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CLINICAL RESEARCH

Baroreflex sensitivity assessed with the sequence method is associated with ventricular arrhythmias in patients implanted with a defibrillator for the primary prevention of sudden cardiac death

La sensibilité du baroréflexe évaluée avec la méthode des séquences est associée aux arythmies ventriculaires chez les patients implantés d'un défibrillateur cardiaque en prévention primaire de la mort subite

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Abbreviations: BRS, baroreflex sensitivity; HF, high frequency; ICD, implantable cardioverter defibrillator; LF, low frequency; LVEF, left ventricular ejection fraction; PNN50, proportion of consecutive normal-to-normal intervals that differ by > 50 ms; SDNN, standard deviation of normal-to-normal intervals.

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KEYWORDS
Baroreflex;
Myocardial infarction;
Ventricular arrhythmia;
Primary prevention;
Sudden cardiac death

Summary

Background. — Left ventricular ejection fraction lacks accuracy in predicting sudden cardiac death, resulting in unnecessary implantation of cardioverter defibrillators for the primary prevention of sudden cardiac death. Baroreflex sensitivity could help to stratify patients at risk of ventricular arrhythmia.

Aim. — To assess the association between cardiac baroreflex sensitivity and ventricular arrhythmias in patients implanted with an implantable cardioverter defibrillator for the primary prevention of sudden cardiac death after myocardial infarction.

Methods. — This case-control single-centre study took place between 2015 and 2016. Cases (n = 10) had experienced ventricular arrhythmias treated by the implantable cardioverter defibrillator in the previous 3 years; controls (n = 22) had no arrhythmia during the same period. Baroreflex sensitivity was assessed using the temporal sequence method (mean slope) and cross-spectral analysis (low-frequency gain and high-frequency gain).

Results. — The mean age was 65 years; 94% of the patients were men. 24-hour Holter electrocardiogram autonomous nervous system variables, left ventricular ejection fraction and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) concentration did not differ between cases and controls. The mean slope was lower in cases than in controls (8 vs. 15 ms/mmHg [P = 0.009] in the supine position; 7 vs. 12 ms/mmHg [P = 0.038] in the standing position). The mean slope in the supine position was still significantly different between groups after adjustment for age, left ventricular ejection fraction and NT-proBNP (P = 0.03). By comparison, low-frequency gain and high-frequency gain did not differ between groups in either the supine or the standing position.

Conclusion. — Patients with ventricular arrhythmias had a lower mean slope compared with those who were free of arrhythmia. A prospective study is needed to confirm this association.

MOTS CLÉS
Baroréflexe ;
Infarctus du myocarde ;
Arythmies ventriculaires ;
Prévention primaire ;
Mort subite

Résumé

Contexte. — La fraction d'éjection du ventricule gauche manque de spécificité pour prédire le risque de mort subite en prévention primaire. La sensibilité du baroréflexe pourrait être un marqueur pronostique plus discriminant.

Objectif. — Nous avons évalué l'association entre la sensibilité du baroréflexe cardiaque et les troubles du rythme ventriculaires chez des patients implantés de défibrillateur en prévention primaire après un infarctus du myocarde.

Méthodes. — Cette étude cas-témoin s'est déroulée entre 2015 et 2016. Les 10 cas avaient eu des arythmies ventriculaires traitées par leur défibrillateur durant les 3 dernières années. Les 22 témoins n'avaient pas eu d'arythmie durant cette même période. La sensibilité du baroréflexe était évaluée par la méthode des séquences (pente moyenne) et par la méthode cross-spectrale (gain LF et gain HF).

Résultats. — La moyenne d'âge était de 65 ans et 94% étaient des hommes. Les paramètres Holter-ECG, la fraction d'éjection du ventricule gauche et le NT-proBNP n'étaient pas différents entre les cas et les témoins. La pente moyenne était plus basse chez les cas que les témoins (8 vs 15 ms/mmHg [p = 0,009] en position allongée ; 7 vs 12 ms/mmHg [p = 0,038] en position debout). Cette différence en position allongée était significative après ajustement sur l'âge, la fraction d'éjection du ventricule gauche et le NT-proBNP (p = 0,03). Au contraire, le gain LF et le gain HF n'étaient pas différents entre les 2 groupes.

