UNIVERSITÀ DEGLI STUDI DI PAVIA

DOTTORATO DI RICERCA

IN MEDICINA SPERIMENTALE

Prognostic Impact of Atrial Rhythm and Dimensions
in Patients with Structural Heart Disease
Undergoing Cardiac Sympathetic Denervation for Ventricular Arrhythmias

Tesi di Dottorato

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Introduction

Structural heart diseases (SHDs), independent of their cause, are characterized by a combination of pathological myocardial substrate and cardiac autonomic nervous system (ANS) remodeling, which promote susceptibility to both atrial arrhythmias (AAs) and ventricular tachyarrhythmias (VTs) (1). Nevertheless, patients with SHD, even at advanced stages, may present with AAs only, VTs only or a combination of both.

From a therapeutic point of view, antiarrhythmic strategies targeting the ANS, as opposed to local interventions such as catheter ablation, have the potential to prevent/treat both AAs and VTs while also affecting other pathophysiological properties of the heart (1).

Left cardiac sympathetic denervation (LCSD) is a well-established therapy for VTs in channelopathies (2). Despite a strong pathophysiological rationale and promising preclinical data, clinical experience with CSD in SHD is limited (3). Data suggest a higher efficacy of bilateral CSD (BCSD) as compared to LCSD in reducing the burden of VTs (4). The prevalence and type of AAs in these patients, the correlation with clinical phenotype (cardiac geometry and function) at CSD and with outcome after CSD are unknown. The impact of CSD on atrial rhythm has never been described either. However, temporary unilateral stellate ganglion block (SGB) was shown to decrease AF inducibility and AF episodes/duration (5).

The purpose of this study was to assess the impact of pre-procedural AAs and left atrial volume index (LAVI) on CSD outcome, as well as the changes in atrial rhythm after CSD.

Methods:

Patient population:

A retrospective analysis of consecutive patients with SHD undergoing CSD for recurrent VTs between 2009 and 2018 at 2 centers was performed. SHD was defined as a left ventricular ejection fraction (LVEF) <55%, hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) or inflammatory cardiomyopathy/ sarcoidosis. Ischemic cardiomyopathy (ICM) was defined by history of myocardial infarction (MI) or myocardial perfusion defect with correlating obstructive disease on coronary angiography. Electrical storm (ES) was defined as ≥ 3 episodes of sustained VT/ICD shock within 24 hours. Clinical history of

AAs included documented and/or treated episodes of atrial tachycardia (AT), atrial flutter (AFL) or atrial fibrillation (AF). Study approval was obtained from the institutional review board of the 2 centers.

For the analysis of atrial rhythm changes after CSD based on ICD monitoring, we only included patients who received BCSD, which provides an almost complete extrinsic sympathetic denervation of atrial chambers. Patients with no atrial sensing, in permanent AF and with < 6 months of ICD monitoring after BCSD were excluded, as well as patients who received renal denervation (RDN) in the first 6 months after BCSD. For patients who received RDN ≥ 6 months after BCSD, follow up was censored at RDN. A drug index was devised to correct for medication use: beta-blockers, mexiletine, verapamil, digoxin and ranolazine were assigned 1 point, sotalol, propafenone, flecainide and dofetilide 2 points and amiodarone 3 points. Drug dosages were not incorporated in the drug index. The ICD threshold for AAs detection (automatic mode switch rate, AMS) was collected for each ICD interrogation.

Surgical procedure

CSD was performed via a minimally invasive (video- or robot-assisted) thoracoscopic surgery under general anesthesia and using single lung ventilation. The lower third to half of the left stellate ganglia, together with T2-T4 thoracic ganglia, were removed. All patients underwent either left or bilateral CSD, at discretion of the treating physician preference.

Echocardiographic assessment

Data was retrospectively obtained from two-dimensional transthoracic exams performed by qualified personnel. To quantify atrial dimensions, single-plane apical four-chamber indexed volumes were used. Further details are reported in table 1.

Table 1: definition of the echocardiographic parameters assessed. Guidelines recommended cut-offs values were used to identify define pathological values (1, 2, 3).

