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STATE-OF-THE-ART PAPER

Heart Rate Turbulence: Standards of Measurement, Physiological Interpretation, and Clinical Use

International Society for Holter and Noninvasive Electrophysiology Consensus

Axel Bauer, MD,* Marek Malik, PHD, MD, FACC,† Georg Schmidt, MD,* Petra Barthel, MD,* Hendrik Bonnemeier, MD,‡ Iwona Cygankiewicz, MD, PHD,§ Przemyslaw Guzik, MD, PHD,‖ Federico Lombardi, MD,¶ Alexander Müller, DIPL-ING (FH),* Ali Oto, MD, FACC,# Raphael Schneider, DIPL-ING (FH),* Mari Watanabe, MD, PHD,** Dan Wichterle, MD, PHD,†† Wojciech Zareba, MD, PHD, FACC§

Munich and Lübeck, Germany; London, United Kingdom; Rochester, New York; Poznan, Poland; Milan, Italy; Ankara, Turkey; St. Louis, Missouri; and Prague, Czech Republic

This consensus statement has been compiled on behalf of the International Society for Holter and Noninvasive Electrophysiology. It reviews the topic of heart rate turbulence (HRT) and concentrates on technologies for measurement, physiologic background and interpretation, and clinical use of HRT. It also lists suggestions for future research. The phenomenon of HRT refers to sinus rhythm cycle-length perturbations after isolated premature ventricular complexes. The physiologic pattern of HRT consists of brief heart rate acceleration (quantified by the so-called turbulence onset) followed by more gradual heart rate deceleration (quantified by the so-called turbulence slope) before the rate returns to a pre-ectopic level. Available physiologic investigations confirm that the initial heart rate acceleration is triggered by transient vagal inhibition in response to the missed baroreflex afferent input caused by hemodynamically inefficient ventricular contraction. A sympathetically mediated overshoot of arterial pressure is responsible for the subsequent heart rate deceleration through vagal recruitment. Hence, the HRT pattern is blunted in patients with reduced baroreflex. The HRT pattern is influenced by a number of factors, provocations, treatments, and pathologies reviewed in this consensus. As HRT measurement provides an indirect assessment of baroreflex, it is useful in those clinical situations that benefit from baroreflex evaluation. The HRT evaluation has thus been found appropriate in risk stratification after acute myocardial infarction, risk prediction, and monitoring of disease progression in heart failure, as well as in several other pathologies.
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The International Society for Holter and Noninvasive Electrophysiology (ISHNE) charged the authors of this text with reviewing the topic of heart rate turbulence (HRT) and providing a written consensus on the standards of measurement, physiologic interpretation, and clinical use of HRT. Consequently, this text is divided into 3 main parts corresponding to the charge given by the Society.

From *Deutsches Herzzentrum and 1. Medizinische Klinik der Technischen Universität München, Munich, Germany; †Division of Cardiac and Vascular Sciences, St. George's, University of London, London, United Kingdom; ‡2nd Department of Internal Medicine, University of Lübeck, Lübeck, Germany; §Heart Research Follow-up Program, University of Rochester, Rochester, New York; ‖University School of Medicine, Poznan, Poland; ¶Cardiology, San Paolo Hospital, University of Milan, Milan, Italy; #Department of Cardiology, Hacettepe University, Ankara, Turkey; **St. Louis University School of Medicine, St. Louis, Missouri; and the ††Institute for Clinical and Experimental Medicine and 1st Faculty of Medicine, Charles University, Prague, Czech Republic. Dr. Schmidt holds a patent on heart rate turbulence.

Drs. Bauer, Malik, and Schmidt compose the Writing Committee on behalf of ISHNE Study Group.

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The Phenomenon of HRT

Concept of HRT. The term HRT describes short-term fluctuations in sinus cycle length that follow spontaneous ventricular premature complexes (VPCs) (1). In normal subjects, sinus rate initially briefly accelerates and subsequently decelerates compared with the pre-VPC rate, before returning to baseline (Fig. 1). A similar pattern can also be induced by pacing, either by programmed ventricular stimulation or by an implanted device such as a cardiac defibrillator (2–5).

Abbreviations and Acronyms

APC = atrial premature complex
HRT = heart rate turbulence
HRV = heart rate variability
LVEF = left ventricular ejection fraction
MI = myocardial infarction
SBP = systolic blood pressure
TO = turbulence onset
TS = turbulence slope
VPC = ventricular premature complex

Quantification and measurement of HRT. Following singular VPCs, the HRT pattern is frequently masked by heart rate variability (HRV) of other origins. Thus, averaging responses to a number of VPCs is needed to characterize the pattern accurately. Consequently, HRT is usually assessed from Holter recordings as an average response to VPCs over longer periods (e.g., 24 h). From such recordings, the so-called VPC tachogram is constructed, aligning and averaging the R-R interval sequences surrounding isolated VPCs. These sequences include at least 2 sinus rhythm R-R intervals before VPCs, the coupling interval and compensatory pause, and at least 15 subsequent sinus R-R intervals. The average needs to include a sufficient number of VPCs (e.g., >5) for reliable construction of the VPC tachogram. Studies involving only very short Holter recordings may not lead to meaningful results (6).

Two phases of HRT, the early sinus rate acceleration and late deceleration, are quantified by 2 parameters termed turbulence onset (TO) and turbulence slope (TS). Turbulence onset is calculated as:

$$TO = \frac{(RR_1 + RR_2) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})} \times 100 \quad [\%]$$

where RR_{-2} and RR_{-1} are the 2 R-R intervals immediately preceding the VPC coupling interval, and RR_1 and RR_2 are 2 R-R intervals immediately following the compensatory pause (Fig. 2). Turbulence slope is defined as the maximum positive regression slope assessed over any 5 consecutive sinus rhythm R-R intervals within the first 15 sinus rhythm R-R intervals after the VPC (Fig. 2).

Hence, in normal subjects, the initial brief acceleration of sinus rate after the VPC is characterized by negative TO, and the subsequent rate deceleration is characterized by positive TS (Fig. 2).

Other parameters characterizing the HRT pattern have also been proposed (7–11) but none was found to improve the HRT description by TO and TS meaningfully.

Analytical settings. To eliminate errors in Holter analysis and to exclude interpolated VPCs (see the Physiologic Background and Pathophysiology of HRT section), HRT calculations are limited to VPCs with prematurity >20% and a compensatory pause of >120% of the mean of the 5 last sinus rhythm intervals preceding the VPC. In actual studies, TO has also been calculated from tachograms surrounding individual VPCs and subsequently averaged, which leads to similar values as when using the averaged tachogram. Turbulence slope always needs to be calculated from the averaged tachogram. (By eliminating the R-R variability due to other sources, averaging also decreased the TS value with increasing number of VPCs.)

