Clinical and haemodynamic correlates of heart rate turbulence as a non-invasive index of baroreflex sensitivity in chronic heart failure

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CLINICAL AND HAEMODYNAMIC CORRELATES OF HEART RATE TURBULENCE AS A NON-INVASIVE INDEX OF BAROREFLEX SENSITIVITY IN CHRONIC HEART FAILURE

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ABSTRACT

Heart Rate Turbulence (HRT) describing the heart rate changes following a premature ventricular contraction, has been regarded as an indirect index of baroreflex function. However limited data are available on its relation to invasive assessment by phenylephrine injection (Phe_Slope).

We therefore compared these methodologies in a series of heart failure (HF) patients in which both measures together with clinical and hemodynamic data were available.

HRT parameters (turbulence onset, TO and turbulence slope, TS, were measured from 24-hour Holter recordings obtained within one week from baroreflex sensitivity assessment and right heart hemodynamic evaluation (Swan-Ganz catheter).

HRT was computable in 135 out of 157 (86%) patients who had both phenylephrine test and hemodynamic evaluation. TO and TS significantly correlated with Phe_Slope ($r=-0.39$, $p<.0001$ and $r=0.66$, $p<.0001$ respectively).

Age, baseline heart rate, left ventricular ejection fraction, pulmonary capillary pressure (PCP), cardiac index (CI) and sodium were significant and independent predictors of Phe_Slope, accounting for 51% of its variability. Similarly, age, baseline heart rate and PCP and NYHA class III-IV were independent predictors for TS and explained 48% of its variability while only CI and LVEF were found to be significantly related to TO and explained a very limited proportion (20%) of the variability.

These data suggest that HRT may be regarded as a surrogate measure of baroreflex sensitivity in clinical and prognostic evaluation in heart failure patients.

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Introduction

The evaluation of baroreflex sensitivity (BRS) provides valuable clinical and prognostic information in a variety of cardiovascular diseases [1]. The original method [2] used intravenous injections of small boluses of angiotensin II to raise intra-arterial blood pressure transiently, and the resultant reflex bradycardia (expressed as the following heart periods) was used as an index of the baroreflex gain. But angiotensin II also causes a later central nervous sympathetic discharge, so phenylephrine (Phe) was later substituted as the pressor agent [3].

Although this method has stood the test of time in many differing clinical conditions [4,5], its invasive nature and the need for a beat to beat measurement of arterial pressure limit its applicability. Non-invasive methods providing (indirect) information on baroreflex control are more suitable for large scale use.

Heart Rate Turbulence (HRT) is the physiological, bi-phasic response of the sinus node to premature ventricular contractions (PVCs) [6]. It consists of a short initial acceleration followed by a deceleration of the heart rate. HRT has been established as an independent risk predictor [6-8]. The physiological mechanisms determining HRT have been extensively investigated and it has been shown that HRT is related to BRS, and perhaps *entirely* dependent on the baroreflex [9, 10]. However, few studies have attempted to evaluate the correlation between HRT – as an indirect index of baroreflex function – and the Phe method, a measure which has long been regarded as the reference method for the evaluation of baroreceptor activity [11, 12]. Moreover, in patients with heart failure (HF) poor hemodynamic status itself reduces baroreflex responses as assessed by the Oxford Phe method [13]. There are so far no data on the impact of hemodynamic variables on HRT.

In this paper we analyzed the relationship between measures of HRT and the Oxford Phe method in patients with HF who also had a direct evaluation of their hemodynamic status.

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Methods

Subjects

We retrospectively analyzed 157 mild-to-moderate HF patients in sinus rhythm consecutively admitted to the Heart Failure Unit of the Scientific Institute of Montescano between 1992 and 1996 for evaluation and treatment of HF, usually in conjunction with evaluation for heart transplantation. Inclusion criteria were: stable clinical conditions (no changes in signs, symptoms or therapy in the 2 weeks preceding the study), standard assessment of baroreflex sensitivity by the Phe method, a 24-hour Holter recording analyzable for at least half of the night-time (00:00-05:00 h) and half of the daytime (09:00-19:00 h), plus a hemodynamic evaluation performed within one week from BRS testing.