Conclusion. — Les patients ayant eu des arythmies ventriculaires avaient une sensibilité du baroréflexe plus basse que les patients n'ayant jamais eu d'arythmies. Une étude prospective est nécessaire pour confirmer cette association.

Background

Implantable cardioverter defibrillators (ICDs) used in primary prevention have proved to be efficient in the reduction of sudden cardiac death. Indeed, they provide a mean reduction of 7.9% in absolute mortality according to different studies [1]. As a result, the number of device implantations is booming [2]. The other side of the coin is that prediction of sudden cardiac death is not accurate enough, as the number of patients that have to be implanted to save a life after 3 years of follow-up ranges from four to 18 [3—5]. Moreover, ICD implantation has numerous serious complications. Lead dysfunction occurs in 40% of patients after 8 years of follow-up, and device infection occurs in 5% of patients after 6 years of implantation [6,7]. Nowadays, international guidelines propose left ventricular ejection fraction (LVEF) as the single tool for predicting sudden cardiac death [8]. All of these facts lead us to consider how we can improve the prediction of sudden cardiac death in patients free from previous ventricular arrhythmia.

Cardiac baroreflex sensitivity (BRS) is a key mechanism contributing to cardiovascular autonomic control; it allows short-term blood pressure regulation and heart rate variability. Indeed, blood pressure fluctuations will activate arterial baroreceptors, inducing compensatory changes in heart rate, cardiac contractility and vascular tone [9,10]. Alteration of this negative feedback loop contributes to sympathetic-parasympathetic imbalance, and has been shown to be strongly associated with the occurrence and progression of many cardiovascular diseases [11,12]. In ischaemic cardiomyopathy, the prognostic value of BRS has been investigated, but the endpoint was cardiac mortality rather than ventricular arrhythmia, which is not accurate enough to determine the extent to which the ICD can prevent sudden cardiac death in primary prevention [13—16].

Given the paucity of tools that can lead to recommendation or non-recommendation of implantation of an ICD for primary prevention, we thought that evaluation of BRS as a possibly valuable tool was warranted. As a first step, in this pilot case-control study, we aimed to determine whether BRS could be associated with the occurrence of ventricular arrhythmias over the 3 most recent years in patients implanted with an ICD for the primary prevention of sudden cardiac death after myocardial infarction.

Methods

Patients

This pilot single-centre case-control study (NCT02930382) took place between February 2015 and February 2016 in the department of cardiology and Clinical Investigation Centre 1402 in Poitiers university hospital (France). All patients with an ICD who were referred to the outpatient cardiology department were screened for eligibility. Inclusion criteria were: ICD implantation for primary prevention of cardiac sudden death; ischaemic cardiomyopathy; and ICD implantation for at least 3 years. Exclusion criteria were: ventricular or atrial pacing $\geq$ 1%; age < 18 years; and history of atrial fibrillation. Cases were defined as patients who had presented one or several episodes of sustained ventricular tachycardia or ventricular fibrillation with appropriate ICD therapy over the last 3 years. Controls were defined as patients who had not experienced any appropriate ICD therapy or sustained ventricular arrhythmia over the last 3 years. The study was conducted according to the ethical principles of the Declaration of Helsinki and the current guidelines for good clinical practice. The local ethics committee (CPP Ouest-III N°◦ 2014-A01917-40) approved the study in February 2015. Written informed consent was obtained from all subjects.