Filtering of R-R interval sequence is also recommended to exclude VPC tachograms containing very short (e.g., <300 ms) or very long (e.g., >2,000 ms) R-R intervals or to include substantial (e.g., >200 ms) beat-to-beat R-R interval difference or substantial difference (e.g., >20%) from the average of preceding (e.g., 5) sinus R-R intervals.

Although lower electrocardiographic sampling frequencies reduce the temporal resolution of R-R intervals, neither

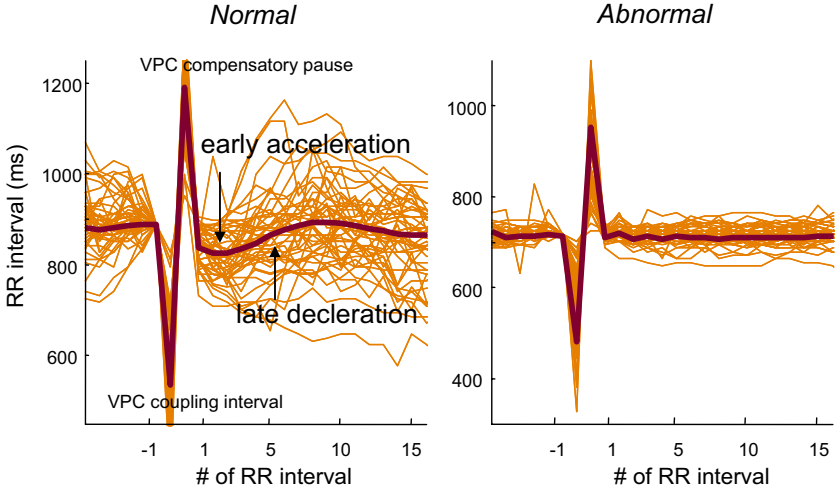

Figure 1 VPC Tachograms

Ventricular premature complex (VPC) tachograms showing normal **(left)** and abnormal **(right)** heart rate turbulence (HRT). HRT is composed of the transient acceleration phase of heart rate (R-R interval shortening) immediately after the compensatory pause followed by a subsequent and gradual deceleration phase (R-R interval prolongation). **Orange curves** show single VPC tachograms. **Bold brown curves** show the averaged VPC tachogram over 24 h.

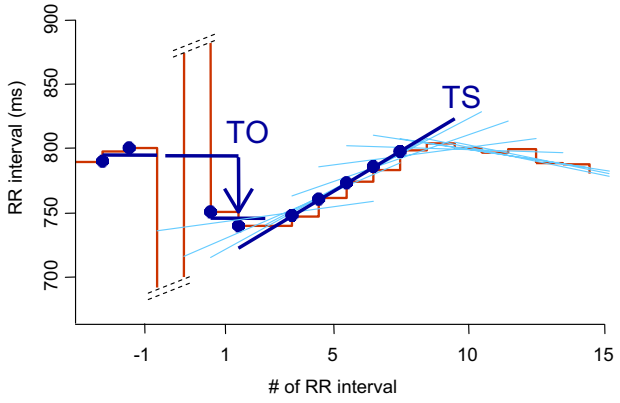

Figure 2 **HRT Calculation**

Calculation of the HRT parameters turbulence onset (TO) and turbulence slope (TS). Turbulence onset is the relative change of R-R intervals **(red lines)** from before to after the VPC. Turbulence slope is the slope of the steepest regression line fitted over the sequences of 5 consecutive sinus rhythm R-R intervals within the 15 R-R intervals after the VPC. The **light blue lines** are the 11 possible regression lines. The **dark blue line** is the steepest one used for TS calculation. Abbreviations as in Figure 1.

TO nor TS are significantly affected unless the sampling rate falls below 50 Hz.

Physiologic Background and Pathophysiology of HRT

The relevant physiological mechanisms of HRT have been extensively studied and reviewed (12–17). Already in early studies, it was hypothesized that the initial heart rate acceleration is triggered by transient vagal inhibition in response to the missed baroreflex afferent input due to hemodynamically inefficient ventricular contraction, and a sympathetically mediated overshoot of arterial pressure is responsible for the subsequent heart rate deceleration through vagal recruitment (18). Although this hypothesis was initially mainly speculative, it was substantiated by later studies.

Physiologic and pathophysiologic considerations. HRT shares some physiological mechanisms with ventriculophasic sinus arrhythmia in which ventricular contractions influence the periods of sinus nodal discharges even in the absence of retrograde atrioventricular conduction (19–21). Arterial baroreceptor activation by ventricular ejection was proposed to be responsible for the reflex slowing of the sinus nodal rate. This interpretation is supported by the latency and dynamics of the effect compatible with vagal action (22–24), as well as by a correlation between intervals between consecutive P waves and invasively measured blood pressure (25).

However, the trigger of HRT is not the same as that of ventriculophasic sinus arrhythmia. Ventriculophasic arrhythmia is associated with atrioventricular block and reflects the hemodynamic impact of idioventricular contractions, but VPCs during normal sinus rhythm have instant deleterious effects on cardiac output and produce different hemodynamic and neural reflex responses. Although the early positive chronotropic effect of VPC was reported already some 3 decades ago (26), both early positive and late negative chronotropic effects of VPC were only described as the components of HRT (1).

The early acceleration of heart rate during HRT is consistent with vagal withdrawal in response to the missed baroreflex afferent input due to hemodynamically inefficient ventricular contraction. This hemodynamic deficiency is caused by several factors including incomplete electrical restitution, a short period of diastolic filling, missing atrial kick, reduced contractility, higher afterload at the time of VPC, and less synchronized ventricular contraction. Because of all of these factors, systolic blood pressure (SBP) produced by VPC is considerably lower than that of normal sinus beats (17).

Both ineffective contraction and compensatory pause also cause diastolic pressure reduction. Moreover, SBP produced by the first post-VPC sinus beat is usually lower (in subjects with normal left ventricular function) compared with the pre-VPC level (17). Hence, not only the instant hemodynamic effect of VPC but also SBP reduction during the subsequent beat activate aortic and carotid baroreceptors causing heart rate increase due to vagal inhibition.

