Heart rate turbulence
— an overview of methods and applications

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Abstract

Heart rate turbulence (HRT) is a relatively new but already well-established non-invasive ECG risk predictor. It has been confirmed as a strong predictor of mortality in large populations of post-infarction patients treated with both classical and modern methods. There have been contradictory results regarding its predictive value in other high-risk populations (idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy and low ejection fraction cohorts). It is important that HRT seems to be particularly useful in identifying high-risk patients with preserved left ventricular function, the group of patients not covered by current indications for implantable cardioverter defibrillators. Further studies are needed to establish the need for correlation with heart rate, number of ventricular premature beats, heart rate variability parameters or clinical covariates in the process of risk stratification by means of HRT. (Folia Cardiol. 2006; 13: 359–368)*

Key words: heart rate turbulence, risk stratification, prognosis, mortality

Introduction

Despite continuous improvement in the treatment and management of cardiovascular diseases, the mortality of patients with cardiac disorders remains high, with sudden cardiac death (SCD) contributing to over half of deaths in this population [1]. Therefore identification of patients at high risk of mortality, who might benefit from primary or secondary prevention, is of major importance. Non-invasive ECG methods provide data on myocardial vulnerability, including the frequency and complexity of ventricular premature beats (VPB), T wave alternans and QT variability, and on autonomic nervous system imbalance in heart rate variability (HRV), both factors contributing to arrhythmogenic conditions. These methods are usually combined with assessment of left-ventricle function based on ejection fraction, reflecting changes in the myocardial substrate, to give complete insight into the risk of the patients studied.

Heart rate turbulence (HRT), a new heart rate derived non-invasive parameter tracking the response of the heart rate to ventricular arrhythmias, was introduced into electrocardiology in 1999 as a strong predictor of mortality in post-infarction patients [2]. The last few years have brought an increasing interest in the analysis of both clinical correlations and the predictive value of this parameter in different subsets of patients. In this review we present, on the basis of published data and our own experience, an overview of the measurement, pathophysiology and predictive value of HRT, as well as some of the limitations of this method.

Heart rate turbulence measurement

Schmidt et al. [2] described HRT as a pattern of response of sinus rhytm (RR) intervals (heart

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rate reflecting sinus node activity) to a premature ventricular beat (VPB). Physiologically, such a response consists of an early acceleration phase and subsequent deceleration following a VPB. The above-mentioned changes in sinus rhythm are observed within 15 RRs following a VPB. Owing to the subtle nature of these changes they require computer algorithms for detection. HRT is described by two numerical parameters: turbulence onset (TO) to describe the initial acceleration, and turbulence slope (TS) to reflect deceleration of the sinus rhythm. TO is a percentage of relative change of the mean of two RR intervals before and two RR intervals after a VPB, while TS is described by a maximum regression line computed in every five consecutive RR intervals following a VPB and is expressed in ms/RR (Fig. 1). The above-mentioned biphasic reaction of a sinus node may be observed in healthy subjects, while in high-risk patients this pattern is blunted or entirely missing. High-risk patients are therefore characterised by a weaker HRT reaction, expressed as the lack of an immediate acceleration or even deceleration of a sinus rhythm (positive values of TO) and a weaker rate of subsequent deceleration with lower TS values (flattened slope). According to the training samples, the authors of the HRT method proposed TO $\geq 0\%$ and TS ≤ 2.5 ms/RR as abnormal values. For risk stratification purposes patients are divided into three groups: HRT0 — both HRT parameters normal, HRT1 — one of the parameters abnormal, and HRT2 — both parameters abnormal. Even though
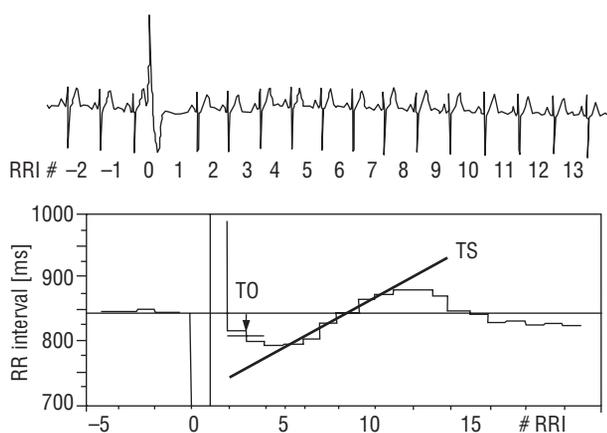
this method was primarily applied to 24-Holter recordings, HRT may also be assessed from shorter recordings or from RR data retrieved from implanted devices. So-called "induced HRT", via intracardiac pacing during electrophysiological studies or via an implantable cardioverter defibrillator (ICD), may also be evaluated [3, 4]. Apart from TO and TS, which are the standard parameters describing HRT, additional parameters such as turbulence jump, turbulence dynamics, turbulence timing or HRT analysis in frequency domain were described and used for risk stratification [5]. Finally papers also appeared which evaluated HRT after premature atrial and not only ventricular beats. This turbulence shows a slightly different pattern, but was also proven to be a mortality predictor [6, 7].

