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Clinical Impact of Aging on Outcomes of Cardioneuroablation for Reflex Syncope or Functional Bradycardia. Results from the cardionEuroabLation: patiEnt selection, imaGe integrAtioN and outComEs. The ELEGANCE multicenter study

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Abstract

Background. Cardioneuroablation (CNA) is a novel treatment for reflex syncope. The effect of aging on CNA efficacy is not fully understood.

Objective. We assessed the impact of aging on candidacy and efficacy of CNA for treating vasovagal syncope (VVS), carotid sinus syndrome (CSS) and functional bradyarrhythmia.

Methods. The ELEGANCE multicenter study assessed CNA in patients with reflex syncope or severe functional bradyarrhythmia. Patients underwent pre-CNA Holter ECG, head-up tilt testing (HUT) and electrophysiologic study. CNA candidacy and efficacy was assessed in 14 young (18-40 years), 26 middle-aged (41-60 years) and 20 older (>60 years) patients.

Results. Sixty patients (37 men; mean age: 51±16 years) underwent CNA. The majority (80%) had VVS, 8% CSS, and 12% functional bradycardia/AV block. Pre-CNA Holter ECG, HUT and EP findings did not differ across age groups. Acute CNA success was 93%, without differences between age groups (p=0.42). Post-CNA HUT response was negative in 53%, vasodepressor in 38%, cardioinhibitory in 7% and mixed in 2%, without differences across age groups (p=0.59). At follow-up (8 months, IQR:4-15), 53 (88%) patients were free of symptoms. Kaplan-Meier curves did not show differences in event-free survival between age groups (p=0.29). The negative predictive value of a negative HUT was 91.7%.

Conclusions. CNA is a viable treatment for reflex syncope and functional bradyarrhythmia in all ages, and is highly effective in mixed VVS. HUT is a key-step of post-ablation clinical assessment.

Keywords. cardioneuroablation, reflex syncope, vasovagal syncope, carotid sinus syndrome, bradycardia, ganglionated plexi, head-up tilt test

Background

Cardioneuroablation (CNA) is a new approach for treating vasovagal syncope (VVS) [1-4], carotid sinus syndrome (CSS) [5], symptomatic sinus bradycardia [6], and atrioventricular (AV) blocks [7,8] caused by autonomic imbalance. Evidence suggests that autonomic control in younger individuals is characterized by the predominance of vagal activity, while in older individuals, sympathetic tone is more prominent [9]. Consistent with this notion, the extent of vagal excitation during CNA varies with age, with younger patients exhibiting greater vagal responses [10]. Therefore, in older patients symptomatic bradyarrhythmia are more likely considered to be related to organic dysfunction of sinus or AV nodes rather than sympatho-vagal imbalance [11,12]. Notwithstanding this, the exact effect of age on the efficacy of CNA in patients with reflex syncope is not yet fully understood. A single study [6] reported that younger patients (<50 years of age) with functional sinus bradycardia treated with CNA have better clinical outcomes and faster recovery of autonomic balance than older patients. However, there has not been a systematic assessment of the impact of aging on CNA candidacy and outcomes in patients presenting with reflex syncope or symptomatic functional bradyarrhythmia [13]. As current guidelines only recommend pacing for recurrent reflex syncope in patients over 40 years old, and pacing has been mostly used in patients aged >60 years [14], determining the efficacy of CNA across these age categories is particularly relevant.

This study aimed to evaluate the impact of aging on the diagnostic work-up for CNA candidacy and on the efficacy of CNA as a treatment for VVS, CSS, and severe functional sinus node bradycardia or advanced AV block.

Methods

Study patients

The cardionEuroabLation: patiEnt selection, imaGe integrAtioN and outComEs (ELEGANCE) study is a multicenter study that assessed CNA in (a) patients with recurrent VVS or carotid sinus syndrome (CSS) and (b) patients with symptomatic functional sinus node bradycardia or advanced AV block in whom a pacemaker implant was considered.