At the same time, transient relative hypotension stimulates the sympathetic arc of autonomic nervous system. The post-VPC drop of diastolic blood pressure initiates a surge of muscle sympathetic nerve activity, which is immediately followed by a period of sympathetic silence (27–31). The magnitude of this burst, which cannot be observed earlier than at the time of the first post-VPC beat, provokes noradrenaline release in perivascular sympathetic endings, leading to an increase of peripheral vascular resistance. It also depends on the blood pressure starting level, VPC coupling interval, post-VPC diastolic pressure fall, baroreflex sensitivity, and basal firing rate of muscle sympathetic nerve activity. Because the latency of hemodynamic response to sympathetic nerve stimulation is approximately 5 s (32), the early heart rate acceleration of HRT is not likely mediated by sympathetic efferent arm activation.

On the contrary, both branches of the autonomic nervous system contribute to the late HRT phase characterized by gradual return of SBP and heart rate to pre-extrasystolic levels. Under physiologic conditions, a significant overshoot of both SBP and heart rate reduction below the baseline values are observed peaking around the 8th post-VPC beat. It is now understood that this late overcompensation is primarily caused by an early sympathetic activation with delayed vasomotor response as well as by vagal activation (Fig. 3) (33,34).

Early heart rate acceleration and late deceleration after single VPCs parallel the corresponding SBP changes with fairly constant delay the pattern of change being fully compatible with baroreflex physiology (3,17,35–38). During

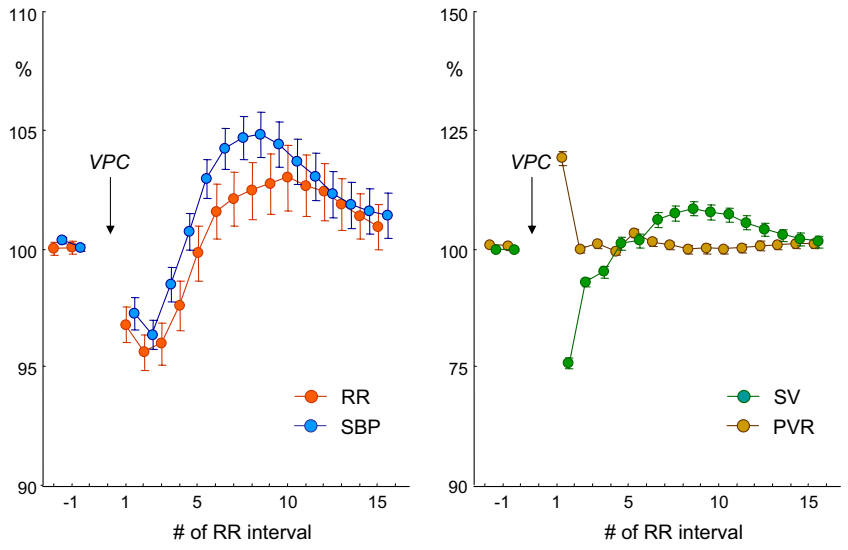

Figure 3 **Normal Post-Ectopic Blood Pressure and R-R Interval Changes**

Averaged profiles (mean ± 95% confidence interval) of R-R intervals, systolic arterial blood pressure (SBP), stroke volume (SV), and peripheral vascular resistance (PVR) after VPCs expressed in relative numbers (with 100% corresponding to pre-VPC value) in patients with normal left ventricular function. R-R intervals numbered −1 and −2 indicate those preceding the VPC; the first 2 post-VPC sinus R-R intervals are numbered 1 and 2. Modified, with permission, from Wichterle et al. (17). Abbreviations as in Figure 1.

the late HRT period, the change of SBP appears constant; thus, HRT slope rather than post-VPC blood pressure dynamic seems to reflect baroreflex sensitivity (35). Both TO and TS were found to correlate with baroreflex sensitivity assessed by the phenylephrine method (39,40). Likewise, post-VPC heart rate patterns simulated by mathematical model of hemodynamics with baroreceptor feedback (with preserved and blunted baroreflex sensitivity) were similar to those observed clinically (41).

Both HRT characteristics are significantly influenced by left ventricular ejection fraction (LVEF) (42). Compared with healthy control patients, HRT indexes are also significantly depressed in patients with congestive heart failure (43) as well as in the presence of structural heart disease with preserved left ventricular function (37,44). Prominent post-extrasystolic potentiation interferes indirectly with the magnitude of HRT dynamics (45). Initial vagal inhibition is promptly upturned and subsequent sympathetic activation (and the dynamics of peripheral vascular resistance) attenuated (17). For all of these reasons, the late overshoot of SBP and R-R intervals after VPC might be missing. Thus, in patients with structural heart disease, both depressed vagal and sympathetic modulations and, indirectly, enhanced post-extrasystolic potentiation all account for attenuated HRT (Fig. 4).

The potentiation of the first post-ectopic beat may trigger electrical alternans with rapid time decay. This is caused by a combination of alternation in hemodynamics variables (end-diastolic pressure and volume) and inotropic state due to alternation of calcium turnover (45). Post-VPC alternans phenomenon was reported in one-third of patients with congestive heart failure (35).

A number of studies investigated the influence of basal autonomic activity on HRT. Normal HRT can practically be abolished by vagal blockade with atropine (2,36,46), but no significant HRT change was observed after beta-blockade with esmolol (36). This agrees with beta-blocker administration not leading to a complete sympathetic blockade as well as acting predominantly on sinus node discharge modulations, while being limited on peripheral vascular resistance. As a result, sympathetically mediated overshoot of SBP in the late HRT phase is not significantly affected by beta-blockade. Consequently, the late heart rate deceleration due to preserved vagal response remains unchanged. Indeed, blood pressure dynamics were not significantly changed after vagal blockade (46), but are significantly blunted in patients with sympathetic neurocirculatory failure and abolished during trimethaphan-induced ganglion blockade in healthy subjects (47).

HRT initiated by premature ventricular paced beats has also been investigated (48). HRT responses were found to be very similar when triggered by spontaneous VPCs or paced beats. Moreover, both the magnitude and the duration of hypotension during short ventricular train drives were highly correlated with HRT heart rate acceleration, confirming the role of sympathetic activation and vagal withdrawal in initial rate acceleration of a standard HRT pattern. This also confirms the importance of a full compensatory pause following isolated VPCs for HRT initiation.