All patients underwent standard clinical and laboratory examinations, including 2D echocardiography and routine blood tests.

This is a retrospective study based on our prospective institutional data-base of HF patients. The Local Ethics Committee approved the study design and waived the need for an informed consent. All patients provided written consent to the scientific treatment of their data in an anonymous form at the time of hospitalization.

Baroreflex Sensitivity Assessment

Subjects were studied as previously described [1]. The Phe test was carried out by injecting an intravenous bolus of the drug (3 to 4 µg/kg) to raise systolic arterial pressure (SAP) by 15-30 mmHg. The injection was repeated twice after a 10-minute interval. In order to measure BRS, RR intervals were plotted against the preceding SAP value and the analysis window was interactively defined as the interval between the beginning and the end of the first significant (> 15 mmHg) increase of SAP following drug injection. The gain of the reflex, in ms/mmHg, was measured as the slope of the regression line fitting the points within this window [1]. BRS was calculated as mean value of computed slopes (and will be referred to as Phe_Slope).

Holter recordings and HRT analysis

Holter recordings were performed using a two-channel recorder and processed using a Synetec System (ElaMedical). Each beat was first automatically labeled as normal or aberrant by the Holter analysis software and then edited by an experienced analyst. Annotated RR time series were transferred to a personal computer and processed to compute HRT indexes [14]. In order to be included in the computation of HRT parameters, only ectopic beats with a minimum prematurity of 20% and a compensatory pause at least 20% longer than the normal interval were considered. Moreover, each ectopic beat had to be preceded by at least 2 sinus rhythm beats, and followed by at least 15 sinus beats. From the RR sequences fulfilling these criteria, turbulence onset (TO) and turbulence slope (TS) were computed.

TO, defined as the percentage difference between the heart rate immediately following PVC and the heart rate immediately preceding PVC, was calculated as follows:

$$TO = ((RR1 + RR2) - (RR\text{-}2 + RR\text{-}1)) / (RR\text{-}2 + RR\text{-}1) * 100$$

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where RR-2 and RR-1 are the first two sinus intervals preceding the PVC and RR1 and RR2 are the first two sinus intervals following the PVC. TO was computed for each suitable PVC and finally averaged over all obtained measurements. Positive values for TO indicate deceleration, negative values indicate acceleration of the sinus rhythm.
TS, defined as the steepest slope of the linear regression line for each sequence of five consecutive normal intervals following the PVC within the first 15 sinus rhythm beats, was computed on the averaged tachogram, obtained after alignment of R-R interval sequences surrounding isolated PVCs. TS is expressed in ms per RR interval.

Hemodynamic evaluation

Catheterization of the right-side of the heart was performed by use of a 7F Swan-Ganz balloon-tipped catheter inserted into the right internal jugular vein and advanced through the right heart into the pulmonary artery. Baseline standard hemodynamic measurements, including pulmonary artery pressure (PAP), pulmonary capillary pressure (PCP), and right atrial pressure (RAP) were made and cardiac output was measured by the thermodilution method as the mean of three consecutive measurements not varying by > 10%.

Statistical analysis

Data are expressed as median (interquartile range) unless otherwise specified. The correlation between BRS (Phe_Slope and HRT) and continuous variables was assessed by Spearman rank correlation coefficient.
To assess the association between BRS (considered as dependent variable) and clinical variables (considered as explanatory variables), we carried out a multiple regression analysis. Due to marked violation of the normality assumptions for the distribution of residuals, TS measurements were log-transformed. Less significant variables were eliminated by a backward elimination procedure at the 0.15 significance level.