All patients underwent comprehensive pre-CNA assessment that included Holter ECG and complete electrophysiologic study with carotid sinus massage and atropine test. Depending on clinical presentation, CNA candidates also underwent HUT. CNA was proposed to young patients (i.e., ≤40 years) when pharmacologic and non-pharmacologic options were ineffective or not desired, and to older patients (i.e. >40 years) when pacemaker implantation was refused. The study was approved from the local Ethic Committee and informed consent was obtained from all participants.

Head-Up tilt test

Antiarrhythmic drugs and drugs which alter autonomic nervous system function were discontinued. After a brief supine control phase, patients were moved to the 70 degrees upright position for 10 min (passive phase). In case of a negative result, sublingual 0,4 mg nitroglycerine was administered in the upright position, and tilting was continued for a maximum of 20 min. During the test, the arterial pressure was monitored. Response to the HUT was classified according to the New Vasovagal Syncope International Study (VASIS) classification [15] as follows. Type 1 (mixed): fall in BP followed by fall in HR producing syncope, without reaching 40bpm. Type 2A (cardio-inhibitory without asystole): HR fall <40 bpm for more than 10 seconds. Type 2B (cardio-inhibitory with asystole): occurrence of asystole that lasts more than 3 seconds. Type 3 (vasodepressor): fall in BP with increase in HR.

Electrophysiologic study and atropine test

A complete EP study was conducted prior to undergo CNA to exclude organic sinus or AV node dysfunction. The corrected sinus node recovery time (cSNRT), AH and HV intervals, Wenckebach cycle and response to carotid sinus massage were assessed. Atropine sulfate (0.04mg/kg, maximum 2 mg) was infused under continuous electrocardiogram (ECG) monitoring. A sinus rate increase of ≥25% in the first 10 min after infusion was considered a positive response.

Cardioneuroablation

Peri-procedural anticoagulation with heparin was performed aiming to achieve an intraprocedural activated clotting time (ACT) of 300–350 seconds. A single transeptal puncture was performed under transesophageal echocardiography guidance. Anatomical map of the LA was acquired using CARTO 3 (Biosense Webster, Diamond Bar, CA) or NavX (Abbott, USA) and fused with CT images. Areas where GPs are usually located [8] were searched for fragmented EGM (fEGMs) (i.e., showing ≥4 deflections) but ablated based on anatomical landmarks independently from the presence of fragmentation. As from June 2022, epicardial fat pads near the area of anticipated GPs with attenuation -190 to -30 Hounsfield Units (HU) were segmented, exported using ADAS3D software (Galgo Inc.), and integrated in electro-anatomical maps for real-time guidance of GP ablation (**Figure 1**). The following GPs were identified and ablated: the left superior GP (LSGP) between the left superior pulmonary vein (PV) and LA appendage, the Marshall tract GP (MTGP) in the carina between left PVs, the left inferior GP (LIGP) posteriorly to the left inferior PV, the inferior paraseptal ganglionated plexus (IPSGP) between the posterior wall of the LA and coronary sinus, the superior paraseptal ganglionated plexus (SPSGP) between the right superior PV and superior vena cava, the right inferior GP (RIGP) between the two right PVs, and aorta-superior vena cava GP (Ao-SVC GP). The SPSGP and the IPSGP were targeted from both the left and right atrium, and the aggregate response to RF delivery is provided. Ablation was performed point-by-

point using a Thermocool SmartTouch 3.5-mm (Biosense Webster, Diamond Bar, CA) or a TactiCath (Abbott, USA) irrigated tip contact force sensing catheter. RF (at least 24 seconds at each site) was limited to 40 W for the posterior and 50 watts for the anterior left atrial wall.

The ablation end-point for each GP was defined as abolition of RF-induced vagal response for LSGP, MTGP and LIGP increase in basal HR ≥25% for the SPSGP, RIGP and Ao-SVC GPs, and shortening of at least 25% of AH interval for the IPSGP [8,16].

Procedural end-points were as following: in patients with VVS or CSS, failure of atropine to increase HR >25% and negativity to carotid sinus massage post-CNA; in patients with AV block due to vagal hyperactivity, reduction of the AH interval of greater than 25% as compared to pre-CNA and failure of atropine to further reduce AH.

