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Practice Guidelines

A novel strategy to treat vaso-vagal syncope: Cardiac neuromodulation by cryoballoon pulmonary vein isolation

Riccardo Maj^{a,1,*}, Thiago Guimarães Osório^{a,1}, Gianluca Borio^a, Saverio Iacopino^b, Erwin Ströker^a, Juan Sieira^a, Murryo Terasawa^a, Shuichiro Kazawa^a, Alessandro Rizzo^a, Alessio Galli^a, Varnavas Varnavas^a, Gezim Bala^a, Xavier Galloo^a, Gaetano Paparella^a, Pedro Brugada^a, Yves De Greef^c, Carlo De Asmundis^a, Gian Battista Chierchia^a

^a Heart Rhythm Management Center, UZ Brussel-VUB, Laarbeeklaan 101, 1090, Brussels, Belgium

^b Electrophysiology Unit, Villa Maria Cecilia, Via Corriera, 1, 48033, Cotignola, RA, Italy

^c Electrophysiology Unit, ZNA Middelheim, Lindendreef 1, 2020, Antwerp, Belgium

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ABSTRACT

Background: Clinical management of vaso-vagal syncope (VVS) remains challenging since no therapy has proven to completely prevent VVS recurrence.

Objective: The purpose of this study was to analyze the mid-term outcome of cryoballoon (CB) cardioneuroablation achieved by pulmonary vein isolation (PVI) in patients with VVS.

Methods: Patients who underwent CB cardioneuroablation in our centers between January 2014 to June 2018 were included. All patients had a history of VVS or pre-syncope despite therapeutic attempts with medical and/or pacing treatments. Patients were excluded in case of structural heart diseases, cerebrovascular diseases or suspected drug-related syncope. Both heart rate (HR) and atrio-ventricular (AV) interval were analyzed on the 12-lead electrocardiogram (ECG) the day before the procedure, the day after, and in the follow-up.

Results: In total, 26 patients (76.9% males, 37.5 ± 9.0 years old) were included. All patients underwent a successful procedure with the 28 mm second-generation Arctic Front Advance CB. No major complication occurred. At a mean follow-up of 20.1 ± 11.6 months the freedom from VVS or reflex pre-syncope was 83.7%, with 22 patients free from any clinical recurrence. Basal HR significantly increased the day after the procedure (57.2 bpm vs 78.3 bpm, $p < 0.001$), while at the final follow-up it stabilized at a value halfway between the 2 previous ones (69.8 bpm, $p = 0.0086$). The AV interval didn't modify significantly after the procedure.

Conclusion: Endocardial autonomic denervation achieved by CB PVI appears to be an effective and safe treatment option for patients with refractory VVS and reflex pre-syncope.

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1. Introduction

Vasovagal syncope (VVS) is a transient loss of consciousness due to a sudden drop of blood pressure (BP) caused by reflex peripheral vasodilatation combined with bradycardia [1]. It is a common

condition in the general population, frequently affecting young patients, as it represents the most frequent cause of syncope [2]. Despite the excellent prognosis of patients with reflex syncope [3], still, VVS can impair significantly the patients' quality of life (QoL), particularly when the episodes of VVS are recurrent [4]. As the exact mechanism underlying and triggering this clinical condition continues to be subject of studies and discussion, at the moment no therapy (i.e. physical maneuvers, tilt training, pharmacological therapy, cardiac pacing) has proven to completely prevent reflex syncope recurrence during long-term follow-up [1,5]. Among all the treatments, endocardial radiofrequency (RF) ablation of the ganglionated plexi (GPs) and parasympathetic network located

* Corresponding author.

E-mail addresses: maj.riccardo@gmail.com, riccardo.maj01@universitadipavia.it (R. Maj).