Results

HRT was computable in 135 out of 157 (86%) patients who had a phenylephrine test and hemodynamic assessment.
Mean Phe_Slope (ms/mmHg), TO (%) and TS (ms/RR) were respectively (mean ± SD) 4.1 ±4.1, 0.08±1.7, and 2.6±3.8.

The main features of the 135 patients who had assessment of both Phe_Slope and HRT are summarized in Table 1.

Table 2 summarizes the results of correlation analyses. It can be seen that HRT was significantly correlated with Phe_Slope, with a stronger association observed for TS (r=0.66, p<.0001) than for TO (r=-0.39, p<.0001). TS and TO were also significantly related (-0.56, p<.0001). Figures 1 and 2 report the scatterplot of respectively TS and TO vs Phe_Slope. The scatterplot of TS vs Phe_Slope represented in Figure 1 shows that the linear association between the two measures while rather satisfactorily for lower values (those of clinical relevance) tends to decrease as the two measures increase.

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In some patients, mainly in association with advanced mitral regurgitation, the estimation of baroreflex gain produced a negative Phe_Slope (3 cases) or a negative TS (8 cases). The activation of sympathoexcitatory reflexes by stretch of cardiac chambers has been claimed to explain the paradoxical tachycardia occurring with the Oxford method [13]. Similar mechanisms are likely to be involved also in the genesis of negative TS, thus these patients were excluded from further analysis.

Multiple regression analysis assessing the association between Phe_Slope, HRT and clinical and hemodynamic variables are summarized in Tables 3-5. We found that age, baseline heart rate, LVEF, PCP, cardiac index (CI) and sodium were significant and independent predictors of Phe_Slope, accounting for 51% of its variability (Table 3). Similarly, age, baseline heart rate, PCP and NYHA class III-IV were also independent predictors for TS (Table 4) and explained 48% of TS variability. At variance, age and baseline heart rate and PCP did not provide any contribution to TO. Only CI and LVEF were found to be significantly related to TO prediction and explained a very limited portion of its variance (20%) (Table 5).

Discussion

This is the first study assessing the relationship between HRT measurements and both baroreflex sensitivity assessed by the Phe test, the reference method for the evaluation of baroreceptor activity, and hemodynamic measures. We have found in a large series of patients with chronic HF that HRT measurements – particularly HRT Slope – are substantially correlated with Phe_Slope and are also significantly associated with hemodynamic parameters.

Measurability of HRT

The recent consensus paper [14] highlighted the technical aspects and clinical use of HRT measures obtained from 24h ECG Holter recordings. The need for an adequate number of ectopic beats meeting the requirements for inclusion in the computation represents the major limitation in HRT use. From this series of 157 consecutively referred patients with a Phe_Slope test and hemodynamic assessment, 135 (86%) had adequate data to calculate HRT. In our patients with HF and a high number of PVCs/hour the lack of “isolated” ectopic beats represented the main reason for not measuring HRT. Although pulsus alternans has been claimed as a reason for not computing HRT because of the problem of post-extrasystolic potentiation [15], this was not observed in our sample population.

Correlation between PE_Slope and HRT

The results of the present study, showing a substantial correlation between Phe_Slope and HRT measurements – mainly TS – strongly support, in patients with HF, that the provoking mechanism of HRT has to be ascribed to the arterial baroreceptor response. Actually, TS showed a highly significant ($p<0.0001$) 0.66 correlation with the Phe_Slope, while a lower (albeit significant) correlation was observed between TO and Phe_Slope.

A lower correlation between TO and Phe_Slope was also found in a retrospective analysis from the ATRAMI study in patients with a previous myocardial infarction [11].

A tight relationship between HRT and BRS, as assessed by the sequence method, was found by Lin et al [16] in 16 patients without structural heart disease who were studied before and after sequential sympathetic, parasympathetic and combined autonomic blockade. They observed that both HRT indexes were significantly affected by atropine and combined autonomic blockade, but were unchanged after esmolol thus suggesting that HRT is critically dependent on vagal mechanisms (namely vagal withdrawal and vagal activation).

