

## Original article

# Heart rate turbulence and variability in patients with ventricular arrhythmias

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**ABSTRACT:** Background: To evaluate the changes in autonomic neural control mechanisms before malignant ventricular arrhythmias, we measured heart rate variability (HRV) and heart rate turbulence (HRT) in patients with ventricular tachycardia or fibrillation (Group I; n=6), non sustained ventricular tachycardia (Group II; n=32), frequent premature ventricular beats (Group III; n=26) and with ICD implantation (Group IV; n=11).

Methods: Time domain parameters of HRV and turbulence onset (TO) and slope (TS) were calculated on 24 hour Holter recordings. Normal values were: SDNN > 70 msec for HRV, TO <0% and TS >2.5 msec/RR-I for HRT.

Results: Whereas SDNN was within normal range and similar in all study groups, HRT parameters were significantly different in patients who experienced VT/VF during Holter recording. Abnormal TO and/or TS were present in 100% of Group I patients and only in about 50% of Group II and IV. On the contrary, normal HRT parameters were present in 40-70% of Group II, III and IV patients and none of Group I.

Conclusions: These data suggest that HRT analysis is more suitable than HRV to detect those transient alterations in autonomic control mechanisms that are likely to play a major trigger role in the genesis of malignant cardiac arrhythmias. (*Heart International* 2007; 3: 51-7)

**KEY WORDS:** Sudden cardiac death, Autonomic nervous system, Risk stratification, Ventricular fibrillation, Holter recordings

## INTRODUCTION

Many non-invasive and invasive parameters have been proposed and tested to identify patients at risk for sudden cardiac death (SCD) (1, 2). More recently, the availability of implantable cardioverter defibrillator (ICD) has made patients' selection an even more relevant issue (3-6). Low left ventricular ejection fraction (7), frequent ventricular ectopic beats (7), fast mean heart rate (8), low heart rate variability (HRV) (9, 10), reduced baro-reflex sensitivity (11), non-sustained ventricular tachycardia (NSVT) (5) and induction of ventricular tachycardia at electrophysiological study (5) were considered markers of either reduced cardiac function, increased electrical instability or abnormal autonomic control me-

chanisms. Nevertheless, when these parameters have been used in prospective studies, the results were often unsatisfactory if not controversial (1, 2).

It is also plausible that risk assessment, performed at the time of discharge after an index event or at the time of study inclusion, could maintain its value only for a limited time as a consequence of disease progression and substrate change. The possibility that before a life threatening arrhythmic event, additional changes in the electrical substrate and autonomic control mechanisms might occur, has therefore to be taken into consideration in the process of risk stratification (12).

Heart Rate Turbulence (HRT) is a recently described (13) method to assess arrhythmic risk in post-myocardial infarction patients based on the evaluation of ven-

tricolophasic sinus arrhythmia following premature ventricular beats (PVBs). HRT has been found effective in identifying SCD victims in post-AMI patients according to retrospective (13, 14) and, more recently, prospective studies (15). Aim of our study was to analyse HRV and HRT in the hours preceding ventricular tachycardia or fibrillation in patients exhibiting these arrhythmias during Holter recordings.

## SUBJECTS AND METHODS

### *Patient population*

The study is based on the analysis of Holter recordings of 64 patients referred to our Institution in the period 2003-2005. The reference group was made by 6 outpatients who experienced sustained ventricular tachycardia or ventricular fibrillation during the 24 hour recording performed for evaluation of palpitations (Group I). Two of these patients died during the Holter recording for ventricular fibrillation. Thirty-two patients who presented NSVT during a Holter recording were also included (Group II). Twenty-six consecutive patients with frequent premature ventricular beats (PVBs), > 10/h, were included in Group III. A fourth group of 11 patients with an implanted cardioverter defibrillator (ICD), but not sustained ventricular arrhythmias during the index Holter recording were also considered. None of the patients presented atrial fibrillation, permanent pacemaker rhythm or artefacts that could affect sinus rhythm fluctuation analysis during the Holter recording.

Complete clinical data were only available for ICD patients and survivors of VT. Demographic data of all the patients are presented in Table I.

The study was approved by the Ethical Committee of our institution.

### *HRV analysis*

After visual inspection and manual editing of the 24 hour recording, standard deviation of normal RR intervals (SDNN) was automatically computed with the Syntec software (ver. 1.20, Ela Medical, France). In all groups the duration of recording was greater than 18 hours and included a nocturnal period.