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¹ Maj Riccardo and Osório Thiago Guimarães contributed equally to the work as co-first authors.

close to the sinus node (SN) and atrio-ventricular node (AVN) has shown excellent long-term results in well-selected patients in some observational studies [6] and case reports [7]. Cryoballoon ablation (CB-A) has shown promising results in achieving freedom from arrhythmia [8], especially since the second-generation version of the CB (Arctic Front Advance, Medtronic, MN, USA) has been released on the market. Moreover, this new technique has shown to be associated with significant autonomic nervous system (ANS) modulation while achieving electrical pulmonary vein isolation (PVI) [9], due to the effect of cryoenergy on the GPs, normally located between the left atrium (LA) and the pulmonary vein (PV) junction. In this study, we analyze the acute success, the complication rates and the mid-term clinical outcomes in terms of VVS recurrences after PVI achieved with CB-A in a series of patients with VVS.

2. Methods

2.1. Study population

The study retrospectively enrolled patients who underwent CB-A cardioablation in our centers (Heart Rhythm Management Centre, UZ Brussels and ZNA Middelheim, Antwerp) between June 2014 and June 2018; all patients had a history of VVS despite therapeutic attempts with both medical (i.e. salt and fluid intake, physical counterpressure training) and/or pacing treatments. The diagnosis of VVS was based on clinical history and diagnostic features like predisposing situations, prodromal symptoms, physical signs, and immediate recovery after the event [1]. All patients included provided detailed medical history and underwent a physical examination, electrocardiography (ECG), *trans*-thoracic echocardiography (TTE), and prolonged ECG monitoring, if needed, to exclude other cardiac causes for syncope. Patients were excluded from this study in case of structural heart diseases (e.g. cardiac valvular diseases, coronary artery disease, pulmonary hypertension and cardiomyopathy), cerebrovascular diseases or suspected drug-related syncope (e.g. vasodilators, antipsychotics, etc). The study was approved by the local Ethical Committee of our Institutions.

2.2. Aim of the study

The main aim of the study was to analyze the mid-term outcome of cryoballoon cardioablation in patients with VVS.

2.3. Pre-procedural management

ATTE was performed within 1 week prior to ablation. To exclude the presence of intracavitary thrombi, all patients underwent transoesophageal echocardiography (TEE) the day before the procedure. All patients underwent a pre-procedural computed tomography (CT) scan to assess detailed LA and PV anatomy. The LA diameter (LAD) was assessed by 2D transthoracic echocardiography as the LA antero-posterior diameter measured during parasternal long-axis M-mode recordings and indexed to body surface area (BSA). All antiarrhythmic drugs (AADs) were discontinued at least 3 days prior to ablation. Both basal heart rate (HR) and atrio-ventricular (AV) interval were analyzed on the 12-lead ECG taken on the day of the procedure.

2.4. Ablation procedure

Our standard ablation procedure has been previously reported in detail [10]. Briefly after having obtained LA access through a single *trans*-septal puncture, an inner-lumen mapping catheter (ILMC) (Achieve mapping catheter, Medtronic, MN, USA) was

advanced to each PV ostium through a steerable 15 Fr sheath (FlexCath Advance, Medtronic, MN, USA). A second-generation 28-mm CB-A (Arctic Front Advance™, Medtronic, MN, USA) was advanced, inflated, and positioned at each PV ostium. Optimal vessel occlusion was defined by selective iodinated contrast injection, showing complete contrast retention, without any backflow into the LA. Once vessel occlusion was deemed satisfactory, delivery of cryoenergy to allow freezing was commenced. Standard cryothermal applications lasted 180 s, and we opted for a single cryoapplication for PV strategy. The usual ablation sequence was treating the left superior PV (LSPV) first, followed by the left inferior (LIPV), the right inferior (RIPV), and finally the right superior (RSPV). PV electrical activity was recorded using the ILMC at a proximal site within each ostium prior to ablation in each PV and then monitored during the whole application time. During the ablation, if PV potentials (PVPs) were visible during energy delivery, time to isolation (TTI) was recorded when PVPs completely disappeared or were dissociated from LA electrical activity. Further additional cryothermal applications were not considered necessary either if PVs were isolated following the initial freeze or, in case of no PVPs available, if the target temperature of -40°C within 60 s was achieved [11]. If needed, pacing from the distal and/or proximal coronary sinus was performed to distinguish far-field atrial signals from PV potentials recorded on the mapping catheter, for left and right-sided PVs, respectively. During the entire procedure, activated clotting time (ACT) was maintained over 250 s by supplementing heparin infusion, as required.