The pathophysiological mechanism of heart rate turbulence

Heart rate turbulence is believed to be mediated via the baroreceptor reflex. Baroreceptors, localised in the aortic arch and carotid sinus, constitute one of the basic mechanisms of heart rate and blood-pressure control. Being more responsive to sudden hypotonia than to an increase in blood pressure, they are constantly stimulated by tonic arterial blood pressure. VPBs provoke a short temporal decrease in blood pressure. This triggers activation of the baroreceptors, which results in a withdrawal of parasympathetic and a predominance of sympathetic activation, resulting in heart rate acceleration. The subsequent increase in blood pressure, explained also by augmented myocardial contractility following the premature contraction, leads to an opposite reaction — activation of the parasympathetic arch and a decrease in the heart rate, also mediated by baroreceptors [8]. These two subsequent phases are reflected as a curve in the HRT reaction. A significant correlation between HRT and baroreflex reaction has been documented in both experimental and clinical studies. Mrowka et al. [9], in a laboratory model, observed that a blunted baroreflex response resembles patterns of HRT. These observations were confirmed by numerous experimental and clinical studies [9–12]. Strong correlations between spontaneous as well as phenylephrine-induced baroreflex sensitivity and HRT were also documented [13]. Further studies confirmed that HRT is highly vagally dependent, as HRT parameters remain significantly attenuated (decreased TS and increased TO) after atropine-induced blockade [14, 15]. Therefore enhanced HRT parameters may reflect the loss of vagal protection against arrhythmic

Figure 1. Heart rate turbulence: RR behaviour after ventricular premature beat with turbulence onset (TO) and turbulense slope (TS) calculated [From: Schmidt G, Malik M. Heart rate turbulence. In: Zareba W, Maison-Blanche P, Locati E (eds). Noninvasive electrocardiology in clinical practice. Futura Publishing Company, Armonk, NY 2001: 207–215].

events. Post-extrasystolic potentiation is the other mechanism, possibly interplaying with different HRT patterns, as documented by Voss et al. [16], in patients with dilated cardiomyopathy.

Heart rate turbulence in risk stratification

Post-infarction patients

The prognostic value of attenuated parameters of HRT for predicting mortality was first confirmed in patients after myocardial infarction enrolled in the Multicenter Postinfarction Program (MPIP) and European Myocardial Infarction Amiodarone Trial (EMIAT) studies [2]. In both populations attenuated HRT parameters were independently associated with total mortality. Patients with abnormal TO and TS had a higher risk of mortality than could be evaluated on the basis of ejection fraction alone. In the MPIP population two-year mortality in patients with both normal, one abnormal, and both abnormal HRT parameters was 9%, 15% and 32% respectively. In EMIAT, these values were 9%, 18% and 34% respectively.

Retrospective application of HRT assessment in the Autonomic Tone and Reflexes after Myocardial Infarction (ATRAMI) trial confirmed a high predictive value of abnormal HRT parameters in the prediction of fatal and non-fatal cardiac arrest in low-risk post-myocardial infarction patients [13]. In this study the combination of abnormal TO and TS parameters was found to be the strongest risk predictor (RR = 4.07), confirming the independent value of HRT in the prediction of cardiac arrhythmic death. This study also confirmed the strong correlation between HRT and baroreflex sensitivity assessed by the phenylephrine test.