### *HRT analysis*

Turbulence Onset (TO) was calculated as the percentage change between the mean of the first 2 sinus RR intervals after a PVB and the last 2 sinus RR intervals before the PVB, as follows:  $TO = [(RR_i - RR_2) - (RR_2 - RR_{-1})] / (RR_2 - RR_{-1})$ , where  $RR_i$  is the  $i$ -th sinus rhythm following ( $i > 0$ ) the compensatory pause of the PVB or preceding ( $i < 0$ ) the coupling interval of the PVB. These measurements were performed for each singular PVB and subsequently averaged. Turbulence Slope (TS) was calculated as the maximum positive slope of a regression line assessed over any sequence of 5 subsequent RR intervals within the tachogram  $RR_1, RR_2, RR_3, \dots, RR_{15}$ , where  $RR_i$  is the average of  $i$ -th sinus rhythm RR intervals after the compensatory pause of a singular PVB (HRT source code 1.1 is available on <http://www.h-r-t.org>).

TO and TS were dichotomized at predefined cut points ( $TO \geq 0\%$  and  $< 0\%$ ,  $TS < 2.5$  and  $\geq 2.5$  ms per normal-to-normal interval) (13).

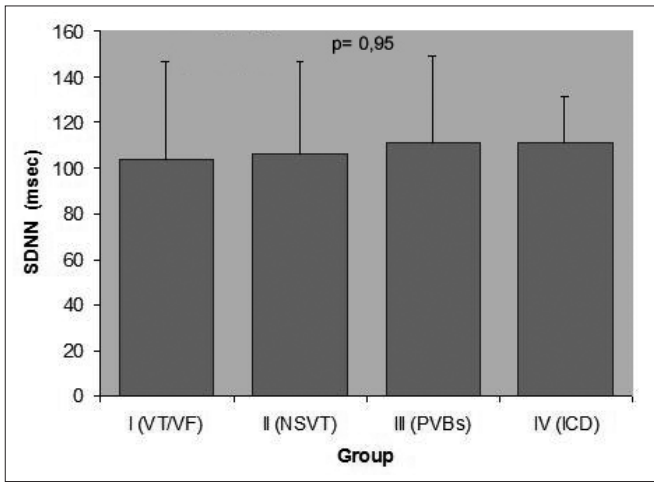
### *Statistical analysis*

Continuous data are presented as mean  $\pm$  SD. Categorical data as number of patients (percentage). PVB number is logarithmic transformed. Significant differences for continuous variables were tested with analysis of variance (ANOVA); Chi-square or Exact Fisher test when appropriate for categorical variables. Post-hoc Bonferroni test was performed after ANOVA to test individual differences. Pearson's coefficients were calculated to correlate HRV and HRT parameters. A significant two-tailed  $p$  level of 0.05 was considered. All statistical analysis were performed with the commercial software SPSS (Release 13.0, SPSS inc., USA).

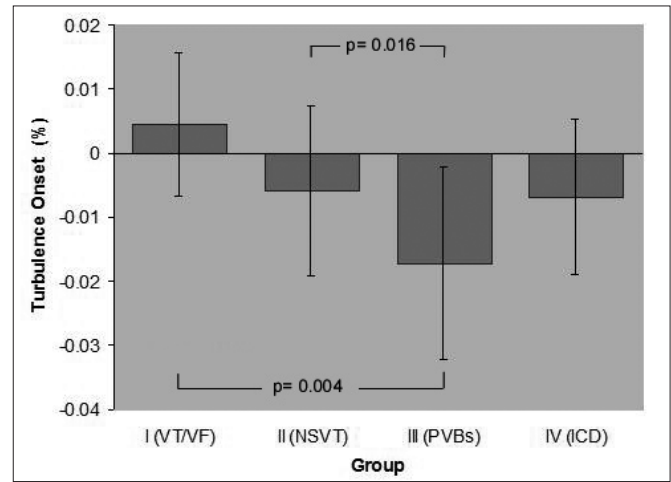
## RESULTS

Clinical characteristics of patients enrolled in the study are presented in Table I. Age and gender did not differ among the four groups. Only a significant lower number of PVBs was present in ICD patients.