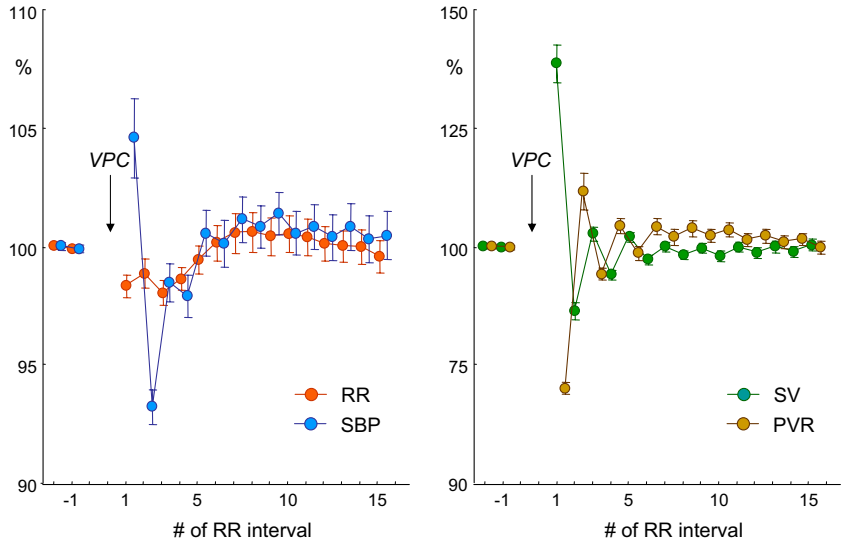

Figure 4 **Post-Ectopic Blood Pressure and R-R Interval Changes in LV Dysfunction**

Profiles of R-R intervals, systolic arterial blood pressure (SBP), stroke volume (SV), and peripheral vascular resistance (PVR) after VPCs in patients with left ventricular (LV) dysfunction. **Symbols and layout** as in Figure 3. Note the post-extrasystolic potentiation of SBP after VPC with subsequent mechanical and electrical alternans. Modified, with permission, from Wichterle et al. (17). Abbreviations as in Figure 1.

Theoretically, the late post-VPC increase in SBP might also be attributed to a transient increase of cardiac output due to purely nonautonomic mechanisms. However, this possibility is unlikely because post-extrasystolic potentiation of contractility has a rapid exponential decay (49–51). Also, no meaningful dynamics of stroke volume in the late phase of HRT were observed when the beat-by-beat stroke volume and peripheral vascular resistance were computed by a nonlinear self-adaptive model of aortic input impedance (17).

Similar to ventriculophasic sinus arrhythmia, other nonautonomic but unlikely mechanisms might also be considered for the early phase of HRT. A positive chronotropic response has been induced by several mechanisms including mechanical stretch of sinus nodal tissue in isolated perfused hearts (52) or of sinus node (53), atrial pressure increase in isolated denervated hearts (54,55), and perfusion pressure reduction of the sinus nodal artery (56). Similarly, it was shown that the positive chronotropic effect produced by traction on the sinus nodal region or on atrial appendages is purely sympathetically mediated (57,58). Presently available data do not support any other retrograde hemodynamic and/or mechanical effects of VPCs on the atria unrelated to the autonomic reflex arch.

Factors affecting HRT. Gender does not influence HRT in healthy control patients (59) or post-infarction patients (60). Increasing age is associated with a decrease in HRT (61), which is consistent with similar reports concerning most measures of autonomic control. Interestingly, however, pre-pubertal children have lower TS than children during puberty, paralleling maturation of the autonomic nervous system (62).

HRT is reduced at a high heart rate (7,11,63–65). The mechanisms responsible for heart rate modulation of HRT are not completely understood. Two possible and nonexclusive explanations have been proposed (66). First, the association of HRT and heart rate can be interpreted as a consequence of shared sympathovagal modulation. Second, heart-rate dependency of HRT may reflect intrinsic sinus nodal properties, specifically the nonlinear relationship between vagal neural activity and the rate of diastolic depolarization of pacemaker cells (67). These observations lead to the possibility of correcting HRT indexes for heart rate (65) but presently available data offer no practical guidance for such a correction.

There is a modest correlation between HRT indexes and HRV measures suggesting other common intrinsic modulators (39,44,65). Presence of circadian rhythm was demonstrated in patients with coronary artery disease and parallels circadian pattern of R-R intervals and HRV indexes (68–70).

The baroreflex source of HRT is in agreement with stronger HRT responses to more premature, and thus less hemodynamically efficient VPCs with longer compensatory pauses (63). The effects of VPC coupling interval on HRT were also directly addressed in 2 pacing studies (7,71) with somewhat conflicting results. In the earlier study, a relationship between VPC coupling interval and HRT parameters was observed only individually but not in the pooled population. In the later study, the correlation between TS

and TO and normalized coupling interval was negative and positive, respectively, in full agreement with HRT physiologic background.

A typical HRT pattern is also observed after short runs of nonsustained ventricular tachycardia (72). The magnitude of these fluctuations is greater than after isolated VPCs, which is again in agreement with the physiologic mechanisms.

The site of VPC origin has no influence on HRT (73), whereas retrograde atrial depolarization, which may reset the sinus node, has rather the opposite effect to the post-VPC autonomic modulation of heart rate and may thus change the dynamics of subsequent sinus R-R intervals (74).

Atrial HRT. A characteristic response of sinus periods is observed not only after ventricular but also after atrial premature complexes (APCs) (71,73,75–78). However, R-R interval dynamics after APCs are different from that after VPCs. Heart rate abruptly decelerates after APCs with a prompt return to baseline, which is followed by subsequent and delayed transitory heart rate deceleration. Initial abrupt deceleration is likely caused by sinus nodal resetting by APCs with subsequent recovery of sinus node automaticity (79). This mechanism overwhelms the autonomic component of the early acceleration phase of HRT. The late deceleration of heart rate after APCs is believed to result from a baroreflex response to blood pressure dynamics following the premature contraction, in the same way as in VPC-triggered HRT. This explanation is supported by significant intra-individual correlation between TS after APCs and VPCs in pacing (71) and Holter studies (75–77), by the inverse relationship between TS and APCs coupling intervals (76), and by the correlation between TS after APCs and phenylephrine baroreflex sensitivity (77).

However, the magnitude of TS after APCs is significantly lower than that after VPCs (76). Two explanations have been proposed. First, physiological ventricular depolarization preceded by atrial contraction produces hemodynamically more effective contraction with a shorter compensatory pause than after VPC. Consequently, APCs lead to less pronounced blood pressure perturbations and baroreflex responses. Second, the magnitude of TS after VPCs is determined not only by the intensity of the late vagal activation but also by the extent of initial heart rate acceleration. Therefore, the discordant behavior of heart rate in both HRT phases augments TS after VPCs. Also, concordant early and late heart rate deceleration might be artificially reducing TS after APCs (76).