The following years brought further evidence that HRT is also an independent predictor when assessed in an acute phase of myocardial infarction in patients treated with modern reperfusion strategies [17–22]. Barthel et al. [17] documented a high predictive value of abnormal HRT parameters in 1455 patients with acute myocardial infarction (ISAR study) with reperfusion obtained in a majority (90%) by percutaneous coronary angioplasty (of this 80% with stenting) and then by thrombolysis and acute coronary artery bypass graft (CABG) surgery. Patients from this population were treated according to recent guidelines; therefore 93% received β-blockers, 90% ACE inhibitors and 85% statins. In this study HRT was evaluated with other classical markers of mortality, such as age, diabetes, left ventricular ejection fraction (LVEF), mean heart rate, HRV and ventricular arrhythmias. HRT2 (both variables abnormal) was found to be an inde-

pendent predictor of two-year mortality, providing the highest hazard ratio (5.9), followed by decreased LVEF, age, diabetes and HRT1 (one abnormal parameter). Two-year mortality in patients with both abnormal, one abnormal and both normal HRT parameters was 15%, 6% and 1% respectively. The other important finding of this study is that HRT was an independent predictor of death in patients with a significantly decreased LVEF of below 30% and those with a LVEF of over 30%. Therefore this observation confirmed that HRT analysis might give us significant information on mortality risk when added to LVEF, identifying high-risk subsets of patients in both subgroups. HRT2, analysed in combination with LVEF, increased the positive predictive value up to 40%. Therefore the simultaneous assessment of HRT with other parameters, especially those reflecting the myocardial substrate, could be recommended. This observation was also confirmed by the study of Sade et al. [18] who found that HRT assessed within the first 24 hours of myocardial infarction was a significant predictor of long-term mortality in patients with an acute myocardial infarction undergoing percutaneous coronary intervention. As with a paper of Barthel et al. [17], it was observed in this study that a combination of LVEF (in this case below 40%) with abnormal HRT parameters increases the positive predictive value, even up to 60% [18]. Regarding the ECG risk parameters assessed in this study, although decreased HRV parameters were found to be significant univariate parameters, multivariate analysis showed that blunted HRT reaction is the only predictive ECG-derived index of mortality in patients with an acute myocardial infarction. Summarizing, in all the above-mentioned studies (MPIP, EMIAT, ATRAMI, and ISAR) a similar pattern was observed, with the highest mortality rate related to HRT2 class (Fig. 2).

Furthermore, analysis of data from the studies of Barthel et al. [17], Sade et al. [18], and Jokinen et al. [19] shows that HRT may be used for risk stratification in patients in the era of primary angioplasty and the broad use of β-blocker therapy, which confirms the superiority of HRT over standard HRV analysis.

Even though numerous studies have demonstrated the usefulness of HRT in the prediction of total mortality, little data existed on HRT as a sudden death risk predictor. Finally the results of a FINGER study published in 2005 documented that HRT, together with non-sustained ventricular tachycardia is a strong risk predictor of both non-sudden and sudden cardiac death in post-infarction patients [21]. In this group of patients TS was a particularly strong SCD predictor among patients
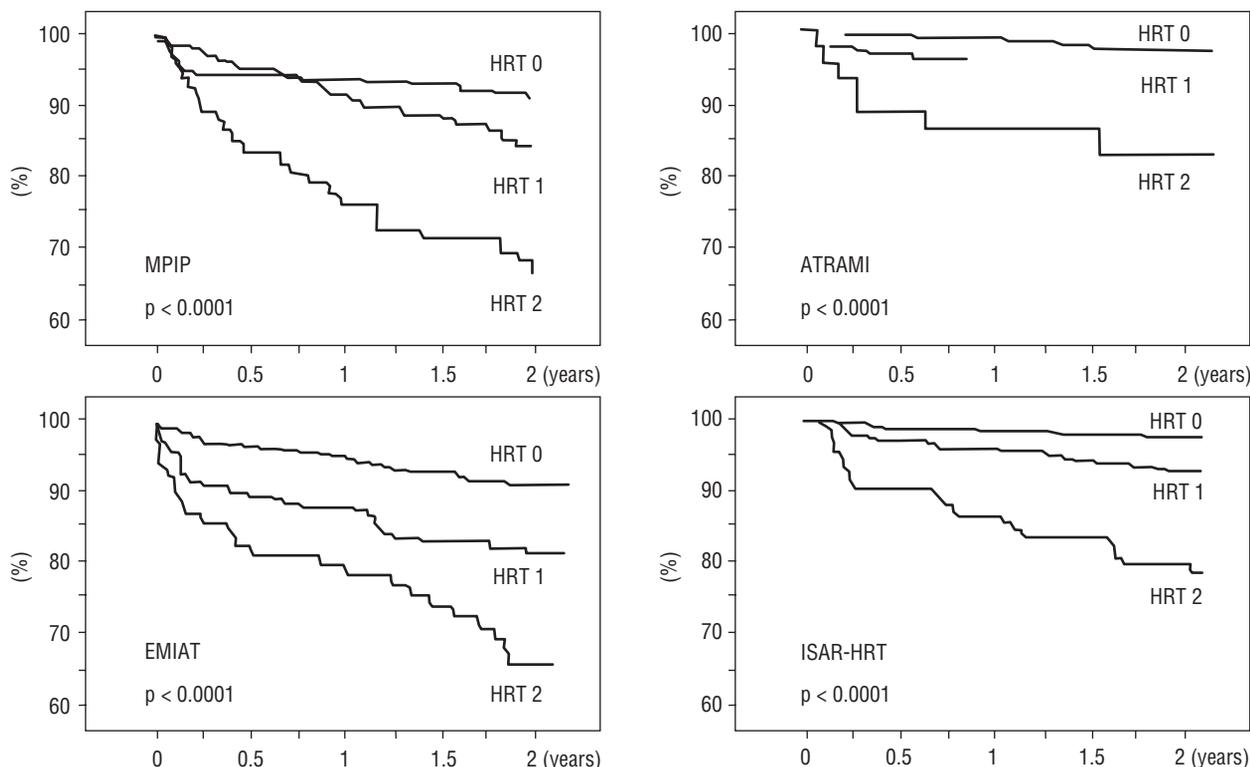
Figure 2. Kaplan-Meier survival curves in MPIP, EMIAT, ATRAMI and ISAR patients stratified to 3 groups: HRT0 (both TO and TS normal); either HRT1 (one of the factors abnormal); or HRT2 (both factors abnormal) [From: Francis J, Watanabe MA, Schmidt G. Heart rate turbulence: a new predictor for risk of sudden cardiac death. Ann Noninvasive Electrocardiol, 2005; 10: 102–109].

