CHARLES UNIVERSITY IN PRAGUE, FIRST FACULTY OF MEDICINE

PHD THESIS

PHYSIOLOGICAL MECHANISMS OF HEART RATE TURBULENCE

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Contents

I. Acknowledgments

The major part of work was carried out at the Department of Cardiac and Vascular Sciences (headed by Prof. John Camm), St. George's Hospital, University of London, United Kingdom under supervision of Prof. Marek Malik, my honourable tutor, who promoted my interest in heart rate turbulence. Since Prof. Malik co-authored the seminal 1999 Lancet paper on heart rate turbulence by Munich working group, we had the chance to start the investigation in this field near the beginning. This opportunity would be almost certainly lost if we had not had concurrently available appropriate technical equipment and expertise in biological signal acquisition and processing at the 3rd Department of Internal Medicine, First Faculty of Medicine, Charles University in Prague (headed by Prof. Josef Marek and later by Prof. Stepan Svacina) under kind supervision of head of cardiology division Prof. Jaromir Hradec. Together with my co-workers Dr. Vojtech Melenovsky and Dr. Jan Simek we were able to perform simultaneous recordings of RR intervals and arterial blood pressure during heart rate turbulence and to offer the first anecdotal evidence of baroreflex involvement in heart rate turbulence at the time when its physiologic background was completely unknown.

My research activities in heart rate turbulence continued during my further position at the Department of Cardiology and Angiology, First Faculty of Medicine, Charles University in Prague (headed by Prof. Michael Aschermann and later by Prof. Ales Linhart) with Dr. Petr Stovicek and Dr. Stepan Havranek as co-workers; and finally at the Department of Cardiology, Institute for Clinical and Experimental Medicine in Prague, headed by Prof. Josef Kautzner, who supervised my thesis overall.

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II. Abbreviations

HRT	heart rate turbulence
VPC	ventricular premature complex
APC	atrial premature complex
SBP	systolic blood pressure
MSNA	muscle sympathetic nerve activity
TO	turbulence onset
TS	turbulence slope
AV	atrioventricular
VA	ventriculoatrial

III. Preamble

The following text was adapted from “Physiology of Heart Rate Turbulence” section that was the authors contribution to the consensus document of International Society for Holter and Noninvasive Electrocardiology (ISHNE) entitled “Heart rate turbulence: Standards of measurement, physiological interpretation, and clinical use” which will be published in Annals of Noninvasive Electrocardiology later this year. The text was designed to serve as a comprehensive referencing source in the field of heart rate turbulence physiology research containing all relevant papers on this topic that were published until June, 2007.

IV. Introduction

Heart rate turbulence (HRT) is a recently recognized electrocardiographic phenomenon in which the small hemodynamic disturbance caused by a ventricular premature beat is enough to induce a response of the sinus node and to provide insights into the regulation properties of the autonomic nervous system. Several retrospective and prospective large-scale studies including more than 5,400 patients have established HRT as one of the strongest and independent risk predictor after myocardial infarction.

Although the standards of HRT measurements are mostly defined, risk stratification strategies based on HRT are still evolving. In contrast, the pathophysiological background of HRT has been clearly identified over the last years.

V. Mechanisms of HRT

Since its original description (Schmidt et al. 1999), considerable efforts have been made to define HRT physiology. Mechanisms underlying HRT were initially suggested by the analysis of Holter-based studies; thereafter, electrophysiological investigations carried out during specific experimental protocols have offered more direct insight into its pathophysiology. The most relevant physiological mechanisms of HRT were recently extensively reviewed (Wichterle et al. 2002; Guzik et al. 2002; Voss et al. 2004; Wichterle et al. 2004b; Watanabe et al. 2004).

From the very beginning, it was hypothesized that initial acceleration of heart rate was triggered by the transient vagal inhibition in response to the missed baroreflex afferent input due to hemodynamically inefficient ventricular contraction. Then, a sympathetically mediated overshoot of arterial pressure was responsible for the subsequent deceleration of heart rate through a vagal recruitment (Malik et al. 1999). Even if this hypothesis was mainly speculative at that time, it was substantially proven afterwards.