Parameter	Assessment and/or definition
LVEF, %	Quantified by the biplane Simpsons method
LVEDD, mm	Parasternal long axis
LVEDVI, ml/m^2	Single-plane apical 4-chamber LVEDV indexed to BSA
LAVI, ml/ m^2	Single-plane apical 4-chamber LA maximum volume indexed to BSA (method of disks)
RAVI, ml/m^2	Single-plane apical 4-chamber RA maximum volume indexed to BSA (method of disks)
RV dilation	Based on proximal RV outflow diameter and/or basal, mid cavity and longitudinal RV diameters
RV dysfunction	Based on TAPSE and/or RV fractional areal change and/or DTI-derived tricuspid lateral annular systolic velocity
Severe diastolic dysfunction (grade III)	Multiparametric evaluation based on mitral E/A ratio, E/e' ratio, e' velocity and deceleration time (± IVRT and PVs flow)

BSA= body surface area; DTI=Doppler Tissue Imaging; IVRT= isovolumic relaxation time; LA=left atrium; LAVI= left atrial volume index; LVEDD= left ventricular end diastolic diameter; LVEDV= left ventricular diastolic volume; LVEDVI= left ventricular end diastolic volume index; LVEF= left ventricular ejection fraction; PVs=pulmonary veins; RA=right atrium; RAVI= right atrial volume index; RV= right ventricle; TAPSE= Tricuspid annular plane systolic excursion.

(1) Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.

(2) Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.

(3) Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314.

Statistical analysis

Continuous variables were assessed as mean ± standard deviation (SD) or median (interquartile range [IQRs]) and categorical variables as percentages. Cox proportional hazard models were used to assess predictors of death/orthotopic heart transplant (OHT), competing risk models for predictors of sustained VT/ICD shocks. Nine potential predictors were assessed: age, LVEF, NYHA class, chronic kidney disease (CKD), history of AAs, LAVI, left ventricular end diastolic volume index (LVEDVI), ratio between LAVI and LVEDVI (LAVI/LVEDVI). A left side procedure only (LCSD) was not included in the models because its independent impact on outcome has already been reported[3] and the majority of patients in this dataset underwent BCSD. The p values for comparing changes before versus after BCSD were computed using the Wilcoxon test for continuous variable and the Chi-Square test for categorical variables. A p value of ≤ 0.05 was considered significant. Computations were carried out using SAS 9.4 (SAS Institute, North Carolina).

Follow up

Follow up data after CSD were obtained through medical records. The primary endpoint included any ICD shock or sustained VT (≥ 30 seconds) below ICD detection, death or OHT. Secondary outcomes included AAs recurrences requiring treatment, inappropriate ICD shocks, need for pacing upgrading, transitory ischemic attack/stroke and need of RDN for VTs. Echocardiographic, clinic and ICD data for each follow up visit were collected. For patients not followed at the institutions where CSD was performed, referring cardiologists were contacted.

Results

Between April 2009 and June 2018, 91 patients (56 ± 13 years, 15% female) with SHD underwent left (n=15, 16%) or bilateral CSD. Baseline clinical characteristics at the time of CSD in the overall study population and in the 2 subgroups (patients with and without AAs) are shown in table 2; echocardiographic characteristics are shown in table 3. Mean LVEF was 34 ±14% (n=91), and most patients presented with NYHA functional class II (54%) or III (30%). ICM was present in 18 patients (21%), non-ischemic cardiomyopathy (NICM) in 68 (75%); 4 patients had mixed cardiomyopathy (CMP), defined as CMP out of proportion to the degree of coronary artery disease and 1 patient had a corrected congenital disorder (transposition of the great arteries) complicated

by MI. Specific etiology for NICM included: HCM (n=7), myocarditis (n=7), valvular heart disease (VHD, n=6), sarcoid/aspecific inflammatory (n=6), Chagas (n=4), ARVC (n=4), drug abuse (n=3), familial dilated CMP (n=2), CMP associated with polymyositis/necrotizing myopathy (n=1), lamin A/C-related CMP (n=1), Birt-Hogg-Dube syndrome (n=1).

A history of AAs before CSD was present in 43 patients (47%), including 4 patients (4%) with permanent AF; the majority had suffered paroxysmal/persistent AF. Yet, among the 46 patients with available dual chamber ICD data before CSD and not in permanent AF (median ICD monitoring time before CSD 8 months, IQR 3-23 months), the burden of AAs was very low (median 0.0%, IQR 0.0-0.1%).

Comparing patients with and without a history of AAs, the only significant clinical difference was a higher prevalence of sleep apnea syndrome in the former (Table 2). Additionally, echocardiographic data shown that patients with AAs had a higher prevalence of left atrial enlargement (LAVI>34 ml/m^2), of RV enlargement and of severe diastolic dysfunction (grade III). They also had a significantly higher LAVI/LVEDVI ratio (Table 3). Finally, except for oral anticoagulants, there were no differences in ongoing drugs at CSD between the 2 groups (Table 5).