Data collection

Sociodemographic and clinical data were collected during patients' visits to the outpatient cardiology department. Electrocardiograms carried out at ICD implantation were retrieved from hospital medical records. PR interval, QRS duration and QT interval corrected according to Bazett's formula were measured and calculated by one trained senior electrophysiologist. The echocardiograms carried out the month before ICD implantation (Vivid™ 6 or 7 echocardiogram; GE Healthcare, Horten, Norway) were reanalysed by a senior echocardiographer (EchoPAC™ 113.1.0; GE Medical Systems, Horten, Norway). LVEF was assessed using the biplane Simpson's method. Left ventricular end-diastolic diameter, end-diastolic septal thickness, left ventricular global longitudinal strain and left atrial volume were also measured. Electrocardiogram and echocardiogram analyses were done blind to case-control status. Data from a 24-hour Holter electrocardiogram carried out before implantation were retrieved. Spiderview™ Holter recorders (Livanova, Milan, Italy) with three-channel recording were used for 24-hour ambulatory Holter electrocardiogram monitoring in each patient. Each beat was automatically classified and labelled by Synescope™ software (Livanova, Milan, Italy), using the template-matching technique. Heart rate variability was analysed in both the time domain and the frequency domain. Regarding time-domain analysis, calculation of the standard deviation of normal-to-normal intervals (SDNN) and the proportion of consecutive normal-to-normal intervals that differed by > 50 ms (PNN50) was performed. The frequency domain consisted of spectral analysis with calculation of spectral powers in the low-frequency (LF) band and the high-frequency (HF) band. Finally, we retrieved N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), creatinine and haemoglobin concentrations at the time of implantation.

Baroreflex sensitivity assessment

Within the 14 days after their selection for the study, cases and controls underwent simultaneously, in the same conditions and blinded to their status, non-invasive plethysmographic recording (Finapres® 2300; Ohmeda SA, Trappes, France), electrocardiogram recording and respiratory rate monitoring via an MP150 workstation (BIOPAC Systems, Goleta, CA, USA) for a duration of 10 minutes in the supine position and 10 minutes in the standing position. The three signals were acquired for a minimal duration of 205 seconds free of premature beats and signal noise (2048 points sampled at 10 Hz). All subjects were asked to breathe regularly and to avoid deep respiration during the recording. Taking into consideration the circadian rhythm of the autonomic tone, all recordings took place between 9 a.m. and 11 a.m. in a quiet room maintained at ≥ 22 °C. The blood pressure signal was digitized (500 Hz) using a 12-bit A/D converter, and processed by an algorithm based on feature extraction to detect and measure the characteristics of a blood pressure cycle (AcqKnowledge® 3.0 software; BioPac Systems, Goleta, CA, USA). Systolic blood pressure and heart rate were stored on a hard disk and sampled at 10 Hz. BRS was evaluated using a specifically designed programme that analysed simultaneous fluctuations in systolic blood pressure and heart rate using both a time-domain technique (sequence method) and a frequency-domain technique (transfer function analysis). The sequence method is based on the detection of three or more cycles with increases or decreases in systolic blood pressure associated with parallel changes in the RR-interval of the following cardiac cycle. A linear regression method was applied to each of these sequences, and an average regression slope was calculated, representing the mean slope of the cardiac BRS. The calculation of the transfer function from systolic blood pressure to heart rate was based on the cross-spectral technique. A Fourier transformation was applied to decompose the signal in a spectrum of different frequencies (HF and LF). Transfer function analysis showed the level of coupling between systolic blood pressure and RR in each frequency. Baroreflex gain was calculated in the LF and HF bands as proposed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (LF = 0.04—0.15 Hz; HF = 0.15—0.40 Hz) [17]. The gain function was the ratio between changes in systolic blood pressure and changes in pulse interval (ms/mmHg). All data were analysed blind to case-control status by a trained researcher. The reproducibility of BRS variables, mean slope calculated with the sequence method and LF and HF gains had been tested previously, in both the supine and the standing position [18].

Statistical analysis

Categorical variables are expressed as numbers and proportions; continuous variables are expressed as mean ± standard deviation or median [interquartile range]. Comparisons of groups were performed using the χ^2 test for categorical variables and Student's *t* test or the Mann-Whitney U test, as appropriate, for quantitative variables. Bivariate or multivariable analyses were performed using logistic regression. The area under the receiver operating characteristic curve was calculated using univariate logistic regression. Analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA). Two-sided *P* values of < 0.05 were considered statistically significant.

Results

Thirty-nine patients implanted with an ICD for at least 3 years had plethysmographic recording. Of these, seven had records that did not allow for BRS evaluation. Therefore, 32 patients were included in the present analysis, corresponding to 10 cases and 22 controls.