without significantly impaired LVEF. Patients with preserved LVEF but abnormal TS values have a higher SCD ratio than those with significantly impaired left ventricular function ($\leq 35\%$) [21]. Similarly, in a paper by Bauer et al. [22], HRT2 was a strong risk predictor of SCD in patients with LVEF over 30%, with a hazard ratio (HR) similar to that of post-infarction patients with significantly impaired LVEF ($\leq 30\%$) (HR 10.8 vs. 10.4 respectively). It is plausible that HRT is predictive both for total mortality and for SCD in patients with preserved LVEF, whereas it might have a predictive value for cardiac death but a limited value for SCD in post-infarction patients with a depressed ejection fraction.

We recently studied the predictive value of HRT parameters in the MADIT II trial, which enrolled post-infarction patients with an EF $\leq 30\%$ [23]. However, the option of calculating HRT parameters based on just a 10-minute resting ECG with a limited number of VPBs was limited. Such a short recording is under criticism for HRT analysis; nevertheless, one can assume that the observed presence of 20 VPBs on average during these 10 minutes should be sufficient to obtain represen-

tative values of HRT parameters. Although in univariate analysis there was a trend toward an association between TS levels and mortality in MADIT II patients, TS was not significant as a predictor of mortality after adjustment for relevant clinical covariates. Similarly, there was no association between TS or TO levels and arrhythmic events documented by ICD interrogation. It is most likely that the substantial damage to the myocardium and the associated impairment of baroreflex response contributed to these unexpected findings. The MADIT II population, with a mean value of TS = 3.9 ms/RR, was in much poorer health than the ATRAMI (mean TS = 12 ms/RR), MPIP (mean TS = 8.5 ms/RR) or EMIAT (mean TS = 6.3 ms/RR) populations and therefore the predictive value of HRT was diminished.

