Circadian Variation in the Occurrences of Ventricular Tachyarrhythmias: Differences between Coronary Artery Disease and Dilated Cardiomyopathy

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Abstract

Aim: This study investigates circadian distribution of ventricular tachyarrhythmias (VT) in coronary artery disease (CAD) and dilated cardiomyopathy (DCM) patients that received an implantable cardioverter defibrillator (ICD) as secondary prevention.

Methods: 37 patients are studied. Times of VT episode are retrieved from data log of the ICD; the analysis includes the separation of different modes of VT-onset. Circadian distributions are fitted using harmonics and polynomial regression models; Goodness of fit is estimated using the coefficient of determination R^2.

Results: 165 VT episodes are recorded from 37 patients: 79 are collected from 26 CAD and 86 from 11 DCM patients. Fitting of the circadian distribution of CAD population gives R^2=0.854 with harmonic and R^2=0.767 with polynomial model. Similarly with DCM patients, fitting with polynomial model led to R^2=0.997 while harmonic regression led to R^2=0.983. Different modes of VT onset show strongly different circadian patterns even when patients have the same etiology.

Conclusion: Circadian distribution of VT episodes from CAD and DCM patients are intrinsically different.

1. Introduction

Several studies have shown a nonuniform circadian distribution of cardiac malignant events. The analysis of ischemic patients with Implantable Cardioverter Defibrillators (ICDs) evidence a morning peak and a secondary afternoon peak [1, 2]. Similar circadian pattern has been noted in acute myocardial infarction [3] and stroke [4]. The circadian distribution of non-ischemic patients treated with ICDs led to controversial results: while in some studies CAD and non-CAD subjects lead to similar conclusions [5], in other paper the morning peak was not observed, but a more uniform distribution of the VT episodes during day-light in non-CAD patients. The latter distribution was observed in non-ischemic patients of different aetiology [6] and in patients with chronic heart failure [7].

The underlying mechanisms involved in circadian variation of ventricular tachyarrhythmias are still unclear, although several efforts are played to explore these mechanisms by studying, among other, the effect of pharmacological treatment, such as beta-blockers [6], and physiological aspects such as the role of the autonomic nervous system in the genesis of arrhythmias [8].

In this study circadian distribution of appropriate ICD shock delivery for VT are analysed. In particular patterns observed in patients with coronary artery disease (CAD) and Dilated CardioMyopathy (DCM) are studied and compared. The investigation considers, as a secondary aim, the circadian distribution obtained from the VT episodes initiated with different modes of onset [9].

2. Methods

2.1. Data set

This retrospective study is based on spontaneous VT episodes from patients with St Jude Medical – Ventritex ICDs (model Angstrom, Contour or Profile) in the framework of the ELECTA (ELECTrogram Analysis) protocol which run at our institutions between December 1998 and October 2002. Visual inspection of the cardiologist identified VT by a sudden increase in heart rate along with a change in EGM morphology from the baseline rhythm; we did not consider supraventricular tachycardia nor atrial fibrillation recordings.

The ICD device allows retrieval of several information about the VT episodes which include, among other, the times of the episode and up to 2 minutes of intracardiac electrograms triggered by each recognized tachyarrhythmia. This allowed us to analyse the VT episode as well as the rhythm immediately preceding its onset which allows us to define the initiation of the VTs.

Both VT episodes requiring ICD therapy (with antitachycardia pacing or shock cardioversion) and non-treated VT that spontaneously recovered before ICD intervention were considered.

Three different modes of VT onset were classified: (i) *PVC onset (PVC):* when VT initiates with a premature ventricular contraction (PVC); (ii) *Short-long-short (SLS) onset* when VT initiation is preceded by a short-long-short cycle; (iii) *Pacemaker (PM) onset* when VT initiates with a PVC immediately after a paced beat. In the latter cases each pause preceding the paced beat was considered appropriate if it correlated to the programmed lower rate interval of the anti-bradycardia system, while we neglected the cases with pause less than the escape interval because representing an ICD undersensing.

2.2. Statistical analysis

Interval and normal variables are expressed as mean ± standard deviation. Mean between groups of these variables were compared using Student T-test, while Chi-square test was used with categorical variables. A value of $p<0.05$ was considered statistically significant. Circadian distribution was made with 3-hour time-interval. For the analysis of circadian distribution both polynomial and harmonic regression were considered. In particular fifth order polynomial models are considered, while the 2 harmonics with greater energy are considered in the harmonic models.