Because the unmyelinated sympathetic nerves are slowly conducting compared to the myelinated vagal fibres to the sinus node, the "immediate" TO response resulting from the drop in blood pressure resulting from the premature ventricular contraction therefore depends, in any individual subject, on the prevailing vagal tone before that beat. Vagal tone is likely to be lower in patients with HF in whom there is an increased firing from cardiac mechanoreceptors stimulated by the mechanical stretching associated with cardiac dilatation leading to the cardio-cardiac sympathetic reflex [17, 18]. The ensuing increased cardiac sympathetic afferent activity produces a tonic restrain of efferent vagal activity thus limiting the ability for vagal activity to withdraw following the hypotension induced baroreceptor deactivation. TS which results from the tracking of arterial baroreflexes of transient hypertension is thus more closely related than TO to the Phe_Slope.

Clinical correlates of HRT and Phe_Slope

Several studies have evaluated HRT measurements with clinical features of HF. In the large cohort of the MUSIC Study [19], HRT parameters especially TS were significantly correlated with the severity of HF and LV dysfunction as assessed by clinical, echocardiographic parameters and by N-terminal-pro-brain natriuretic peptide levels. Similarly, in the series of 553 ambulant outpatients from the UK-Heart study HRT parameters showed significant associations with HF [8].

Our analysis, by including also invasive hemodynamic parameters adds to these previous observations. More specifically, mean PCP played a significant role in the prediction of both Phe_Slope and TS. Experimental data support the relationship between reduced baroreceptor responsiveness and increased cardiac filling pressure. In dogs with pacing-induced HF, nitroprusside administration was found to increase BRS by about 60%, and the change correlated significantly with the magnitude of decrease in left atrial pressure, while BRS did not change by decreasing left atrial pressure in normal dogs [20].

The importance of age and baseline heart rate as "physiologic determinants" of BRS have largely been recognized. Kardos et al [21] found that age, heart rate, systolic and diastolic blood pressure, gender, body mass index and smoking were independent "physiologic" predictors of BRS in a large population of healthy volunteers.

Following the first evidence of an effect of age and high blood pressure on the arterial baroreceptor control of heart rate [22], many factors have been shown to be

responsible for the age-associated decline in baroreflex function including increased levels of oxidative stress, vascular stiffening, sinoatrial node responsiveness to acethilcholine [23].

The limited number of patients under beta-blockers clearly emphasizes the role of baseline heart rate. Actually, beta-blocker treatment seems to blunt the relationship between Phe_Slope and baseline heart rate as shown in a group of 103 HF patients who had Phe_Slope assessed under chronic beta-blockade in whom we found only a borderline significance for baseline heart rate [5].

However, it has also to be taken into account that clinical and hemodynamic parameters accounted for about 50% of the inter-individual variation in both Phe_Slope and TS thus suggesting that other factors including genetic variations, have a role in the clinical value of BRS assessment.

It might not be surprising that CI was the most important predictor of TO. Indeed, in the presence of a low cardiac output, systolic blood pressure during normal sinus rhythm is rather low. The ensuing carotid pressures may well often be located in the lower non linear portion of the reflex, thus severely blunting the heart rate reflex at the time of a premature ventricular contraction [24].

Clinical implications and conclusions

There are pros and contra in the clinical use of the two techniques. While the Phe method has a higher rate of measurability, it requires a drug administration and it is time consuming. HRT is completely non-invasive and automatically computed by a dedicated software; however, not only the lack of but also an excessive number of arrhythmias may limit its measurability. The argument can be made that the increase in blood pressure brought about by the post-extrasystolic beat might not be comparable with the one obtained by drug administration. However, both methods are substantially concordant in identifying patients with depressed baroreceptor activity.