2.5. Phrenic nerve monitoring

Prior to ablation of the right-sided PVs, a standard decapolar catheter was placed in the superior vena cava (SVC), just cranial to the RSPV, or in the right subclavian vein in order to pace the right phrenic nerve (20 mA at 2.0 msec pulse width at a cycle length of 1200 msec) during ablation. Phrenic nerve capture was monitored both by the femoral venous pressure waveform (VPW) analysis and by the contraction of the right hemidiaphragm, which was observable both by fluoroscopic imaging and with manual palpation of the abdomen. Phrenic nerve pacing started once the temperature during the application reached -20°C , in order to avoid balloon dislodgement due to diaphragmatic contraction in the very first phase of cryoenergy application. Pacing was continued throughout the entire duration of cryoenergy delivery. Cryoenergy application was immediately stopped, with immediate deflation of the CB [12], in case of VPW decrease of more than 50% of the peak-to-peak initial value, and/or if weakening or loss of right diaphragmatic movement was noted.

2.6. Post-ablation management

After the procedure, patients underwent continuous ECG telemetric monitoring until discharge from the hospital. Before discharge, TTE was performed in all patients in order to exclude post-procedural pericardial effusion, and a chest X-ray was also performed. Oral anticoagulation was initiated from the evening of the procedure and continued for at least 3 months. In all patients, AADs were discontinued after the procedure. Both HR and AV interval were analyzed on the 12-lead ECG the day after the procedure.

2.7. Follow-up

After discharge from the hospital, patients were scheduled for follow-up visits at 1, 6, and 12 months (when available) and then every 9–12 months or according to patients' preferences. Resting

ECG and/or 24-h Holter-ECG recordings were obtained at each follow-up visit. Spontaneous recurrences of syncope or pre-syncope were carefully recorded. Both HR and AV interval were analyzed at each follow-up visit. Both resting ECG and 24-h Holter-ECG were reexamined in case of recurrences. All documented AF episodes lasting >30 s after the index procedure were also collected. All reports of Holter monitoring or ECG recordings having been performed in other centers were sent to the Heart Rhythm Management Centre, UZ Brussels or to ZNA Middelheim, Antwerp, for diagnosis confirmation during follow-up.

2.8. Statistical analysis

Categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as mean \pm standard deviation or median and range as appropriate. Event-free survival rates were estimated by the method of Kaplan–Meier. Comparisons of continuous variables were done with a Student's t-test and binomial variables with χ^2 or Fisher's test as appropriate. For each variable, hazard ratio (HR), 95% confidence interval (CI), and P values of the final model are displayed. A 2-tailed probability value of 0,05 was deemed significant. Statistical analyses were conducted using SPSS data analytical software (SPSS v22, Chicago, IL, USA).

3. Results

3.1. Study population

Twenty-six patients (76.9% males, 37.5 ± 9.0 years old) were taken into consideration for our analysis. All patients had neurally-mediated reflex syncope or pre-syncope with recurrent episodes (mean of 2.6 ± 0.8 episodes/patient), refractory to conventional treatments. Sixteen patients (61.5%) had also previously documented episodes of paroxysmal AF. Seven patients (26.9%) were receiving AADs at the time of the procedure: one patient was taking class I AADs and beta-blocker therapy, 3 patients were taking flecainide while 3 other patients were under beta-blocker therapy only. All patients included in the study had a CHADS-VASc score of 0 and no clinical or imaging finding suggestive of any kind of structural heart disease (SHD) was documented. Four patients (15.4%) were considered competitive athletes according to the ESC

Table 1

Baseline characteristics of the study population (AF, atrial fibrillation; BMI, body mass index; BSA, body surface area; CT, computed tomography; LA, left atrium; PV, pulmonary vein; AADs, antiarrhythmic drugs).