Modifications of HRT by specific interventions. In patients without structural heart disease, HRT was reportedly unaffected by recently initiated beta-blockade (36). Different effects of selective and nonselective antiadrenergic therapy on HRT were reported (80). In a randomized study comparing metoprolol ($beta_1$-blocker) and carvedilol ($beta_1$-, $beta_2$-, $alpha_1$-blocker) in the subacute phase of myocardial infarction (MI), there was a trend toward lower TO in the carvedilol group and significantly higher TS in the metoprolol group, indicating differential effects of additional $alpha_1$-adrenoceptor blockade on baroreceptor response.

Chronic beta-blockade has been suggested to restore abnormal HRT. In a small uncontrolled series of patients with advanced congestive heart failure receiving titrated atenolol therapy, TS was significantly elevated within a 3-month follow-up, whereas no alterations were observed in TO (81). However, the observation was made during a period of a significant cardiac function recovery when concomitant medication for congestive heart failure was also administered. Hence, the selective role of beta-blockers in improving HRT in congestive heart failure remains unclear. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have also been shown to increase significantly both HRT components in advanced congestive heart failure (82,83).

The effects of chronic beta-blockade on HRT after MI have recently been investigated in 2 large longitudinal trials assessing HRT in the subacute phase and 12 months after MI in patients with beta-blocker treatment (>90%) optimized according to the present clinical guidelines (84,85). In both studies, TS remained unchanged within the observation period. Interestingly, although TO remained unaffected in the subpopulation with 100% revascularization therapy and >80% concomitant angiotensin-converting enzyme inhibitor medication (84), it significantly decreased in the remainder of the population (85).

The effects of muscarinic receptor blockade with atropine were also investigated (2,36,86). In patients without structural heart disease, atropine caused a significant TS decrease and a significant TO increase. These effects of atropine were observed both with and without concomitant beta-blocker therapy, confirming that HRT is critically dependent on reflex parasympathetic activity.

Data on the HRT effects of amiodarone are sparse. In the only presently available study in dilated cardiomyopathy (87), all patients on amiodarone had abnormal TO, and almost 40% of patients with abnormal TO had also abnormal TS. However, it is unclear whether these abnormalities are due to direct amiodarone effects, or whether the investigated patients on amiodarone had more advanced cardiac dysfunction reflected by blunted HRT.

Successful coronary reperfusion was found associated with a significant TS increase and TO decrease. The changes appeared within 2 h after reperfusion without further significant alterations (Fig. 5) (88). In patients with incomplete reperfusion, however, HRT measures were unaffected by the procedure.

Traditional coronary artery bypass grafting procedure requires clamping of the aorta with extracorporeal circulation. This may interfere with cardiac autonomic control through various mechanisms. Thus, not surprisingly, significant HRT blunting was reported during the post-operative period (89). Only after 1 year, HRV parameters and TO

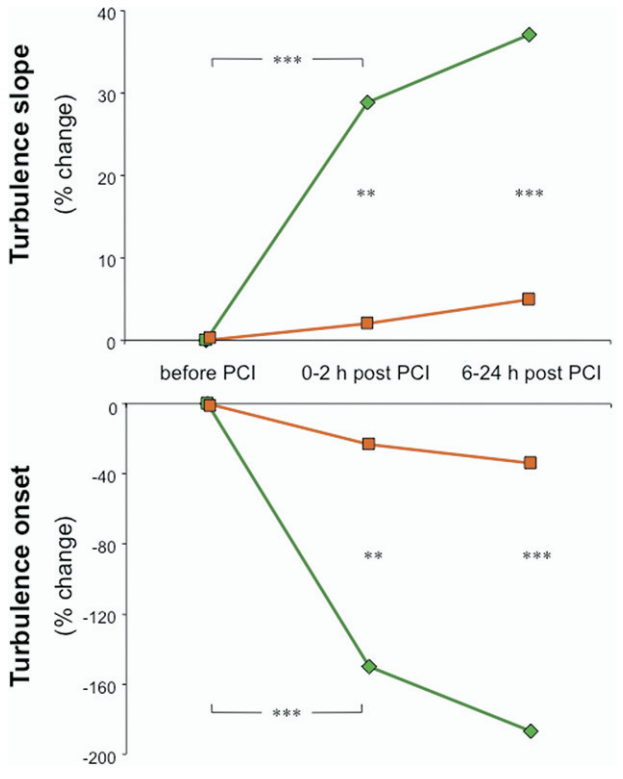

Figure 5 HRT Changes After PCI

Percentage change of turbulence slope and turbulence onset during the first 2 h after percutaneous coronary intervention (PCI) and during hours 6 to 24 after PCI in patients with complete reperfusion (Thrombolysis In Myocardial Infarction [TIMI] risk score III, **green**) and incomplete reperfusion (TIMI II, **red**) after PCI for acute myocardial infarction. **p < 0.01; ***p < 0.001. Abbreviations as in Figure 1.

returned to pre-operative values while TS remained significantly attenuated. Unfavorable post-operative tachycardia and impairment of baroreflex sensitivity caused by mechanical damage of autonomic nervous fibers by aorta clamping might be considered the underlying mechanism, despite successful revascularization and improvement in blood supply to the heart.

Clinical Use of HRT

Normal and abnormal values. Four studies have reported TO and TS values in healthy volunteers (59,75,90,91). In these studies, mean TO ranged from −2.7% to −2.3% and mean TS ranged from 11.0 to 19.2 ms/R-R interval.

In most clinical studies, however, TO <0% and TS >2.5 ms/R-R interval are considered normal. These originally proposed cutoff values were validated in the data of 3 large post-infarction studies (totaling 2,646 patients) (1,92).

The TO and TS variables can be used as separate clinical variables or in a combination. In risk stratification studies (see the subsequent section), HRT values are usually classified into 3 categories: 1) HRT category 0 means TO *and* TS are normal; 2) HRT category 1 means 1 of TO *or* TS is abnormal; and 3) HRT category 2 means both TO *and* TS are abnormal. If HRT cannot be calculated because no or too few suitable VPC tachograms are found in the recording, patients who are otherwise in sinus rhythm are classified as HRT category 0 (92).

