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High Atrioventricular Phase Index on Near-Field Intracardiac Electrogram is Associated with Risk of Ventricular Arrhythmia

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Abstract

The purpose of this study was to characterize and quantify concordance between consecutive atrial and ventricular activation time points through analysis of phases and to explore its association with outcomes in patients with implantable cardioverter-defibrillator (ICD). Patients with structural heart disease and dual-chamber ICDs underwent 5min baseline right ventricular (V) near-field and atrial (A) electrogram (EGM) recording. The cross-dependencies of phase dynamics of the changes in consecutive A (AA') and V (VV') were quantified and the AV phase dependency index was determined. In Cox regression analysis, a high AV phase index (in the highest quartile, >0.259) was significantly associated with higher risk of ventricular tachyarrhythmias (HR 2.84; 95% CI 1.05–7.67; P=0.04). In conclusion, in ICD patients with structural heart disease, high sinus AV phase dependency index on EGM is associated with the risk of ventricular arrhythmia.

Keywords

symbolic dynamics; sympathetic; phase dependency; atrial; ventricular

Introduction

Implantable cardioverter-defibrillators (ICDs) are widely used in eligible patients to prevent sudden cardiac death (SCD). Despite effective termination of ventricular tachycardia (VT) / ventricular fibrillation (VF), the occurrence of VT/VF is associated with increased mortality and heart failure hospitalizations in ICD patients.¹ Timely (within 1–3 months window) prediction of sustained VT/VF² might trigger timely adjustment in patients' management and therefore, prevent appropriate, but undesirable ICD therapies, and improve patients outcomes. It is important to identify novel risk markers of VT/VF in ICD patients, which would help to develop robust risk score of VT/VF events in the future.

We recently showed that increased percentage of near-field (NF) right ventricular (RV) intracardiac electrogram (EGM) VV' alternans (i.e. short-long-short, or long-short-long sequences of VV' intervals) was associated with increased mortality in ICD patients³. However, it is unknown whether VV' alternans appearance is mainly driven by the sinus node, or if atrioventricular (AV) node contribute to it. No prior studies have analysed the

phase dependency between atrial AA' intervals (measured on atrial EGM) and VV' intervals (measured on NF RV EGM), and the prognostic value of this measure. The purpose of this study was to characterize the dependency between phase changes of atrial and ventricular activation intervals in patients with implanted ICD and to determine their association with sustained VT/VF events with appropriate ICD therapies.

Methods

We analysed data collected for the ICD-EGMs study (NCT00916435).⁴ The study conformed to principles outlined in the Declaration of Helsinki and was approved by the Johns Hopkins University and Washington University Human Studies Committees. All participants provided written informed consent.

1. Study population

Inclusion and exclusion in the ICD-EGMs study have been previously described.⁴ For this study, we included only study participants with implanted dual-chamber ICD. Participants with implanted single-chamber ICD, or cardiac resynchronization device (CDR) have been excluded. We further excluded patients if they had more than 15% of non-sinus beats on baseline EGM or were paced either from right atrium or ventricle more than 5% during the preceding 3 months. In addition, we excluded patients if no EGM recording in sinus rhythm was available for analysis. Only sinus rhythm EGM recordings were analyzed in this study.

2. Atrial and ventricular EGM analysis

Intracardiac EGMs have been recorded during regular office visit, as previously described.⁴ Only non-paced recordings in sinus rhythm were included in this study. For our analysis, we selected 50 consecutive sinus beats. Atrial (A) and ventricular (V) NF RV EGM peaks were detected as the dominant deflections in the EGM recordings as previously described³, using custom Matlab software (MathWorks, Natick, MA, USA) and were visually scanned. AA' and VV' intervals were measured between consecutive A or V EGM dominant deflections, respectively. AV' interval was measured as the interval between each A and V EGM dominant deflection. Joint symbolic dynamics (JSD) was used to measure AA', VV' and AV' changes. Applied equations are described in the online supplement.⁵ Symbolic dynamics is an approach that involves coarse-graining of observed time series into sequences of symbols, providing significant patterns for quantification of system dynamics.⁶⁻⁸

Figure 1(A) and 1(B) shows the atrial and ventricular electrograms and their corresponding sequence of symbols generated from AA' and VV' intervals. Symbolic patterns were generated using three successive symbols and were grouped into three families⁹: 1) V0: no variations between consecutive symbols; 2) V1: two consecutive symbols are similar while the remaining is different; 3) V2: all consecutive symbols are different.