Among the cases, the ventricular arrhythmia that triggered the ICD therapy was ventricular tachycardia in seven patients and ventricular fibrillation in three patients. The median delay between ICD implantation and ICD therapy was 5 [2; 7] years.

Clinical characteristics at implantation

Patients' clinical characteristics at implantation are given in Table 1. There was no significant difference between cases and controls regarding sex ratio, age, cardiovascular risk factors (hypertension, dyslipidaemia, diabetes, smoking status), medical history or drug use.

Electrocardiogram variables (QRS duration, PR and corrected QT interval), measured at implantation were quite similar in cases and controls (Table 1), as were echocardiographic variables (left ventricular end-diastolic diameter, diastolic septum thickness, global longitudinal strain and left atrial volume). LVEF was not significantly different in cases and controls: 29 ± 6% and 27 ± 7%, respectively.

Regarding biological determinations at implantation, creatinine, haemoglobin and NT-proBNP concentrations did not differ significantly in cases compared with controls (Table 1).

Autonomic nervous system activity evaluated at implantation by 24-hour Holter electrocardiogram did not show significant differences between cases and controls, in either temporal domains (SDNN, PNN50) or frequency domains (LF power, HF power, LF/HF) (Table 1).

BRS assessment in cases and controls

The evaluation of BRS calculated from the Finapres® recording more than 3 years after implantation of the ICD (median delay 6 [4; 10] years) is described in Table 2. The mean slope was significantly lower in cases compared with controls, in both the supine and standing positions (8 vs. 15 ms/mmHg [*P* = 0.009] in the supine position and 7 vs. 12 ms/mmHg [*P* = 0.038] in the standing position, respectively).

The supine mean slope difference between cases and controls was still significant after adjustment for age (*P* = 0.035), LVEF (*P* = 0.02), NT-proBNP concentration (*P* = 0.01), and also when adjusted simultaneously for these three factors taken together (*P* = 0.03). Of note, age, LVEF and NT-proBNP were not significantly associated with case/control status.

The standing mean slope remained significantly different between cases and controls after adjustment for LVEF (*P* = 0.039), NT-proBNP concentration (*P* = 0.048) and both together (*P* = 0.041). However, the difference in standing mean slope between cases and controls was no longer significantly different when adjusted for age (*P* = 0.09).

The receiver operating characteristic curve analysing the mean slope in the supine position is shown in Fig. 1. The area under the curve was 79.5% [61.8%; 97.2%]. The cut-off value maximizing the likelihood ratio was 10.45 ms/mmHg and the related sensitivity and specificity were 80% (95% confidence interval 44.4—97.5) and 80% (95% confidence interval: 56.3—94.3), respectively.

BRS evaluated by cross-spectral analysis tended to be lower in cases than in controls, but the difference did not reach statistical significance in either the supine or standing positions, or for LF and HF gain variables (Table 2).

Table 1 Characteristics of patients at implantation.