Follow-up and end-points

The follow-up consisted of a clinical evaluation with ECG at 1, 3, 6 and every 6 months thereafter. Post-CNA serial Holter ECG and HUT were encouraged but performed according to the clinical practice of the referring physicians. The primary study endpoint was the spontaneous recurrence of symptoms that led to CNA.

Statistical analysis

Continuous variables are given as mean ± standard deviation for normally distributed data or median (interquartile range, IQR) in case of skewed distribution. Categorical variables are given as absolute numbers and percentages. Group comparison was assessed by one-way ANOVA followed by the Bonferroni post-hoc test or Kruskal-Wallis test, as appropriate. Proportions were compared using the Chi-square or Fisher's exact test. Standardized residuals were used to assess the contribution of each cell to the overall chi-square statistic. The cumulative probability of the primary endpoint over time was estimated using the Kaplan-Meier method. Predictors of syncope

recurrence were assessed by Cox regression analysis. A p value <0.05 was considered as significant. Statistical analysis was performed using IBM SPSS Statistics, version 27.0 (IBM Corp; Armonk, NY, USA).

Results

From February 2021 to February 2023, 60 patients (37 men; mean age: 51±16 years) underwent CNA. One patient had ischemic and one hypertensive heart disease, while the remaining 58 had no structural heart disease. The majority (n= 48, 80 %) had multiple recurrent VVS, 5 (8%) had CSS, and 7 (12%) symptomatic functional bradycardia or advanced AV block. The mean number of syncope episodes in the last 12 months was 3 (IQR: 2-7). Ten patients with documented symptomatic sinus pauses or AV block and typical reflex prodromes that occurred in the setting of prolonged standing or stressors (emotional stress, pain) refused pre-CNA HUT. In all the remaining patients, a HUT was performed.

Patients were divided in 3 groups according to age: young, 18-40 years (n= 14); middle-aged, 41-60 years (n= 26); older: >60 years (n= 20). The clinical characteristics are illustrated in **Table 1**. Holter ECG findings and HUT response did not differ across groups, although a slighter higher prevalence of HUT mixed response was observed in younger patients (**Table 1**). At EP study, older patients showed a non-significant trend towards longer HV interval and blunted HR increase in response to atropine (**Table 1**).

CNA

Biatrial CNA was performed in all 60 patients under general anesthesia. The LSGP was targeted in 59 patients (98%), the MTGP in 60 (100%), the LIGP in 56 (93%), the SPSGP in 60 (100%), the RIGP in 59 (98%), the IPSGP in 57 (95%), and the Ao-SVC GP in 60 (100%). Response to RF

applications to each GP according to age group is reported in **Table 2**. A non-significant trend towards lower HR increase following RF application on the SPSGP was observed in older patients. The MTGP responded only in 4 individuals belonging to the older group. The remaining GPs responded comparably between age groups. During CNA, one patient developed AF and did not undergo post-procedural atropine test. Out of the remaining 59 patients, acute success as determined by atropine administration was achieved in 54 (92%) without differences between age groups (**Table 2**). Mean procedural time was 75±31 minutes. One patient had pericardial effusion that was drained the day after ablation. There were no further procedure-related complications.

Follow-up

As compared to pre-CNA, in young and middle-aged patients Holter ECGs at 1 and 3-6 months showed a significant increase in mean HR that persisted over time. In older patients this increase was less pronounced and did not persist at 3-6 months (**Figure 2**).

Out of 45 patients that underwent follow-up HUT, 24 (53%) had a negative test (including 2 patients that did not undergo pre-CNA HUT), 17 (38%) a vasodepressor, 3 (7%) a cardio-inhibitory, and one (2%) a mixed response (**Figure 3**). One patient with cardio-inhibitory response was observed in each age group, while the single patient with mixed response was a 61 years-old man ($p= 0.59$).

After a median follow-up of 8 months (IQR: 4-15), 53 (88%) patients were free of symptoms, while 6 had recurrence of VVS and one had persistent symptomatic functional sinus bradycardia.