In order to quantify A–V dependencies, we computed the directionality index rather than calculating percentage of dependency using JSD. Phase is defined as the fractional part of a cycle, measured from an arbitrary origin, through which the time has advanced, and is often expressed as an angle. We used the Hilbert transform to calculate the phases of the A and V

EGMs and the phases at each A and V activation time points were recorded. The phase dependencies and directionality were calculated as described in the online supplement.¹⁰

For the assessment of the directionality index three consecutive cardiac cycles were considered every time. In this study, the direction and strength of dependency is determined based on the directionality index, $d^{(A,V)}$: (1) $0 < d \leq 1$ indicates strength of dependency of VV' on AA', which means that prolongation of AA' interval in the previous cardiac cycle will result in the prolongation of VV' interval in the subsequent sinus cardiac cycle. Similarly, shortening of the AA' interval in the previous cardiac cycle will result in the shortening of VV' interval in the subsequent cardiac cycle; (2) $-1 \leq d < 0$ indicates strength of dependency of AA' on VV', which means that prolongation of VV' interval in the previous cardiac cycle will result in the prolongation of AA' interval in the subsequent sinus cardiac cycle. Similarly, shortening of the VV' interval in the previous cardiac cycle will result in the shortening of AA' interval in the subsequent cardiac cycle; (3) $d=0$ indicates that AA' and VV' are equally interdependent, i.e. change of VV' or AA' interval in the previous cardiac cycle did not change VV' or AA' interval in the subsequent cardiac cycle, or if the change was in the opposite direction (i.e. increasing AA' interval in previous cycle is associated with decreasing VV' interval in subsequent cycle, or vice versa).

In order to estimate the percentage of cardiac cycles with specific pattern, the directionality indices of the range -1 to $+1$ was divided into 20 segments (10 on each side of 0) and with 0 as the centre (50%), the percentage was calculated as:

$$\text{Percentage of cardiac cycles} = 50 + d * 50 \%$$

4. Study outcome

Sustained VT or VF event with appropriate ICD therapies (ICD shock or antitachycardia pacing) served as the primary outcome in this study.

5. Statistical analysis

Data were analysed using STATA 13 (StataCorp LP, College Station, TX, USA) and GraphPad Prism v6.05 for Windows (GraphPad Software, San Diego, CA, USA). Directionality index was considered as a continuous variable and was also categorized in quartiles. The directionality index was dichotomized into 1–3 quartiles (Q1-3 phase index) and 4th quartile (Q4 phase index). Cox regression analysis was performed to determine whether directionality index in the highest quartile is associated with the primary outcome. Due to small statistical power, Cox regression analysis was adjusted one-by-one by potential confounders. Several Cox models were constructed to adjust for age (Model 1), sex (Model 2), race (Model 3) left ventricular ejection fraction (Model 4), ICD indication (Model 5), and type of cardiomyopathy (Model 6). Results are presented as mean $\pm$ standard deviation. A P-value of <0.05 was considered significant.

Results

1. Patient population

Clinical characteristics of the participants are given in Table 1. The study population consisted of 59 participants (mean age: 59.5 ± 14.1 yrs; 28.8% female; 88.1% white). First degree AV block (AV interval > 200 ms) was observed in 20 study participants (34%). During a median follow-up of 2.4 years, 17 patients developed VT/VF and received appropriate rescue ICD shock. Mean left ventricular ejection fraction (LVEF) was $35.2 \pm 11.7\%$. Baseline clinical characteristics were not associated with directionality index in this study population (Table 1). Symbolic measures were not significantly different between patients with and without VT/VF (Table 2).

