

# Normalization of RR Sequences: A New Approach for Quantitative Assessment of Heart Rate Turbulence by Abnormal Post Stimulation Response

A Berkowitsch, N Guettler, B Schulte, T Neumann, D Vukajlovich, A Erdogan, HF Pitschner

Kerckhoff-Clinic, Bad Nauheim, Germany

## Abstract

In our previous studies we observed different patterns of abnormal post ectopic sinus response. In some cases the conventional HRT parameter Turbulence Slope (TS) could not be correctly used. The normalization of RR sequences allows to estimate a rate independent parameter  $TS_{norm}$ .

Aim of the present study was to investigate the effect of normalization of tachograms and to define new descriptors of HRT which may predict recurrence of VT/VF in ICD patients.

## 1. Introduction

HRT - Heart Rate Turbulence - is the physiological, biphasic response of the sinus node to a premature ventricular beat (PVB). It consists of a short initial acceleration followed by a deceleration of the heart rate (Fig. 1).

Schmidt et al [1] defined parameters quantifying HRT, Turbulence Onset (TO: the percentage difference between the heart rate immediately following PVB and the heart rate immediately preceding PVB) characterizing acceleration and Turbulence Slope (TS: the steepest slope of the linear regression line for each sequence of five consecutive sinus rhythm intervals within 20 post paced RR intervals (RRI)) describing deceleration. The normal HRT is characterized by  $TO < 0$  and a high value of TS (Fig. 1a,b).

Schmidt et al [1] and Malik et al [2] investigated relationship between HRT and cardiac mortality in patients with coronary artery disease (CAD). These studies suggested that impaired HRT can be a strong risk predictor for sudden cardiac death.

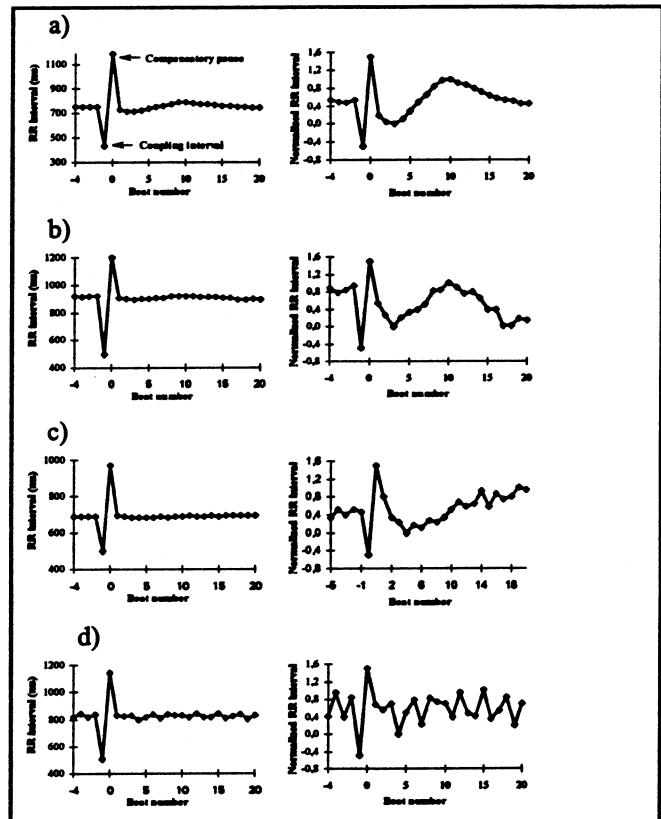


Figure 1. Originally averaged tachograms on the left, normalized tachograms on the right. a) normal HRT in a healthy patient,  $TS_{abs}=13.4$ ,  $TS_{norm}=0.23$ ; b) clearly seen biphasic reaction on the PVB in a CAD patient without VT/VF,  $TS_{abs}=4.08$ ,  $TS_{norm}=0.15$ ; c) a blunted response in a CAD patient with VT/VF,  $TS_{abs}=1.18$ ,  $TS_{norm}=0.05$ ; d) CAD patient with stored VT/VF. Fluctuating postectopic tachogram,  $TS_{abs}=6.7$ ,  $TS_{norm}=0.14$ . All tachograms are an average over 10 paced PVBs

The approach of Schmidt et al. [1] was based on averaging over all PVBs found in a Holter -ECG. However, spontaneous PVBs cannot be obtained in all risk patients. In our previous studies [3,4] we analyzed the relationship between HRT after induced PVBs and recurrence of VT/VF in ICD patients. We observed an abnormal type of the postectopic sinus response being characterized by a randomly fluctuating tachogram depicted in figure 2. The absolute values of TS in this case can be higher than TS in the normal post ectopic response (Fig. 1). Therefore, we found that the original approach [1,2] can be further optimized for our study.

