8). Distances ranged from 0 to 42.6 mm.

Postmortem study

The most cited publication (Sanchez 2005) [15] of RPN relation to the right side of the heart has a very interesting and unique methodology. The distance was measured from the vein margins to the presence of the RPN, with minimal and maximal distances on the right side of the heart, and not from the vein ostium. The differences of the minimal and maximal values for the same RPV are because of the shape of the cross-section of RPV, but most notably, the veins in postmortem studies were without blood pressure and their shape differs from a working heart. The minimal value from this publication was taken into meta-analysis because its distance relationships were often taken into discussion in many publications [22]. Randhawa 2014 [24] used the same methodology and had different measurements, more similar to the endocardial distances. Finally, Smith 2017 [25] combined both of these techniques to create a reliable landmark for operators. The values were comparable with those from pacing or CT imaging

Table 3: RPN-RIPV distance

Publication	Type of study	N	Mean	SD	Min	max	(95%CI)
SANCHEZ 2005 [15]	PM	19	7.8	1.2	6	10	7.68 – 7.92
RANDHAVA 2014[26]	PM	30	16.86	6.88	0.4	28.55	14.77 – 18.95
SMITH 2017 [17]	PM	28			Not measured		
NIETO - TOLOSA 2011 [18]	CT	10			Not measured		
CANPOLAT 2014 [20]	CT	145			Not measured		
WANG 2016 [16]	CT	62	17.24	7.78	7.2	33.94	13.35 – 21.13
HORTON 2010 [21]	CT	71			Not measured		
HORTON 2010 [21]	CT	37			Not measured		
HORTON 2010 [21]	P	71			Not measured		
ISO 2016 [23]	3D/P	20			Not measured		
SCHMIDT 2008 [22]	3D/P	7	28.2	15.3	11	68	20.04 – 36.32
GOFF 2016 [24]	CT/3D	7	21	6.9	10	30	17.87 – 24.13
overall	125		16.53	8.92	0.4	68	11.77 – 21.28
Group 1	62		17.24	7.78	7.2	33.94	13.35 – 21.13
Group 2	14		25.07	14.04	10	68	29.59 – 20.54
Group 3	49		13.21	6.5	0.4	28.55	11.11 – 15.31

CT imaging/Preoperative visualization

In CT imaging, the RPN is not directly visualized, but the course of RPPB is. Among these structures, the exact course of the RPN may be variable. Delineation of the PN is highly dependent on image quality, which may raise the question of whether this technique can be commonly used before the procedure [23]. The best example was illustrated by Nieto-Tolosa[18] in which RPN detection was on the 20% level. The authors suggested that patients in whom RPPB could be visualized tended to have a higher BMI. Canpolat [20] three years later proved that this technique might be used both in average and higher BMI patients.

Nevertheless, distance measurement before the procedure will only keep the operator more alert during RSPV freeze. This information should be correlated with RPV ostium size and depth setting of the CB during the procedure. Thus, the preoperative assessment of RPPB will only have informative value for an operator.

Pacing/3D mapping

Intraoperative measurements are most precise in detecting RPN. Stimulation from the place of cryoapplication may be the most accurate. However, many factors which play a role in proper RPN localization, such as the strength of stimulation impulse, usage of the 3D system, and force of balloon setting. Another issue is comparing stimulation from the SVC to the balloon tip in AP view [6], which showed no significant compatibility to other studies. Stimulation strength plays a role in depicting RPN, and the bias margin rises with the power output [6,21,27] or wall thickness [15]. Usage of the 3D system in CBA is relatively rare, however, Iso study[23] was a milestone into understanding how the CB changes the shape of PV ostium[23]. Iso uses both methods of measuring the RPN distance: from RSPV orifice to pacing the RPN capture, and the postmortem type method, from RSPV to the PN location corresponding with the RA in a 3D system.

Interestingly the distances in the second method were significantly longer than in the real postmortem studies (2,1mm Sánchez-Quintana; 7,74 Randhava; vs. 11,4 Iso p<0,05). The reason is that the RPN location is somewhere between RSPV and RA, including wall thickness, pericardial sack, and epicardial adipose tissue presence. The last thing which plays a role in RPN distance is the deep setting of the CB. The distances before and after the balloon setting to the RPN significantly differ on average, by about 3.4mm [23]. The same results were presented in Goff research [24]. He proved that small variations in balloon placement could lead to substantial changes in phrenic – to – balloon distances. In summary, RPN pacing is clinically useful for delineating the precise course of the RPN. The RPN capture is dependent on the relative distance between the pacing site and the nerve position and course. Relative distance is dependent fromforce balloon setting in the RPV ostium, possibly decreasing the distance to the danger zone.