Other populations

Heart rate turbulence, which was primarily designed to predict mortality in post-infarction patients, was subsequently applied in different subsets of patients. Blunted HRT parameters were found to predict mortality in patients with chronic coronary artery disease out of the acute phase of
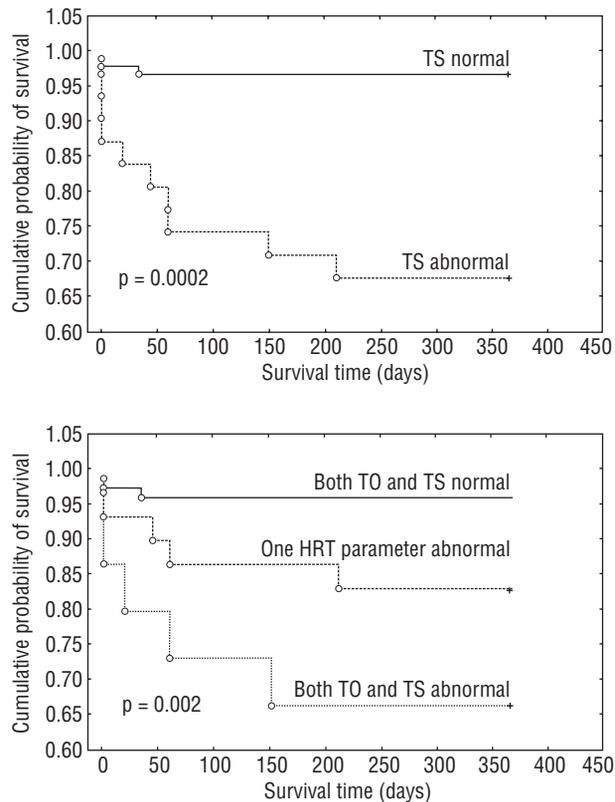
Figure 3. Cumulative probability of survival by heart rate turbulence parameters. P values computed with the log-rank test [From: Cygankiewicz I et al. Prognostic significance of heart rate turbulence in patients undergoing coronary artery bypass grafting. Am J Cardiol, 2003; 91: 1471–1474].

myocardial infarction. In a study of 146 patients with angiographically documented coronary artery disease undergoing coronary artery bypass grafting we observed that an abnormal TS (analysed both as continuous and low-quartile-based dichotomised values) was predictive for cardiac death during a one-year follow-up after cardiac surgery (Fig. 3) [20].

In post-infarction patients HRT was predictive for total mortality, cardiac death and arrhythmic events [2, 13]. Contradictory results are obtained from patients with chronic heart failure and non-ischaemic cardiomyopathies. In a study by Koyama et al. [24] in a population of 50 patients with heart failure (72% with non-ischaemic cardiomyopathy), HRT was highly predictive for death as regards heart failure progression and the rehospitalisation rate but failed to predict arrhythmic events. Similarly, in a study by Moore et al. [25], TS was an independent predictor of death from decompensated heart failure in a group of 533 outpatients with mild-to-moderate heart failure. The Magdeburg study [26] showed that HRT was predictive for total mortality

and heart transplantation in a group of 242 patients with idiopathic dilated cardiomyopathy. Nevertheless, no significance was found which would predict arrhythmic events in this group of patients. On the other hand, there are data that the ICD-induced HRT reaction is predictive for cardiac mortality and appropriate ICD-discharge in patients with idiopathic dilated cardiomyopathy and an implanted cardioverter defibrillator device [27]. In patients with hypertrophic cardiomyopathy HRT parameters neither differed from the control group nor proved predictive for clinical prognosis [28].

Table 1 summarises the predictive value of HRT parameters in risk stratification in different subsets of patients.

What are the cut-off values for predicting outcome?

As shown in the above comparison of TS values between various post-infarction populations, it is difficult to define normal values of HRT or the cut-off values used for risk stratification. Cut-off values of 0% for TO and 2.5 ms/RR, as proposed by the authors of the method [2], are widely accepted, although these were developed following myocardial infarction in patients not treated with modern strategies. It is probable that other values should be applied for risk stratification in coronary patients widely treated with pharmacology and interventional strategies. Similarly, other values might be used in patients with non-ischaemic dilated cardiomyopathy or hypertrophic cardiomyopathy. A high number of false-positive abnormal TO parameters (19%) defined as over 0% was reported by Grimm et al. [29] in patients with no structural heart disease. The cut-off value of 3 ms/RR for TS was proposed as the optimal stratification value for patients with congestive heart failure [24]. Therefore quartile values, the lower quartile for TS and upper quartile for TO, might be considered more adequate [20, 23].

Similarly, no consensus exists on when HRT parameters should be assessed. Temporal and circadian changes in HRT parameters have been observed. TS values have been reported to be lowest in the afternoon hours in coronary in-patients, while no significant changes in TO values have been observed [30]. According to Hallstrom et al [31], daytime (8 am – – 6 pm) ECG recording should be chosen in TS evaluation for prognostic purposes. HRT parameter dynamics after the acute phase of myocardial infarction were evaluated in a study by Jokinen et al. [19]. Restoration of blunted TO values was observed in the 12 months after acute myocardial infarction,

Table 1. The predictive value of heart rate turbulence parameters in risk stratification in different subsets of patients.