	Whole population (n = 32)	Cases (n = 10)	Controls (n = 22)	P
Clinical characteristics				
Age (years)	65 ± 11	67 ± 10	63 ± 12	0.30
Male sex	30 (94)	9 (90)	21 (95)	0.55
Height (cm)	171 ± 8	169 ± 8	172 ± 9	0.53
Weight (kg)	85 ± 14	90 ± 16	82 ± 12	0.26
Body mass index (kg/m^2)	29 ± 5	31 ± 5	28 ± 4	0.08
Systolic blood pressure (mmHg)	117 ± 12	113 ± 6	118 ± 13	0.19
Diastolic blood pressure (mmHg)	74 ± 13	69 ± 11	76 ± 14	0.19
Medical history and medication				
Hyperlipidaemia	18 (56)	5 (50)	13 (59)	0.71
Hypertension	13 (41)	4 (40)	9 (41)	0.99
Diabetes	9 (28)	3 (30)	6 (27)	0.99
Active smoking	4 (13)	1 (10)	3 (14)	0.66
Stroke	3 (9)	2 (20)	1 (5)	0.22
Carotid stenosis	2 (6)	0 (0)	2 (9)	0.32
Lower limb arterial disease	1 (3)	1 (10)	0 (0)	0.31
Drug use				
Beta-blockers	31 (97)	9 (90)	22 (100)	0.31
ACEIs	31 (97)	9 (90)	22 (100)	0.31
Diuretics	24 (75)	7 (70)	17 (77)	0.68
Anticoagulants	10 (31)	3 (30)	7 (32)	0.99
Antiplatelet agents	27 (84)	9 (90)	18 (82)	0.99
12-lead electrocardiogram				
Heart rate (beats/min)	60 ± 13	63 ± 16	59 ± 11	0.44
PR interval (ms)	211 ± 43	204 ± 33	214 ± 47	0.68
QRS duration (ms)	121 ± 34	121 ± 27	121 ± 38	0.6
Corrected QT interval[a] (ms)	449 ± 48	448 ± 60	450 ± 44	0.74
Echocardiography				
LVEF (%)	28 ± 6	29 ± 6	27 ± 7	0.27
LV end-diastolic diameter (mm)	64 ± 11	64 ± 12	63 ± 10	0.81
Diastolic septum thickness (mm)	11 ± 2	10 ± 3	11 ± 2	0.84
Global longitudinal strain (%)	−8.06 ± 2.9	−8.1 ± 2.68	−8.05 ± 3.05	0.95
Left atrial volume (mL/m^2)	42 ± 17	40 ± 10	43 ± 19	0.85
Biology				
NT-proBNP (pg/mL)	916 ± 905	772 ± 1102	980 ± 821	0.14
Creatinine (μmol/L)	104 ± 35	99 ± 31	106 ± 37	0.60
Haemoglobin (g/dL)	14.0 ± 1.6	14.3 ± 1.4	13.9 ± 1.7	0.55
Heart rate variability				
PNN50 (%)	5.13 ± 4.39	4.00 ± 2.95	5.64 ± 4.88	0.36
SDNN (ms)	106.59 ± 41.82	91.77 ± 24.07	113.33 ± 46.7	0.37
LF (ms^2)	355.91 ± 294.55	399.6 ± 408.13	336.05 ± 235.3	0.74
HF (ms^2)	113.66 ± 2.21	123 ± 66.97	109.41 ± 61.08	0.49
LF/HF	3.55 ± 3.26	3.69 ± 3.99	3.5 ± 2.98	0.51

Data are expressed as mean ± standard deviation or number (%). ACEI: angiotensin-converting enzyme inhibitor; HF: high frequency; LF: low frequency; LF/HF ratio: low frequency/high frequency component; LV: left ventricular; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone of B-type natriuretic peptide; PNN50: proportion of consecutive normal-to-normal intervals that differ by > 50 ms; SDNN: standard deviation of normal-to-normal intervals.

[a] QT interval corrected with Bazett's formula.

Discussion

Our study showed that, in a population with a low ejection fraction, BRS assessed by the sequence method in the supine and standing positions was lower in patients who had experienced ventricular arrhythmias, while no clinical, biological or structural variables differed significantly between cases and controls. This important finding has not been reported previously, to the best of our knowledge. On the other hand, we did not show any difference between cases and controls when BRS was evaluated by the cross-spectral method.

Table 2 Baroreflex sensitivity assessment.

	Cases ($n = 10$)	Controls ($n = 22$)	P
Supine mean slope (ms/mmHg)	8.04 ± 5.66	14.87 ± 6.92	0.009
Supine LF gain (ms/mmHg)	3.61 ± 2.73	4.78 ± 3.77	0.63
Supine HF gain (ms/mmHg)	4.22 ± 3.75	6.61 ± 5.88	0.19
Standing mean slope (ms/mmHg)	7.27 ± 4.55	11.61 ± 6.69	0.038
Standing LF gain (ms/mmHg)	2.44 ± 0.79	4.11 ± 4.08	0.29
Standing HF gain (ms/mmHg)	2.73 ± 1.15	5.61 ± 7.39	0.33

Data are expressed as mean ± standard deviation. HF: high frequency; LF: low frequency.