2. Relationship between AA' and VV'

Mean AA' and VV' intervals were 841.3 ± 201.4 and 841.1 ± 201.3 ms, respectively. Dependencies of V on A (figure 1C) and A on V (figure 1D) have been illustrated by plotting their corresponding phases (see online supplement). Overall, VV' phase change showed higher dependency on AA' in our study group with mean directionality index of 0.11 ± 0.2 . This means that prolongation (or shortening) in AA' interval was associated with respective prolongation (or shortening) in VV' interval in 55.5% of three consecutive sinus cardiac cycles. In other words, on average, there were no strong interdependency of AA' and VV' intervals from each other. However, in one quarter of study populations in 62.9% of cardiac cycles ($d > 0.259$), AA' interval prolongation (or shortening) was strongly associated with respective prolongation (or shortening) in VV' interval.

Baseline AV interval did not affect directionality index. There was no difference in directionality index in patients with vs. without AV block I.

3. Survival analysis

In univariable analysis association of directionality index with primary outcome was borderline (Table 3). However, in Cox regression analysis adjusted for LVEF, Q4 phase index (directionality index in the highest quartile, > 0.259) indicating higher dependency of VV' on AA', was significantly associated with higher risk of VT/VF with appropriate ICD therapies (hazard ratio [HR] 2.84; 95% confidence interval [CI] 1.05–7.67; $P = 0.04$). Adjustment for demographic characteristics and an underlying heart disease (type of cardiomyopathy) attenuated association.

Discussion

The major finding of this study is the demonstration of the association of increased dependency of changes in VV' intervals on AA' interval changes with elevated risk of ventricular tachyarrhythmia. Our study suggests that the atrioventricular node is capable of mitigating the effect of sympathetic overflow on the ventricles of the heart. Further studies of AA' and VV' phase dependencies are needed.

The concept of symbolic dynamics drops the detailed information but preserves the robust properties of a system's dynamics by employing a coarse-graining procedure, thus allowing

easy interpretation of physiological data through a simplified description, and has been widely used to study ECG beat-to-beat dynamics.^{7,8,11} Considering the fact that weak coupling first affects the phases of the oscillators rather than their amplitudes, we quantified the strength of AA' and VV' interaction by analyzing the relation between their phases. Subsequently, we calculated the deviations from the synchrony to obtain the dependency/direction of coupling.

From our study it appears that the directionality index in the highest quartile, indicating higher dependency of VV' on AA', was significantly associated with higher risk of VT/VF. Activation of sympathetic nerve activity increases conduction velocity in the AV node, which reduces the time between atrial and ventricular contraction. On the other hand, parasympathetic activation decreases velocity of conduction at the AV node, excessive of which could produce AV block. Vagal activation is assumed to help alleviate certain arrhythmias;¹² however, some vagal activity may occur as discrete bursts within each cardiac cycle.¹³ Such vagal bursts can appear at different times in successive cardiac cycles that can occur just before the AV node is excited, causing a prolongation of AV conduction.¹⁴ It is expected that changes in atrial intervals would predict the changes and hence control ventricular intervals. This possibly explains the finding that a strong dependency of changes in subsequent ventricular intervals on atrial interval changes is associated with VT/VF outcome. In future studies, it would be interesting to determine whether the calculation of AV phase index can be incorporated into pacing algorithms that can mitigate strong sympathetic influence, presented by AA' sequence.

Several limitations of this study should be considered. The proposed approach is not applicable to patients with cardiac channelopathies, frequent atrial and ventricular pacing, and those with frequent ectopies. This study was carried out on a small number of subjects. The findings of this study needs to be validated in larger population in future studies. Selection of 50 beats was arbitrary and requires further investigation.