One approach is normalization of the originally averaged tachogram as depicted in the figures 1. In our previous studies [3,4] we suggested a rate independent parameter based on the normalized RR sequence:

$$RR_{nrm} = \frac{RR_{abs} - RR_{min}}{RR_{max} - RR_{min}} \quad (1)$$

with  $RR_{max}$  and  $RR_{min}$  maximum and minimum RRI within 20 post paced RRI. This parameter was termed Normalized Turbulence Slope ( $TS_{nrm}$ ) and was calculated within 10 post paced RR intervals.

However, the normalization alone is not capable to reduce possible effects of the fluctuations in the post ectopic period. Moreover, the effect of fluctuations can increase in case of post ectopic pulsus alternans (PA) as presented below.

A previous study of Ceri Davies et al [5] has demonstrated that patients with a low LVEF have a high prevalence of PA in the post ectopic period (Fig. 2). The absolute value of TS in these patients was significantly lower than in patients without PA. However, as depicted in figure 2 the normalization of RR sequences can lead to overestimation in this case.

During routine analysis of HRT we cannot predict a pattern of possible post ectopic response. Hence, additional descriptors of HRT are required. Aim of this study was to analyze the effect of normalization on TS, and to define new parameters, which may correlate with the recurrence of VT/VF in ICD patients with coronary artery disease and dilated cardiomyopathy (DCM).

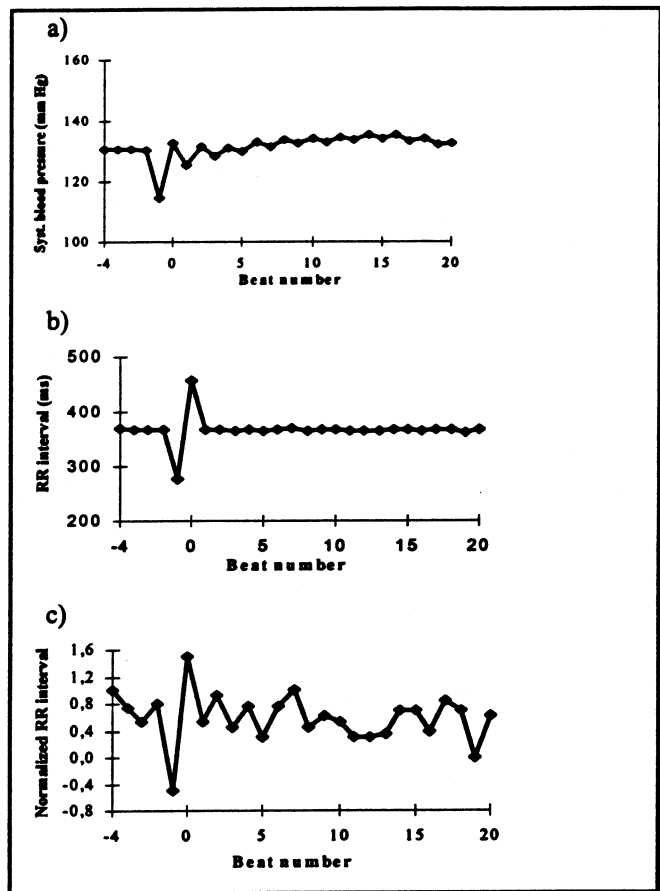


Figure 2. a) blood pressure pattern typical for pulsus alternans, b) blunted sinus response,  $TS=0.56$ , c) normalized tachogram showing alternating cycle lengths,  $TS_{nrm}=0.11$ .

## 2. Methods

### 2.1. Data acquisition and processing

In each patient 10 PVBs were induced via the implanted device during sinus rhythm. Five RRI prior to and 20 RRI after the PVB were averaged.

TS was calculated within the first 10 post paced RRI according to two modes: a) for originally averaged RR sequence ( $TS_{abs}$ ), b) for the normalized RR sequence.