In this respect, we have demonstrated in a large series of patients with HF that the hemodynamic correlates of HRT measurements – particularly HRT Slope – are similar to the Phe_Slope. By adding invasive hemodynamic measurements to the already explored clinical parameters, our study further support the concept that HRT slope might be regarded as a surrogate measure of baroreflex sensitivity in clinical and prognostic evaluation in heart failure patients.

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Legends for Figures

Figure 1. Scatterplot of the correlation between arterial baroreflex gain (PE_Slope) and Turbulence Slope

Figure 2. Scatterplot of the correlation between arterial baroreflex gain (PE_Slope) and Turbulence Onset

Table 1: Descriptive statistics in 135 patients

Characteristic	
Age (years)	**54** (46-58)
Sex (% male)	**86**
NYHA II-III (%)	**87**
Baseline RR interval (ms)	**775** (677-861)
Resting Systolic Arterial Pressure (mmHg)	**110** (100-115)
Resting Diastolic Arterial Pressure (mmHg)	**70** (70-80)
LVEF (%)	**23** (19-28)
LVESD (mm)	**62** (56-69)
LVEDD (mm)	**73** (68-79)
Severe Mitral regurgitation (3-4) %	**40**
Peak VO_2 ml/kg/min	**14** (11-18)
PAP (mmHg)	**25** (16-36)
PCP (mmHg)	**15** (9-26)
RAP (mmHg)	**3** (1-7)
CI (l/min/m^2)	**2.3** (1.9-2.7)
VPCs (n/hour)	**13** (4-49)
NSVT (%)	**40**
BUN (mg/dl)	**51** (41-60)
Sodium (mEq/l)	**138** (136-140)
Creatinine (mg/dl)	**1.17** (1.04-1.31)
Potassium (mEq/l)	**4.3** (4.1-4.6)
Bilirubine (mg/dl)	**1.06** (0.80-1.45)
PE_Slope (ms/mmHg)	**2.8** (1.1 -6.2)
SDNN (ms)	**88** (60-120)
TO (%)	**0.12** (-0.69-0.70)
TS (ms/RR)	**1.4** (0.5-3.4)
Medical theraphy (%):	
- **ACE-inhibitors**	**89**
- **Beta-blockers**	**6**
- **Diuretics**	**95**
- **Digitalis**	**76**
- **Amiodarone**	**24**

Continuous variables are expressed as median (lower quartile – upper quartile). LVEF= left ventricular ejection fraction; LVESD, LVEDD = left ventricular end systolic and diastolic diameter; PAP= mean pulmonary artery pressure; PCP= pulmonary capillary pressure; RAP= right atrial pressure; CI= cardiac index; VPCs/h= ventricular premature contractions/hour; NSVT= non-sustained ventricular tachycardia; BUN= blood urea nitrogen; SDNN= standard deviation of normal-to-normal RR intervals.

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Table 2. Correlation matrix

	PE_Slope	TS	TO	Mean RR
PE_Slope		0.66	-0.39	0.38
TS	0.66		-0.56	0.58
TO	-0.39	-0.56		-0.48
Mean RR	0.38	0.58	-0.48	

$p < 0.0001$ for all correlations reported

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Table 3. Results from multiple regression analysis assessing the association between clinical and functional covariates and PE-Slope

Variable	Beta	F-value	p-value
Age	-0.237	51.60	<0.0001
Mean RR	0.009	11.82	0.001
LVEF	-0.109	4.39	0.038
PCP	-0.133	17.61	<0.0001
CI	1.335	6.66	0.011
Sodium	0.209	5.16	0.025

Table 4. Results from multiple regression analysis assessing the association between clinical and functional covariates and HRT Slope*.

Variable	Beta	F-value	p-value
Age	-0.044	16.18	0.0001
Mean RR	0.005	42.75	<0.0001
PCP	-0.032	11.03	0.001
NYHA III-IV	-0.414	3.82	0.053

*HRT Slope measurements were log-transformed before analysis

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Table 5. Results from multiple regression analysis assessing the association between clinical and functional covariates and HRT Onset.

