

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

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A B S T R A C T

HRT (heart rate turbulence), 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 relationship with invasive assessment by phenylephrine injection (Phe-slope). In the present study, we therefore compared these methodologies in a series of patients with HF (heart failure) in which both measures together with clinical and haemodynamic data were available. HRT parameters [TO (turbulence onset) and TS (turbulence slope)] were measured from 24-h Holter recordings obtained within 1 week of baroreflex sensitivity assessment and right heart haemodynamic evaluation (Swan-Ganz catheter). HRT was computable in 135 out of 157 (86%) patients who had both a phenylephrine test and haemodynamic evaluation. TO and TS significantly correlated with Phe-slope ($r = -0.39$, $P < 0.0001$ and $r = 0.66$, $P < 0.0001$ respectively). Age, baseline heart rate, LVEF (left ventricular ejection fraction), PCP (pulmonary capillary pressure), CI (cardiac index) 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 (New York Heart Association) classes III–IV were independent predictors for TS and explained 48% of its variability, whereas only CI and LVEF were found to be significantly related to TO and explained a very limited proportion (20%) of the variability. In conclusion, these results suggest that HRT may be regarded as a surrogate measure of baroreflex sensitivity in clinical and prognostic evaluation in patients with HF.

INTRODUCTION

The evaluation of BRS (baroreflex sensitivity) provides valuable clinical and prognostic information in a variety of cardiovascular diseases [1]. The original method [2] used intravenous injections of small boluses of AngII (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. However, AngII also causes a later central nervous sympathetic discharge, so Phe (phenylephrine) 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

Key words: age, autonomic control, baroreflex, heart failure, heart rate turbulence, phenylephrine.

Abbreviations: AngII, angiotensin II; BRS, baroreflex sensitivity; CI, cardiac index; HF, heart failure; HRT, heart rate turbulence; LAP, left atrial pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PCP, pulmonary capillary pressure; Phe, phenylephrine; PVC, premature ventricular contraction; RAP, right atrial pressure; SAP, systolic arterial pressure; TO, turbulence onset; TS, turbulence slope.

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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.

HRT (heart rate turbulence) is the physiological bi-phasic response of the sinus node to PVCs (premature ventricular contractions) [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 investigated extensively and it has been shown that HRT is related to BRS and is 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 HF (heart failure), poor haemodynamic status itself reduces baroreflex responses as assessed by the Oxford Phe method [13]. There are so far no data on the impact of haemodynamic variables on HRT.

In the present study, we analysed the relationship between measures of HRT and the Oxford Phe method in patients with HF who also had a direct evaluation of their haemodynamic status.

MATERIALS AND METHODS

Subjects

We retrospectively analysed 157 patients with mild-to-moderate HF 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 BRS by the Phe method, a 24-h Holter recording analysable 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 haemodynamic evaluation performed within 1 week of BRS testing.

All patients underwent standard clinical and laboratory examinations, including two-dimensional echocardiography and routine blood tests.

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

BRS assessment

Subjects were studied as described previously [1]. The Phe test was carried out by injecting an intravenous

bolus of the drug (3–4 $\mu\text{g}/\text{kg}$ of body weight) to increase SAP (systolic arterial pressure) by 15–30 mmHg. The injection was repeated twice after a 10-min 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 in 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 were processed using a Synetec system (ElaMedical). Each beat was first automatically labelled 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 two sinus rhythm beats and followed by at least 15 sinus beats. From the RR sequences fulfilling these criteria, TO (turbulence onset) and TS (turbulence slope) 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:

$$\text{TO} = \frac{[(\text{RR1} + \text{RR2}) - (\text{RR} - 2 + \text{RR} - 1)]}{(\text{RR} - 2 + \text{RR} - 1)} \times 100$$

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 of the obtained measurements. Positive values for TO indicate deceleration, whereas 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 RR interval sequences surrounding isolated PVCs. TS is expressed in ms/RR interval.

Haemodynamic evaluation

Catheterization of the right side of the heart was performed by use of a 7 French Swan-Ganz balloon-tipped catheter inserted into the right internal jugular vein and advanced through the right heart into the pulmonary

artery. Baseline standard haemodynamic measurements, including PAP (pulmonary artery pressure), PCP (pulmonary capillary pressure) and RAP (right atrial pressure), were made and cardiac output was measured by the thermodilution method as the mean of three consecutive measurements not varying by >10%.