As mentioned above the physiologically normal HRT (Fig. 1a) is expressed by an early acceleration within first

2-3 post paced RRI followed by a late deceleration within the next 4-7 RRI. Mathematically TS reflects the averaged velocity of the deceleration, but does not provide full information about the HRT pattern. In order to obtain additional information we defined the following descriptors 1)-Turbulence Jump- (TJ) calculated as a maximal proportional difference between two consecutive RRI within 10 post paced RRI, 2) Deceleration Length - (DL) defined as the maximal number of consecutive increasing RRI within the first 10 post paced RRI, 3) Number of Turn -off points - (NTP) - calculated as the number of tachogram turn-off points within first 10 post paced RRI.

## 2.2. Study patients

Fifty two consecutive ICD patients with CAD ( 48 male, mean age:  $65 \pm 8$  years, mean LVEF:  $33 \pm 11$  %, in 19 pts. VT/VF was terminated by the device, follow up prior to data acquisition  $30 \pm 27$  months.) and 32 patients with DCM (28 male, mean age:  $59 \pm 10$  years, mean LVEF:  $25 \pm 10$  %, therapy was delivered in 17 pts, follow up prior to data acquisition  $31 \pm 24$  months. ) were enrolled in the prospective study during routine ICD-follow up at our institution. The medians of parameters were used as cut-off points in the prospective analysis

## 3. Results

A retrospective analysis provided no significant differences between both CAD patient groups regarding age, TO,  $TS_{abs}$ . As depicted in table 1, NTP provided the highest significance followed by DL,  $TS_{norm}$ , TJ and LVEF. The test revealed a significant difference between DCM patients without and with stored VT/VF in TJ, followed by NTP and LVEF. The data in the table are given as median  $\pm$ SD.

During follow up after the data acquisition in 13 CAD patients and in 10 DCM patients occurred VT/VF were treated by the device. The Kaplan-Meier analysis revealed significance of the NTP as a strong independent predictor for the recurrence of VT/VF in CAD patients (Fig. 3a). The significance was also confirmed for DL and  $TS_{norm}$ . The results of a prospective analysis for CAD and DCM patients are depicted in the table 2.

Table 1. Differences between patients without and with stored VT/VF (retrospective analysis).

Descriptor	No VT/VF	VT/VF	p
<b>CAD</b>			
LVEF (%)	35 $\pm$ 9	30 $\pm$ 13	<0.03
$TS_{norm}$ (%)	8.1 $\pm$ 3.0	5.5 $\pm$ 3.4	<0.01
TJ (%)	35 $\pm$ 11	46 $\pm$ 17	<0.003
DL	3.9 $\pm$ 1.9	2.0 $\pm$ 1.2	<0.002
NTP	3.4 $\pm$ 1.6	4.8 $\pm$ 1.4	<0.001
<b>DCM</b>			
LVEF (%)	29 $\pm$ 13	22 $\pm$ 6	<0.05
NTP	4.5 $\pm$ 1.4	5.6 $\pm$ 1.3	<0.04
TJ (%)	39 $\pm$ 13	57 $\pm$ 16	<0.002

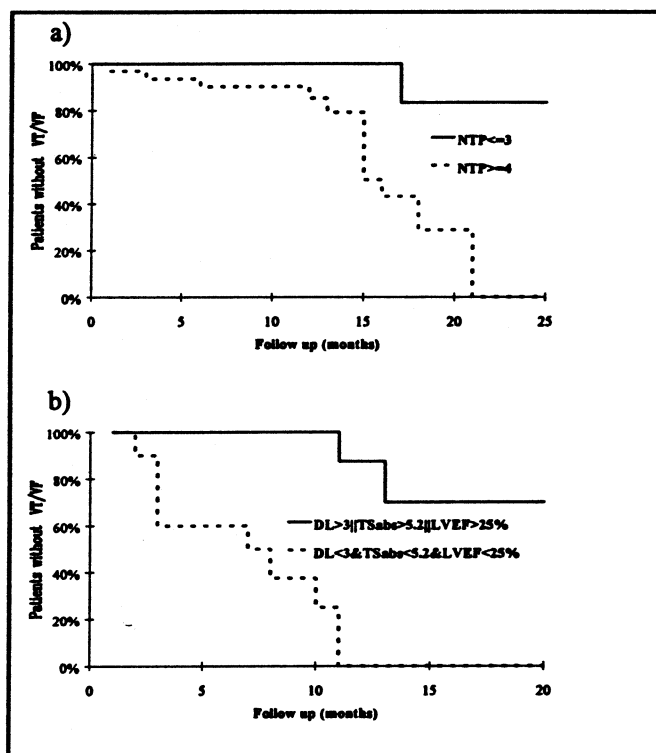


Figure 3. Probability of the therapy free outcome for a) CAD patients and b) DCM patients.