References

1. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med*. 2008; 359:1009–17. [PubMed: 18768944]
2. Tereshchenko LG, Ghanem RN, Abeyratne A, Swerdlow CD. Intracardiac QT integral on far-field ICD electrogram predicts sustained ventricular tachyarrhythmias in ICD patients. *Heart Rhythm*. 2011; 8:1889–94. [PubMed: 21802390]
3. Baumert M, Kabir MM, Dalouk K, Henrikson CA, Tereshchenko LG. VV' Alternans Triplets on Near-Field ICD Intracardiac Electrogram is Associated with Mortality. *Pacing Clin Electrophysiol*. 2015; 38:547–57. [PubMed: 25752990]
4. Tereshchenko LG, Fetis BJ, Domitrovich PP, Lindsay BD, Berger RD. Prediction of ventricular tachyarrhythmias by intracardiac repolarization variability analysis. *Circ Arrhythm Electrophysiol*. 2009; 2:276–84. [PubMed: 19808478]
5. Baumert M, Kabir MM, Dalouk K, Henrikson CA, Tereshchenko LG. VV' Alternans Triplets on Near-Field ICD Intracardiac Electrogram is Associated with Mortality. *Pacing Clin Electrophysiol*. 2015; 38:547–57. [PubMed: 25752990]
6. Baumert M, Javorka M, Kabir M. Joint symbolic dynamics for the assessment of cardiovascular and cardiorespiratory interactions. *Philos Trans A Math Phys Eng Sci*. 2015:373.

7. Baumert M, Baier V, Truebner S, Schirdewan A, Voss A. Short- and long-term joint symbolic dynamics of heart rate and blood pressure in dilated cardiomyopathy. *IEEE Trans Biomed Eng.* 2005; 52:2112–5. [PubMed: 16366235]
8. Kabir MM, Saint DA, Nalivaiko E, Abbott D, Voss A, Baumert M. Quantification of cardiorespiratory interactions based on joint symbolic dynamics. *Ann Biomed Eng.* 2011; 39:2604–14. [PubMed: 21618043]
9. Moura-Tonello SCG, Takahashi ACM, Francisco CO, Lopes SLB, Del Vale AM, Borghi-Silva A, et al. Influence of type 2 diabetes on symbolic analysis and complexity of heart rate variability in men. *Diabetology & Metabolic Syndrome.* 2014; 6:1–11. [PubMed: 24383616]
10. Rosenblum MG, Pikovsky AS. Detecting direction of coupling in interacting oscillators. *Phys Rev E Stat Nonlin Soft Matter Phys.* 2001; 64(1–4):045202. [PubMed: 11690077]
11. Voss A, Kurths J, Kleiner HJ, Witt A, Wessel N, Saparin P, et al. The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death. *Cardiovasc Res.* 1996; 31:419–33. [PubMed: 8681329]
12. Levitt B, Cagin N, Kleid J, Somberg J, Gillis R. Role of the nervous system in the genesis of cardiac rhythm disorders. *Am J Cardiol.* 1976; 37:1111–3. [PubMed: 1274874]
13. Martin P. Dynamic vagal control of atrial-ventricular condition: Theoretical and experimental studies. *Annals of Biomedical Engineering.* 1975; 3:275–95. [PubMed: 1220583]
14. Martin P. Depression of atrioventricular sensitivity in the dog by successive brief bursts of vagal stimulation. *Circulation Research.* 1976; 38:448–53. [PubMed: 1269084]

Figure 1.

Illustration of symbolic dynamics and phase dependency of atrial and ventricular electrograms (EGM). A – Selected beats of simultaneous atrial and ventricular EGM recordings with the corresponding intervals in ms shown in-between the beats; B – plot of symbolic sequences of AA' and VV' intervals calculated from atrial and ventricular EGMs as described in the methods section. During the first 11 beats AA' is driving VV' while VV' is driving AA' from beat 17 to 24; C – Phase plot indicating the influence of phase of VV' on phase of AA' (as increments can be observed in ϕ_V while ϕ_A shows no changes); D – similar phase plot as C, showing the phase of AA' is influenced by VV' phases.

Figure 2.