Statistical analysis

Results are expressed as medians (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. Owing to the 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 Phe test and haemodynamic assessment. Mean Phe-slope, TO and TS were 4.1 ± 4.1 ms/mmHg, $0.08 \pm 1.7\%$ and 2.6 ± 3.8 ms/RR interval respectively (values are means \pm S.D). 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 the correlation analyses. It can be seen that HRT was significantly correlated with Phe-slope, with a stronger association observed for TS ($r = 0.66$, $P < 0.0001$) than for TO ($r = -0.39$, $P < 0.0001$). TS and TO were also significantly related (-0.56 , $P < 0.0001$). Figures 1 and 2 show the scatterplots of TS and TO against the Phe-slope respectively. The scatterplot of TS against Phe-slope shown in Figure 1 indicates that the linear association between the two measures, although satisfactory for lower values (those of clinical relevance), tended to decrease as the two measures increased.

In some patients, mainly in association with advanced mitral regurgitation, the estimation of baroreflex gain produced a negative Phe-slope (three cases) or a negative TS (eight 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 also likely to be involved in the genesis of a negative TS, thus these patients were excluded from further analysis.

Multiple regression analysis assessing the association between Phe-slope, HRT and clinical and haemodynamic variables is summarized in Tables 3–5. We found that

Table 1 Descriptive statistics of the 135 patients analysed

Continuous variables are expressed as medians (interquartile range). ACE, angiotensin-converting enzyme; DAP, diastolic arterial pressure; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; V_{O_2} , oxygen consumption; NSVT, non-sustained ventricular tachycardia; BUN, blood urea nitrogen; SDNN, S.D. of normal-to-normal RR intervals.

Characteristic	Value
Age (years)	54 (46–58)
Sex (% male)	86
NYHA classes II–III (%)	87
Baseline RR interval (ms)	775 (677–861)
Resting SAP (mmHg)	110 (100–115)
Resting DAP (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 V_{O_2} ($\text{ml}\cdot\text{kg}^{-1}$ of body weight $\cdot\text{min}^{-1}$)	14 (11–18)
PAP (mmHg)	25 (16–36)
PCP (mmHg)	15 (9–26)
RAP (mmHg)	3 (1–7)
CI ($\text{l}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$)	2.3 (1.9–2.7)
PVCs (n/h)	13 (4–49)
NSVT (%)	40
BUN (mg/dl)	51 (41–60)
Sodium (mmol/l)	138 (136–140)
Creatinine (mg/dl)	1.17 (1.04–1.31)
Potassium (mmol/l)	4.3 (4.1–4.6)
Bilirubin (mg/dl)	1.06 (0.80–1.45)
Phe-slope (ms/mmHg)	2.8 (1.1–6.2)
SDNN (ms)	88 (60–120)
TO (%)	0.12 (–0.69 to 0.70)
TS (ms/RR)	1.4 (0.5–3.4)
Medical therapy (%)	
ACE-inhibitors	89
β -Blockers	6
Diuretics	95
Digitalis	76
Amiodarone	24

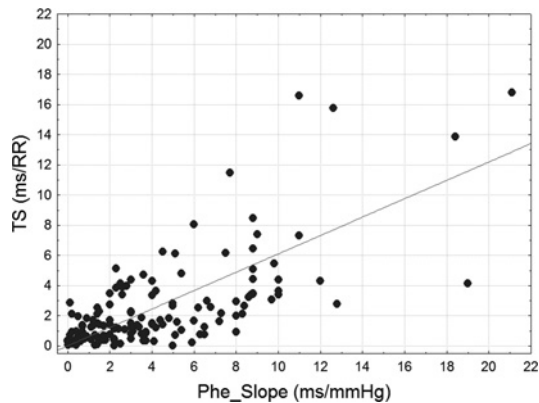
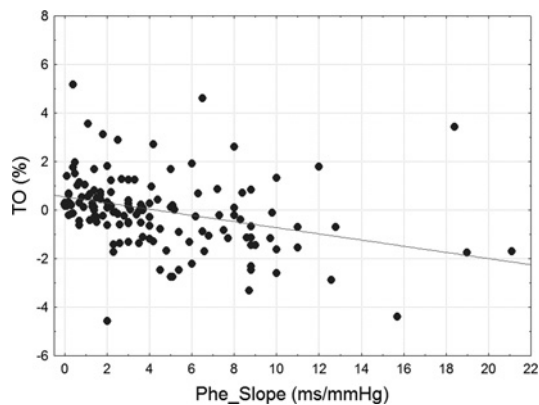
age, baseline heart rate, LVEF (left ventricular ejection fraction), PCP, CI (cardiac index) and sodium were significant and independent predictors of Phe-slope, accounting for 51% of its variability (Table 3). Similarly, age, baseline heart rate, PCP and NYHA (New York Heart Association) classes III–IV were also independent predictors for TS (Table 4) and explained 48% of TS variability. In contrast, 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).