Authors	Acronym	No. of patients	Popula- tion type	Mean LVEF	Follow-up [months]	End-points	Predictive value in multivariate analysis (HR)	Comments
Schmidt et al. [2]	MPIP	715	Post-MI	45%	22	Total mortality	2.5 for TS 3.2 for HRT2	
Schmidt et al. [2]	EMIAT	732	Post-MI	30%	21	Total mortality	1.9 for TS 1.7 for TO 3.2 for HRT2	
Ghuran et al. [13]	ATRAMI	1212	Post-MI	49%	21	Combination of FCA and NFCA	2.47 for TS 1.21 for HRT 1 4.07 for HRT2	8.67 for combined index
Barthel et al. [17]	ISAR	1455	Post-MI	56%	22	Total mortality	2.4 for HRT1 5.9 for HRT2	2.8 for HRT2 in patients with LVEF < 30%
Jokinen et al. [19]	MRFAT	675	Post-MI	46%	40	Total mortality Cardiac deaths	1.9 for TO 2.2 for TS 2.2 for TO 2.5 for TS	Predictive also if assessed 1 year after MI
Mäkikallio et al. [21]	FINGER	2130	Post-MI	51%	34	SCD Non-SCD	2.9 for TS	4.7 in patients with LVEF > 35%
Berkowitsch et al. [23]	MADIT II	884	Post-MI	23%	22	Total mortality SCD	Not predictive	Short-term recordings (10 min)
Cygankiewicz et al. [20]		146	Chronic CAD	54%	12	Cardiac deaths	1.03 for TO 8,93 for TS 3.36 for HRT2	Cut-offs: TO ≥ 0.37% (Q4) TS ≤ 4.25 (Q1)
Sade et al. [18]		128	Post-MI	49%	12	Total mortality	3.8 for TO 12 for TS 8.3 for HRT2	14 for HRT2 + LVEF < 40%
Kawasaki et al. [28]		104	HCM	41%	27	Cardiac mortality	Not predictive	
Grimm et al. [26]		242	DCM	30%	41	Transplant-free survival, MAE	Not predictive	
Koyama et al. [24]		50	CHF	39%	26	CHF events (death, hospitalisation)	10.09 for TS	
Moore et al. [25]		533	CHF		60	CHF decompensation	0.84 for 10% increment of TS	Cut off TS < 3 ms/RR

TO — turbulence onset, TS — turbulence slope, HRT — heart rate turbulence, post-MI — patients who have suffered a myocardial infarction; CAD — coronary artery disease, HCM — hypertrophic cardiomyopathy; DCM — dilated cardiomyopathy; CHF — congestive heart failure; LVEF — left ventricular ejection fraction, RR — relative risk, FCA — fatal cardiac arrhythmia, NFCA — non-fatal cardiac arrhythmia, MAE — major arrhythmic events, Abn — abnormal

while TS remained unchanged over this period. Nevertheless, HRT retained its prognostic value, assessed either in the early or in the late phases of myocardial infarction. Changes in HRT values during the acute phase of infarction were observed in patients undergoing percutaneous coronary intervention. Revascularisation resulted in the restoration of HRT parameters assessed within 12 hours of the procedure when comparison was made with pre-procedure values, but only in patients who retained TIMI-3 flow. In patients with TIMI-2 coronary flow no improvement in HRT was observed [32]. It was postulated that attenuated microcirculation might be responsible for this finding. Significant attenuation of HRT parameters was observed in patients undergoing CABG surgery [33]. Revascularisation significantly attenuated both HRT parameters, which might be explained by impairment of autonomic nervous fibres in the course of aorta clamping; a similar mechanism was postulated to explain postoperative impairment of the HRV parameters. TO returned to preoperative values after 12 months, while TS remained attenuated. This observation suggests that HRT should not be used for risk stratification purposes during the 12 months following CABG surgery.

Other applications of heart rate turbulence

Heart rate turbulence was primarily designed as a predictor of mortality. However, it has also been used as a simple marker of autonomic nervous system balance. An alteration in heart rate dynamics, expressed as increasing TO after premature atrial beats, was found in the hours before atrial fibrillation onset, suggesting enhanced vagal activity in this period [34].

Heart rate turbulence was also suggested as an autonomic nervous system marker in patients with congestive heart failure. Abnormal HRT parameters attributed to heart failure were restored by three-month beta-blocker therapy in ten patients with heart failure. The evolution of TS was accompanied by parallel changes in HRV parameters reflecting parasympathetic tone [35]. Our own experience (data not published) showed that HRT may be considered as a marker of congestive heart failure advancement, giving insight into haemodynamic changes as well as changes to the autonomic nervous system.