Table 2: Baseline characteristics of the study population at CSD

	All patients, N=91	History of AAs, N=43	No AAs, N=48
Age	56 ± 13	59 ± 13	54 ± 13
Body mass index	29 ± 6	29 ± 5	29 ± 6
Female gender	14 (15)	5 (12)	9 (19)
Hypertension	52 (57)	28 (65)	24 (50)
Hyperlipidemia	47 (52)	23 (54)	24 (50)
Diabetes	21 (23)	7 (16)	14 (29)
TIA/Stroke	12 (13)	7 (16)	5 (10)
Sleep Apnea Syndrome	19 (21)	13 (30)	6 (12)**
COPD	8 (9)	4 (9)	4 (8)
CKD (GFR <60 ml/min/m^2)	31 (34)	16 (37)	15 (31)
Creatinine (mg/dL)	1.2 ± 0.7	1.3± 0.8	1.2 ± 0.4
NICM	68 (75)	33 (77)	35 (73)
Previous heart surgery, excluding LVAD	24 (26)	11 (26)	13 (27)
- **CABG**	9 (10)	5 (12)	4 (8)
- **Aortic valve replacement**	7 (8)	3 (7)	4 (8)
- **Mitral valve replacement/repair**	6 (7)	2 (5)	4 (8)
ICD	89 (98)	43 (100)	46 (96)
CRT-D	30 (33)	17 (40)	13 (27)
Age from first ICD implant to CSD	5 (3-9)	5 (2-9)	5 (3-9)
Atrial lead/sensing	76 (83)	39 (91)	37 (77)
Atrial lead	71 (78)	37 (86)	34 (71)
NYHA Class I/II/III/IV	9/49/27/6 (10/54/30/6)	4/25/11/3 (9/58/26/7)	5/24/16/3 (10/50/33/6)
LVAD	3 (3)	1 (2)	2 (4)
ES history	67 (74)	32 (74)	35 (73)
Previous VT ablation	74 (81)	33 (77)	42 (85)
History of AAs	43 (47)	43 (100)	
- AT/AFL only	4 (4)	4 (9)	
- Paroxysmal/Persistent AF	35 (38)	35 (81)	
- Permanent AF	4 (4)	4 (9)	
Previous AT/AF ablation	9 (10)	9 (21)	
Previous AV node ablation	3 (3)	3 (7)	
Inappropriate ICD shocks	6 (7)	3 (7)	3 (6)
- Due to atrial arrhythmias	4 (4)	3 (7)	1 (2)
BNP at CSD admission*	277 (83-762)	562 (118-809)	196 (75-682)
Number of sustained VT/ICD shocks in the year before CSD	8 (4-17)	7 (4-16)	10 (5-17)

Values are reported as mean ± SD, n (%), or median (interquartile range). AAs= atrial arrhythmias; AF= atrial fibrillation; AFL= atrial flutter; AT= atrial tachycardia; AV= atrioventricular; BNP= brain natriuretic peptide; CABG= coronary artery bypass graft, CKD= chronic kidney disease; COPD= chronic obstructive pulmonary disorder; CRT-D= cardiac resynchronization therapy-defibrillation; CSD= cardiac sympathetic denervation; ES= electrical storm; LVAD= left ventricular assist device, NICM= nonischemic cardiomyopathy; NYHA= New York Heart Association; TIA= transitory ischemic attack; VT= ventricular tachyarrhythmias. *BNP data was available for 60 of 91 patients. **= $p<0.05$ between the 2 groups (patients with and without AAs).

Table 3: Echocardiographic data at CSD according to the history of atrial arrhythmias

	Available, n	History of AAs, n=43	No AAs, n=48
Body surface area, m^2	43/48	2.1 ± 0.2	2.0 ± 0.2
LVEF, %	43/48	33 ± 15	35± 12
LVEDD, mm	38/44	61 ± 11	60 ± 9
LVEDVI, ml/m^2	40/43	90 ± 53	87 ± 34
- LVEDVI> 75		19 (47)	26 (60)
LAVI, ml/ m^2	40/43	50 ± 31	35 ± 18
- LAVI > 34		27 (68)	17 (35)*
LAVI/LVEDVI	40/43	0.62 ± 0.44	0.43 ± 0.19*
RAVI, ml/m^2	31/36	34 ± 20	30 ± 12
RV dilation	42/46	23 (55)	13 (28)*
RV dysfunction	41/47	21 (51)	21 (46)
Valvular stenosis/regurgitation ≥ moderate	43/47	7 (16)	5 (11)
-Mitral regurgitation ≥ moderate		5 (12)	4 (8)
Systolic PAP, mmHg	36/41	34 ± 13	30 ± 9
Severe diastolic dysfunction (grade III)	33/39	14 (42)	7 (18)*

Values are reported as mean ± SD, n (%), or median (interquartile range). AAs= atrial arrhythmias; LAVI= left atrial volume index; LVEDD= left ventricular end diastolic diameter; LVEDVI= Left ventricular end diastolic volume index; LVEF= left ventricular ejection fraction; PAP= pulmonary arterial pressure; RAVI= right atrial volume index; RV= right ventricle.
*= $p<0.05$ between groups.