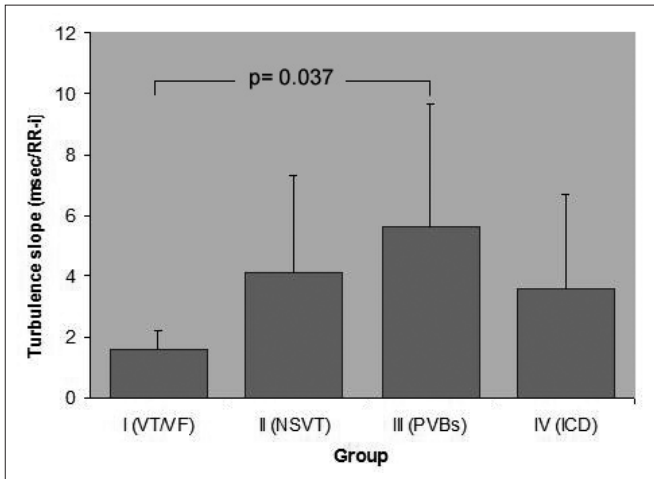
Mean heart rate and SDNN were similar in the four groups. Of interest was the finding that all mean values of 24 hour SDNN were above 70 msec; the cut-off value used in our laboratory to identify high risk post-MI patients (Fig. 1).



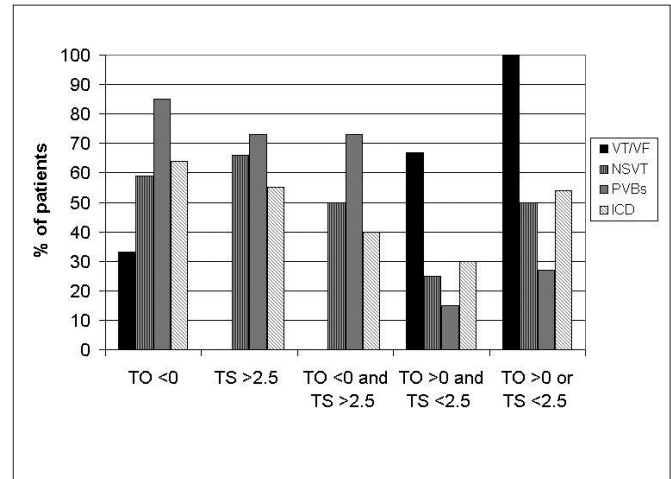
**Fig. 1** - Mean values of 24 hour SDNN in patients with VT/VF (group I), non sustained ventricular tachycardia (Group II), frequent premature ventricular beats (Group III) and ICD (Group IV).



**Fig. 2** - Comparison of TO absolute values in the four study groups. A significant difference between Group I and III was evident.



**Fig. 3** - Comparison of TS absolute values in the four study groups. A significant difference between Group I and III was evident.



**Fig. 4** - Distribution of normal and abnormal HRT parameters in the different study groups according to cut-off values of <0% for TO and >2.5 msec/RR-I for TS. At least one abnormal parameter (5th set of data) was present in all VT/VF patients, whereas in only about 50% of ICD or NSVT patients. Normal HRT parameters were present (3rd set of data) in none of VT/VF patients but in about 40-70% of Group II, III and IV patients.

On the contrary, we observed a significant difference of HRT parameters in patients who presented VT or VF during Holter recordings (Group I) in comparison to Group II and III patients (Figs. 2 and 3; Tab. II). When considering data as categorical variables, the difference was more evident : TS value < 2.5 msec/RR interval was detectable in all Group I subjects and only in 34% and 27% of, respectively, Group II and III patients. A TO  $\geq$  0% was present in 67% of VT/VF patients and in 41% and 15% of, respectively, NSVT (Group II) and frequent PVB (Group III) patients.

In ICD patients, abnormal TO and TS values were observed in 36% and 45% of cases; these percentages were significantly different from that of Group I (VT/VF) but similar to patients with NSVT (Tab. III).

TS, as previously reported (11-13), appeared more sensitive in revealing differences among groups when considered either as a continuous or categorical variable (Fig. 4)

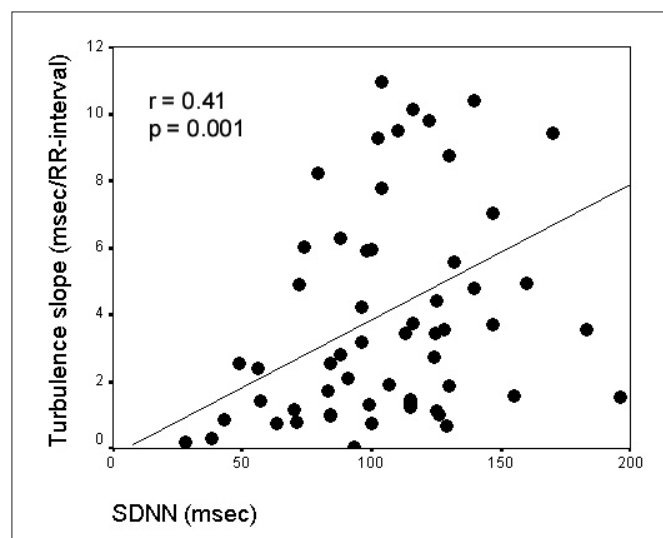


Fig. 5 - Linear correlation between TS and SDNN in all study population.

