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Compound motor action potentials in transient and persistent phrenic nerve injury — metanalysis

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Abstract: Background: The right phrenic nerve is vulnerable to injury (PNI) during cryoballoon ablation (CBA) isolation of the right pulmonary veins. The complication can be transient or persistent. The reported incidence of PNI fluctuates from 4.73% to 24.7% depending on changes over time, CBA generation, and selected protective methods.

Methods: Through September 2019, a database search was performed on MEDLINE, EMBASE, and Cochrane Database. In the selected articles, the references were also extensively searched. The study provides a comprehensive meta-analysis of the overall prevalence of PNI, assesses the transient to persistent PNI ratio, the outcome of using compound motor action potentials (CMAP), and estimated average time to nerve recovery.

Results: From 2008 to 2019, 10,341 records from 48 trials were included. Out of 783 PNI retrieved from the studies, 589 (5.7%) and 194 (1.9%) were persistent. CMAP caused a significant reduction in the risk of persistent PNI from 2.3% to 1.1% ($p = 0.05$; odds ratio [OR] 2.13) in all CBA groups. The mean time to PNI recovery extended beyond the hospital discharge was significantly shorter in CMAP group at three months on average versus non CMAP at six months ($p = 0.012$). CMAP (in contrast to non-CMAP procedures) detects PNI earlier from 4 to 16 sec ($p <0.05$; $I_2 = 74.53\%$) and 3 to 9° ($p <0.05$; $I_2 = 97.24\%$) earlier.

Conclusions: Right PNI extending beyond hospitalization is a relatively rare complication. CMAP use causes a significant decrease in the risk of prolonged injury and shortens the time to recovery.

Keywords: compound motor action potentials (CMAP), cryoballoon ablation (CBA), phrenic nerve injury.

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Introduction

Since 2006, the cryoballoon ablation (CBA) technique has revolutionized the treatment of paroxysmal atrial fibrillation and has become the gold standard treatment method since 2012. The main reason behind its efficacy is its simplifying pulmonary vein (PV) isolation, making it a highly standardized and reproducible procedure [1–3]. Nevertheless, CBA is associated with a significant risk of right phrenic nerve injury (PNI) because of the proximity between the right phrenic nerves and the right-sided PVs during balloon-based ablations [4]. The PNI can be transient or persistent, and that feature depends on the time to recovery. Transient phrenic nerve paralysis/injury (TPNI) is defined either as completely resolved before the end of the procedure [5, 6], lasting less than 24 hours [7], or until discharge as demonstrated by chest fluoroscopy [8]. Any longer period of diaphragmatic paralysis is defined as persistent or sustained phrenic nerve injury (PPNI). In a systematic review, the reported incidences of transient and persistent right PNI resulting from ablation with the first-generation CB were 6.48% and 4.73%, respectively [9]. The risk of PNI associated with the second-generation CB is even higher with a reported incidence of transient and persistent PNI being 16.0%–24.7% and 5.4%–7.0%, respectively [10–13]. The anatomical relationship of the relevant structures makes the risk unavoidable; however, various techniques have been implemented throughout the last decade for preventing prolonged PNI [14]. The most used technique involves the use of compound motor action potentials (CMAP). The first record of CMAP was published in 2011 by Franceschi [15]; later, two studies, including multiple patients, were published in 2014 with a significant PPNI reduction [16, 17].

In this article, we aimed to perform a systematic review of PNI based on all cryoballoon generations from the last 12 years by conducting a meta-analysis to assess the efficacy of diaphragmatic stimulation and CMAP use for PNI protection. Intraoperative physical conditions both with and without right dome diaphragmatic stimulation and time to recovery data were collected.

Methods

Through September 2019, literature searches were performed using the MEDLINE, EMBASE, and Cochrane databases to identify eligible articles. This review was performed according to the Preferred Reporting Items for Systematic Reviews and meta-analysis guidelines (PRISMA) guidelines [18]. The exhaustive search strategy used for the 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 the Newcastle–Ottawa Scale (NOS) to further evaluate the quality of the observational studies, and NOS ≥7 was regarded as a good quality score [19].

Table 1. Baseline characteristics of the included studies. Column 13: Detailed information of phrenic nerve injury (PNI): 1 PNI record, 2 PN stimulation data, 3 compound motor action potential (CMAP) usage, 4 intraoperative median time to PNI, 5 intraoperative median temperatures to PNI, 6 locations of cryoballoon ablation (CBA) during PNI, 7 detailed list of PNI, 8 follow up of PPNI; * Cassado-Arroyo 2013 HRM Brussel used in bigger database by Mugnai while intra-operative data were used.

Author (year)	Centre	Number of procedures CB-1/CB-2 /CB-ST	Mean age	Males	BMI	AF duration (months)	LA size (LAD)	HT	DM	CAD	LVEF (%)	Detailed informa-tion	PNI (%)	TPNI (%)	PPNI (%)
Malmborg 2008 [20]	Uppsala	43	56.3	90%	25.5	110.4	44	30.2%	NA	7.0%		1,6,8	4.651	2.33	2.33
Neumann 2008 [21]	Bad Neu-man, Bo-hum	346	59	63.8%	NA	80.4	41	44.5%	NA	16.8%	60	1,6,8	7.514	0.58	6.94
Van belle 2008 [22]	Rotherdam	141	56	74.1%	NA	NA	42	13.5%	NA	3.5%		1,6,8	4.255	1.42	2.84
Chun 2009 [23]	ASKLEPIOS	27	56	79.2%	NA	72	41	33.3%	NA	11.1%		1,2,4, 6,7	11.11	11.1	0
Linhart 2009 [24]	Bonn	20	59.9	88.2%	28.38	84	41	60.0%	NA	NA	59.5	1,6	15	15	0
Kojodjojo 2010 [25]	Londyn	124	57.3	54.9%	NA	67.2	39.6	33.9%	NA	4.0%	65	1,2,6,8	1.613	0	1.61
Dorwarth 2011 [26]	Munich	141	59	72.7%	NA		41	45.4%	NA	NA		1,6	9.22	8.51	0.71
Guiot 2012 [27]	Rouen	66	57	63.9%	26	64.8		27.3%	7.6%	NA		1,6,8	7.576	6.06	1.52
Jackson 2012 [28]	Newcastle AU	200	61.2	76.2%	NA	57	42.2	50.0%	7.5%	NA	60.2	1	7.5	4.5	3

Table 1. cont.

Author (year)	Centre	Number of procedures CB-1/CB-2 /CB-ST	Mean age	Males	BMI	AF duration (months)	LA size (LAD)	HT	DM	CAD	LVEF (%)	Detailed informa-tion	PNI (%)	TPNI (%)	PPNI (%)
Kuhne 2012 [29]	Basel	65	58	78.7%	NA	54	40	20.0%	NA	7.7%	59	1,2,4, 6,7,8	6.154	4.62	1.54
Ghosh 2013 [30]	Australia	130	57.8	90.7%	NA	NA		0.0%	NA	NA		1,4,5,6	16.92	16.9	0
Mugnai 2013 [31, 62]	HRM Brus-sel	136	57	78.4%	26.2	22.1	41.6	25.7%	2.9%	5.1%		1,2,4,5, 6,7,8	8.088	6.62	1.47
Packer 2013 [2]	MAYO Clinic	163	57	93.3%	NA	NA	40	41.1%	6.7%	4.9%	60	1,6,8	17.79	15.3	2.45
Vogt 2013 [32]	Bad Oeyn-hausen	605	59	70.2%	NA	50	42.1	41.7%	NA	NA	57.1	1,6,8	4.463	2.48	1.98
Ang 2014 [33]	London	38	57	96.2%	NA	50	40	39.5%	NA	28.9%	55	1,6,8	31.58	23.7	7.89
Aryana 2014 [34]	Sacramento	140	63	66%	29.7	52.8	44	59%	13.6%	12.9%	58	1,2,6,8	12.14	11.4	0.71
Aytemir 2014 [35]	Ankara	306	54.65	49.3%	25	NA	40	41.8%	13.4%	11.1%	64	1,2,6	4.575	0	4.58
Mondesert 2014 [36]	Montreal	200	59.9	80.8%	28	73.2	37.7	36.5%	10.0%	NA	59.7	1,2,3, 4,6	16.5	15	1.5
Jourda 2014 [37]	Paris	75	59.9	88.7%	28.2	45.6	42.8	34.7%	10.7%	10.7%	64.4	1,6	17.33	17.3	0
Lakhani 2014 [17]	New York	109	61.1	71.6%	NA	NA		70.6%	15.6%	NA	52	1,2,3, 4,6	6.422	6.42	0

Table 1. cont.