RIPV - We harvest possible data from publications used for this study. The only parameter to estimate was the mean distance of the RPN to the ostium from the RIPV. The mean distance (n-125) was 16.53mm (±8.92) with distances from 0.4 – 68mm and was significantly longer than from RSPV (p<0,05). From that reason the risk of RPNI is significantly lower than from RSPV. Because of a small amount of RPNI in RIPV, insufficient data makes meta-analysis unattainable. The interesting fact presented in the publications was the presence of a right common ostium (RCO) and vigorous wedging against a large PV ostium will provoke the balloon's distal displacement close to the RPN [30,31].

Danger zone of RPNI

In our analysis, the mean risk of RPNI was surprisingly high: 12.46% from RSPV, and 3.5% from RIPV. This high value occurred because the publications were concentrated on RPNI and were from the early period of cryoballoon ablation using the first-generation CB. There was no research in the database of CB studies without the risk of RPNI. This value is decreasing over the years, due to new balloon generations, novel techniques in avoiding RPNI risk and volume of procedures. The lowest risk was in Franceschi's research with feasible usage of CMAP with a risk of incidence of 0.7% [32]. The danger zone was estimated at 7.36mm from the RSPV ostium, i.e., it was close to the diaphragmatic nerve distance average in the postmortemexamination. It is slightly closer than proposed by Canpolat [20]: -8mm. Again, the distance is not the only risk predictor. Many research papers noticed that the balloon tip was often significantly further from the projected distance relative to a given phrenic nerve without RPNI [6,20,21,24]. Preparing this meta-analysis, we harvest the PNP data from over 10K CBA, finding 783 RPNI in 54 significant publications from 2008, estimating the mean risk level to be 7.7% - but that was not the problematic aspect in this research. These studies suggest that the location of the nerve near the PV ostium is associated with a higher risk of RPNI.

Questions for further investigation

After obtaining the distance information on relatively large groups of measurements (n-507), the first question is, will further research may contribute to a change in average distances? From our analysis, we know that a minimal amount of publications – with different values – need to exceed at least 16 in the Orwin method while in Rosenthal's, 72 research publications.

Another question concerns the idea that phrenic nerve injury may not only be dependent on course proximity to the PV ostia, but of other issues such as flow size through vessels accompanying RPN in RPPB or thickness of fat surrounding the bundle. Interestingly, not every RPN in the range of balloon freeze was paralyzed.

Finally – how to prevent or decrease the risk of RPNI? Still, the five main strategies play a role in preventing RPNI during cryoablation. From most commonly used fluoroscopy and palpation, through electromyography – CMAP, to intracardiac echocardiography (ICE) and auditory cardiotocography least often[28]. The most crucial direct protection of the RPN during CBA, in our perspective, is CMAP [29].

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Appendix

Table 1: Appendix Avardage difference data

Meta-analysis (average difference);Variable effect; significance p < 0,05

Study	D	SE	Lower limit 95% PU	Upper limit 95% PU	P	share %
HORTON CT	-5,41	0,85	-7,08	-3,74	0,0000	24,32%
CANPOLAT CT	-5,40	1,08	-7,52	-3,28	0,0000	22,87%
TOLOSA CT	-10,40	5,62	-21,42	0,62	0,0643	4,54%
ISO 3D	-4,50	1,23	-6,92	-2,08	0,0003	21,85%
SCHMIDT 3D	-2,70	3,59	-9,74	4,34	0,4523	8,94%
MARTINS FLUORO	-13,50	1,87	-17,16	-9,84	0,0000	17,48%
Summary	-6,61	1,31	-9,18	-4,04	0,0000	100,00%

Avardage difference data D = average for damage - average with no damage SE – standard error, RSD relative standard deviation