Risk stratification after MI. In large post-infarction studies, the prevalence of abnormal HRT ranges from 22% to 31% for HRT category 1 and from 8% to 13% for HRT category 2, depending on the acute treatment (1,92). HRT is also reduced in patients suffering from coronary artery disease without a history of previous MI (44). This reduction was shown to be independent of clinical covariates including left ventricular dysfunction and age.

Clinical evidence of HRT being a powerful post-MI risk predictor comes from retrospective analyses of 6 large-scale studies (1,39,68,93) and from 2 prospective studies (92,94), both of which have been specifically designed to validate the prognostic value of HRT in post-MI patients receiving state-of-the-art treatment. The retrospective analyses included the MPIP (Multicenter Post-Infarction Program) trial (1,95), the placebo arm of the EMIAT (European Myocardial Infarction Amiodarone Trial) (1,96), the ATRAMI (Autonomic Tone and Reflexes after Acute Myocardial Infarction) trial (39,97), the CAST (Cardiac Arrhythmia Suppression Trials) I and II (68,98,99), and the FINGER (Finland and Germany post-infarction trial) (92,93). The prospective studies were the ISAR (Innovative Stratification of Arrhythmic Risk) HRT trial (92) and the REFINE (Risk Estimation Following Infarction Noninvasive Evaluation) trial (94). Details of HRT post-infarction studies are shown in Table 1. All of these studies, with the exception of CAST data analysis, used the same cutoff values for dichotomization of TO and TS, that is, 0% and 2.5 ms/R-R interval, respectively. In all of these studies, impaired HRT was the strongest electrocardiographic risk predictor. On univariate analysis, patients with HRT category 2 (i.e., TO ≥0% and TS ≤2.5 ms/R-R interval) had a 4.4- to 11.3-fold risk of subsequent death within 2 years compared with patients with normal HRT. The risk of subsequent deaths associated with HRT category 2 was consistently similarly high as in patients with left ventricular dysfunction. Figure 6 illustrates the cumulative 2-year mortality rates for the patients of the MPIP, EMIAT, and ISAR-HRT populations stratified by HRT categories. The prognostic value of HRT was independent of other predictors such as LVEF, HRV, and arrhythmias. Multivariate relative risks of HRT category 2 adjusted for known risk variables ranged from 3.2 to 5.9. Recently, the REFINE trial investigated the capacity of combined assessment of autonomic tone and cardiac electrical substrate to predict the development of serious outcomes after MI (94). HRT category 1 combined with abnormal T-wave alternans assessed 10 to 14 weeks after MI reliably predicted cardiac death or cardiac arrest, death from any cause, and fatal or nonfatal cardiac arrest.

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Table 1 Studies (or Substudies) Investigating HRT as a Post-Infarction Risk Predictor

	MPIP	EMIAT	ATRAMI	CAST	ISAR-HRT	FINGER	REFINE
Number of patients	577	614	1,212	744	1,455	2,130	322
Inclusion criteria*	MI ≤4 weeks Age ≤70 yrs	MI ≤4 weeks Age ≤75 yrs LVEF ≤40%	MI ≤4 weeks Age ≤80 yrs	MI ≥6 VPC/h	MI ≤4 weeks Age ≤75 yrs	MI ≤4 weeks Age ≤75 yrs	MI LVEF <50%
Follow-up (months)	22	21	20	55	22	33	47
End point	Mortality	Mortality	Cardiac mortality†	Mortality	Mortality	Sudden death	Cardiac death
End points reached (%)	13	14	4	29‡	5	2	9
Treatment of acute MI	None	60% lysis	63% lysis	28% lysis	90% PCI 6% lysis	70% PCI 14% lysis	45% PCI 21% lysis
Mean LVEF (%)	45	30	49	37	56	Not specified	47
Beta-blockers (%)	55	32	20§	30	93	94	92
Univariate analysis							
HRT category 2	5.0 (2.8–8.8)	4.4 (2.6–7.5)	6.9 (3.1–15.5)	Not specified	11.4 (5.7–22.8)	4.6 (2.6–8.1)‖	2.9 (1.1–7.5)¶
LVEF ≤30%	4.0 (2.5–6.4)	2.2 (1.4–3.5)	4.7 (2.6–8.3)	Not specified	7.1 (4.2–12.1)	4.5 (2.5–8.0)#	3.3 (1.4–7.6)
Multivariate analysis							
HRT category 2	3.2 (1.7–6.0)	3.2 (1.8–5.6)	4.1 (1.7–9.8)	20.4 (10.2–30.6)**	5.9 (2.9–12.2)	2.9 (1.6–5.5)	Not specified
LVEF ≤30%	2.9 (1.8–4.9)	1.7 (1.1–2.7)	3.5 (1.8–7.1)	Not specified	4.5 (2.6–7.8)	Not specified	Not specified

*Sinus rhythm was an inclusion criterion in all studies. †Cardiac mortality included fatal and nonfatal cardiac arrest. ‡Cumulative mortality rate only presented for total study population of CAST after 5 years. §At time of Holter recording. ‖Relative risks presented for turbulence slope ≤2.5 ms/R-R interval. ¶HRT category ≥1 versus 0 tested; HRT was assessed 10 to 14 weeks after MI. #Left ventricular ejection fraction was dichotomized at 35%. **The logarithm of turbulence slope was corrected for heart rate and VPC count (optimized in CAST data). Data for the MPIP (Multicenter Post-Infarction Program) and EMIAT (European Myocardial Infarction Amiodarone Trial) studies are from Schmidt et al. (1), for the ATRAMI (Autonomic Tone and Reflexes after Acute Myocardial Infarction) study from Ghuran et al. (39), for the CAST I and II (Cardiac Arrhythmia Suppression Trials) studies are from Hallstrom et al. (68), for the ISAR-HRT (Innovative Stratification of Arrhythmic Risk HRT) study from Barthel et al. (92), for the FINGER (Finland and Germany post-infarction trial) study from Makikallio et al. (93), and for the REFINE (Risk Estimation Following Infarction Noninvasive Evaluation) study from Exner et al. (94).
HRT = heart rate turbulence; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; VPC = ventricular premature complex.

The present data do not allow for identifying the optimum time after acute MI for HRT assessment. For logistic reasons, Holter recordings have mostly been made during the second week after the index infarction (1,39,68,92,93). However, 2 studies raised questions about the optimum time for HRT assessment after MI (94,100). In a comparably small Turkish study (100), HRT assessed within hours after hospital admission was shown to be a highly significant risk predictor. In the REFINE study, however, HRT-based risk assessment months after MI was more effective than risk assessment early after MI (94). From the practical point of view, HRT assessment prior to hospital discharge seems to be a reasonable standard in survivors of acute MI.