Author (year)	Centre	Number of procedures CB-1/CB-2 /CB-ST	Mean age	Males	BMI	AF duration (months)	LA size (LAD)	HT	DM	CAD	LVEF (%)	Detailed information	PNI (%)	TPNI (%)	PPNI (%)
Martins 2014 [10]	Rennes	147	60.1	86.4%	NA	852	41	0.0%	NA	NA	65.1	1,2,6	19.73	19.7	0
Metzner 2014 [38]	ASKLEPIOS	115	61	65.8%	NA	NA	43	0.0%	NA	NA		1,2,5,8	3.478	0	3.48
Arayana 2015 [6]	USA	773	63	76.9%	NA	51.6	44	64.4%	12.2%	12.0%	57	1,2	8.797	7.63	1.16
Franceschi 2015 [15]	Marseille	140	60.3	79.7%	NA	NA	41.2	37.9%	0.0%	NA	60.7	1,2,3,4, 5,6,7,8	7.1	6.43	0.7
Furnkrantz 2015 [8]	Frankfurt	360	64	39.2%	NA	NA	40	37.5%	5.0%	18.3%		1,2,4, 6,7	7.778	5.28	2.5
Greiss 2015 [39]	Bad Nauheim	376	59	67.3%	NA	50.4	41	59.3%	6.4%	NA	62	1,3,6	2.394	2.39	0
Liu 2015 [40]	Fuwai i Berlin	125	62	73.2%	28	NA	45	64.8%	13.6%	15.2%	62	1,2,6	1.6	1.6	0
Luik 2015 [41]	Freiburg	156	61	68.0%	NA	NA		61.5%	9.0%	12.2%		1,6,8	5.769	2.56	3.21
Meissner 2015 [42]	Cologne, Bohum	166	63	59.0%	NA	32.6	48	81.9%	16.3%	25.3%		1,2,3,4, 5,6,7,8	6.024	4.22	1.81
Wasserlauf 2015 [43]	Chicago	101	62.9	67.0%	NA	51.6	37	43.6%	6.9%	NA	58	1,3,6,8	0.99	0	0.99

Table 1. cont.

Author (year)	Centre	Number of procedures CB-1/CB-2 /CB-ST	Mean age	Males	BMI	AF duration (months)	LA size (LAD)	HT	DM	CAD	LVEF (%)	Detailed informa-tion	PNI (%)	TPNI (%)	PPNI (%)
Okishige 2016 [7]	Yokohama	197	63.7	82.0%	NA	29.2		46.7%	11.2%	6.6%	64	1,2,3, 6,8	12.69	9.14	3.55
Aryana 2016 [44]	USA	355	64	70.6%	30	NA	44	68.2%	23.1%	20.8%	55	1,2,6,8	3.099	2.54	0.56
Guhl 2016 [45]	Pittsburgh	450	59.1	83.3%	31.3	NA	43	57.6%	13.3%	16.0%	55	1,3,6,8	10.89	9.78	1.11
Kardos 2016 [46]	Budapest, Rotterdam	40	59	73.0%	NA	NA	41.3	42.5%	5.0%	12.5%		1,6,8	7.5	5	2.5
Mugnai 2016 [47, 62]	HRM Brus-sel	550	57.5	71.4%	26.8	21.4	41.9	40.2%	8.9%	7.6%	58.4	1,2,4, 5,6,8	7.273	5.27	2
Paylos 2016 [48]	Madrid	128	58	81.5%	NA	66	37	28.1%	4.7%	NA		1,4,5, 6,7,8	7.031	5.47	1.56
Providencia 2016 [49]	Touluse, London, Grnoble	393	60.1	68.4%	26.7	55.2	39.5	0.0%	NA	NA	55	1,6	1.781	0	1.78
Straube 2016 [50]	Monachium	173	64	71.9%	27.3	29	46	0.0%	NA	NA	54	1,6,8	1.156	0	1.16
Yalin 2017 [51]	Luebeck, Usak	133	66	63.0%	29	26.1	42	78.2%	20.3%	38.3%	51	1,6,8	4.511	3.01	1.5
Miyazaki 2017 [52]	FUKUI	550	63.5	0.0%	24.3		37.9	0.0%	NA	NA	65.4	1,2,3, 4,5,6,8	6.182	3.82	2.36

Table 1. cont.

Author (year)	Centre	Number of procedures CB-1/CB-2 /CB-ST	Mean age	Males	BMI	AF duration (months)	LA size (LAD)	HT	DM	CAD	LVEF (%)	Detailed informa-tion	PNI (%)	TPNI (%)	PPNI (%)
Okishinge 2018 [53]	Yokohama, Tokyo	284	64	56.8%	NA	44	39	41.2%	6.0%	8.8%	65	1,3,6,8	25	24.3	0.7
Mortsell 2018 [54]	Uppsala	139	61.9	70.6%	27.9	78.3	40.9	42.0%	11.6%	4.3%		1,6,8	3.6	2.9	0.7
Akkaya 2018 [55]	Bad Nau-heim	457	61	63.5%	27.3	19		67.0%	9.6%	NA	62	1,3,6	3.501	2.19	1.31
Su 2018 [56]	RADICOOL trial	452	69	50.8%	NA	10.8	47	0.0%	NA	NA		1,3	1.549	1.55	0
Molenaar 2019 [57]	Nederlands	222	58	64.41%	27	NA	NA	35.1%	4.1%	4.1%		1,6,8	19.8	13.5	6.3
Chikata 2019 [58]	Toyama	92	66.5	74.7%	24.3	NA	38.6	54.3%	15.2%	8.7%	66.1	1,3,6	5.435	5.43	0
Chan 2019 [59]	Hong Kong	67	57.4	76.2%	25.1	48.8	37	76.1%	17.9%	34.3%		1,3,6,8	5.97	0	5.97
Sano 2019 [60]	Hamamatsu	70	60	88.9%	24.6	NA	38.4	50.0%	14.3%	12.9%	60.9	1,3,6	10	10	0

Study Selection

Studies that were eligible for meta-analysis using the keywords/phrases, right phrenic nerve protection, right PNI, and CMAP were included under certain conditions: (1) reported clear, data that was easy to extract for further analysis, (2) studies were retrospective and observational in nature. The exclusion criteria included case studies, case reports, conference abstracts, and letters to the editor, incomplete and unclear data, studies on animals, or those not related to CBA procedures. All studies were independently evaluated for inclusion by two investigators. 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 and quality assessment

All publication pieces of data were extracted: (1) publication information (the first author's name, publication year), (2) cohort demographics (sample size, gender constituent ratio, mean age, comorbidity), (3) atrial fibrillation (AF) duration, (4) body mass index (BMI), (5) echocardiographic parameters (left ventricular ejection fraction (LVEF), (6) left atrial dimension (LAD), (7) procedural data, including cryoballoon generation (first generation: CB-1, second generation (advanced): CB-2, third generation (short tip): CB-ST), balloon dimension (23 or 28 mm), balloon location (right superior pulmonary vein right [RSPV] or inferior pulmonary vein [RIPV]), time and nadir temperature to PNI, diaphragmatic protection (fluoroscopy, palpation, stimulation, including cycle, strength of impulse, positioning of pacing electrode and CMAP), procedural and delayed complications of phrenic nerve palsy. Whenever the data of interest were incomplete, the investigators did not use the study in the meta-analysis. In some publications, only a selected group was used for analysis once the same data were found in other publications.

Statistical analysis

Statistical analyses were performed using the Statistica (TIBCO v.13.3) software. Continuous variables are expressed as mean ± standard deviation (SD) or median range as appropriate. Confidence intervals (95% CI) for individual groups and the whole group were 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 (for example, time to PNI or temperature to PNI) and pooled OR for binary variables (for example, PNI with CMAP and no phrenic nerve injury). All pooled estimates were displayed with a 95% CI. For PNI resolution the Wilcoxon Peto's log-rank test was used because higher sensitivity at early survival times than late ones. The existence of heterogeneity among effect sizes of individual studies was assessed using an I2 of higher than 50% with p value of <0.1, *Q* test, and the T^2 index with a value of ≥95%, indicating medium-to-high heterogeneity. A funnel plot and Begg and Mazumdar's test were used to investigate publication bias for the primary clinical outcome.