Clinical characteristics n = 26	
Age at time of procedure (years \pm SD)	37.5 \pm 9.0
Male gender, n (%)	20 (76.9)
Episodes of syncope/presyncope (episodes \pm SD)	2.6 \pm 0.8
Paroxysmal AF, n (%)	16 (61.5)
BMI (kg/m ² \pm SD)	23.9 \pm 3.4
BSA (m ² \pm SD)	1.9 \pm 0.2
Creatinine before the procedure (mg/kg \pm SD)	0.93 \pm 0.2
Pacemaker recipients, n (%)	4 (18.2)
Anatomical characteristics (echo and CT scan)	
LA indexed diameter (mm/mq \pm SD)	19.4 \pm 2.0
PV: normal anatomy, n (%)	21 (80.7)
PV: left common ostium, n (%)	3 (11.5)
PV: right middle vein, n (%)	2 (7.7)
Therapy pre-ablation	
AADs class I, n (%)	4 (15.4)
Beta-blockers, n (%)	4 (15.4)

Categorical variables are expressed as absolute and percentage (in brackets). Continuous variables are expressed as mean \pm SD.

definition [13]. The mean left atrial volume was 35.8 ± 4.3 ml/mq and the mean index diameter was 19.4 ± 2.4 mm. Detailed baseline characteristics are shown in Table 1.

3.2. Cryoballoon ablation procedure

The baseline rhythm at the time of the procedure was sinus rhythm (SR) in all patients. A 28 mm second-generation CB-A was used in all patients. Either the 20 mm Achieve mapping catheter or the 25 mm Achieve mapping catheter (Medtronic, MN, USA) were used as ILMC during the procedure. Three patients showed left common ostium (LCO) at the CT scan while 2 patients had an accessory right middle pulmonary vein (RMPV). Mean procedure time (i.e. the time taken from first groin puncture to complete sheath extraction) was 67.1 ± 15.0 min while the mean fluoroscopic time was 14.8 ± 7.5 min (Table 2). All 103 PVs were successfully isolated with CB-A without the need for additional focal-tip ablation; at the end of each procedure, all PVs were confirmed to be isolated. Procedural details are shown in Table 2.

3.3. Complications

Two patients (7.7%) experienced periprocedural complications. One patient experienced impending phrenic nerve palsy (PNP) without actual loss of diaphragmatic contraction, and therefore without any clinical consequence while another patient experienced a complication related to the vascular access, which anyway didn't require any subsequent invasive treatment.

3.4. Outcome

Mean follow-up was 20.1 ± 11.6 months. The freedom from VVS or reflex pre-syncope during the mean follow period was 83.7% with 22 patients free from any clinical recurrence (Fig. 1). The type or recurrence was VVS in one patient and reflex pre-syncope in the other 3 patients (Table 3). No clinical or anatomical predictors of recurrence of VVS or reflex pre-syncope were documented. No documented recurrence of AF or any other atrial arrhythmia was documented in the follow-up. No patient underwent pacemaker implantation in the follow-up. Both HR and AV interval were collected before the CB-A, the day after the procedure and in the follow-up. Basal HR significantly increased the day after the procedure (57.2 bpm vs 78.3 bpm, $p < 0.001$), while at the final follow-up it stabilized at a value halfway between the 2 previous ones

Table 2

Procedural characteristics (LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; PNP, phrenic nerve palsy).

Procedure characteristics, n = 26	
Procedure time, min \pm SD	67.1 \pm 15.0
Fluoroscopy time, min \pm SD	14.8 \pm 7.5
SR at the time of procedure, n (%)	26 (100.0)
LSPV freeze >1, n (%)	6 (23.1)
LIPV freeze >1, n (%)	5 (19.2)
RSPV freeze >1, n (%)	5 (19.2)
RIPV freeze >1, n (%)	5 (19.2)
LSPV min temperature, C \pm SD	-48.7 \pm 4.5
LIPV min temperature, C \pm SD	-42.8 \pm 19.2
RSPV min temperature, C \pm SD	-47.4 \pm 5.5
RIPV min temperature, C \pm SD	-48.9 \pm 5.6
Impending PNP, n (%)	1 (4.5)
Major complications, n (%)	0 (0)
Vascular complications, n (%)	1 (4.5)

Categorical variables are expressed as absolute and percentage (in brackets). Continuous variables are expressed as mean \pm SD.