Table 4: Secondary outcomes after CSD

	All patients, n=91	Subgroup of 34 with ICD data before and after BCSD
AF electrical cardioversion	1 (1)	1 (1)
ICD inappropriate shocks	1 (1)	0 (0)
- **Due to AF**	1 (1)	
Transition to permanent AF	1 (1)	1 (1)
ICD Upgrading	4 (4)	1 (3)
- **Right atrium lead**	2 (2)	0 (0)
- **Right atrium + left ventricle lead**	2 (2)	1 (3)
Stroke/TIA	1 (1), TIA*	1 (3)
AV node ablation	0 (0)	0 (0)
RDN for VTs	8 (9)	4 (12)

Values are reported as n (%). AF=atrial fibrillation; AV= atrioventricular; RDN=renal denervation; TIA= transitory ischemic attack; VTs= ventricular tachyarrhythmias. *In absence of documented AF.

Table 5: Changes before vs after BCSD in the subset of 34 patients with atrial sensing and at least 6 months of ICD data after BCSD

	n*	Before BCSD	After BCSD	p value-change
ICD data				
AAs burden, %	34	0.0 (0-0.7)	0.0 (0-0.1)	0.49
Atrial pacing, %	29	28 (9-77)	72 (27-92)	<0.01
At least one episode of AAs	34	14 (41)	12 (35)	0.80
Longest AAs ≥ 24 hours	32	2 (6)	2 (6)	1.00
AMS rate, bpm	33	174 ± 15	171 ± 14	0.13
Rate response function on	33	11 (33)	17 (52)	0.21
Lower rate interval, ppm	33	59 ± 12	64 ± 11	<0.01
Right ventricular pacing (dual chamber ICD), %	22	1.1 (1-6.7)	3 (0.7-20.3)	0.21
Biventricular pacing, %	8	95.5 (91.9-96.4)	97.1 (95.7-98.3)	0.64
Echocardiographic data				
LVEF, %	27	40 ±12	37 ± 13	0.17
LVEDVI, ml/m^2	21	72 ± 26	75 ± 22	0.49
LVEDD, mm	23	57 ± 8	60 ± 9	<0.01
LAVI, ml/m^2	22	30 ± 17	35 ± 22	0.51
RAVI, ml/ m^2	19	26 ± 10	34 ± 21	0.34
RV dysfunction	24	7 (29)	7 (29)	1.00
Valvular stenosis/regurgitation ≥ moderate	25	3 (12)	7 (28)	0.16
Clinical data				
Number of sustained VT/ ICD shocks	34	8 (3-15)	1 (0-4)	<0.01
NYHA class	34	2.0 (2-2)	2.1 (2-3)	0.50
Drug Index/Month	34	91 (61-122)	91 (59-122)	0.76

Values are reported as mean ± SD, n (%), or median (interquartile range). AAs= atrial arrhythmias; AMS= automatic mode switch; ICD=implantable cardioverter defibrillator; LAVI= left atrial volume index; LVEDD= left ventricular end diastolic diameter; LVEDVI= left ventricular diastolic volume index; LVEF= left ventricular ejection fraction; NYHA= New York Heart Association; RAVI= right atrial volume index; RV= right ventricle. n* = patients with paired data (before and after BCSD).

Table 5: Chronic drugs at CSD

Ongoing chronic drugs at CSD	All patients, n=91	History of AAs, N=43	No AAs, N=48
Beta blockers	85 (93)	39 (91)	46 (96)
-Metoprolol	29 (32)	14 (33)	15 (31)
-Carvedilol	52 (57)	25 (58)	27 (56)
-Bisoprolol	3 (3)	1 (2)	2 (4)
-Atenolol	1 (1)	1 (2)	0 (0)
ACE-inhibitor/ARB	62 (68)	31 (72)	31 (65)
ARNI	1 (1)	1 (2)	0 (0)
Aspirin	38 (42)	16 (37)	22 (46)
Clopidogrel	3 (3)	0 (0)	3 (1)
Oral anticoagulant	42 (46)	27 (63)	15 (31)*
>1 AAD	29 (32)	12 (28)	17 (35)
Amiodarone	55 (60)	25 (58)	30 (62)
Sotalol	18 (20)	8 (19)	10 (23)
Mexiletine	30 (33)	10 (23)	20 (42)
Dofetilide	5 (5)	2 (5)	3 (1)
Ranolazine	1 (1)	1 (2)	0 (0)
Digoxin	15 (16)	10 (23)	5 (10)
Ivabradine	1 (1)	0 (0)	1 (2)
Previously on amiodarone, permanently stopped because of side effects	14 (15)	8 (17)	6 (12)
- **Previous AIT**	4 (4)	2 (5)	2 (4)