Results

Eligible studies

For the most precise study selection, each database was scanned through combination of two key words: (1) cryoballoon ablation *AND* phrenic nerve injury and cryoballoon ablation *AND* compound motor potential action OR (2) CMAP. Initially, 301 potentially relevant articles were identified according to the adopted search strategy. As illustrated in the flow diagram (Fig. 1), the first review excluded 216 papers based on screening the titles and abstracts, and an additional 21 articles were excluded after

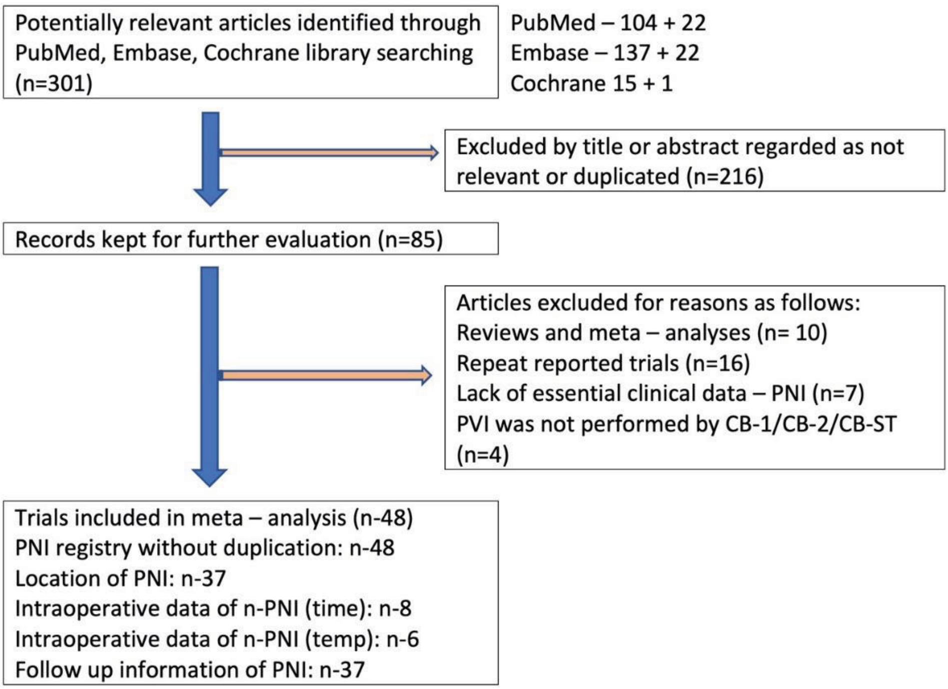

Fig. 1. A flow diagram for the selection process of published articles. PNI — phrenic nerve injury, PVI — pulmonary vein isolation, CB-1 first generation of cryoballoon, CB-2 second generation of cryoballoon, CB-ST — short tip cryoballoon.

a detailed evaluation in addition to 64 articles thoroughly enrolled with timeline and centers origin with intermeshing of records. Finally, 48 eligible observational controlled and noncontrolled trials that fulfilled all inclusion criteria for PNI registry [2, 5–17, 20–60] Fig. 1. For metanalysis of PN protection, location of PNI, and time to resolution of PNI, different criteria ware used; thus, a significantly less papers met the final criteria, and each part of the analysis was estimated separately. Nevertheless, the method and equipment of CBA is unified so that they can be analyzed together and in dependent subgroups.

The studies included in this meta-analysis were published between September 2008 [21] and May 2019 [60]. Two randomized controlled trials met the inclusion criteria [54, 57]. The reasons for final exclusion were lack of essential clinical outcome data, repeated records in databases, review articles, duplicated studies, and non-controlled trials. As to the quality of those included studies forty-eight full-text studies were allocated a NOS score of ≥7 [19].

Baseline characteristics of included study

All enrolled clinical studies were published form 2008 [20] to 2019 [60]. The first enrollment of CBA: CB-1 was found in 2007 [61]; however, records from this study were used later in 2008 in a larger observational registry [22]. The total number of patients in this meta-analysis reached 10,341 with 4164 patients undergoing first generation CBA: CB-1 (23 mm [1164 patients] and 28 mm [3328 patients]), 6075 with second generation CBA: CB-2 (23 mm [192 patients] and 28 mm [5765 patients]) and finally 102 patients who had an ablation with the third generation CB-ST procedure, 28 mm. Discrepancies in the number of 23 28 mm and number of procedures could have resulted from the use of two types of diameters in one procedure.

All trials (n = 48) for PNI with relevant baseline information included patients comparable on mean age, gender ratio, body mass index (BMI), atrial fibrillation (AF) duration, comorbidities, left ventricular ejection fraction (LVEF), and left atrium size between the CB generations (Table 1). Each study describes the method of phrenic nerve control and protection (supplemental publication material Table 1), number of PNI (n = 48), and time to recovery (n = 37), if not in days, at least at check-up periods. Intraoperative data was found in 13 studies [8, 15, 17, 23, 29, 30, 36, 38, 42, 47, 48, 52, 62] providing a detailed time to PNI, only eight [15, 30, 38, 42, 47, 48, 52, 62] studies delivered information about nadir disruption of temperature to PNI while only five [15, 38, 42, 48, 62] detailed time, temperature, and balloon location of the right superior pulmonary vein/right inferior pulmonary vein (RSPV/RIPV) In 20 studies, we found information about diaphragmatic stimulation, 17 described the strength of power to stimulation, 30 studies described the time of freezing as shown in the supplemental publication material.

CMAP was used in 15 studies, four used immediate balloon deflation (IBD; one CMAP + IBD), 30 studies used fluoroscopy control with palpation, and two studies did not use any phrenic nerve protection [20, 21]. Detailed information of data included in certain studies are shown in column 13, Table 1. Except for statistical significance of hypertension diagnosis between the CMAP and non-CMAP group, almost all the other demographic characteristics (age, gender, AF duration) and echocardiographic data (left atrium diameter [LAD], left LVEF) were comparable between these two groups. Statistical analyses of the baseline demographic and echocardiographic data are presented in Table 2. The study did not compare the 6-month or 1-year efficacy because of different balloon generations, sizes, and selected techniques. The average success rate ranged from 59.7% in CB-1 [40] to 90.83% in CB-2 [35] with a mean of 75.82% overall.

Table 2. Statistical analysis of the baseline demographic and echocardiographic data; BMI — body mass index, AF — atrial fibrillation, LAD — left atrial diameter, LVEF — left ventricle ejection fraction, HT — hypertension, DM — diabetes mellitus, CAD — coronary artery disease.

Variable	Studies included	CRYO no CMAP	CRYO CMAP	P value
Number of patients	48	6650	3691	NA
Age	48	59.95 [58.99-60.91] OR = 0.49	61.83 [60.72-62.94] OR = 0.57	p = 0.79 OR = 0.94
BMI	25	27.21 [26.53-27.89] OR = 0.35	26.64 [24.47-28.82] OR = 1.11	p = 0.59 OR = 0.28
AF duration	32	52.49 [42.78-62.20] OR = 4.96	45.29 [33.39-57.18] OR = 6.07	p = 0.62 OR = 3.6
LAD (mm, [SD])	41	41.72 [41.02-42.41] OR = 0.35	39.73 [38.53-40.93] OR = 0.61	p = 0.60 OR = 0.99
LVEF (%, [SD])	31	58.98 [57.74-60.23] OR = 0.63	60.91 [58.94-62.89] OR = 1.01	p = 0.82 OR = 0.96
Male sex (% mean)	48	65.17%	62.51%	p = 0.2
HT	41	46.92%	55.5%	**p <0.05**
DM	31	10.69%	10.47%	p = 0.80
CAD	28	12.71%	13.42%	p = 0.56

Transient versus persistent phrenic nerve injury (primary outcome)

From 10,341 records, information about 783 PNI (7.7%) was found; 589 (5.7%) were transient, while 194 (1.9%) were persistent. In the CB-1 generation (n = 4164 records with 4492 CB-1 balloons), PNI was found in 302 cases (7.2%), in the CB-2 generation (n = 5957) was found in 466 cases (7.8%), and in the CB-ST (n =102), 15 (1.96%) were found. After obtaining the results from studies reporting relevant detailed data, we observed that the number of PNI in the CMAP and non-CMAP groups was similar and did show statistical difference (p = 0.56, odds ratio [OR]: 0.96; 95% CI [0.82–1.11]). The transient subgroup was seen significantly more often in the CMAP group, while the PPNI was present more often without CMAP use (Table 3).

Table 3. Summary table of PNI data with CMAP and non-CMAP usage; CB-1 first generation of cryoballoon, CB-2 first generation of cryoballoon, PNI — phrenic nerve injury.