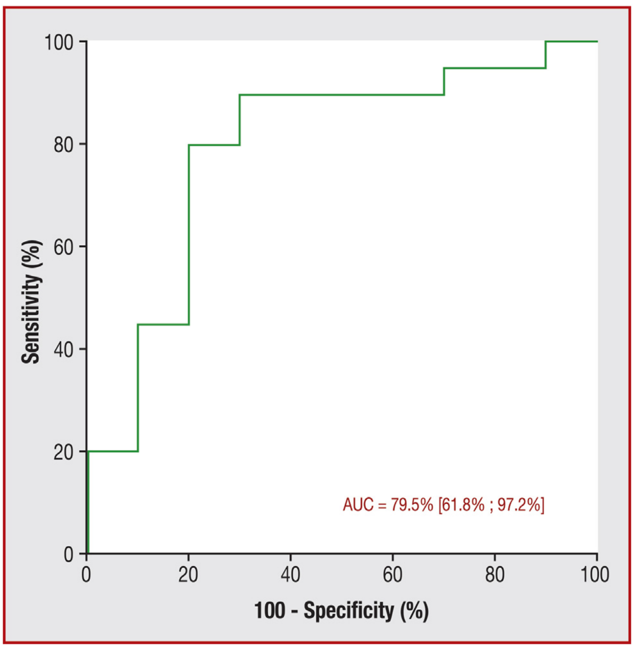

Figure 1. Receiver operating characteristic curve analysing the mean slope in the supine position; the endpoint was ventricular arrhythmia. AUC: area under the curve.

BRS evaluates the capability of the autonomic nervous system to increase vagal activity and decrease sympathetic activity after a sudden increase in blood pressure. By the early 1970s, some experimental studies had shed light on the pathophysiological implications of baroreflex impairment in various heart diseases. Animal models were used to demonstrate that, after myocardial infarction, impaired BRS was associated with ventricular fibrillation, whereas parasympathetic activation decreased ventricular arrhythmias [19,20].

Prediction of sudden cardiac death

Attempting to predict sudden cardiac death in primary prevention is a long story. The first study demonstrating the usefulness of defibrillators for the primary prevention of sudden cardiac death was published 15 years ago; since then, several studies have confirmed those results [21—23]. The cornerstone for prediction of sudden cardiac death in those studies was reduced LVEF, and current guidelines recommend implantation of a defibrillator when LVEF is $\leq$ 35% with symptomatic heart failure [8]. Most of the time, LVEF is evaluated using echocardiography, with variability approximating 16% [24]. Numerous other markers have been tested to improve the prediction of sudden cardiac death: electrocardiogram QRS fragmentation; left ventricle scarring; and serum biomarkers of inflammation and neurohumoral activation [25—28]. Scores have also been developed to predict non-arrhythmic death [29]. Unfortunately, none has been reproducible or powerful enough to be considered in international guidelines.

In this study, we demonstrated that BRS assessed with the sequence method was lower in patients who had experienced ventricular arrhythmias, even though cases and controls had similar LVEFs and non-different 24-hour Holter heart rate variability at implantation. Our results are in agreement with those in the literature, which showed heart rate variability to be a poor predictive tool regarding sudden cardiac death, whereas BRS seems to be more promising.

In the ATRAMI study, a low value for BRS assessed with the sequence method was associated with a 2.8-fold [1.24-fold; 6.15-fold] higher risk of cardiac death ($P = 0.01$) [16].

Previous studies aimed to assess the predictive value of BRS regarding cardiovascular mortality, but not regarding arrhythmic sudden cardiac death. The originality of this pilot study stems from its assessment of the relationship between BRS and ventricular arrhythmias rather than cardiac mortality. Several studies have demonstrated that BRS is associated with cardiovascular mortality [13—16]. On the other hand, a recent meta-analysis showed appropriate shocks to be associated with higher New York Heart Association class, lower LVEF, no beta-blocker therapy and single-chamber ICD (versus dual-chamber ICD), but BRS was not assessed [30]. According to our results, depressed BRS could be associated with ventricular arrhythmia in patients with ischaemic cardiomyopathy, and patients with a depressed BRS could be considered as being at high risk of sudden cardiac death, which is a very sensitive public health problem [31,32].