Six out of 7 patients with symptoms recurrence had a post-CNA HUT: 2 had a negative test, while the others had a cardio-inhibitory type 2A (n= 1), mixed (n= 1), or vasodepressive (n= 2) response (**Figure 3**). The negative predictive value of a negative HUT was 91.7%. All patients with pre-CNA mixed response had a negative or vasodepressive post-CNA HUT, and none of them had symptoms recurrence.

As far as atropine test is concerned, out of 7 patients with symptoms recurrence, one had positive post-CNA atropine test, one did not undergo the test due to intraprocedural AF, an all the others exhibited negative results, indicating an effective CNA (NPV: 90.7%). On the other hand, out of 5 patients with positive post-CNA atropine test, only one had symptoms recurrence over a median follow-up of 4 months (IQR: 2-7) (PPV: 20.0%)

Overall, 4 patients were implanted with a dual-chamber pacemaker, 2 refused further therapies, and one underwent a second CNA with no further symptoms thereafter. Five CNA failures occurred in middle-aged and 2 in older patients. Kaplan-Meier curves did not show statistically significant differences in cumulative event-free survival neither across predefined age groups (**Figure 4A)**, nor after dichotomizing patients in ≤40 vs >40 years of age (**Figure 4B**), although a trend for lower rate of symptoms recurrence in young patients was observed. In Cox regression analysis, age as a continuous variable did not predict recurrence of symptoms (HR: 1.00; 95% CI: 0.96-1.05; p= 0.73).

Discussion

We aimed to assess how aging affects the diagnostic work-up and efficacy of CNA as a treatment for VVS, CSS or functional sinus node bradycardia/AV block. In our population of CNA candidates, we found that age did not have a significant impact on Holter ECG findings, HUT response, or electrophysiological characteristics of the sinus and AV node. While CNA was more effective in younger patients, age per se did not predict CNA success, and most older patients benefited from CNA. Moreover, we report that CNA is highly effective in patients with VVS and HUT mixed response, and that a negative post-CNA HUT has high negative predictive value for symptoms recurrence.

Pre-CNA clinical assessment

Holter ECG showed similar values for minimum, mean, and maximum heart rate across all age categories. The detection of spontaneous RR pauses >3 seconds was comparable as well.

The distribution of HUT outcomes was similar to that reported by Vandenberk et al. in their recent metanalysis [2] and did not differ between young, middle-aged, and older individuals. This finding is in disagreement with a large retrospective study [17] reporting that the prevalence of HUT cardioinhibitory response is higher in younger patients, while vasodepressor response prevails in older groups [18,19]. This difference can be attributed to our highly selected population of CNA candidates, who exhibited syncope in the setting of typical neuroautonomic symptoms and absence of organic sinus and AV node dysfunction. Indeed, the prevalence of a negative HUT in our study was only 10%, which is significantly lower than the reported 40% in unselected patients with VVS[17].

In keeping with previous studies [6,20,21], we found that older patients displayed a trend towards longer HV interval and blunted HR increase in response to atropine, but otherwise, there were no other differences between age groups.

CNA endpoints

As previously reported [6,22], we did not observe a clear increase in HR after ablation of the LSGP, LIGP, and RIGP, while ablation of the RS and Ao-SVC GPs greatly increased HR. This finding would support the concept that ablation of all ganglionated plexi is needed infrequently, as recently suggested [14]. Of note, although the response to RF applications across age groups was overall comparable, we observed a blunted HR increase after SPSGP ablation in older patients, which is in agreement with what observed in individuals >50 years of age by Qin et al. [6].

Notably, acute CNA success as determined by failure of HR to increase after atropine administration was achieved in most patients, with no significant differences between age groups.

Post-ablation clinical assessment

In keeping with previous findings [6,23], in young and middle-aged patients serial Holter ECGs at 1 and 3-6 months showed a significant and durable increase in mean HR. However, in older patients this increase was less pronounced and did not persist at 3-6 months, consistent with an overall less substantial impact of neuromodulation on sinus rate in this age category. Failure of CNA to increase heart rate in older patients, despite a comparable incidence of symptoms recurrence to younger patients, may indicate that symptoms in the older age group were triggered by isolated reflex stressors rather than functional bradycardia. However, it cannot be ruled out that the lack of sustained heart rate increase after CNA reflects underlying reduced intrinsic sinus node activity, which could result in symptoms recurrence during a longer follow-up.