The goodness of fit of the regression models was tested using the *coefficient of determination* R^2:

$$R^2(y) = 1 - \frac{\sum_i (y_i - \hat{y}_i)^2}{\sum_i (y_i - \bar{y})^2} \qquad (1)$$

In equation (1) The value of y_i represents the measured variable for each 3-hour interval, $\bar{y}_i$ is its mean value, and $\hat{y}_i$ is the approximation obtained by the regression model. In practice R^2 is defined as 1 minus the ratio between the residual sum of squares and the total sum of squares. R^2 assumes values between 0 and 1, and it is often interpreted as the fraction of variation explained by the regression model. Extreme cases are: $R^2=1$ (obtained when the approximated and the measured values equals) indicating that the fitted model describes all the variability of the data set, and $R^2=0$ (obtained when the model is identical to the mean value of the data set) indicating that the fitted model does not describes the variability of the data set. Eventually $R^2=1$ indicates an excellent regression model, and $R^2=0$ indicates a poor regression model.

3. Results

Between December 1998 and October 2002 sixty-eight patients were implanted with a third-generation St Jude Medical – Ventritex ICD device for secondary prevention. Among them 23 did not experienced VT episodes, 3 patients had aetiology different from CAD or DCM, and from 5 subjects only bipolar recordings were retrieved. Eventually 37 patients (26 CAD and 11 DCM) matched the required criteria. From these 37 patients 165 VT episodes, 79 from CAD and 86 form DCM, have been collected. Baseline Characteristics of Patient Population are resumed in Table 1.

Table 1: Baseline characteristics of the patients.

	CAD	DCM	p
N of pats with VT/VF	26	11	
Age (years)	70±10	64±12	n.s.
Gender (male/female)	23 / 3	10 / 1	n.s.*
Follow-up (months)	33±10	24±13	<0.03
Ejection Fraction	35 ± 8	31±9	n.s.
NYHA Class: I/II+III	2 / 24	2 / 9	n.s.*
Treatment at implant:			
Treated / Non-treated	18 / 8	5 / 6	n.s.*

Figure 1 shows circadian distributions of CAD and DCM population along with corresponding polynomial (dotted line) and harmonic (solid line) regressions models.

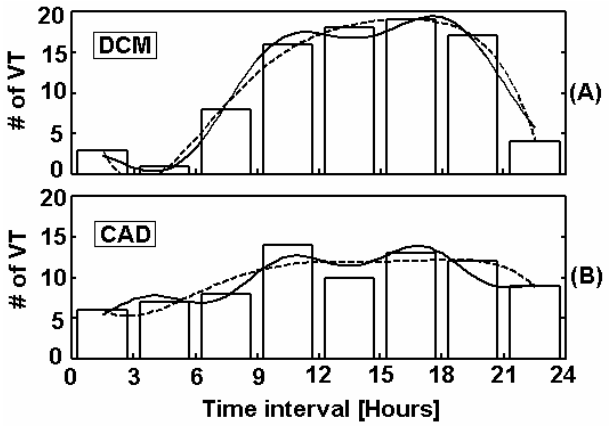

Figure 1: Circadian distribution of CAD and DCM patients along with polynomial (dashed line) and harmonic (solid line) regression models.

The coefficient of determination with CAD group was $R^2=0.963$ for harmonic regression and $R^2=0.767$ for polynomial regression. With DCM patients the values of $R^2=0.983$ for harmonic regression and $R^2=0.997$ for polynomial regression were obtained.

Circadian distribution of SLS, PVC, and PM onsets

are shown for CAD (Fig. 2) and DCM patients (Fig. 3).

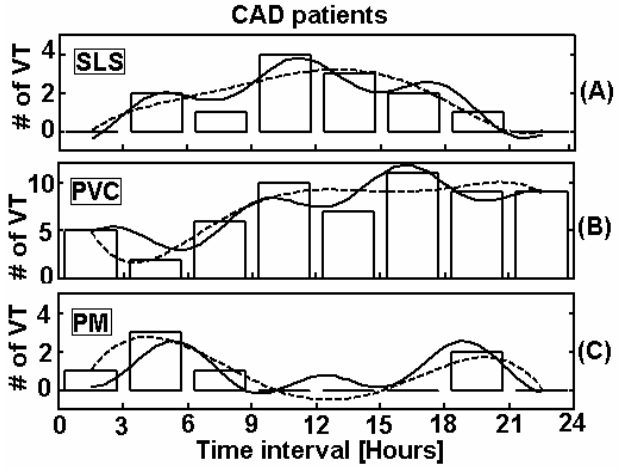

Figure 2: Circadian distribution of the VT episodes initiated with different modes of onset along with polynomial and harmonic regressions for CAD patients. Panel (A) regards SLS-onset, Panel (B) is related to PVC-onset, and Panel (C) is referred to PM-onsets.