	CMAP **3691**	No CMAP **6650**	
No PNI/PNI	3404/287 (7.77%)	6154/496 (7.46%)	p = 0.56 OR 0.98
Transient PNI	247 (6.7%)	342 (5.1%)	**p <0.05 OR = 0.77**
Persistent PNI	40 (1.1%)	154 (2.3%)	**p <0.05 OR = 2.13**
CB-1 Transient PNI	913/81 (8,87%)	3251/139 (4.3%)	**p <0.05 OR = 0.47**
CB-1 Persistent PNI	913/6 (0,6%)	3251/75 (2.3%)	**p <0.05 OR = 3.4**
CB-2 Transient PNI	2778/166 (5,97%)	3297/201 (6.1%)	p = 0.75 OR = 1.03
CB-2 Persistent PNI	2778/34 (1,22%)	3297/79 (2.4%)	**p <0.05 OR = 1.99**

Dividing PNI into transient and persistent PNI in CMAP and non-CMAP group showed statistical significance for all variants except transient PNI in the CB-2 group. A statistical difference was found in almost all CBA generations with the highest incidence in persistent PNI in CB-1 (OR 3.4) and CB-2 (OR: 3.4 and 1.99, respectively). The inverse situation was found in transient PNI in the CB-1 group (OR: 0.47). Combined data from different CBA generations with and without CMAP use are presented in the Forrest plot in Fig. 2A. The funnel plot of the selected studies for

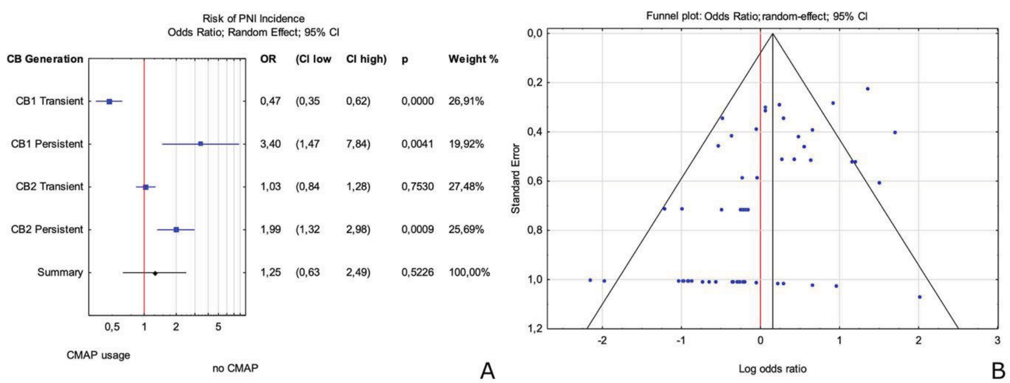

Fig. 2. A: Forrest plot of subgroups in PNI analysis; Significance of CMAP usage in persistent PNI. **B**: Persistent PNI: Heterogeneity of included studies: I2 46.62%, T2 0.23, p = 0.018 Q 29.97; Funnel plot for PPNI of included studies, Begg Mazumdar test for assessment the publication bias p = 0.65; PNI — phrenic nerve injury.

the analysis shows the risk of bias in Fig. 2B. The only insignificance was noticed between TPNI in the CB-2 generation (CMAP/nonCMAP) ($p = 0.75$; OR: 1.03). For this record, a Kaplan Meier's log-rank test was preformed and yielded a value of $p = 0.77$.

By obtaining the results from studies reporting relevant, detailed, intra-operative data regarding PNI, including time to PNI ($n = 243$) and temperature to PNI ($n = 150$), a significant difference between CMAP and non-CMAP groups was noticed. The mean difference for time to PNI was significant for CMAP and non-CMAP groups. The shortest time to PNI was found in the CMAP CB-1 and CB-2 groups (both 137 s). The longest time to PNI was observed in non-CMAP groups reaching 153 and 141 s for CB-1 and CB-2, respectively. The mean difference nadir temperature to PNI was lowest for CB1 (–59°C at which the CMAP value could not be dispersed), for CB-2 non-CMAP and CMAP (–53 and –50°C), which achieved statistical significance. The summarized graphs with heterogeneity values are shown in Fig. 3.

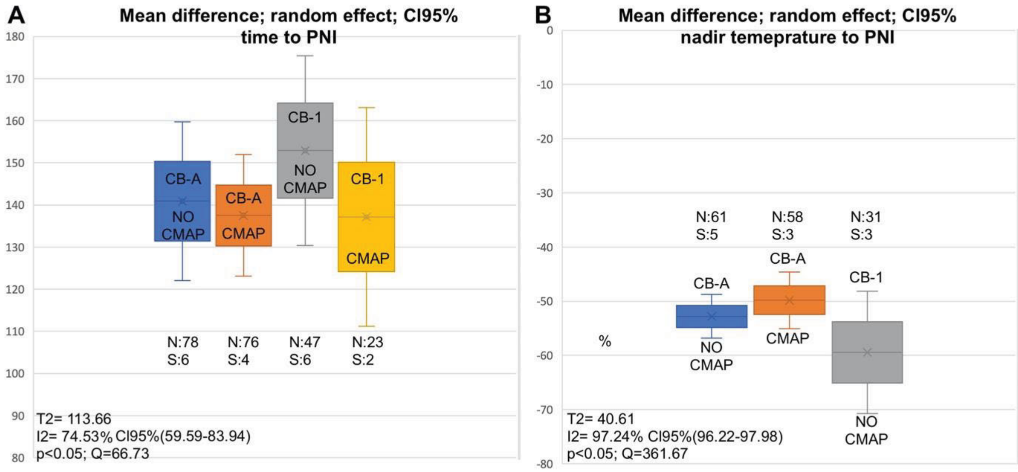

Fig. 3. Summarized graphs with Cl 95% from difference of time to PNI (A) and temperature to PNI (B). For CMAP the breakpoint was amplitude reduction of 30%m for no CMAP lack of diaphragmatic stimulation. N — number of records, S — number of studies; PNI — phrenic nerve injury.

The location of the PNI

The number of instances of PNI from the records reached $n = 783$ (studies: 48) while the precise location as to right superior or inferior phrenic nerve was found in $n = 627$ (studies: 40). It was not surprising, according to relationship, that PNI were most frequently found in RSPV as shown in Fig. 4. Five-hundred eighteen PNI (82.6%)

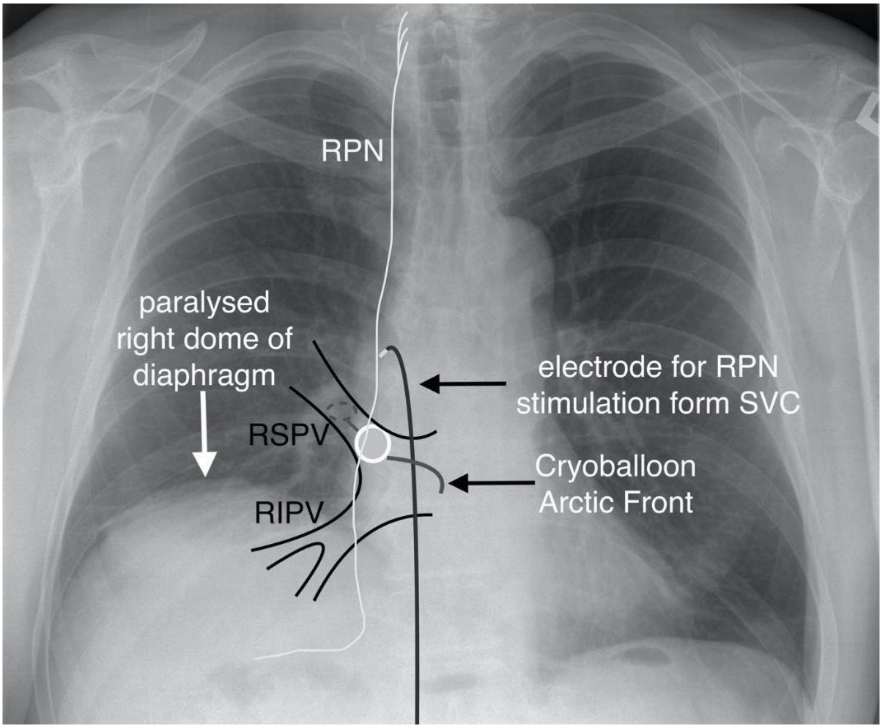

Fig. 4. RTG with right phrenic nerve injury (PNI) with schematic location of right phrenic nerve (RPN) and stimulating electrode in superior vena cava (SVC); RSPV — right superior pulmonary vent, RIPV — right inferior pulmonary vein.

occurred in RSPV and 109 (17.4%) in RIPV (p <0.005). In the CMAP/no-CMAP group, 206 were found in RSPV (77.4%), 60 in RIPV (23.6%), 312 in RSPV (86.4%), and 49 in RIPV (13.6%) based on results from the chi-square test (p = 0.003). It was impossible to collect precise data concerning the transition of transient PNI to persistent PNI combined with vein location in selected studies.