Clinical and ECG covariates of heart rate turbulence

Heart rate turbulence has been found to correlate with several clinical (age, LVEF, coexisting diabetes) and ECG factors (mean heart rate, HRV,

BRS) [36–38]. TS decreases and TO increases with age. Lower TS values and higher TO values are observed in patients with decreased LVEF. Age-related changes might be explained as an effect of a reduced arterial compliance. Lower HRT parameters are observed in patients with attenuation of the autonomic nervous system, as in diabetes.

Heart rate turbulence parameters, especially TS, have been found to correlate with mean heart rate and the number of VPBs [31, 38]. Patients with a lower heart rate and a low number of VPBs have steeper (better) values of TS. Whether this is a purely mathematical relationship or the expression of real lower risk remains controversial. HRT was also found to correlate significantly with HRV parameters both in the time and the frequency domains [38] (Fig. 4).
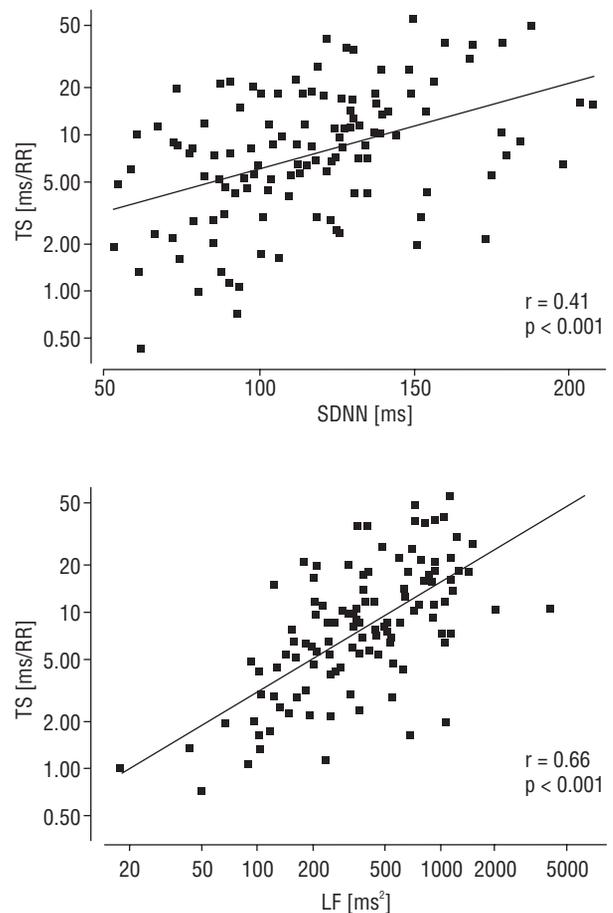
Figure 4. Relationship between turbulence slope (TS) and standard deviation of all RR intervals of sinus rhythm (SDNN) and low frequency power (LF) parameters [From: Cygankiewicz I et al. Relationship between heart rate turbulence and heart rate, heart rate variability, and number of ventricular premature beats in coronary patients. J Cardiovasc Electrophysiol, 2004; 15: 731–737].

A strong correlation between TS and low frequency power may confirm that HRT reflects baroreflex sensitivity.

Heart rate turbulence dependence on heart rate and number of VPBs and the strong correlations with baroreflex sensitivity and HRV should not be surprising, as HRT combines all these factors. Whether these correlations strengthen or weaken the predictive value of HRT remains controversial. On the one hand the optimal risk predictor should be independent overall, while on the other a combination of risk predictors reflecting different mechanisms participating in the chain of events leading to sudden death may increase the positive predictive value and lead to a more accurate identification of high-risk patients.

Heart rate turbulence assessment: limitations and questions

Heart rate turbulence is considered one of the most useful Holter-derived risk predictors. Nevertheless, HRT-based risk assessment has several limitations. The first and most important of these is that this method is limited only to patients with a sinus rhythm presenting with a VPB and characteristics which allow for HRT calculation. An ECG strip, including a VPB with neighbouring 20 RR intervals free of artefacts and other premature beats, is required for HRT analysis. Additionally, as it is considered that only a VPB provoking a correspondingly long compensatory pause may trigger the classical biphasic HRT reaction, different algorithms were applied to exclude interpolated VPBs [2]. Therefore a high percentage of patients (ranging from 20% to 40%) may be encountered in whom, despite the presence of sinus rhythm and a VPB detected on Holter monitoring, HRT analysis cannot be performed because of the elimination of all VPBs by filtering algorithms. Nevertheless, as documented in the ISAR study, patients with no VPBs on Holter monitoring had similar survival rates as those with HRT0 (both parameters normal) [17].