Variable	Beta	F-value	p-value
LVEF	-0.065	5.94	0.016
CI	-0.73	7.91	0.006

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Figure 1 .

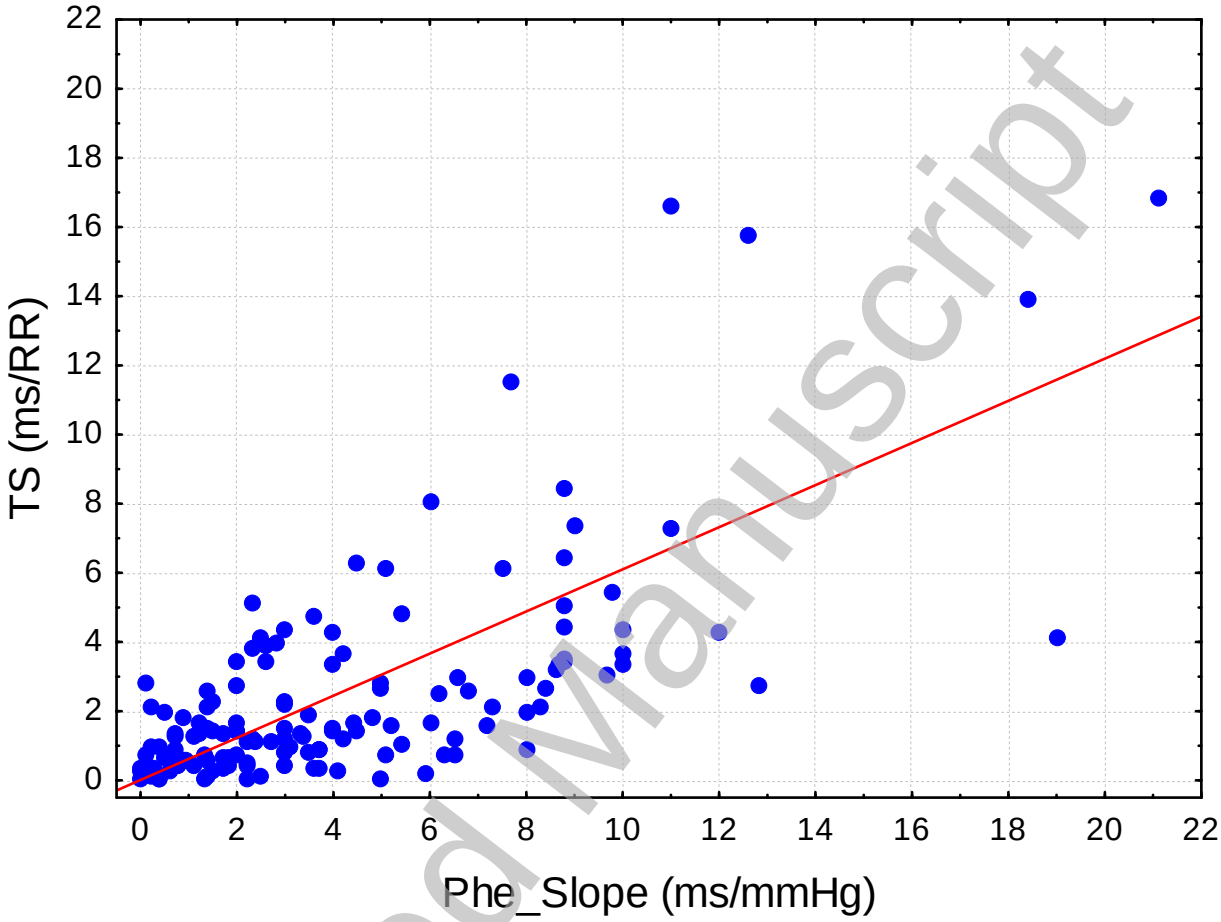

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Figure 2.