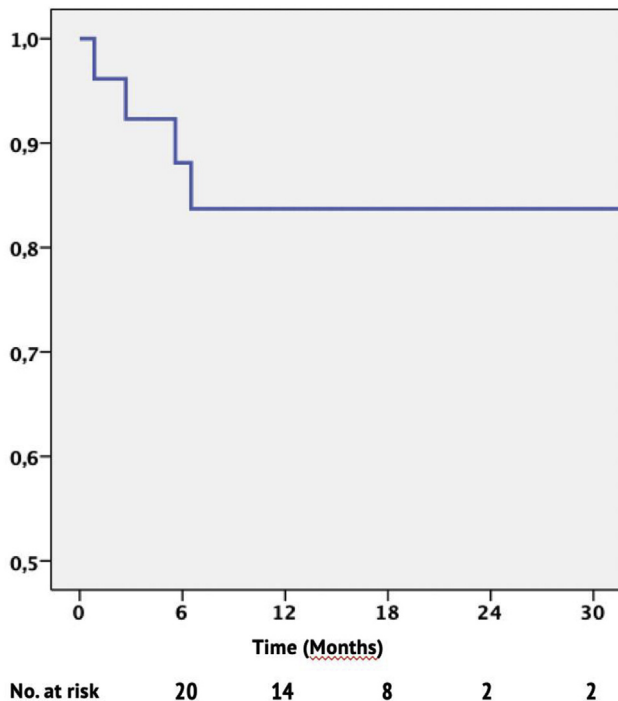


Fig. 1. Kaplan–Meyer curve showing the event-free survival of vaso-vagal syncope and pre-syncope recurrence.

Table 3

Outcome (VVS, vaso-vagal syncope).

Clinical follow-up, n = 26	
Mean follow-up in month, mean \pm SD	20.1 \pm 11.6
Patients who experienced clinical recurrences, n (%)	4 (15.4)
Mean time to recurrence in months, mean \pm SD	3.9 \pm 1.1
Recurrence of VVS, n (%)	1 (3.8)
Recurrence of reflex pre-syncope, n (%)	3 (11.5)

Categorical variables are expressed as absolute and percentage (in brackets). Continuous variables are expressed as mean \pm SD.

(69.8 bpm, $p = 0.0086$) (Fig. 2). On the other hand, the AV interval showed a trend toward prolongation right after the CB-A (165.0 msec vs 157.0 msec, $p = 0.3012$), without reaching significance.

4. Discussion

The main findings of the study are that: (i) the overall success rate of a single CB-A ablation performed in patients with VVS or reflex pre-syncope was 83.7% at 20.1 ± 11.6 months of follow-up; (ii) no patient underwent pacemaker implantation in the follow-up; (iii) HR showed a very specific change after the CB-A ablation, as a result of the modification of cardiac autonomic innervation; and (iv) procedure-related complication rate was low as CB-A ablation confirmed to be safe and feasible in this specific population.

The intrinsic cardiac autonomic nervous system (ICANS) is part of the autonomic nervous system and works as a communication centre between the heart and the central nervous system (CNS) [14–17]; it comprises autonomic cell bodies (GPs), that are located within the heart (i.e. inside the atrial wall, on the epicardium, in the endocardium, or in the epicardial fat pads) [6], and specifically adjacent to PV ostia, possibly enabling a selective vagal denervation

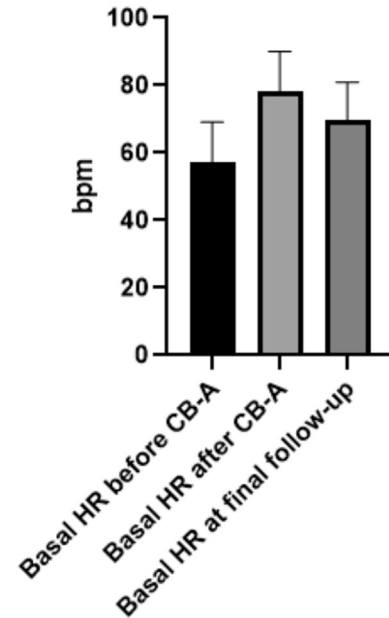


Fig. 2. Bar chart showing the basal heart rate evolution before the procedure, after the procedure and at the final follow-up. HR: heart rate; CB-A: cryoballoon ablation.