CNA also exerted profound changes in the pattern of response to HUT. Most patients with pre-CNA cardio-inhibitory or mixed syncope showed a negative or vasodepressor response to HUT, independently from age. These findings are consistent with previous reports [24,25]. Of note, our study enrolled a significant proportion of patients with mixed response to HUT, which is fully representative of the general population typically referred to a syncope unit [17]. None of the patients with pre-CNA HUT mixed response had neither post-ablation positive HUT, nor symptoms recurrences. This would indicate that CNA, regardless of age, is a useful therapeutic option also in patients with mixed-type HUT response.

Follow-up and clinical endpoints

Follow-up data showed that 88% of patients were free of symptoms after a median observation of 8 months, with no significant differences between age groups. It is worth noting that all instances of symptoms recurrence were observed in patients aged over 40 years, which is a clinically significant cutoff. However, it should also be mentioned that 85% of patients above the age of 40 were still free of symptoms at follow-up. This finding suggests that restricting CNA candidacy to younger

patients leaves older untreated, despite their potential to substantially benefit from CNA. While Qin et al. [6] reported that patients over 50 years of age are less likely to benefit from CNA, it is essential to note that their study only investigated patients with functional bradycardia. Moreover, only 14% of patients over 50 years of age in their study required pacemaker implantation, a percentage that aligns with our findings. Furthermore, in studies that enrolled both young and older patients, CNA failures encompass all ages and is not limited to older patients [23].

Of note, the absence of cardio-inhibitory or vasodepressor syncope at post-CNA HUT had high negative predictive value for symptoms recurrence. Nonetheless, the low event rate does not allow to draw definitive conclusions. Post-CNA results of HUT have been reported with differences among studies, possibly depending on variable HUT timing and protocols [24-26]. Our study found that syncope was more likely to recur in patients who had a pre-ablation cardioinhibitory HUT response and still had a positive HUT after CNA, even if with a vasodepressive mechanism. As CNA does not affect neuroautonomic vascular control, it is tempting to conclude that abolition of the cardio-inhibitory component of reflex syncope might be effective despite persistence of a positive HUT.

Study limitations

This study has important limitations. First, it does not have a control group, which leaves unanswered the question of whether the low rate of recurrence of syncope post-CNA is entirely attributable to the efficacy of ablation. Second, as the follow-up is relatively short, our findings do not provide sufficient evidence to draw conclusions about the duration of CNA effects in the different age groups. Further research, including studies with longer follow-up comparing GP ablation with cardiac pacing [27], is necessary to investigate the impact of aging on the long-term efficacy of CNA.

Conclusions

Our findings are consistent with previous studies suggesting that CNA is effective in treating reflex syncope and functional bradyarrhythmia, particularly in younger patients. However, we do extend previous knowledge showing that CNA can be a treatment option for VVS, CSS or functional bradyarrhythmia in patients of all ages, provided that appropriate candidate selection is performed. While there is no current reason to restrict the use of CNA to patients with reflex syncope under the age of 40 or 60, a controlled trial should be conducted to demonstrate that CNA is not inferior to pacemaker implantation in this age group.

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Figure legends

Figure 1. Anatomic localization of targeted GPs.

Left panels. Left atrial CT scans showing two areas of attenuated signal intensity (-190 to -30 Hounsfield Units) corresponding to epicardial fat pads at the level of the SPSGP (A) and LSGP (B). **Right panels.** Fusion of anatomical map and CT of the left atrium, right atrium, aorta, and segmented epicardial fat pads near the area of anticipated GPs. LA, left atrium; RSPV, right superior pulmonary vein; LSPV, left superior pulmonary vein; LSGP, left superior GP; SPSGP, superior paraseptal GP; MTGP, Marshall tract GP; LIGP, left inferior GP; IPSGP, inferior paraseptal GP; RIGP, right inferior GP; Ao-SVC GP, aorta-superior vena cava GP.