Similarly, no agreement exists on the number of VPBs required for proper HRT analysis. As proposed by the authors of the method, at least one VBP is sufficient. However, data exist indicating that HRT parameter values strongly depend on the number of VPBs as well as the mean heart rate [31, 38]. Significantly higher values of TS were observed in patients with fewer than 10 VPBs and in those with a lower heart rate. Whether this is due to the fact that patients with fewer VPBs or a lower heart rate really present a lower risk of death or whether it is a purely mathematical association is not clear.
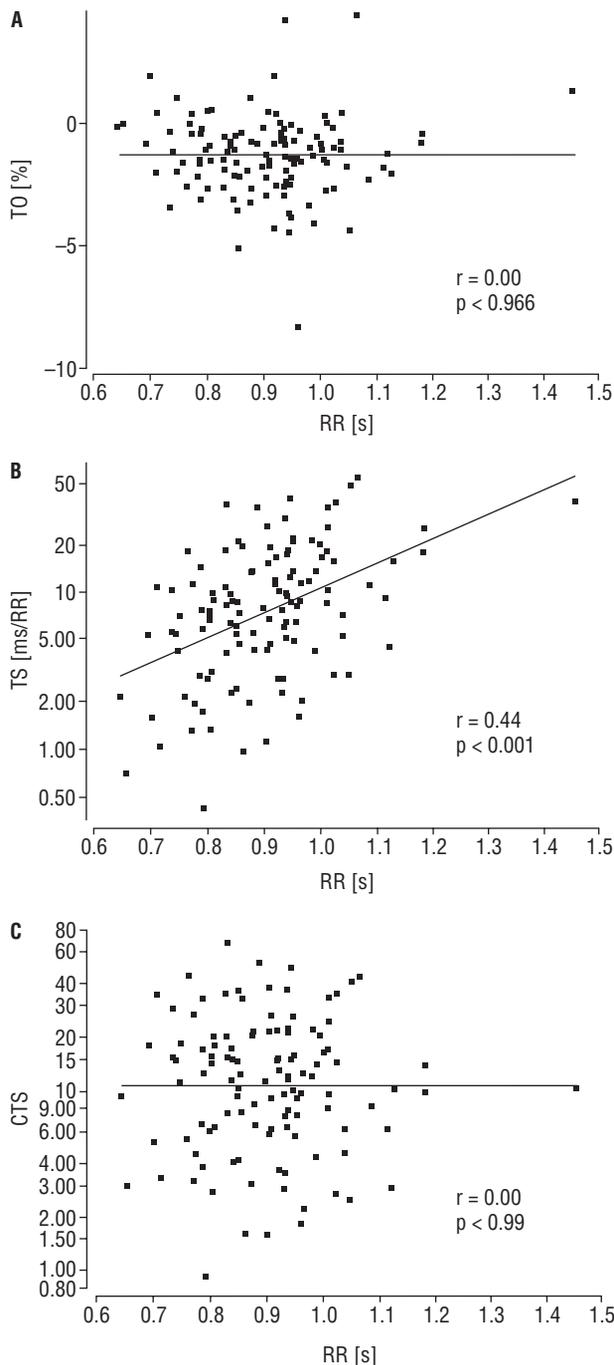
Figure 5. Heart rate turbulence parameters and heart rate. Relationship between mean heart rate (expressed as mean RR) and turbulence onset (TO) (**A**), turbulence slope (TS) (**B**) and corrected turbulence slope (CTS) (**C**) [From: Cygankiewicz I et al. Relationship between heart rate turbulence and heart rate, heart rate variability, and number of ventricular premature beats in coronary patients. J Cardiovasc Electrophysiol, 2004; 15: 731–737].

Therefore we suggest that HRT should only be calculated for stratification purposes in patients with more than 10 VPBs on Holter monitoring.

Whether HRT should be corrected for heart rate is a matter of debate. Our own data indicate that there is a significant correlation between TS and heart rate, indicating the need for such correction. It is difficult to propose a universal correction but one could consider a population-based correction as an option (Fig. 5).

In summary, heart rate turbulence was established as effective method predicting mortality in patients with cardiovascular disorders. By virtue of combining predictive value of frequent premature ventricular beats with predictive value of baroreflex sensitivity, heart rate turbulence indicates high-risk subset of patients who might require more aggressive treatement toward preventing sudden death (ICD) and/or preventing progression of heart failure. Current mostly research use of the method should be followed by clinical use based on standard algorithm posted on the HRT website.

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