HRT is mostly depressed during the acute phase of MI when the coronary artery is occluded, but recovers immediately if blood flow is restored by percutaneous coronary intervention (84,88). Turbulence slope remains constant up to 1 year after MI, but there are conflicting reports on TO changes over time (84,85). In a study of 416 post-infarction patients, TO improved 12 months after MI (85), but in a more recent study involving 100 patients, TO remained unchanged (84).

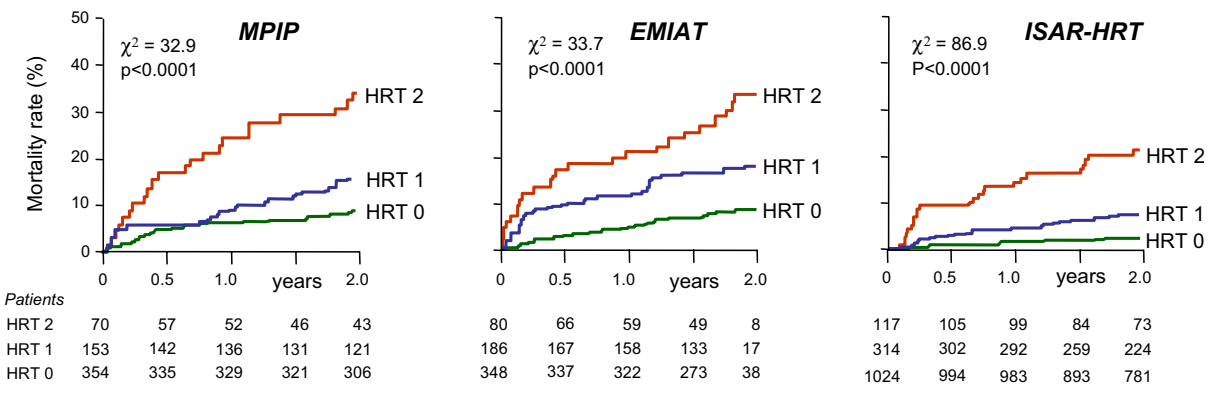

Figure 6 HRT Post-Infarction Risk Stratification

Cumulative mortality rates of patients stratified by HRT categories in the populations of MPIP (Multicenter Post-Infarction Program) **(left)**, EMIAT (European Myocardial Infarction Amiodarone Trial) **(middle)**, and ISAR-HRT (Innovative Stratification of Arrhythmic Risk HRT) studies **(right)**. The numbers of patients in the individual groups involved in the analyses at 0, 6, 12, 18, and 24 months are shown under each graph. Data for the MPIP and EMIAT studies are from Schmidt et al. (1) and for the ISAR-HRT study from Barthel et al. (92). Abbreviations as in Figure 1.

Persistent impairment of HRT after percutaneous coronary intervention in patients with incomplete reperfusion implies prolonged baroreflex impairment and is consistent with poor prognosis. In a recent study, when HRT was assessed within 24 h after early revascularization (mostly thrombolytic) therapy, blunted HRT in the acute phase of MI was a strong and independent predictor of long-term mortality (100). Thus, early assessment of HRT may be detecting pathological loss of reflex autonomic response due to incomplete reperfusion or severe microvascular dysfunction after percutaneous coronary intervention.

The HRT-based risk assessment was also reported for coronary artery bypass grafting. Although pre-operatively assessed HRT has been shown to be a good predictor of outcome (101), the surgery was found to be associated with a significant worsening of HRT parameters in the post-operative period (89). Predictive usefulness seems thus to be lost during the post-operative period.

Prognostic studies have consistently demonstrated that the HRT-based risk prediction is unaffected by beta-blocker therapy, regardless of whether beta-blocker medication was used infrequently (<20%, ATRAMI; 32%, MPIP) (1,39), moderately (45%, EMIAT) (1), or frequently (>90%, ISAR-HRT) (92), and independently from the frequency of reperfusion therapy and left ventricular function. This contrasts with most of the other mortality predictors after MI and in congestive heart failure for which data in patients on beta-blockers are presently sparse. The HRT-based risk assessment might therefore have an advantage in the beta-blocker era.

In most risk stratification studies, patient age was restricted at 70 to 75 years. Therefore, conclusions drawn from these studies cannot be easily extrapolated to older patients. Presently unpublished findings in the ISAR-HRT trial suggest that HRT loses prognostic power in elderly post-infarction patients (e.g., >80 years of age) (102). This is likely related to the physiologic age-related baroreflex decline.

HRT cannot be measured without VPCs in the Holter recording. In most studies, patients without VPCs have therefore been excluded from the analysis. However, patients without VPCs and otherwise in sinus rhythm have an equally good prognosis as do patients with normal HRT (92).

Little controversy exists about the length of the Holter recording used for HRT assessment. All studies that reported high predictive values of HRT used 24-h recordings. A retrospective analysis of HRT in the MADIT II (Multicenter Automatic Defibrillator Implantation Trial 2) that used only 10-min recordings showed the inappropriateness of shorter recordings (6).

Most post-infarction HRT studies (namely MPIP, EMIAT, CAST, and ISAR-HRT) used total mortality as the primary end point (1,68,92). The ATRAMI trial used the composite of fatal and nonfatal cardiac arrest (39). The FINGER trial was designed to assess the value of HRT in sudden cardiac death prediction (93). Because HRT was found to be a strong end point predictor in all of these studies, prognostic values of HRT do not seem to be exclusively associated with any specific mechanism of death, which is consistent with the predictive value of other autonomic markers.

In the ISAR-HRT trial, HRT category 2 alone yielded a positive predictive accuracy of 21% at a sensitivity level of 34% (92). These values were comparable with those yielded by LVEF ≤30% (23% and 27%, respectively) (92). As with other risk factors, risk prediction after MI can be substantially improved if HRT is combined with LVEF and other predictors such as QRS duration, presence of diabetes mellitus, or advanced age. The HRT-based risk prediction is also meaningfully powerful in post-MI patients with preserved ejection fraction (e.g., >30%). Although most of the statistical results of combinations of different variables are based on multivariate Cox models, score schemes might be more useful in clinical practice. Compared with HRT category 2 alone, combination with other predictors can increase sensitivity by 58% at a comparable level of positive predictive accuracy. Alternatively, positive predictive accuracy may be increased by 66% at a comparable level of sensitivity (92,103).