Table 2 Correlation matrix $P < 0.0001$ for all of the correlations reported.

Variable	Phe-slope	TS	TO	Mean RR
Phe-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	—

Table 3 Multiple regression analysis assessing the association between clinical and functional covariates and Phe-slope

Variable	β	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

**Figure 1** Correlation between arterial baroreflex gain (Phe-slope) and TS**Figure 2** Correlation between arterial baroreflex gain (Phe-slope) and TO**Table 4** Multiple regression analysis assessing the association between clinical and functional covariates and HRT-slope

HRT-slope measurements were log-transformed before analysis.

Variable	β	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 classes III-IV	-0.414	3.82	0.053

Table 5 Multiple regression analysis assessing the association between clinical and functional covariates and HRT onset

Variable	β	F value	P value
LVEF	-0.065	5.94	0.016
CI	-0.730	7.91	0.006

DISCUSSION

The present study is the first to assess the relationship between HRT measurements and both BRS assessed by the Phe test, the reference method for the evaluation of baroreceptor activity, and haemodynamic 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 haemodynamic parameters.

Measurability of HRT

The consensus paper [14] highlighted the technical aspects and clinical use of HRT measures obtained from 24-h 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 the present series of 157 consecutively referred patients with a Phe-slope test and haemodynamic assessment, 135 (86%) had adequate data to calculate HRT. In our patients with HF and a high number of PVCs/h 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 present sample population.

Correlation between Phe-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 had a highly significant ($P < 0.0001$) 0.66 correlation with the

Phe-slope, whereas 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 (Autonomic Tone and Reflexes After Myocardial Infarction) study in patients with a previous myocardial infarction [11].

A close 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 with the myelinated vagal fibres to the sinus node, the 'immediate' TO response resulting from the fall in blood pressure as a consequence of the PVC 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 restraint of efferent vagal activity thus limiting the ability of vagal activity to withdraw following the hypotension-induced baroreceptor unloading. 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 (MUerte Subita en Insuficiencia Cardiaca) study [19], HRT parameters especially TS were significantly correlated with the severity of HF and left ventricular dysfunction as assessed by clinical and echocardiographic parameters and by NT-BNP (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 present analysis, by also including invasive haemodynamic 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 approximately 60%, and the change correlated significantly with the magnitude of decrease in LAP

(left atrial pressure), whereas BRS did not change by decreasing LAP in normal dogs [20].

The importance of age and baseline heart rate as 'physiological 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 'physiological' 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 and sinoatrial node responsiveness to acetylcholine [23].

The limited number of patients taking β -blockers clearly emphasizes the role of baseline heart rate. Actually, β -blocker treatment seems to blunt the relationship between Phe-slope and baseline heart rate, as shown in a group of 103 patients with HF who had Phe-slope assessed under chronic β -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 haemodynamic parameters accounted for approximately 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 PVC [24].

Clinical implications and conclusions

There are arguments for and against the clinical use of the two techniques. Although the Phe method has a higher rate of measurability, it requires a drug administration and 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 essentially comparable in identifying patients with depressed baroreceptor activity.

In this respect, we have demonstrated in a large series of patients with HF that the haemodynamic correlates of HRT measurements, particularly HRT-slope, are similar to the Phe-slope. By adding invasive haemodynamic measurements to the already explored clinical parameters,

our present study further supports the concept that HRT-slope might be regarded as a surrogate measure of BRS in the clinical and prognostic evaluation in patients with HF.

AUTHOR CONTRIBUTION

Maria Teresa La Rovere designed the experiments, collected and analysed the data, and prepared the paper. Roberto Maestri developed the analysis software, managed the database, performed the statistical analysis and prepared the paper. Gian Domenico Pinna developed the analysis software, managed the database, performed the statistical analysis and was involved in revising the paper. Peter Sleight designed the experiments and was involved in revising the paper. Oreste Febo collected the data and was involved in revising the paper.

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