When we correlated HRV and HRT parameters of all study group, a modest but significant correlation between SDNN and TO ( $r=-0.38$ ;  $p=0.003$ ) or TS ( $r=0.41$ ;  $p=0.001$ ) was detectable (Fig. 5).

## DISCUSSION

In this study, we reported that HRT was superior to HRV to reflect those alterations in autonomic control of sinus node before VT or VF episodes during Holter recordings. This was evident when considering HRT parameters either as continuous or, more consistently, as categorical variable. On the contrary, patients with ICD (Group IV), i.e. with history of previous cardiac arrest or sustained VT but no sustained ventricular arrhythmias in the index Holter recording, presented values of HRT similar to patients with NSVT or frequent ectopic beats.

TABLE I - CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

	Group I (n=6)	Group II (n=32)	Group III (n=26)	Group IV (n=11)	p value
Age (years)	72 ± 6	66.8 ± 11	65.5 ± 14	70 ± 7	0.569
Gender (male)	5 (83.3%)	18 (56.3%)	15 (57.7%)	9 (81.8%)	0.572
Indications to 24 hour Holter recording:					
Rhythm control	0 (0%)	5 (15.6%)	4 (15.4%)	0 (0%)	
Palpitations	0 (0%)	0 (0%)	3 (11.5%)	0 (0%)	
PVBs (%)	0 (0%)	3 (9.3%)	3 (11.5%)	0 (0%)	
Cardiomyopathy	1 (16.6%)	4 (12.5%)	2 (7.7%)	0 (0%)	
Syncope	1 (16.6%)	4 (12.5%)	5 (19.2%)	0 (0%)	
ICD control	3 (50%)	0 (0%)	0 (0%)	10 (90.9%)	
CAD	1 (16.6%)	6 (18.75%)	1 (3.8%)	1 (9.1%)	
Unknown	0 (0%)	12 (37.5%)	8 (30.7%)	0 (0%)	
Ln PVBs (number)	5.0 ± 1.5	5.4 ± 1.5	4.9 ± 1.3	3.2 ± 1.6	0.004

PVB= premature ventricular beats; ICD= implantable cardioverter defibrillator; CAD= coronary artery disease

TABLE II - HRV AND HRT PARAMETERS IN THE STUDY POPULATION

	Group I (n=6)	Group II (n=32)	Group III (n=26)	Group IV (n=11)	p value
SDNN (msec)	104 ± 43	106 ± 41	111 ± 38	111 ± 20	0.951
Mean RR interval (msec)	825 ± 156	833 ± 153	824 ± 137	904 ± 134	0.565
Turbulence onset (%)	0.04507 ± 0.011	-0.0058 ± 0.013	-0.0171 ± 0.015	-0.0068 ± 0.012	0.001
Turbulence slope (msec/RR-i)	1.624 ± 0.58	4.117 ± 3.18	5.607 ± 4.06	3.608 ± 3.12	0.053

SDNN= standard deviation of normal RR intervals

**TABLE III - DIFFERENT DISTRIBUTION OF NORMAL AND ABNORMAL HRT PARAMETERS IN THE STUDY POPULATION**

	Group I (n=6)	Group II (n=32)	Group III (n=26)	Group IV (n=11)	P value
T Onset <0%	33%	59%	85%	64%	0.056
T slope >2.5 msec/RR-i	0%	66%	73%	55%	<0.01
TO <0% and TS >2.5 ms/RR-I ("normal")	0%	50%	73%	40%	<0.01
TO >0% and TS <2.5 ms/RR-I ("abnormal")	67%	25%	15%	30%	0.077
TO >0% or TS <2.5 ms/RR-I ("one of two abnormal")	100%	50%	27%	54%	0.01

### HRV and arrhythmic mortality

It's well established HRV parameters may predict worse prognosis with increased risk for cardiovascular and overall mortality in many cardiovascular diseases (10). Most of evidences came from studies investigating risk for sudden cardiac death after an acute MI or in survivors of cardiac arrest (10, 16-18). The association between HRV reduction and prediction of arrhythmic mortality remains, however, controversial as recent reports have failed to demonstrate a distinct HRV pattern in relation to the type of death (15, 19). In the ATRAMI study (20), for example, HRV reduction was associated with increased total but not arrhythmic mortality. More recently, Huikuri et al (19) also reported that HRV was more related to total cardiac rather than arrhythmic mortality. Being the mechanisms of arrhythmic and non-arrhythmic cardiac mortality quite different, the interpretation of HRV reduction remains difficult from both a physiological and risk stratification point of view (10, 21, 22). This issue is even more controversial when considering heart failure patients (10, 23, 24).