Values are reported as n (%). AAD=antiarrhythmic drugs; AAs= atrial arrhythmias; AIT= amiodarone induced thyrotoxicosis. ARB=angiotensin receptor blocker. ARNI=Angiotensin receptor-neprilysin inhibitor. *= $p<0.05$ between the 2 groups (patients with and without AAs).

Table 6: Ongoing chronic AADs at CSD and at last follow up visit (type and dosages) in the subset of 34 patients

	At CSD, n=34	Mean Daily Dose (mg)	At last visit after CSD, n=34	Mean Daily Dose (mg)
Beta blockers (%)	30 (88)		32 (94)	
-Metoprolol	12 (35)	129 ± 98	17 (50)	87 ± 60
-Carvedilol	17 (50)	38 ± 32	12 (35)	43 ± 31
-Bisoprolol	2 (6)	2.5 ± 1.8	3 (9)	5 ±3.8
> 1 AAD (%)	9 (26)		8 (24)	
Amiodarone	14 (41)	279 ± 94	15 (45)	196 ± 118 *
Sotalol	10 (29)	212 ± 65	6 (18)	193 ± 53
Mexiletine	9 (26)	457 ± 139	7 (21)	467 ± 178
Dofetilide	2 (6)	1000 ± 0	1 (3)	1000
Digoxin	2 (6)	0.156 ± 0.133	0 (0)	
Verapamil	3 (9)	147 ± 83	2 (6)	180 ± 85
Propafenone	2 (6)	450 ± 0	0 (0)	
Ranolazine	0 (0)		2 (6)	1250 ± 354

Values are reported as mean ± SD, n (%), or median (interquartile range). AAD=antiarrhythmic drugs; *= $p<0.05$ between the dosage before CSD and at last visit after CSD.

AAs and LAVI impact on CSD outcome

The median follow up after CSD was 14 months (IQR 4-37). Overall, 27 patients (30%) died before being transplanted, 17 patients underwent OHT (19%) and 53 had sustained VT/appropriate ICD shocks (58%) during follow-up.

In the competing risk model for sustained VT/ICD shock neither LAVI nor a history of AAs was associated with the outcome, not even at the univariable (unadjusted) analysis. A pre-procedural NYHA class III (HR= 7.23, 95% CI 1.50-35.39, p=0.01) and IV (HR= 9.07, 95% CI 1.18-69.5, p=0.03), as compared to class I, were the only independent predictors of sustained VT/ICD shocks, while NYHA class II had a borderline significance (HR= 3.77, 95% CI 0.85-16.64, p=0.08,

In the Cox models for death/OHT a history of AAs was not predictive, while LAVI was statistically significant both at univariable (HR= 1.02 per unit, 95% CI 1.01-1.03, p<0.01, c stat for LAVI alone: 0.720) and at multivariable analysis (figure 1). In the multivariable model controlled for age, three independent predictors for death/OHT were identified: LAVI (HR=1.02 per unit, 95% CI 1.005-1.035, p<0.01), LVEF (HR=0.95 per unit, 95% CI 0.92-0.98, p <0.01) and CKD (HR= 2.04, 95% CI 1.08-3.87, p=0.03) (c stat=0.779 for model).