Risk prediction in heart failure. Neurohumoral activation with sympathetic overdrive and progressive hemodynamic deterioration are the main features of heart failure independent of etiology. Consequently, patients with congestive heart failure are known to have significantly impaired baroreflex sensitivity as well as reduced HRV. It is thus not surprising that a high percentage of patients with cardiomyopathies and/or heart failure also present with abnormal HRT (87). A recent analysis of the MUSIC (Muerte Subita e Insuficiencia Cardiaca [Sudden Death in Heart Failure]) trial reported strong correlations of TO and TS with the extent of heart failure (104). This may suggest the possibility of guiding pharmacological therapy in heart failure patients. The HRT assessment might become a useful tool for this purpose, because both TO and TS recover after effective pharmacological treatment (81,105).

Data on prognostic value of HRT in patients with congestive heart failure is limited. Two large studies (UK-Heart Trial and MUSIC study) investigated the prognostic role of HRT in patients with mild-to-moderate heart failure of ischemic and nonischemic etiology (106,107). In the UK-HEART (United Kingdom Heart Failure Evaluation and Assessment of Risk) trial, abnormal TS was found to be an independent predictor of heart failure decompensation (106). The MUSIC study confirmed prognostic value of TS in predicting heart failure death, and also suggested that abnormal TS predicts sudden death in congestive heart failure patients (107). The prognostic value of HRT in patients with heart failure seems to be strongly dependent on the underlying mechanism. Unpublished analyses of HRT in the EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study)

(108,109) and in the DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) (110,111) suggest that HRT is a powerful predictor of mortality in patients with post-MI heart failure.

On the contrary, in patients with nonischemic heart failure, HRT seems to have a minor role in predicting outcome. The largest series of patients with nonischemic heart failure in whom HRT was investigated comprised 242 patients with idiopathic dilated cardiomyopathy taken from the Marburg Cardiomyopathy database (87). In these patients, TO predicted transplant-free survival. However, neither TO nor TS predicted arrhythmic events. In patients included in the Frankfurt dilated cardiomyopathy database, HRT also failed to predict any arrhythmic events (112). In patients with hypertrophic cardiomyopathy, HRT did not differ from control subjects and was not associated with prognosis (113).

Other clinical potential and specific pathologies. Impaired HRT is found in diabetic patients, both with (42,60,114) and without previous MI (115,116). The HRT impairment is independent of apparent diabetic neuropathy but, as with the reduction of other autonomic markers, it reflects cardiac autonomic dysfunction. In a large post-infarction population, 14% of patients with diabetes mellitus had HRT category 2, twice the incidence in patients without diabetes mellitus (114). In diabetic patients suffering from MI, HRT is a particularly strong predictor of mortality (114,116).

Patients suffering from mitral valve prolapse have also impaired HRT compared with control patients (117). The finding is likely related to the underlying autonomic dysfunction rather than to hemodynamic alterations because impairment of HRT was not found in mitral regurgitation (117). In patients with mitral stenosis, TO was observed to be related to the severity of symptoms (118).

Turbulence slope measured at nighttime correlates significantly with the apnea-hypopnea index in patients with obstructive sleep apnea (119). This was not found for TO in the original study, but in a more recent study, both TO and TS were abnormal during apnea episodes (120).

Smaller studies investigated HRT in a large variety of pathologies ranging from Chagas' disease (121,122), children with dilated cardiomyopathy (123), children with adenotonsillar hypertrophy (124) and obesity (125). Among other findings, HRT was found to be impaired in patients with overt hyperthyroidism compared with control patients (126). After antithyroid treatment, TS normalizes while TO remains impaired, suggesting ongoing abnormalities of autonomic function. In depressed post-MI patients, HRT is impaired compared with nondepressed patients (127). In a small study, HRT was shown to predict restenosis after coronary intervention (128). The prognostic value of HRT in patients with congenital heart disease was recently evaluated in a heterogeneous study of 43 patients, 50% of whom had a systemic right ventricle (129). During follow-up of 27 ± 13 months, HRT category 2 indicated a 70-fold risk of a combined end point of death and successful resuscitation and was the strongest predictor on multivariate analysis. Surgical denervation abolishes HRT as suggested by a small study in 10 patients after heart transplantation (115). A recent study analyzed HRT in 29 patients with myotonic dystrophy type 1 (130). Turbulence onset (but not TS) was not only significantly impaired compared with control patients but also identified those patients who were inducible at electrophysiological testing.

Future Directions

Despite significant research progress of the HRT field, a number of issues (in addition to those already discussed) remain poorly understood and in need of further investigation.

Because of the need to obtain nominal 24-h Holter recordings for clinically meaningful HRT assessment, short-term pacing studies would have some practical appeal. Presently available data do not allow us to propose a gold-standard protocol for such studies although is seems obvious that they should include repeated ventricular extrastimuli with different coupling intervals. In patients with implanted defibrillators, frequent assessment of provoked HRT might also predict the likelihood of impending tachyarrhythmias (131,132).

Reproducibility data are lacking in most clinical populations. Practically, short-term day-to-day reproducibility in post-infarction patients and short- to long-term reproducibility in patients with stabilized congestive failure would be of clear interest.

Because of the importance of diabetic neuropathies, the possible value of HRT monitoring should also be assessed in diabetic patients without clinically manifested heart disease. The same applies to patients with metabolic syndromes in whom easily accessible autonomic monitoring would have obvious clinical potential.

Most importantly, however, prospective multivariate intervention (e.g., defibrillator) studies in post-MI patients, including not only HRT but a complete spectrum of established risk predictors are needed to reach a verified consensus on how independent risk factors should ideally be combined and practically used for the improvement of ejection fraction–based risk assessment that has many known shortcomings.

Conclusions

HRT is a recently recognized electrocardiographic phenomenon reflecting minute hemodynamic disturbance caused by a VPC. This disturbance is sufficient to induce a baroreflex mediated response of the sinus node and thus to provide insight into the regulation properties of the autonomic nervous system. The standards of measurements are mostly defined although some details need further investigation. Similarly, the pathophysiologic background has been clearly identified. Several large-scale retrospective and prospective studies have established beyond any doubt that HRT is one of the strongest independent risk predictors after MI. It thus appears that the

stage has now been reached when HRT might be used in large prospective intervention studies.

Reprint requests and correspondence: Dr. Marek Malik, Division of Cardiac and Vascular Sciences, St. George's, University of London, Cranmer Terrace, London SW17 0RE, United Kingdom. E-mail: marek.malik@btinternet.com.

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