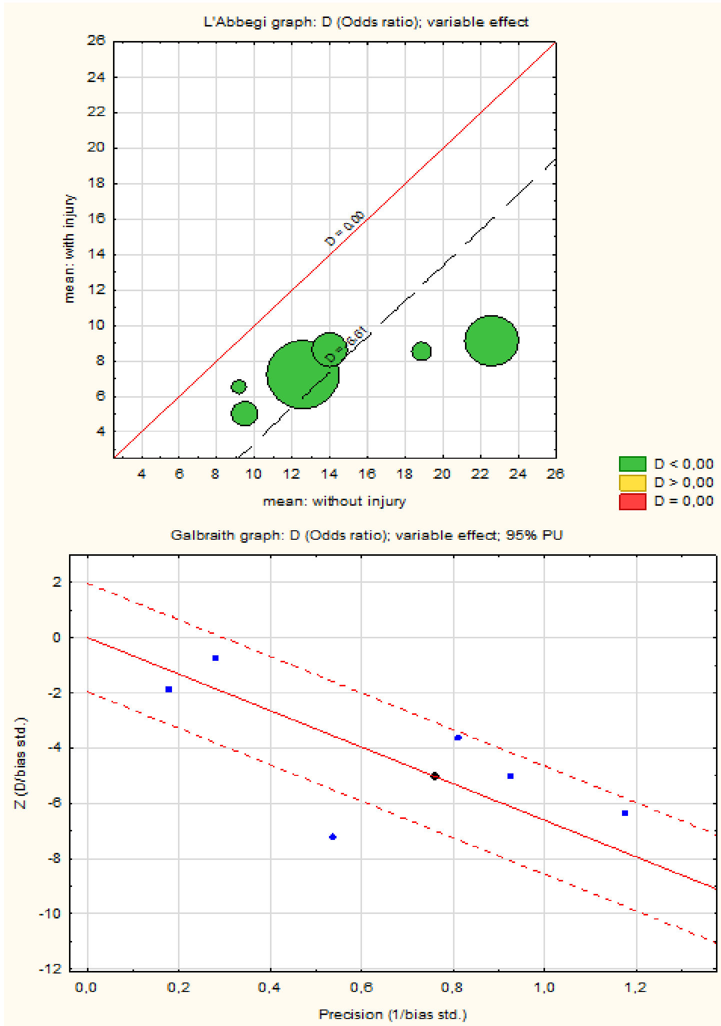

Figure: Appendix Heterogeneity analysis Galbraith graph

Table 2: Appendix Cumulative analysisdata

Meta-analysis (average difference); Variable effectcumulative analysis (by year); significance p < 0,05										
Study	year	D	SE	Lower limit 95% CI	Upper limit 95% CI	p	Cumulative share	N1 cum	N2 cum	RSD
SCHMIDT 3D	2008	-2,70	3,59	-9,74	4,34	0,4523	8,94%	2	5	
HORTON CT	2010	-5,27	0,83	-6,89	-3,65	0,0000	33,26%	9	35	-76,98%
TOLOSA CT	2011	-5,38	0,82	-6,98	-3,77	0,0000	37,80%	11	45	-1,06%
CANPOLAT CT	2013	-5,38	0,65	-6,66	-4,11	0,0000	60,67%	15	186	-20,24%
MARTINS FLUORO	2014	-7,25	1,68	-10,53	-3,96	0,0000	78,15%	28	254	157,15%
ISO 3D	2016	-6,61	1,31	-9,18	-4,04	0,0000	100,00%	31	271	-21,79%

D = average for damage - average with no damageSE – standarderror, RSD relative standard deviation;

Table 3: AppendixSensitivity analysis for each publication - data

Sensitivity analysis D (Odds ratio); variable effecthighlited p < 0,05								
Includedstudy	Group	D	SE	Lower limit 95% CI	Upper limit 95% CI	P	share %	dSE
ISO 3D	2	-7,42	2,12	-11,57	-3,27	0,0005	77,02%	37,45%
SCHMIDT 3D	2	-7,28	1,68	-10,57	-3,99	0,0000	89,06%	8,90%
MARTINS FLUORO	3	-5,13	0,66	-6,42	-3,84	0,0000	80,69%	-57,36%
HORTON CT	1	-7,19	2,32	-11,74	-2,65	0,0019	75,08%	50,33%
CANPOLAT CT	1	-7,04	1,81	-10,60	-3,49	0,0001	84,03%	17,71%
TOLOSA CT	1	-6,53	1,62	-9,71	-3,35	0,0001	94,12%	5,15%
Withoutexclusion		-6,76	1,54	-9,78	-3,74	0,0000	100,00%	0,00%

D = average for damage - average with no damage SE – standard error, RSD relative standard deviation; dSE – deviation for standar error;