Schematic illustration of A–V dependency. A – prolongation of AA' interval in the previous cardiac cycle resulting in the prolongation of VV' interval in the subsequent sinus cardiac cycle; B – shortening of the VV' interval in the previous cardiac cycle resulting in the shortening of AA' interval in the subsequent cardiac cycle; C – change of VV' or AA' interval in the previous cardiac cycle did not change VV' or AA' interval in the subsequent cardiac cycle.

Table 1

Clinical characteristics of study participants

Characteristic	All (n=59)	Q1-3 Phase index (n=42)	Q4 Phase index (n=17)	P
Age, y (SD)	59.5 (14.1)	61.1(14.2)	55.7(13.4)	0.180
Female, n(%)	17 (28.8)	14(33.3)	3(17.7)	0.228
White, n(%)	52 (88.1)	38(90.5)	14(82.4)	0.382
Ischemic cardiomyopathy	34 (57.6)	18(42.9)	7(41.2)	0.906
Primary prevention of SCD	46 (78.0)	32(76.2)	14(82.4)	0.605
Diabetes	21 (35.6)	15(35.7)	6(35.3)	0.976
Hypertension	43 (72.9)	33(78.6)	10(58.8)	0.122
NYHA class II–III	25 (42.4)	19 (45.2)	6(35.3)	0.484
LVEF, % (SD)	35.2 (11.7)	35.1(11.8)	35.5(11.7)	0.907

Table 2

Comparison of symbolic analysis results in patients with vs. without VT/VF

	VT/VF no (n=42)	VT/VF yes (n=17)	P-value
Mean AA, ms	840.3(205.6)	843.8(196.9)	0.952
Mean VV, ms	840.0(205.4)	843.6(197.1)	0.951
Mean AV, ms	191.3(51.6)	194.0(54.2)	0.860
SD AA, ms	58.0(30.8)	53.5(31.9)	0.623
SD VV, ms	56.6(30.6)	55.6(38.4)	0.923
SD AV, ms	23.4(16.6)	36.6(65.0)	0.418
RMSSD AA, ms	842.9(205.2)	846.2(196.1)	0.954
RMSSD VV, ms	842.6(204.9)	846.4(196.1)	0.947
RMSSD AV, ms	193.6(50.9)	202.8(69.0)	0.621
AA V0, %	8.7(7.2)	7.6(8.5)	0.642
AA V1, %	44.1(13.4)	44.2(13.6)	0.967
AA V2, %	2.2(3.2)	2.8(5.9)	0.680
VV V0, %	9.2(6.6)	7.2(5.6)	0.258
VV V1, %	45.2(11.0)	44.1(9.9)	0.709
VV V2, %	2.3(3.5)	2.3(3.0)	0.956
AV V0, %	9.8(9.5)	9.4(9.2)	0.869
AV V1, %	42.6(12.0)	41.5(11.6)	0.737
AV V2, %	3.9(4.1)	5.5(5.4)	0.275
Mean $d^{(A,V)}$, a.u.	0.08(0.2)	0.14(0.2)	0.593

AA=AA interval; VV=VV interval; AV=AV interval; SD=Standard deviation; RMSSD=Root mean square of successive differences; V0=No variations between consecutive symbols; V1=Two consecutive symbols are similar while the remaining is different; V2=All consecutive symbols are different; $d^{(A,V)}$ =Directionality index.

Table 3

Cox regression hazard ratios for ICD-EGMs study participants with directionality index in the highest quartile, Q4PhaseIndex (> 0.259)

Predictor	HR (95%CI)	P
Unadjusted	2.26(0.84–6.10)	0.106
Model 1	2.21(0.79–6.15)	0.129
Model 2	2.05(0.76–5.54)	0.159
Model 3	2.50(0.92–6.80)	0.072
Model 4	2.84(1.05–7.67)	0.040
Model 5	2.69(0.96–7.54)	0.060
Model 6	2.24(0.83–6.06)	0.111

Model 1 is adjusted by age; Model 2 is adjusted by sex; Model 3 is adjusted by race; Model 4 is adjusted by LVEF; Model 5 is adjusted by primary prevention of sudden cardiac death; Model 6 is adjusted by ischemic cardiomyopathy.