Figure 2. **Holter ECG.**

Changes in Holter ECG mean sinus rate from pre-CNA to 1 and 3-6 months after CNA according to the study group. Significances are by ANOVA followed by Bonferroni post-hoc test.

Figure 3. Outcome of pre- and post-CNA HUT.

Horizontal bands represent the outcome categories of HUT. On the left, patients evaluated pre-CNA are divided according to HUT outcome (in blue, type 2B cardioinhibitory syncope; in red, type 2A cardioinhibitory syncope; in green, mixed syncope; in yellow, vasodepressive syncope; and in gray, negative HUT). On the right, patients are represented within the diagnostic categories of post-CNA HUT, retaining the color of the original category. In the lower band, on the left patients with pre-CNA HUT but without follow-up testing are represented; on the right, patients with follow-up HUT without pre-CNA testing are depicted. The squares identify patients who experienced recurrence of syncope post-CNA.

Figure 4. **CNA outcomes.**

Cumulative survival free from syncope in the three predefined age groups (A) and in patients young (≤40 years) vs older (>40 years) (B). The p-values are by the log-rank test.

Tables

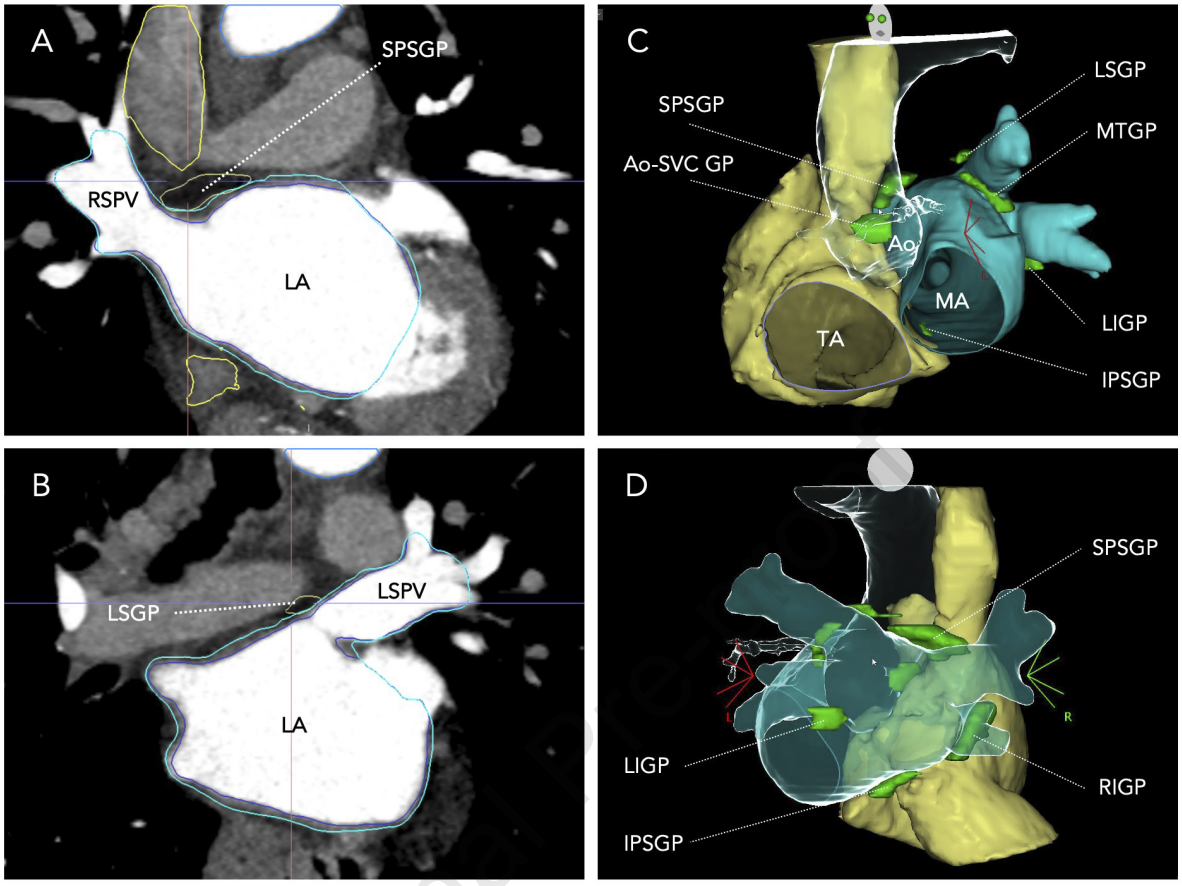
Table 1. Clinical characteristics of study patients according to age category.