Time to recovery PPNI (secondary outcome)

From various definitions of persistent phrenic nerve injury (beyond procedure/discharge), we established the definition as impairment of diagrammatic stimulation beyond the time of hospitalization. In 37 studies with 194 cases it was decided that after recalculating those occurrences after the procedure but not after hospitalization to define that group as transient PNI. Eighty-one persistent PNI after CB-1 and 113 after CB-2 generation were noted. In the CB-1 group, almost half of the nerve injuries (40 PPNI; 49,4%) were associated with 23 mm, although the use of CB1-23 mm accounted for almost a quarter of the total first generation (n = 1164; 25.9%).

In CB-2, the use of 23 mm significantly decreased to n = 192 (3.3%) after which the incidence with 23 mm became statistically insignificant. In CB-2, CMAP usage became a marker. Seventy-three (64.6%) PPNI occurred without the CMAP, and 40 (35.4%) occurred with CMAP use ($p < 0.05$).

We investigated the time to recovery based on the registries. The information was found in 27 studies by observing 150 PPNI, 66 from CB-1 and 84 from CB-2. Precise data with time to resolution were collected from 138 PNI and divided into persistent PNI-CMAP and persistent PNI non-CMAP protection groups. The median time to recovery in the persistent PNI with CMAP group was three months (standard deviation [SD] 3.45; 95%CI 1.9–4.1) while without CMAP protection, this time was prolonged to six months (SD 4.1; 95%CI 5.2–6.8) with statical significance based on Wilcoxon Peto's log-rank test ($p = 0.012$) as shown in Fig. 5. Only 12 results were described as unresolved ranging over 24 months beyond the observation period. The longest time of observation of unresolved persistent PNI reach over 36 month [46]. Detailed information of PNI follow-up can be found in the supplemental publication material.

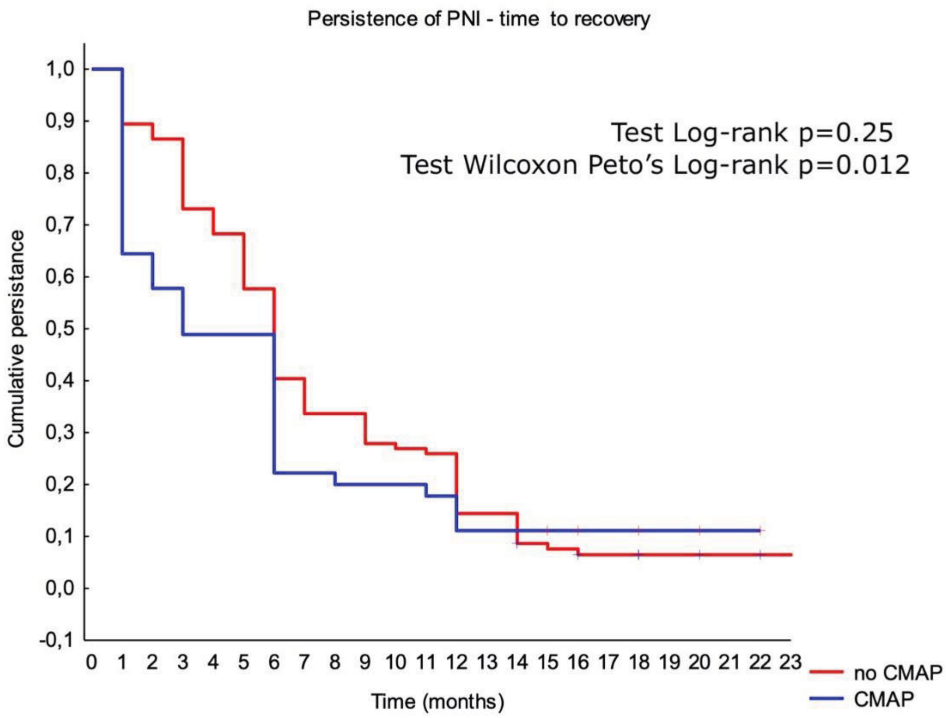

Fig. 5. Kaplan–Meier survival plot of time to recovery from persistent phrenic nerve injury. CMAP — compound motor action potentials, PNI — phrenic nerve injury.

Discussion

From the very beginning of the CBA procedure, PNI was associated with right-sided pulmonary vein isolation. No CBA registry in literature without PNI can be found, and every comparison or meta-analysis between RF ablation and cryo-registry shows a disadvantage in this field [6, 24, 31, 37, 41, 43, 49, 63, 64]. The reason for this issue is a combination of the right phrenic nerve course and cryo-energy dispersion delivered during the procedure [4, 65]. Any assessment of distance between PVI ostium and PN may only alert for potential, upcoming complications [4]. Nevertheless, PNI complication is heterogeneous. From our perspective, TPNI (5.7%), resolving until the end of the procedure is a mild complication resulting incomplete or short time vein isolation and up to the day of discharge, also requires an additional X-ray. The serious problem occurs with PPNI (1.9%) that extends beyond the hospital discharge. Most patients have no symptoms during rest, whereas physical activity induces symptoms, such as dyspnea [66, 67]. The time for PNI resolution varies significantly. Most can take up to six months to resolve, and almost all are resolved by 12 months. Patients with PPNI need regular checkups and fluoroscopic or sonographic evaluation [64]. We conducted that the first-generation of CB (CB-1) 23 mm CB-1 (deeper seating), which increased the risk of PNI almost three-fold [9]. In the second-generation CBA, a redesigned cooling area caused an increase in the incidence rate, reaching almost 20% overall in some trials [2, 10, 33, 37, 57]. Various anatomical predictors were proposed for preventing PNI [68]. The CMAP presented by Franceschi [15] can be called a game-changer by decreasing the amount of persistent PNI. After implementing this method, the PNI decreased significantly from 2.3 to 1.1%. Monitoring diaphragmatic CMAP during phrenic nerve injury capture allows earlier detection of phrenic nerve dysfunction [15, 30, 36]. The mean difference in time to PNI between CMAP and the non-CMAP group was shorter, and the temperature was higher, thus causing a benign injury. Lower temperatures and longer applications caused an increase in the risk of PNI, which was also observed by other authors [48]. Analysis of cycle length of phrenic nerve stimulation with the impulse strength did not reveal any statistical favorites; however the Okishige *et al.* proved that the PNI manifested earlier with weaker power of stimulation [53]. This effect might by intensified among patients with superior vena cava compression [69] or wall thickening observed in multi electrode pacing devices [70–72].

Nevertheless, no technique eliminates the risk of PNI associated with CBA. From this record, long, persistent PNI lasting beyond the time of observation have been reported with and without CMAP [34, 35, 47, 48]. Finally, the amount of PPNI with CMAP decreased and the median time to resolution was shortened from six to three months. This meta-analysis summarizes the findings that CMAP should be obligatorily implemented during each CBA.

Contributions

M.K.: the concept and design, data collection, statistical analysis, writing the manuscript. M.K.: the inspiration, concept and design, revising article critically for important intellectual content, final approval of the version to be submitted. N.J.: English language support. G.K, T.R, R.B, J.L.: revising article critically for important intellectual content. All authors have approved the final article.

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Disclosures

None declared.

Conflict of interest

None declared.