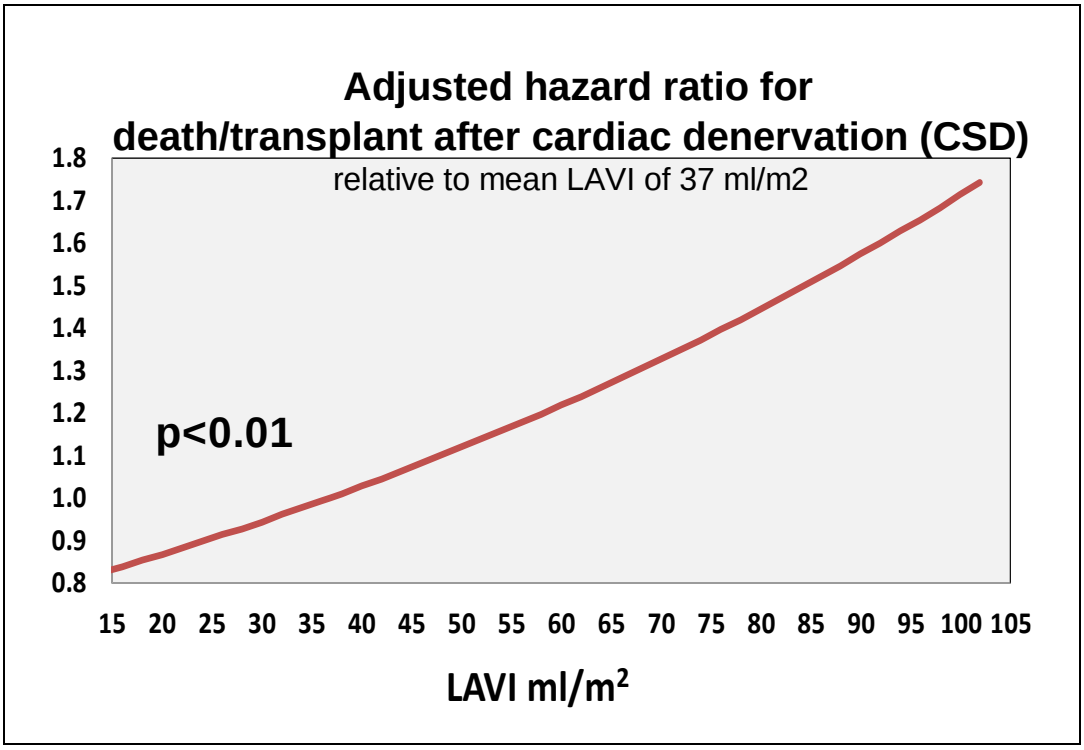

Figure 1: adjusted hazard ratio for death/transplant after cardiac denervation relative to the mean value of LAVI of the study population (37 ml/m^2).

Secondary outcomes after CSD

Excluding the 4 patients in permanent AF at the time of CSD, only 3/87 patients had either episode of AAs requiring treatment (n=2, electrical cardioversion in one case, three inappropriate ICD shocks in the other) or progression to permanent AF (n=1) after CSD (Table 4). Overall, only 1 patient who had not undergone AV node ablation before CSD (1%) suffered inappropriate ICD shocks due to AAs after CSD, as compared to 4/85 patients (5%) before; none of the 4 patients suffering inappropriate ICD shocks due AAs before CSD (mean 4 ± 2 shocks/patient) had recurrences after CSD.

Finally, 4/20 patients (20%) with a single right ventricular lead at the time of CSD, underwent ICD upgrading during follow up: 2 with the addition of an atrial lead only (respectively 110 and 123 days after BCSD), the remaining with the addition of both an atrial and a left ventricular lead (respectively 35 and 345 days after BCSD). The need for upgrading was 4/18 (22%) in patients who received BCSD and 0/2 (0%) in those undergoing LCSD (p=1.00)

Changes in atrial rhythm after BCSD (N=34)

Dual chamber (or single lead with atrial sensing) ICD data before and after BCSD were available for 34 patients (52± 14 years, 24% female, mean LVEF 41± 12%, 41% with a clinical history of AAs, 12% with previous AA ablation), including 2 ICM, 1 mixed CMP and 31 NICM (11 idiopathic CMP).

Available ICD, clinical and echocardiographic data of these patients before and after BCSD is reported in Table 5. The median ICD monitoring time was 8 months (IQR 5-17) before and 15 months (IQR 8-21) after BCSD (p=0.01). During follow-up, 2 patients died (6%) and 6 had OHT (18%, table 4). The AT/AF burden, already low before BCSD, remained stable after the procedure; the percentage of patients with AAs episodes lasting more than 24 hours was unchanged as well. However, the percentage of atrial pacing increased from a median of 28% to 72% (p <0.01, figure 2), in association with a significant increase in the programmed lower rate interval (LRI) for atrial pacing (from 59 ± 12 to 64 ± 11 bpm, p<0.01). At the same time, ventricular pacing percentages, NYHA functional class, cardiac chambers volumes and biventricular function were stable, but a mild increase in LV end diastolic diameter (from 57 to 60 mm, p <0.01) was noticed. Of note, the monthly drug index did not change, but the mean daily dose of amiodarone/patient was significantly lower at last follow-up (from 279 ± 94 mg to 196 ± 118, p=0.04), as reported in table

6. Finally, the number of ICD shock/patient was significantly reduced after BCSD from a median of 8 to a median of 1 ($p < 0.01$).