achieved through energy (e.g. RF) applied to the endocardium. It has been shown that the high-frequency stimulation (HFS) performed at the endocardial LA wall at the vicinity of the antra of the PVs can elicit a positive vagal response (i.e. a transient ventricular asystole, atrioventricular AV block, or an increase in mean R-R interval by 50%), like it has been observed in an early work from Yao et al. [18], with subsequent LA vagal denervation accomplished by RF lesions delivered at these very sites. In another elegant work, Pachon et al. [19] described their endocardial anatomical ablation mainly aimed at 3 main parasympathetic ganglia located in paracardiac fat-pads (Fig. 3):

1. Ganglion A: localized between the aortic root and the medial superior vena cava;
2. Ganglion B: localized between the right PVs and the right atrium (RA);
3. Ganglion C: localized in the infero-posterior interatrial septum.

After being evaluated in the setting of AF ablation [20–24], cardioneuromodulation through endocardial approach has been tested in VVS patients, first with sporadic case reports [7] and then in small sample clinical trials [6,18,25], showing the potential therapeutic effects of the technique in this population. In the first study designed to evaluate the effectiveness of GPs RF ablation in the clinical control of neurocardiogenic syncope, functional AV blocks and sinus node dysfunction, Pachon et al. [19] have shown complete relief from symptoms in all 21 patients at a mean follow-up of 9.2 months. Later on, the same group [6] presented the long-term outcome (at a mean follow-up of 45.1 ± 22 months) of the cardioneuroablation performed with the endocardial RF catheter ablation of the cardiac vagal nervous system; while there was no pacemaker implantation in the follow-up, long-term vagal denervation was achieved in all but 3 patients (6.9%), as confirmed by atropine test results. In a larger cohort of patients [25], left-sided GP ablations performed in 57 patients with refractory VVS showed 91.2% success rate during a follow-up of 36.4 ± 22 months. Of note, all the studies above-mentioned were performed using RF as the chosen energy technique, and no study to the best of our

knowledge was ever conducted with cryoenergy. In this study, we retrospectively assessed mid-term outcome of cryoballoon cardioablation in VVS patients and we found out that freedom from VVS or reflex pre-syncope was achieved in 83,7% of patients from after a mean follow-up of 20.1 ± 11.6 months. Although sub-optimal when compared to previous studies [6,25], this result still carries a relevant clinical significance, especially considering that it has been achieved through a very reproducible [26] and feasible [27] procedure. Furthermore, given the low rate of procedure-related complications, this technique can be considered extremely safe, and that represents a crucial point when dealing with young patients (the mean age in our population was 37.5 ± 9.0), in which all the consequences related to definitive pacemaker implantation (i.e. psychological impact, lead or device malfunctioning, hospitalization, etc) should be avoided. Moreover, the efficacy of pacemaker implantation in this specific population has still been questioned, as emerges from the recent ISSUE-3 registry on syncope of uncertain etiology [28].

Besides, some grade of cardiac neuromodulation achieved by CB-A has already been described in previous studies [29–31], due to the proximity of left atrial GPs to the PVs and the wide antral area targeted by the device [32]. Interestingly, while vagally-mediated episodes of bradycardia were mostly described following CB application to the left-sided PVs [33], the lasting impact of CB-A on the parasympathetic system seems to be associated with right-sided PVs applications. In an elegant work from Mori et al. [34] conducted on 54 paroxysmal AF patients who underwent CB-A (25 patients starting from the right-side PVs and 29 patients targeting the left-side PVs first), a vagal response was observed in 61.5% of the left-first group of patients while only in the 9.5% of the patients from the right-first group, suggesting that the initial CB ablation of the RSPV may affect the anterior right GP and may suppress its function as an integration centre for the SN. More recently, Hu et al. [35] have retrospectively assessed ablation response of all GPs in LA in a population of 115 VVS patients, showing that all GPs could produce vagal response but the RAGP ablation showed the highest increase in heart rate among the points studied. This result may confirm that the ARGV, located close to the RSPV, is the integration centre for the SN [17] and therefore a favorable target for