List of Abbreviations

CB-1	—	first cryoballoon generation
CB-2	—	second cryoballoon generation
CBA	—	cryoballoon ablation
CB-ST	—	short tip cryoballoon generation
CMAP	—	compound motor action potentials
IBD	—	immediate balloon deflation
PNI	—	phrenic nerve injury
PPNI	—	persistent phrenic nerve injury
RIPV	—	right interior pulmonary vein
RSPV	—	right superior pulmonary vein
TPNI	—	transient phrenic nerve injury

References

1. *Sorgente A., Chierchia G.B., de Asmundis C., Capulzini L., Sarkozy A., Brugada P.*: Cryoballoon ablation of atrial fibrillation: state of the art 10 years after its invention. Recent Pat Cardiovasc Drug Discov. 2010 Nov; 5 (3): 177–183. doi: 10.2174/157489010793351917. PMID: 20874670.
2. *Packer D.L., Kowal R.C., Wheelan K.R., et al.*: STOP AF Cryoablation Investigators. 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 Apr 23; 61 (16): 1713–1723. doi: 10.1016/j.jacc.2012.11.064. Epub 2013 Mar 21. PMID: 23500312.
3. *Calkins H., Kuck K.H., Cappato R., et al.*: 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural

techniques, patient management and follow-up, definitions, endpoints, and research trial design. J Interv Card Electrophysiol. 2012 Mar; 33 (2): 171–257. doi: 10.1007/s10840-012-9672-7. PMID: 22382715.
4. *Kuniewicz M., Mazur M., Karkowski G., Budnicka K., Przybycień W., Walocha J., Lelakowski J.*: Tracing The Right Phrenic Nerve — A Systematic Review and Meta-Analysis. J Atr Fibrillation. 2020 Oct 13; 3: 1–8.
5. *Saitoh Y., Irfan G., Ciconte G., et al.*: Persistence of Phrenic Nerve Palsy Following 28-mm Cryoballoon Ablation: A Four-Year Single Center Experience. Pacing Clin Electrophysiol. 2015 Jul; 38 (7): 807–814. doi: 10.1111/pace.12636. Epub 2015 Apr 27. PMID: 25851416.
6. *Aryana A., Singh S.M., Kowalski M., et al.*: Acute and Long-Term Outcomes of Catheter Ablation of Atrial Fibrillation Using the Second-Generation Cryoballoon versus Open-Irrigated Radiofrequency: A Multicenter Experience. J Cardiovasc Electrophysiol. 2015 Aug; 26 (8): 832–839. doi: 10.1111/jce.12695. Epub 2015 Jun 4. PMID: 25917655.
7. *Okishige K., Aoyagi H., Kawaguchi N., et al.*: Novel method for earlier detection of phrenic nerve injury during cryoballoon applications for electrical isolation of pulmonary veins in patients with atrial fibrillation. Heart Rhythm. 2016 Sep; 13 (9): 1810–1816. doi: 10.1016/j.hrthm.2016.05.003. Epub 2016 May 3. PMID: 27154231.
8. *Fürnkranz A., Bordignon S., Schmidt B., et al.*: Incidence and characteristics of phrenic nerve palsy following pulmonary vein isolation with the second-generation as compared with the first-generation cryoballoon in 360 consecutive patients. 2015 Apr; 17 (4): 574–578. doi: 10.1093/europace/euu320. Epub 2015 Jan 6. PMID: 25564551.
9. *Andrade J.G., Khairy P., Guerra P.G., et al.*: Efficacy and safety of cryoballoon ablation for atrial fibrillation: a systematic review of published studies. Heart Rhythm. 2011 Sep; 8 (9): 1444–1451. doi: 10.1016/j.hrthm.2011.03.050. Epub 2011 Mar 30. Erratum in: Heart Rhythm. 2011 Nov; 8 (11): 1828. PMID: 21457789.
10. *Martins R.P., Hamon D., Césari O., et al.*: Safety and efficacy of a second-generation cryoballoon in the ablation of paroxysmal atrial fibrillation. Heart Rhythm. 2014 Mar; 11 (3): 386–393. doi: 10.1016/j.hrthm.2014.01.002. Epub 2014 Jan 1. PMID: 24389575.
11. *Fürnkranz A., Bordignon S., Dugo D., et al.*: Improved 1-year clinical success rate of pulmonary vein isolation with the second-generation cryoballoon in patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2014 Aug; 25 (8): 840–844. doi: 10.1111/jce.12417. Epub 2014 May 2. PMID: 24654794.
12. *Giovanni G.D., Wauters K., Chierchia G.B., et al.*: One-year follow-up after single procedure Cryoballoon ablation: a comparison between the first and second generation balloon. J Cardiovasc Electrophysiol. 2014 Aug; 25 (8): 834–839. doi: 10.1111/jce.12409. Epub 2014 Apr 9. PMID: 24641307.
13. *Casado-Arroyo R., Chierchia G.B., Conte G., et al.*: Phrenic nerve paralysis during cryoballoon ablation for atrial fibrillation: a comparison between the first- and second-generation balloon. Heart Rhythm. 2013 Sep; 10 (9): 1318–1324. doi: 10.1016/j.hrthm.2013.07.005. Epub 2013 Jul 24. PMID: 23891574.
14. *Su W., Kowal R., Kowalski M., Metzner A., Svinarich J.T., Wheelan K., Wang P.*: Best practice guide for cryoballoon ablation in atrial fibrillation: The compilation experience of more than 3000 procedures. Heart Rhythm. 2015 Jul; 12 (7): 1658–1666. doi: 10.1016/j.hrthm.2015.03.021. Epub 2015 Mar 14. PMID: 25778428.
15. *Franceschi F., Dubuc M., Guerra P.G., Khairy P.*: Phrenic nerve monitoring with diaphragmatic electromyography during cryoballoon ablation for atrial fibrillation: the first human application. Heart Rhythm. 2011 Jul; 8 (7): 1068–1071. doi: 10.1016/j.hrthm.2011.01.047. Epub 2011 Feb 9. PMID: 21315843.
16. *Mondésert B., Andrade J.G., Khairy P., et al.*: Clinical experience with a novel electromyographic approach to preventing phrenic nerve injury during cryoballoon ablation in atrial fibrillation. Circ Arrhythm Electrophysiol. 2014 Aug; 7 (4): 605–611. doi: 10.1161/CIRCEP.113.001238. Epub 2014 Jul 13. Erratum in: Circ Arrhythm Electrophysiol. 2014 Oct; 7 (5): 995. Shohoudi, Azadeh [added]. PMID: 25017398.

17. *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 Mar; 11 (3): 369–374. doi: 10.1016/j.hrthm.2013.11.015. Epub 2013 Nov 16. PMID: 24252287.
18. *Moher D., Liberati A., Tetzlaff J., Altman D.G., Group P.*: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010; 8 (5): 336–341.
19. *Wells G., Shea B., O'Connell D., Robertson J., Peterson J., Welch V., et al.*: The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses Ottawa Health Research Institute. 2013. Available at: http: //www.ohri. ca/programs/clinical-epidemiology/oxford.Asp.
20. *Malmborg H., Lönnerholm S., Blomström-Lundqvist C.*: Acute and clinical effects of cryoballoon pulmonary vein isolation in patients with symptomatic paroxysmal and persistent atrial fibrillation. Europace. 2008 Nov; 10 (11): 1277–1280. doi: 10.1093/europace/eun286. PMID: 18955410.
21. *Neumann T., Vogt J., Schumacher B., et al.*: Circumferential pulmonary vein isolation with the cryoballoon technique results from a prospective 3-center study. J Am Coll Cardiol. 2008 Jul 22; 52 (4): 273–278. doi: 10.1016/j.jacc.2008.04.021. PMID: 18634982.
22. *Van Belle Y., Janse P., Theuns D., Szili-Torok T., Jordaens L.*: One year follow-up after cryoballoon isolation of the pulmonary veins in patients with paroxysmal atrial fibrillation. Europace. 2008 Nov; 10 (11): 1271–1276. doi: 10.1093/europace/eun218. PMID: 18955409; PMCID: PMC2573029.
23. *Chun K.R., Schmidt B., Metzner A., et al.*: The 'single big cryoballoon' technique for acute pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a prospective observational single centre study. Eur Heart J. 2009 Mar; 30 (6): 699–709. doi: 10.1093/eurheartj/ehn570. Epub 2008 Dec 24. PMID: 19109353; PMCID: PMC2655313.
24. *Linhart M., Bellmann B., Mittmann-Braun E., et al.*: Comparison of cryoballoon and radiofrequency ablation of pulmonary veins in 40 patients with paroxysmal atrial fibrillation: a case-control study. J Cardiovasc Electrophysiol. 2009 Dec; 20 (12): 1343–1348. doi: 10.1111/j.1540-8167.2009.01560.x. PMID: 19656254.
25. *Kojodjojo P., O'Neill M.D., Lim P.B., et al.*: Pulmonary venous isolation by antral ablation with a large cryoballoon for treatment of paroxysmal and persistent atrial fibrillation: medium-term outcomes and non-randomised comparison with pulmonary venous isolation by radiofrequency ablation. Heart. 2010 Sep; 96 (17): 1379–1384. doi: 10.1136/hrt.2009.192419. PMID: 20801856; PMCID: PMC2976075.
26. *Dorwarth U., Schmidt M., Wankerl M., Krieg J., Straube F., Hoffmann E.*: Pulmonary vein electrophysiology during cryoballoon ablation as a predictor for procedural success. J Interv Card Electrophysiol. 2011 Dec; 32 (3): 205–211. doi: 10.1007/s10840-011-9585-x. Epub 2011 May 19. PMID: 21594628.
27. *Guiot A., Savouré A., Godin B., Anselme F.*: Collateral nervous damages after cryoballoon pulmonary vein isolation. J Cardiovasc Electrophysiol. 2012 Apr; 23 (4): 346–351. doi: 10.1111/j.1540-8167.2011.02219.x. Epub 2011 Nov 14. PMID: 22081875.
28. *Jackson N., Barlow M., Leitch J., Attia J.*: Treating atrial fibrillation: pulmonary vein isolation with the cryoballoon technique. Heart Lung Circ. 2012 Aug; 21 (8): 427–432. doi: 10.1016/j.hlc.2012.03.123. Epub 2012 May 2. PMID: 22554875.
29. *Kühne M., Knecht S., Altmann D., et al.*: Phrenic nerve palsy during ablation of atrial fibrillation using a 28-mm cryoballoon catheter: predictors and prevention. J Interv Card Electrophysiol. 2013 Jan; 36 (1): 47–54; discussion 54. doi: 10.1007/s10840-012-9740-z. Epub 2012 Oct 23. PMID: 23090778.
30. *Ghosh J., Sepahpour A., Chan K.H., Singarayar S., McGuire M.A.*: Immediate balloon deflation for prevention of persistent phrenic nerve palsy during pulmonary vein isolation by balloon cryoablation. Heart Rhythm. 2013 May; 10 (5): 646–652. doi: 10.1016/j.hrthm.2013.01.011. Epub 2013 Jan 16. PMID: 23333737.
31. *Mugnai G., Chierchia G.B., de Asmundis C., et al.*: Comparison of pulmonary vein isolation using cryoballoon versus conventional radiofrequency for paroxysmal atrial fibrillation. Am J Cardiol. 2014 May 1; 113 (9): 1509–1513. doi: 10.1016/j.amjcard.2014.01.425. Epub 2014 Feb 12. PMID: 24630388.