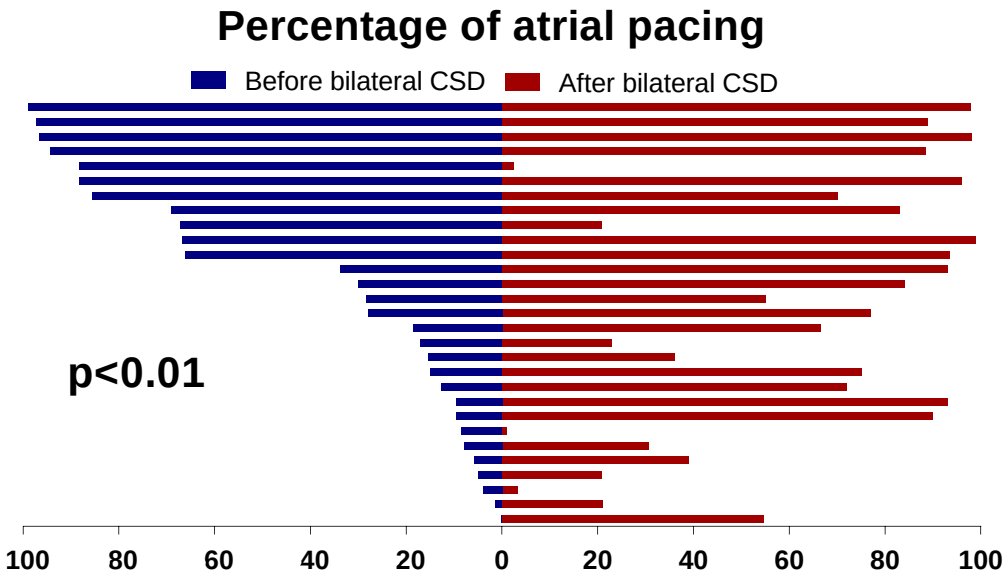

Figure 2: percentage of atrial pacing before and after bilateral cardiac sympathetic denervation

Discussion

AAs and LAVI impact on CSD outcome

In our cohort of patients with SHD undergoing CSD a history of AAs (mainly AF) was common; yet, excluding the few patients with permanent AF, AAs burden before CSD was very low. A history of AAs was not associated with VT recurrences or with mortality/OHT risk after CSD, while LAVI was independently associated with death/OHT occurrence.

The association between SHD, HF and AAs is well known. Yet, the prevalence and the prognostic impact of AAs in patients with SHD vary consistently across studies. A large meta- analysis (6) of patients with an ICD (including both primary and secondary prevention studies) recently showed that AF increases the risk of both mortality and ICD appropriate shocks. Of note, the definition of AF was heterogeneous across studies and the prevalence ranged from 9 to 50%. The association between AF and mortality/VT recurrences in patients with SHD seems to be lost after VT ablation. Recent data from the International VT Ablation Center Collaborative Group (7), failed to demonstrate an association between AF and outcomes after VT ablation. Yet, AF was more common in patients presenting at VT ablation with a history of ES (8), in agreement with the association between AAs and VTs in SHD. Finally, a previous paper (3) suggested a potential association between AF and mortality/OHT after CSD. However, this hypothesis was never assessed in a multivariable model. Our study is characterized by a long follow-up, a detailed characterization of AAs type and burden before CSD and an adequate power to specifically assess the impact on AAs on outcomes after CSD. Importantly, since the burden of AAs detected through the ICD was not provided in any of the abovementioned studies, the lack of association with outcomes could be partially related to a very low AT/AF burden at the time of VT ablation/CSD, as underlined by our data.

Left atrial enlargement as assessed by LAVI is strongly related to LV filling pressure independently from LVEF (9). Of note, in our population only 10% of patients presented with significant mitral valve regurgitation (MR); therefore, this variable was not included in our models, despite its established prognostic value in CMP patients (10). Potential explanations for the observed prevalence of MR include relatively preserved LV dimensions in our study population, different types of CMPs and previous successful mitral valve surgery. LAVI has been associated with an increased risk of all-cause mortality, cardiovascular mortality and HF hospitalization in a broad spectrum of cardiomyopathies including ICM, NICM and HCM (11). Yet, LAVI prognostic

impact in patients with SHD and refractory VTs is largely unexplored. Our data show that in patients undergoing CSD for VTs (largely in sinus rhythm at the time of CSD) LAVI is independently associated with overall mortality and OHT but not with VT recurrences. The lack of association between LAVI and VTs in our population could be related to the ongoing antiarrhythmic interventions, including AADs, VT ablation and CSD. It is particularly tempting to speculate that the potential detrimental effect of left atrial enlargement in terms of increased sympathetic signaling and VTs susceptibility might be mitigated by CSD.