Table 2. Predictors of VT/VF in patients with ICD.

Descriptor	Sen	SpC	PPA	NPA	p
CAD					
NTP $\leq$ 3/ $\geq$ 4.	0.92	0.47	0.39	0.95	<0.001
DL $\geq$ / $\leq$ 3	0.77	0.63	0.42	0.89	<0.02
TS <sub>nm</sub> $\geq$ / $\leq$ 0.12	0.67	0.51	0.30	0.83	<0.05
DCM					
DL $\geq$ / $\leq$ 3	0.90	0.68	0.56	0.94	<0.01
TS <sub>abs</sub> $\geq$ / $\leq$ 5.2	0.70	0.64	0.47	0.82	<0.04
LVEF $\geq$ / $\leq$ 25%	0.80	0.55	0.44	0.86	<0.05

The strongest independent predictor for VT/VF in DCM patients was DL $\leq$ 3 RRI (p<0.01) followed by TS<sub>abs</sub> and LVEF. The combination of these parameters provided a high significance p<0.001, Sen=80%, Spc=90%, PPA=78%, NPA=88%. (Fig. 3b). Although NTP could not reach significance as an independent predictor for VT/VF in DCM patients the combination of NTP $\geq$ 4 with TS<sub>abs</sub>  $\leq$ 5.2 ms/beat and LVEF  $\leq$ 25 % provided the same power of predictability.

#### 4 Discussion and conclusion

The modification of the original algorithm suggested by Schmidt et al [1] performed in this study allowed to obtain additional information on the post ectopic activity of the sinus node which may be used for improved predictability of tachyarrhythmic events in CAD as well as in DCM patients.

The main finding of our study is that the importance of the defined descriptors of HRT, DL and NTP was confirmed for CAD as well as for DCM patients. By the physiologically normal reaction of sinus node on the PVB all random TNP should be eliminated after averaging over 10 PVBs. If this is not the case, the post ectopic response is impaired even the value of TS is formally high. Both of these parameters provided significance in the retrospective as well as in the prospective analysis.

In future this method of inducing at least 10 PVBs and calculating HRT descriptors could also be used during invasive electrophysiologic examinations as a short test for risk stratification., especially for patients with DCM because even programmed ventricular stimulation is not helpful for the risk prediction of DCM patients in contrast to patients with CAD [6].

#### Acknowledgment

The authors wish to express their appreciation to Prof. Dr. Georg Schmidt and to Dipl. Ing. Raphael Schneider from the 1st Medical Clinic of the Technical University Munich, Germany, for their valuable critical remarks and contribution to this study.

#### References

- [1] Schmidt G, Malik M, Barthel P, et al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction, *The Lancet* 1999, 353: 1390-96.
- [2] Malik M, Wichterle D, Schmidt G. Heart-rate turbulence. *G Ital Cardiol* 1999, 29, Suppl. 5: 65-69.
- [3] Berkowitsch A, Guettler N, Schulte B, et al. Heart-rate turbulence slope after paced premature ventricular beats as a predictor for the recurrence of ventricular tachyarrhythmias. A study in defibrillator patients *Circulation*, 2000, 102, Suppl. II-525
- [4] Berkowitsch A, Guettler N, Neumann T et al. Turbulence jump- a new descriptor of heart-rate turbulence after paced premature ventricular beats. A study in dilated cardiomyopathy patients. *Eur Heart J* 2001, 22, Suppl: 547
- [5] Davies LC, Francis DP, Ponikowski P, et al. Relation of heart rate and blood pressure turbulence following premature ventricular complexes to baroreflex sensitivity in chronic congestive heart failure. *Am J Cardio* 2001, 87: 737-742
- [6] Grimm W, Glaveris C, Hoffmann J, et al. Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: design and first results of the Marburg Cardiomyopathy Study. *Pacing Clin Electrophysiol* 1998, 21: 2551-56.

Address for correspondence

Dr. Alexander Berkowitsch,  
Kerckhoff-Clinic, Beneke Strasse 2-8, 61231,  
Bad Nauheim, Germany.

E-mail: alexander.berkowitsch@kerckhoff.med.uni-giessen.de