32. *Vogt J., Heintze J., Gutleben K.J., Muntean B., Horstkotte D., Nölker G.*: Long-term outcomes after cryoballoon pulmonary vein isolation: results from a prospective study in 605 patients. J Am Coll Cardiol. 2013 Apr 23; 61 (16): 1707–1712. doi: 10.1016/j.jacc.2012.09.033. Epub 2012 Nov 28. PMID: 23199518.
33. *Ang R., Hunter R.J., Baker V., et al.*: Pulmonary vein measurements on pre-procedural CT/MR imaging can predict difficult pulmonary vein isolation and phrenic nerve injury during cryoballoon ablation for paroxysmal atrial fibrillation. Int J Cardiol. 2015 Sep 15; 195: 253–258. doi: 10.1016/j.ijcard.2015.05.089. Epub 2015 May 21. PMID: 26048388.
34. *Aryana A., Morkoch S., Bailey S., Lim H.W., Sara R., d'Avila A., O'Neill P.G.*: Acute procedural and cryoballoon characteristics from cryoablation of atrial fibrillation using the first- and second-generation cryoballoon: a retrospective comparative study with follow-up outcomes. J Interv Card Electrophysiol. 2014 Nov; 41 (2): 177–186. doi: 10.1007/s10840-014-9942-7. Epub 2014 Sep 17. PMID: 25227868.
35. *Aytemir K., Gurses K.M., Yalcin M.U., et al.*: Safety and efficacy outcomes in patients undergoing pulmonary vein isolation with second-generation cryoballoon. Europace. 2015 Mar; 17 (3): 379–387. doi: 10.1093/europace/euu273. Epub 2014 Nov 5. PMID: 25376699.
36. *Mondésert B., Andrade J.G., Khairy P., et al.*: Clinical experience with a novel electromyographic approach to preventing phrenic nerve injury during cryoballoon ablation in atrial fibrillation. Circ Arrhythm Electrophysiol. 2014 Aug; 7 (4): 605–611. doi: 10.1161/CIRCEP.113.001238. Epub 2014 Jul 13. Erratum in: Circ Arrhythm Electrophysiol. 2014 Oct; 7 (5): 995. Shohoudi, Azadeh [added]. PMID: 25017398.
37. *Jourda F., Providencia R., Marijon E., et al.*: Contact-force guided radiofrequency vs. second-generation balloon cryotherapy for pulmonary vein isolation in patients with paroxysmal atrial fibrillation-a prospective evaluation. Europace. 2015 Feb; 17 (2): 225–231. doi: 10.1093/europace/euu215. Epub 2014 Sep 3. PMID: 25186456.
38. *Metzner A., Rausch P., Lemes C., et al.*: The incidence of phrenic nerve injury during pulmonary vein isolation using the second-generation 28 mm cryoballoon. J Cardiovasc Electrophysiol. 2014 May; 25 (5): 466–470. doi: 10.1111/jce.12358. Epub 2014 Jan 30. PMID: 24400647.
39. *Greiss H., Berkowitsch A., Wojcik M., et al.*: The Impact of Left Atrial Surface Area and the Second Generation Cryoballoon on Clinical Outcome of Atrial Fibrillation Cryoablation. Pacing Clin Electrophysiol. 2015 Jul; 38 (7): 815–824. doi: 10.1111/pace.12637. Epub 2015 May 15. PMID: 25851511.
40. *Liu J., Kaufmann J., Kriatselis C., Fleck E., Gerds-Li J.H.*: Second generation of cryoballoons can improve efficiency of cryoablation for atrial fibrillation. Pacing Clin Electrophysiol. 2015 Jan; 38 (1): 129–135. doi: 10.1111/pace.12538. Epub 2014 Dec 12. PMID: 25494851.
41. *Luik A., Radzewitz A., Kieser M., et al.*: Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study. Circulation. 2015 Oct 6; 132 (14): 1311–1319. doi: 10.1161/CIRCULATIONAHA.115.016871. Epub 2015 Aug 17. PMID: 26283655; PMCID: PMC4590523.
42. *Meissner A., Maagh P., Christoph A., Oernek A., Plehn G.*: ECG-Guided Surveillance Technique in Cryoballoon Ablation for Paroxysmal and Persistent Atrial Fibrillation: A Strategy to Prevent From Phrenic Nerve Palsy. Int J Med Sci. 2016 May 10; 13 (6): 403–411. doi: 10.7150/ijms.14383. PMID: 27279788; PMCID: PMC4893553.
43. *Wasserlauf J., Pelchovitz D.J., Rhyner J., et al.*: Cryoballoon versus radiofrequency catheter ablation for paroxysmal atrial fibrillation. Pacing Clin Electrophysiol. 2015 Apr; 38 (4): 483–489. doi: 10.1111/pace.12582. Epub 2015 Jan 28. PMID: 25627795.
44. *Aryana A., Kowalski M., O'Neill PG, 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 Dec; 13 (12): 2306–2313. doi: 10.1016/j.hrthm.2016.08.011. Epub 2016 Aug 5. PMID: 27503480.
45. *Guhl E.N., Siddoway D., Adelstein E., et al.*: Incidence and Predictors of Complications During Cryoballoon Pulmonary Vein Isolation for Atrial Fibrillation. J Am Heart Assoc. 2016 Jul 21; 5 (7): e003724. doi: 10.1161/JAHA.116.003724. PMID: 27444510; PMCID: PMC5015404.