Changes in atrial rhythm after CSD

The analysis of patients who underwent BCSD did not show significant changes in the AAs burden detected by the ICD, despite a mild increase in LV end diastolic diameter and an almost double ICD monitoring time after BCSD as compared to before. Of note, AAs burden was already low before BCSD, despite almost half of the patients had a history of AAs. The high use of class III AADs because of VTs is likely to have contributed to these findings, together with the small % of patients who had previously received catheter ablation for AAs. Nevertheless, an additional protective effect of BCSD towards AAs onset/progression seems plausible, also taking into account that the mean doses of amiodarone were significantly reduced after BCSD.

The mechanisms involved in AAs onset and maintenance in SHDs are complex, but cardiac ANS is certainly involved (1). Pre-clinical data showed that the sympathetic neuronal sprouting that follows ventricular MI affects the entire heart and leads to an increased AF susceptibility (12). Sympathetic activation is thought to promote AAs mainly through focal mechanisms such as enhanced automaticity and triggered activity. Such mechanisms may act as trigger for AF on a susceptible substrate or as AT/AF maintaining driver in case of persistent rapid firing (1). Yet, in patients with paroxysmal AF undergoing AF ablation, temporary unilateral SGB not only reduced AF inducibility/duration, but also prolonged atrial effective refractory period, potentially suggesting additional re-entrant related functional mechanisms for sympathetic activation mediated pro-arrhythmic effects (5). The relatively small LA dimensions in our population underscore the potential contribution of local/functional mechanisms as opposed to mechanisms mainly related to LA enlargement/fibrosis in promoting susceptibility to AAs.

Finally, we described for the first time the impact of CSD on cardiac chronotropy in patients with SHD. In our cohort, almost one fourth of patients with a single ventricular lead before CSD

underwent atrial catheter implantation after the procedure; all of them had received BCSD. Among patients who already had a dual chamber ICD before BCSD, a mild but significant increase in the programmed lower rate interval (LRI) for atrial pacing was noticed after BCSD, in association with a consistent increase in the percentage of atrial pacing over time.

Previous canine experiments (13), combined with recent optogenetic studies in mouse (14), suggest that the right stellate ganglion plays a pivotal role in the neuronal circuits that control heart rate (HR). In conscious dogs both right and bilateral stellectomy (but not left) were associated with significantly lower resting HR and peak HR during exercise (13). The impact of temporary right SGB on HR in humans is more controversial (5, 15). Patients with SHD have detectable clinical signs of autonomic imbalance characterized by sympathetic hyperactivity and parasympathetic withdrawal. Additionally, stellate ganglia from subjects undergoing BCSD for refractory VTs showed signs of inflammation, neurochemical remodeling, and oxidative stress (16). In this setting BCSD is expected not only to reduce sympathetic drive to the heart, but also to improve vagal control both at the central and at the peripheral level (17). The increased parasympathetic drive to the sinus node after BCSD may contribute to explain the impact on resting HR despite ongoing polytherapy with BBs and AADs. Of note, patients are expected to be more active in the months after CSD due to an overall improvement in the quality of life related to the highly significant reduction of ICD shocks (18).

Taken all together, our findings suggest that patients with a single lead ICD and/or without ICD undergoing BCSD should be monitored for the potential need of atrial pacing, particularly in case of preexisting bradycardia. Of course AADs down titration should be tried first, albeit the optimal timing for trying AADs down titration after BCSD has not being established yet.

Limitations

Data were collected retrospectively and are not complete for all variables; yet, the percentage of missing data is overall low. ICD programming was left to the discretion of the treating physician, therefore was not uniform. Finally, despite being performed by qualified personnel, the echocardiographic evaluations were neither centralized nor blinded.

Conclusions

A history of atrial arrhythmias was frequent in patients with SHD and refractory ventricular arrhythmias undergoing CSD but did not affect the outcome. LAVI, on the other hand, was an independent predictor of death/orthotopic heart transplant. The burden of atrial arrhythmias, already low at baseline, stayed stable after BCSD despite a mild progression of left ventricular enlargement, suggesting a protective effect of BCSD.

Finally, a relatively high need for dual chamber upgrading was observed after BCSD, combined with a significant increase in the percentage of atrial pacing in subjects who already had an atrial catheter. These findings suggest that subjects with a single lead ICD and/or without ICD undergoing BCSD should be monitored for the potential need of atrial pacing.

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