A reduction in time domain parameters of HRV in patients with cardiac arrest during Holter recordings was first reported by Martin et al (25). Subsequently, Huikuri et al (26) and Valkama et al (27) observed a reduction of SDNN in patients with a history of sustained ventricular tachycardia in comparison to patients without repetitive ventricular arrhythmias during Holter recordings. In the present study carried out in ambulatory patients we found, instead, a preserved HRV in all four groups, with mean SDNN above the cut-off value of 70 msec. It must be recalled that, in the literature, discordant results in SDNN calculation were observed in relation to the dura-

tion of the observational period before arrhythmic event: SDNN values were found to be reduced when calculated in the 5-minutes interval immediately before arrhythmia onset (28), whereas it was found unchanged, increased or reduced when longer recordings were analysed (10, 26-28). Data from the analysis of ICD memory seems to support this hypothesis. Indeed Pruvot et al (29) and Lombardi et al (30) found consistent alterations of time and frequency domain parameters of HRV only in the minutes preceding the detected arrhythmic event. A possible explanation of the above findings is that HRV parameters measured over a 24 hour period may reflect those chronic alterations of autonomic control mechanisms that may predispose ventricular arrhythmias rather than unmasking sudden variations in autonomic modulation that may play as a trigger for arrhythmias occurrence.

### HRT and HRV analysis before VT/VF

HRT was described for the first time in 1999 and validated on the data base of three large clinical trials (13,14). More recently, the results of a large prospective study have been published confirming the predictive value of HRT for risk stratification of post-MI patients (15). In these studies, alteration of both TO and TS parameters were associated with increased all-cause mortality. In the ATRAMI study (15), TO and TS were the most important independent risk predictors for cardiac mortality together with LVEF. Moreover, when HRT was compared with other accepted risk parameters like SDNN, baroreflex sensitivity, presence of NSVT at Holter recording, only TS, i.e. the most sensitive parameter of HRT, showed a significant association with increased mortality (15).

The results of our study confirm the greater sensi-



re-activity of HRT parameters in comparison to SDNN in reflecting those alterations of autonomic control mechanisms that precede the onset of malignant ventricular arrhythmias. Indeed more than 60% of patients with a history of aborted SCD had normal HRV and HRT, whereas all patients who experienced VT/VF during the Holter recording had an abnormal HRT. Of interest were the findings that SDNN was >70 msec in 4 out of 6 Group I patients and that the percentage of alteration of HRT parameters in ICD patients (Group IV) was similar to that of NSVT patients (Group II). All these findings seem therefore to confirm the capability of HRT to detect not only those substrate alterations that may predispose to arrhythmias but also those additional transient alterations in autonomic control mechanisms likely to play a major pro-arrhythmic role.

The underlying mechanisms advocated to explain changes in HRV and HRT may partially explain our results. SDNN has been considered to reflect global autonomic balance: its reduction is commonly interpreted as an indirect evidence of a diminished vagal tone and an increased sympathetic modulation of sinus node (10). HRT, which is known to reflect ventriculophasic sinus arrhythmia, is highly correlated with baroreflex sensitivity. Consequently, abnormal HRT parameters more directly reflect a reduced vagal reflex efferent activity caused by impaired baroreflex mechanisms (31-33). Indeed, it has been previously reported that HRT and, in particular TS, is significantly correlated to baroreflex sensitivity, whereas in the present as in previous reports, the correlation between HRT and HRV parameters was less strong.

An additional point that may explain the greater sensitivity of HRT in comparison to HRV is the effect of editing premature ventricular beats in HRV analysis: ventricular ectopies are a prerequisite to compute HRT whereas they represent a limitation requiring time-consuming editing of data, interpolations of RR intervals and possibility of distortion of the tachogram when HRV computed. The clinical significance of this processing has never been evaluated in HRV studies and could have prevented a more appropriate evaluation of abnormal autonomic control mechanisms in patients with cardiac electrical instability.

### Study limitations

There are few but important limitations in the present study: First of all, population was quite small and heterogeneous being based on outpatient clinic; second, patients were distributed in the different groups according to arrhythmias number and complexity rather than on clinical characteristics. Third, complete clinical data were not available being the study based on outpatient records.

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