46. *Kardos A., Kis Z., Som Z., Nagy Z., Foldesi C.*: Two-Year Follow-Up after Contact Force Sensing Radiofrequency Catheter and Second-Generation Cryoballoon Ablation for Paroxysmal Atrial Fibrillation: A Comparative Single Centre Study. Biomed Res Int. 2016; 2016: 6495753. doi: 10.1155/2016/6495753. Epub 2016 May 22. PMID: 27314032; PMCID: PMC4893449.
47. *Mugnai G., de Asmundis C., Velagic V., et al.*: Phrenic nerve injury during ablation with the second-generation cryoballoon: analysis of the temperature drop behaviour in a large cohort of patients. Europace. 2016 May; 18 (5): 702–709. doi: 10.1093/europace/euv346. Epub 2015 Nov 11. PMID: 26564954.
48. *Paylos J.M., Morales A., Azcona L., et al.*: Long-Term Evolution of Patients Treated for Paroxysmal Atrial Fibrillation with First and Second Generation Cryoballoon Catheter Ablation with a Prospective Protocol Guided by Complete Bidirectional Left Atrium-Pulmonary Veins Disconnection after Adenosine as Main Target end Point to achieved. Seven Years Follow-up of Patients with a rough estimation profile of Low ALARMEc Score. A Single Center Report. J Atr Fibrillation. 2016 Apr 30; 8 (6): 1400. doi: 10.4022/jafib.1400. PMID: 27909504; PMCID: PMC5089479.
49. *Providencia R., Defaye P., Lambiase P.D., et al.*: Results from a multicentre comparison of cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: is cryoablation more reproducible? Europace. 2017 Jan; 19 (1): 48–57. doi: 10.1093/europace/euw080. Epub 2016 Jun 5. PMID: 27267554.
50. *Straube F., Hartl S., Dorwarth U., Wankerl M., Bunz B., Ebersberger U., Hoffmann E.*: Cryoballoon ablation for persistent atrial fibrillation — Large single-center experience. J Cardiol. 2016 Dec; 68 (6): 492–497. doi: 10.1016/j.jjcc.2016.02.007. Epub 2016 Mar 11. PMID: 26976341.
51. *Yalin K., Abdin A., Lyan E., et al.*: Safety and efficacy of persistent atrial fibrillation ablation using the second-generation cryoballoon. Clin Res Cardiol. 2018 Jul; 107 (7): 570–577. doi: 10.1007/s00392-018-1219-1. Epub 2018 Feb 28. PMID: 29492703.
52. *Miyazaki S., Kajiyama T., Watanabe T., 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 Mar 24; 7 (7): e008249. doi: 10.1161/JAHA.117.008249. PMID: 29574457; PMCID: PMC5907598.
53. *Okishige K., Aoyagi H., Shigeta T., et al.*: Quick, safe, and effective maneuver to prevent phrenic nerve injury during cryoballoon ablation of atrial fibrillation. J Interv Card Electrophysiol. 2018 Nov; 53 (2): 233–238. doi: 10.1007/s10840-018-0379-2. Epub 2018 May 24. PMID: 29797153.
54. *Mörtsell D., Malmborg H., Lönnerholm S., Jansson V., Blomström-Lundqvist C.*: Acute and long-term efficacy and safety with a single cryoballoon application as compared with the standard dual application strategy: a prospective randomized study using the second-generation cryoballoon for pulmonary vein isolation in patients with symptomatic atrial fibrillation. Europace. 2018 Oct 1; 20 (10): 1598–1605. doi: 10.1093/europace/euy014. PMID: 29420721.
55. *Akkaya E., Berkowitsch A., Zaltsberg S., et al.*: Five-year outcome and predictors of success after second-generation cryoballoon ablation for treatment of symptomatic atrial fibrillation. Int J Cardiol. 2018 Sep 1; 266: 106–111. doi: 10.1016/j.ijcard.2018.03.069. PMID: 29887425.
56. *Su W., Orme G.J., Hoyt R., et al.*: Retrospective review of Arctic Front Advance Cryoballoon Ablation: a multicenter examination of second-generation cryoballoon (RADICOOL trial). J Interv Card Electrophysiol. 2018 Apr; 51 (3): 199–204. doi: 10.1007/s10840-018-0335-1. Epub 2018 Feb 24. PMID: 29478173.
57. *Molenaar M.M.D., Timmermans C.C., Hesselink T., 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 May; 42 (5): 508–514. doi: 10.1111/pace.13626. Epub 2019 Mar 5. PMID: 30756393; PMCID: PMC6850154.
58. *Chikata A., Kato T., Usuda K., et al.*: Coronary sinus catheter placement via left cubital vein for phrenic nerve stimulation during pulmonary vein isolation. Heart Vessels. 2019 Oct; 34 (10): 1710–1716. doi: 10.1007/s00380-019-01402-4. Epub 2019 Apr 10. PMID: 30972550.

59. *Chan N.Y., Choy C.C., Yuen H.C., Chow H.F., Fong H.F.*: Long-term outcomes of cryoballoon pulmonary vein isolation for paroxysmal and persistent atrial fibrillation in Chinese patients. J Interv Card Electrophysiol. 2020 Apr; 57 (3): 425–434. doi: 10.1007/s10840-019-00542-x. Epub 2019 Apr 23. PMID: 31016428.
60. *Sano M., Urushida T., Matsukura G., et al.*: Clinical feasibility of pulmonary vein orifice pacing for the prediction of phrenic nerve injury during cryoballoon ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2019 Aug; 30 (8): 1200–1206. doi: 10.1111/jce.13962. Epub 2019 May 15. PMID: 31045300.
61. *Van Belle Y., Janse P., Rivero-Ayerza M.J., Thornton A.S., Jessurun E.R., Theuns D., Jordaens L.*: Pulmonary vein isolation using an occluding cryoballoon for circumferential ablation: feasibility, complications, and short-term outcome. Eur Heart J. 2007 Sep; 28 (18): 2231–2237. doi: 10.1093/eurheartj/ehm227. Epub 2007 Jun 14. PMID: 17569680.
62. *Ströker E., de Asmundis C., Saitoh Y., et al.*: Anatomic predictors of phrenic nerve injury in the setting of pulmonary vein isolation using the 28-mm second-generation cryoballoon. Heart Rhythm. 2016 Feb; 13 (2): 342–351. doi: 10.1016/j.hrthm.2015.10.017. Epub 2015 Oct 13. PMID: 26573972.
63. *Whiteman S., Saker E., Courant V., Salandy S., Gielecki J., Zurada A., Loukas M.*: An Anatomical Review of the Left Atrium. Transl Res Anat. 2019; 17: 100052.
64. *Cheng X., Hu Q., Zhou C., Liu L.Q., Chen T., Liu Z., Tang X.*: The long-term efficacy of cryoballoon vs irrigated radiofrequency ablation for the treatment of atrial fibrillation: A meta-analysis. Int J Cardiol. 2015 Feb 15; 181: 297–302. doi: 10.1016/j.ijcard.2014.12.002. Epub 2014 Dec 3. PMID: 25540844.
65. *Ciconte G., Baltogiannis G., de Asmundis C., et al.*: Circumferential pulmonary vein isolation as index procedure for persistent atrial fibrillation: a comparison between radiofrequency catheter ablation and second-generation cryoballoon ablation. Europace. 2015 Apr; 17 (4): 559–565. doi: 10.1093/europace/euu350. Epub 2015 Jan 12. PMID: 25582875.
66. *Heeger C.H., Pott A., Sohns C., et al.*: Phrenic nerve injury during pulmonary vein isolation using the second-generation cryoballoon: characteristics and follow-up — The YETI registry. European Heart Journal. 2019; 40 (Suppl 1): 6121.
67. *Sacher F., Monahan K.H., Thomas S.P., et al.*: Phrenic nerve injury after atrial fibrillation catheter ablation: characterization and outcome in a multicenter study. J Am Coll Cardiol. 2006 Jun 20; 47 (12): 2498–2503. doi: 10.1016/j.jacc.2006.02.050. PMID: 16781380.
68. *Knecht S., Kühne M., Altmann D., Ammann P., Schaer B., Osswald S., Sticherling C.*: Anatomical predictors for acute and mid-term success of cryoballoon ablation of atrial fibrillation using the 28 mm balloon. J Cardiovasc Electrophysiol. 2013 Feb; 24 (2): 132–138. doi: 10.1111/jce.12003. Epub 2012 Nov 6. PMID: 23130991.
69. *Matusik P.T., Tomala I., Piekarz I., Karkowski G., Kuniewicz M., Lelakowski J.*: Thyroid goiter: implications for implantation of cardiovascular implantable electronic devices and cannulation of the superior vena cava confluence. Pol Arch Med Wewn. 2016 Jun 30; 126 (6): 432–434. doi: 10.20452/pamw.3459. Epub 2016 Jun 30. PMID: 27362396.
70. *Dębski M., Ulman M., Ząbek A., et al.*: Association of selected factors with long-term prognosis and mortality after dual-chamber pacemaker implant. Cardiol J. 2019; 26 (6): 717–726. doi: 10.5603/CJ.a2018.0093. Epub 2018 Aug 29. PMID: 30155863; PMCID: PMC8083035.
71. *Dębski M., Maniecka-Bryła I., Dziankowska-Zaborszczyk E., et al.*: Years of life lost as a measure of premature death among dual-chamber pacemaker recipients from Małopolska Province. Kardiol Pol. 2019 Aug 23; 77 (7–8): 683–687. doi: 10.33963/KP.14839. Epub 2019 May 21. PMID: 31113926.
72. *Kuniewicz M., Walocha J.A., Budnicka K., Mazur M., Walocha E., Jurczyk M.*: Electrode ingrowths revealed during cadaveric dissection of a 5y old implanted pacemaker — the case report. Folia Med Cracov. 2019; 59 (2): 61–66. PMID: 31659349.