Study limitations

The main limitation of this study was its cross-sectional design, requiring retrospective analysis of ICD use, indicative of ventricular arrhythmia. However, such a first step was necessary before considering a prospective cohort study that would necessitate a large number of subjects. Another limitation was patient selection, which was very restrictive. Indeed, BRS assessment required exclusion of patients with atrial fibrillation and cardiac stimulation. Patients implanted with an ICD for primary prevention who have an LVEF < 35% are often subject to atrial fibrillation or are paced because of beta-blockers or cardiac resynchronization therapy.

Estimation of spontaneous BRS

Assessment of BRS is very tricky. In most studies dealing with the relationship between BRS and morbimortality, BRS was quantified in response to intravenous phenylephrine [11,15,16]. This method is invasive and, from a methodological point of view, blood pressure response after phenylephrine administration has shown high interindividual variability. Moreover, phenylephrine may have a direct effect on baroreceptors, as has been demonstrated in a rat model [33]. In our study, BRS assessment was totally non-invasive, as blood pressure was estimated using a non-invasive plethysmographic system. This method is easily feasible in daily clinical settings, and has been shown to be appropriate after myocardial infarction and in a wide variety of clinical situations [11]. Various techniques exist to estimate spontaneous BRS from non-invasive recordings, and substantial differences can be observed in the estimates [34]. Therefore, we chose to report three currently used estimates, the reproducibility of which had been tested before the start of the study [31]. The mean values of BRS found in the present work were consistent with expected values, given the techniques used, as well as the age and clinical condition of the studied patients [11].

Conclusions

This case-control study was the first study aiming to specifically assess the association between BRS and ventricular arrhythmias. In this population of patients with ischaemic cardiomyopathy and LVEF < 35%, BRS assessed with the sequence method was lower in patients with ventricular arrhythmias compared with in patients free of arrhythmia. As the number of patients that have to be implanted to save a life is tremendously high, we need to predict the risk of ventricular arrhythmia more accurately. A prospective study to assess the prognostic value of BRS for ventricular arrhythmia before primary prevention ICD implantation seems indispensable.

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Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Nanthakumar K, Epstein AE, Kay GN, Plumb VJ, Lee DS. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials. J Am Coll Cardiol 2004;44:2166—72.
[2] Raatikainen MJ, Arnar DO, Merkely B, Camm AJ, Hindricks G. Access to and clinical use of cardiac implantable electronic devices and interventional electrophysiological procedures in the European Society of Cardiology Countries: 2016 Report from the European Heart Rhythm Association. Europace 2016;18(Suppl 3):iii1—79.
[3] Algalarrondo V, Perault R, Bories MC, et al. Prophylactic implantable cardioverter defibrillators for primary prevention: From implantation to heart transplantation. Arch Cardiovasc Dis 2018;111:758—65.
[4] Betts TR, Sadarmin PP, Tomlinson DR, et al. Absolute risk reduction in total mortality with implantable cardioverter defibrillators: analysis of primary and secondary prevention trial data to aid risk/benefit analysis. Europace 2013;15:813—9.
[5] Weeke P, Johansen JB, Jorgensen OD, et al. Mortality and appropriate and inappropriate therapy in patients with ischaemic heart disease and implanted cardioverter-defibrillators for primary prevention: data from the Danish ICD Register. Europace 2013;15:1150—7.
[6] de Bie MK, van Rees JB, Thijssen J, et al. Cardiac device infections are associated with a significant mortality risk. Heart Rhythm 2012;9:494—8.
[7] Kleemann T, Becker T, Doenges K, et al. Annual rate of transvenous defibrillation lead defects in implantable cardioverter-defibrillators over a period of > 10 years. Circulation 2007;115:2474—80.
[8] Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 2015;36:2793—867.
[9] Levy MN, Pappano AJ. Cardiovascular physiology. 9th ed Philadelphia: Mosby Elsevier; 2007.
[10] Parati G, Di Rienzo M, Bertinieri G, et al. Evaluation of the baroreceptor-heart rate reflex by 24-hour intra-arterial blood pressure monitoring in humans. Hypertension 1988;12:214—22.
[11] Herpin D, Ragot S, Le Henaff J, et al. [Short term blood pressure variability and baroreflex sensitivity in mild and moderate hypertensive patients ''dipper and non dipper'']. Arch Mal Coeur Vaiss 1996;89:1087—90.
[12] Thomson HL, Morris-Thurgood J, Atherton J, Frenneaux M. Reduced cardiopulmonary baroreflex sensitivity in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 1998;31:1377—82.
[13] De Ferrari GM, Sanzo A, Bertoletti A, Specchia G, Vanoli E, Schwartz PJ. Baroreflex sensitivity predicts long-term cardiovascular mortality after myocardial infarction even in patients with preserved left ventricular function. J Am Coll Cardiol 2007;50:2285—90.
[14] Exner DV, Kavanagh KM, Slawnych MP, et al. Noninvasive risk assessment early after a myocardial infarction the REFINE study. J Am Coll Cardiol 2007;50:2275—84.