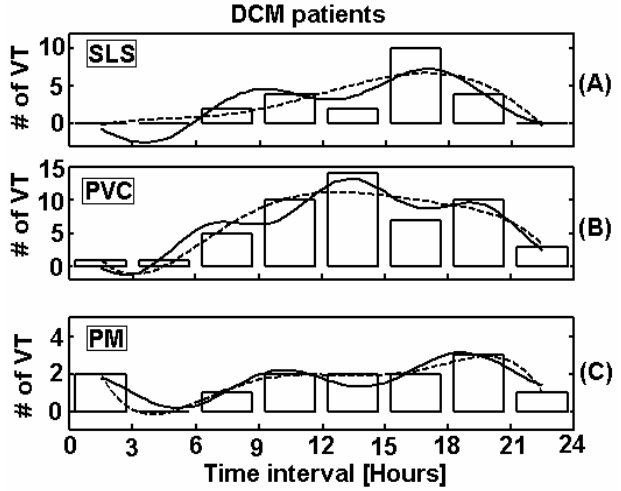

Figure 3: Circadian distribution of the VT episodes initiated with the considered modes of onset along with polynomial and harmonic regressions for DCM patients. Panel (A) regards SLS-onset, Panel (B) is related to PVC-onset, and Panel (C) is referred to PM-onsets.

In Table 2 the coefficient of determination R^2 for the goodness of fit of harmonic and polynomial regression models of SLS, PVC and PM modes of onset are reported for CAD and DCM populations.

Note how SLS and PVC onset are better described by an harmonic model, while VT initiated with PM mode have a behaviour which can be better approximated using a polynomial model.

Table 2: Value of the coefficient of determination R^2 of polynomial and harmonic regressions for the fitting of the SLS, PVC and PM circadian distribution.

Regression	CAD patients			DCM patients		
Model	sls	pvc	pm	sls	pvc	pm
N. of VT	13	59	7	22	51	13
Harmonic	0.92	0.84	0.71	0.78	0.91	0.85
Polynomial	0.77	0.83	0.90	0.68	0.86	0.98

4. Discussion and conclusions

4.1. Methodological observations

From the methodological point of view at least two observations should be done.

The first regards the presence of negative values in the regression models, when circadian distributions were related to different modes of VT-onset. Of course the outcomes of the models shoulkd never assume negative values, thus this is a wrong result. Nevertheless this happen because the number of episodes is small, and it is the opinion of the authors that, with a larger data base and a greater number of VT episodes this problem should be eliminated.

The second methodological observation regards the intrinsic characteristic that can be observed from harmonic rather than polynomial models, and the important role that can be played by the coefficient of determination. Indeed harmonic regression tries to evidence the presence of peaks even when the peak is not real. This error occurs, for example, in the first peak of Figure 1A, where it is shown a morning peak in DCM patients; in the third peak of Figure 2A related to an afternoon peak (arout 6 pm) in SLS-onset episodes from CAD patients; in the middle peak of Figure 2C related to circadian distribution of PM-onset in CAD patients. On the contrary the polynomial model may ignore the presence of existent peaks. This error occurs, for example, in Figure 1B where no peaks are evidenced in the circadian distribution of CAD patients, in Figure 2A and 2B where the morning peaks are quite evident in SLS onset, but they are eliminated by polynomial regressions. The role of the coefficient of determination may then become the key to understand the intrinsic behaviour of the distribution: namely to evaluate if the distribution can be better modelled by peaks and dumb-peaks (better described by an harmonic model), or if it can have a more smooth behaviour (better modelled as a polynomial).

4.2. Clinical observations

From the clinical point of view at least two observations should be done.

The first comment is focused on the difference between circadian distribution obtained from CAD or DCM patients. In CAD subjects, it is convincing the presence of two peaks, one between 9 and 12 and the second between 15 and 18, as shown in figure 1B. These peaks are made clear by using harmonic regression, which reaches R^2=0.963, while they are neglected by the polynomial regression (which obtained R^2=0.767). On the contrary DCM patients do not evidence clear peaks, but rather an almost uniform distribution of the VT episodes during day-light hours and a dumb peak during night. In this case the polynomial model better represents the data and it reaches a higher coefficient of determination (R2=0.997) than the harmonic model (R2=0.983). This lead to the conclusion that circadian distribution of VT onset for CAD and DCM patients could be intrinsically different because better modelled by intrinsically different regression models.

The second comment is focused on VT initiated with PM onset. It is evident that the timing of these VTs is different from the others, both with CAD and DCM patients. In fact both morning and afternoon peaks are negligible, while VT episodes with PM-onset occur more often during the evening or during the night. This is in agreement with our previous results [10] were we observed that the presence of PM onset is associated with a slow heart rhythm immediately preceding the initiation of the VT episode. It is accepted that in the evening and during the night the heart rhythm is usually slower that during day-light hours.

5. Conclusion

In this paper it is observed that the circadian distribution of CAD patients is optimally described by an harmonic regression models, with the presence of two peaks, one in the morning and a second in the afternoon. On the contrary DCM patients, presenting a pattern with an almost uniform distribution during day-light hours and a dumb peak in the night, are optimally described by a polynomial model. We conclude that CAD and DCM patients show intrinsically different circadian patterns in the occurrences of VT episodes. It is also observed that circadian distribution of VT episodes initiated with different modes of onset lead to unexpected results, that might be helpful for the understanding of the mechanisms involved in VT initiation.

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