	Young 18-40 y (n= 14)	**Middle-aged 41-60 y (n= 26)**	**Older >60 y (n= 20)**	**p**
Males, n (%)	9 (64)	14 (54)	14 (70)	0.55
Age (years)	29±7	52±6	67±7	<0.01
CNA indication				
VVS, (%)	12 (86)	22 (84)	14 (70)	0.57
CSS, n (%)	0	2 (8)	3 (15)	
Functional bradycardia/AVB ,n (%)	2 (14)	2 (8)	3 (15)	
Holter ECG				
Min HR, (bpm)	39±8	43±13	42±8	0.52
Mean HR, (bpm)	62±9	66±14	65±9	0.73
Max HR, (bpm)	112±19	110±25	109±14	0.92
Patients with RR>3 sec, n (%)	7 (50)	7 (27)	7 (25)	0.34
HUT (n= 50)				
Mixed (type 1), n (%)	5 (42)	3 (14)	3 (19)	0.35
Cardio-inhibitory type 2A, n (%)	1 (8)	5 (23)	5 (31)	
Cardio-inhibitory type 2B, n (%)	5 (42)	11 (50)	5 (31)	
Vasodepressor (type 3), n (%)	0	2 (9)	0	
Negative, n (%)	1 (8)	1 (4)	3 (19)	
EP study				
AH, ms	87 (72-103)	89 (72-114)	100 (75-142)	0.29
HV, ms	50±7	49±5	54±8	0.07
Wenckebach CL, ms	550 (485-695)	420 (350-420)	430 (340-510)	0.11
cSNRT, ms	300 (189-344)	250 (150-360)	260 (120-440)	0.74
Atropine HR increase, (%)	72 (53-90)	57 (50-92)	53 (35-76)	0.19

Table 2. GP response to RF application

	Young 18-40 y n= 14	**Middle-aged 41-60 y n= 26**	**Older >60 y n= 20**	**p**
LSGP - Abolition of vagal response, n (%)	5 (36)	13 (50)	7 (37)	0.66
MTGP - Abolition of vagal response, n (%)	0	0	4 (20)	0.01
LIGP - Abolition of vagal response, n (%)	0	1 (4)	0	1.00
SPSGP - HR increase, % (IQR)	31 (9-55)	29 (13-43)	14 (8-33)	0.29
RIGP - HR increase, % (IQR)	0 (-1.7-0)	0 (-1.5-0.28)	0 (0-4.2)	0.28
Ao-SVC GP - HR increase, % (IQR)	6 (2-18)	6 (0-13)	9 (2-17)	0.66
IPSGP - AH reduction, n (%)	2 (15)	2 (9)	0	0.46
Atropine HR incr. post-CNA, % (IQR)	2 (-0.3-19)	0 (0-8)	2 (-1-15)	0.77
Acute CNA success, n (%)	13 (93)	24 (96)	17 (85)	0.42

LSGP, left superior GP; MTGP, Marshall tract GP; LIGP, left inferior GP; IPSGP, inferior paraseptal ganglionated plexus; SPSGP, superior paraseptal ganglionated plexus; RIGP, right inferior GP, Ao-SVC GP, aorta-superior vena cava GP


A
SPSGP
RSPV
LA
C
LSGP
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MTGP
Ao-SVC GP
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