[15] Garcia R, Sosner P, Laude D, Hadjadj S, Herpin D, Ragot S. Spontaneous baroreflex sensitivity measured early after acute myocardial infarction is an independent predictor of cardiovascular mortality: results from a 12-year follow-up study. Int J Cardiol 2014;177:120—2.
[16] La Rovere MT, Bigger Jr JT, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998;351:478—84.
[17] Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17:354—81.
[18] Herpin D, Ragot S. Mid- and long-term reproducibility of noninvasive measurements of spontaneous arterial baroreflex sensitivity in healthy volunteers. Am J Hypertens 1997;10:790—7.
[19] Billman GE, Schwartz PJ, Stone HL. Baroreceptor reflex control of heart rate: a predictor of sudden cardiac death. Circulation 1982;66:874—80.
[20] Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull Jr SS, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ Res 1991;68:1471—81.
[21] Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225—37.
[22] Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877—83.
[23] Sjoblom J, Kalm T, Gadler F, et al. Efficacy of primary preventive ICD therapy in an unselected population of patients with reduced left ventricular ejection fraction. Europace 2015;17:255—61.
[24] McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. Am Heart J 2003;146:388—97.
[25] Cheng A, Zhang Y, Blasco-Colmenares E, et al. Protein biomarkers identify patients unlikely to benefit from primary prevention implantable cardioverter defibrillators: findings from the Prospective Observational Study of Implantable Cardioverter Defibrillators (PROSE-ICD). Circ Arrhythm Electrophysiol 2014;7:1084—91.
[26] Das MK, Maskoun W, Shen C, et al., Fragmented QRS. on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. Heart Rhythm 2010;7:74—80.
[27] Escande W, Boveda S, Defaye P, et al. Outcomes in guideline-based versus off-guideline primary prevention implantable cardioverter-defibrillator recipients. J Am Coll Cardiol 2017;70:1302—3.
[28] Klem I, Weinsaft JW, Bahnson TD, et al. Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. J Am Coll Cardiol 2012;60:408—20.
[29] Providencia R, Boveda S, Lambiase P, et al. Prediction of nonarrhythmic mortality in primary prevention implantable cardioverter-defibrillator patients with ischemic and nonischemic cardiomyopathy. JACC Clin Electrophysiol 2015;1:29—37.
[30] Zeitler EP, Al-Khatib SM, Friedman DJ, et al. Predicting appropriate shocks in patients with heart failure: patient level meta-analysis from SCD-HeFT and MADIT II. J Cardiovasc Electrophysiol 2017;28:1345—51.
[31] Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. Circ Res 2015;116:1887—906.
[32] Risgaard B, Winkel BG, Jabbari R, et al. Burden of sudden cardiac death in persons aged 1 to 49 years: nationwide study in Denmark. Circ Arrhythm Electrophysiol 2014;7:205—11.
[33] Goldman WF, Saum WR. A direct excitatory action of catecholamines on rat aortic baroreceptors in vitro. Circ Res 1984;55:18—30.
[34] Laude D, Elghozi JL, Girard A, et al. Comparison of various techniques used to estimate spontaneous baroreflex sensitivity (the EuroBaVar study). Am J Physiol Regul Integr Comp Physiol 2004;286:R226—31.