cardioneuroablation. This data seems to be confirmed by our work, as proven by both our clinical results and ECG modifications. In fact, while sympathetic reinnervation may be almost complete at 3 months [9], late vagal reinnervation may be less significant due to the loss of neuronal bodies achieved during endocardial ablation [36]. This finds a very clear correlation with the ECG modifications of HR in our population, as the acute response right after CB-A (i.e. basal HR increase) has then shown a clear trend towards a stabilization to an in-between value in the follow-up (Fig. 3). Of note, in the above-mentioned work [35], only minimal HR showed significant increase during all follow-up time points (all $p < 0.05$), suggesting a specific impact of the procedure on the cardiac autonomic balance mostly in basal conditions. Furthermore, the complete vagal denervation may not be necessary to eliminate VVS on a middle-term follow-up, as the attenuation of the cardioinhibitory reflex may be sufficient for reducing the symptoms burden.

4.1. Limitations

Our study has several limitations. The most important limitation of this study is related to its retrospective cohort design. Furthermore, the study has been conducted on a limited number of patients and for a limited timespan, which may restrict our ability to draw substantial conclusions, especially considering the extremely variable natural history of the clinical condition. We didn't systematically evaluate the presence of an important cardio-inhibitory response at the head-up tilt test. No patient was been implanted with an internal loop recorder (ILR) before or after the procedure. The CB-A procedure in these patients has been performed in our centers in a standard fashion, therefore no intracardiac mapping neither HFS was performed during these procedures.

5. Conclusion

Endocardial autonomic denervation achieved by CB-A PVI appears to be an effective and safe treatment option for patients with refractory VVS and reflex pre-syncope. Further larger and randomized controlled trials are required to promote this alternative treatment in this specific clinical context.

Declaration of competing interest

Gian-Battista Chierchia and Carlo de Asmundis receive compensation for teaching purposes and proctoring from AF solutions, Medtronic, and Biosense-Webster. Pedro Brugada receives research grants on behalf of the centre from Medtronic. Other authors: no relationships that could be construed as a conflict of interests.

CRediT authorship contribution statement

Riccardo Maj: Data curation, Writing - review & editing. **Thiago Guimarães Osório:** Conceptualization. **Gianluca Borio:** Data curation. **Saverio Iacopino:** Software. **Erwin Ströker:** Methodology. **Juan Sieira:** Methodology. **Muryo Terasawa:** Investigation. **Shuichiro Kazawa:** Investigation. **Alessandro Rizzo:** Visualization. **Alessio Galli:** Visualization. **Varnavas Varnavas:** Software. **Gezim Bala:** Methodology. **Xavier Galloo:** Validation. **Gaetano Paparella:** Validation. **Pedro Brugada:** Writing - review & editing. **Yves De Greef:** Writing - review & editing. **Carlo De Asmundis:** Writing - review & editing. **Gian Battista Chierchia:** Writing - review & editing.

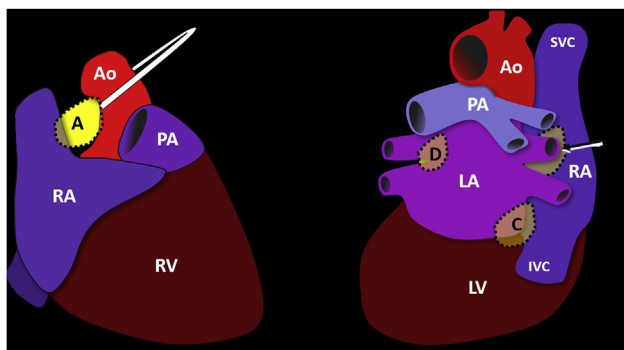


Fig. 3. Schematic view of the epicardial ganglionated plexus corresponding to: Ganglion A, between the superior vena cava and the aortic root just above the right upper pulmonary vein; Ganglion B, between the right upper pulmonary vein and the right atrium; Ganglion C, between the inferior vena cava and the right left atrium; Ganglion D, between left pulmonary vein and left pulmonary artery. Note the anatomical proximity between the ganglions and the wide antral area normally targeted by the cryoballoon. A,B, C, D: ganglionated plexi; Ao: aorta; IVC: inferior vena cava; SVC: superior vena cava; LA: left atrium; LV: left ventricle; PA: pulmonary artery; RA: right atrium; RV: right ventricle.

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