VI. HRT and ventriculophasic sinus arrhythmia

HRT shares some physiological features of ventriculophasic sinus arrhythmia, a phenomenon in which ventricular contractions influence the periods of sinus nodal discharges, even in the absence of retrograde atrioventricular conduction (Erlanger et al. 1909; Hecht et al. 1914; Chung et al. 1970). Arterial baroreceptor activation by ventricular ejection was proposed as the mechanism responsible for the reflex slowing of sinus nodal rate. This interpretation was supported by the observations that the latency and dynamics of this effect was compatible with vagal action (Wilson et al. 1918; Parsonnet et al. 1944; Roth et al. 1948), as well as by the correlation between PP intervals and invasively measured blood pressure (Bevegard et al. 1967). The trigger of HRT, however, is not the same as that of ventriculophasic sinus arrhythmia associated with atrioventricular block where the idioventricular contractions have an important hemodynamic impact. In fact, ventricular premature complexes (VPCs) during normal sinus rhythm have deleterious effects on instant cardiac output and produce different hemodynamic and neural reflex responses.

Although early positive chronotropic effect of VPC was originally reported almost three decades ago (Döhlemann et al. 1979), both early positive chronotropic and late negative chronotropic effects of VPC were described as the components of HRT only recently (Schmidt et al.1999).

VII. Physiological interpretation of HRT

The rapid, but gradual (usually culminating in the second postectopic RR interval) 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: incomplete electrical restitution; 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 these factors, systolic blood pressure (SBP) produced by VPC is considerably lower than that produced by normal sinus beat.

Both ineffective VPC and fully compensatory pause participate at diastolic pressure drop. Moreover, SBP produced by first post-VPC sinus beat is usually lower (at least in subjects with normal left ventricular function) than pre-VPC level since postextrasystolic potentiation is not able to compensate the preceding drop of post-VPC diastolic pressure. Hence, not only instant hemodynamic effect of VPC ("missing" beat) but also prolonged

reduction in SBP in subsequent beat activates the aortic and carotid baroreceptors, which determine an increase in heart rate due to vagal inhibition.

At the same time, transient relative hypotension stimulates the sympathetic arc of autonomic nervous system. It has been well documented in human and animal studies (Herre et al. 1987; Lombardi et al. 1989; Welch et al. 1989; Smith et al. 1995; Grassi et al. 2002) that the drop of diastolic blood pressure after a VPC initiates a surge of muscle sympathetic nerve traffic (MSNA), which is instantaneously followed by a period of sympathetic silence. The magnitude of this burst, which can be observed not earlier than at the time of the first post-VPC beat, provokes noradrenalin release in perivascular sympathetic endings leading to 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 MSNA. Because the latency of hemodynamic response to sympathetic nerve stimulation is approximately 5 seconds (Hainsworth et al. 1987), it seems unlikely that the early heart rate acceleration of HRT might be mediated by sympathetic efferent arm activation. On the contrary, both branches of the autonomic nervous system operate during the late phase of HRT, which is characterized by gradual return of SBP and heart rate to pre-extrasystolic values. Under physiologic conditions, a significant overshoot of both SBP (transient hypertension peaking around 8^{th} post-VPC beat) and heart rate reduction below the baseline values are observed. It is now believed that this late “overcompensation”, which occurs in agreement with spontaneous periodicity of baroreflex mechanisms, is primarily caused by an early sympathetic activation with delayed vasomotor response and, secondarily, by vagal activation. Recently observed correlations between MSNA and indices of heart rate turbulence further supported this hypothesis (Segerson et al. 2007).

VIII. Autonomic background of HRT

Numerous studies recently investigated the influence of basal autonomic activity on HRT. Indeed, it was shown that preserved vagal influence on sinus node is an essential condition for normal HRT, which can be almost abolished by vagal blockade with atropine (Güttler et al. 2001; Marine et al. 2002; Lin et al. 2002). No significant change of HRT was observed after beta-blockade with esmolol (Lin et al. 2002). It must be pointed out that beta-blocker administration does not provide a complete sympathetic blockade: the effect is predominant on modulation of sinus node discharge and limited on peripheral vascular resistance. As a result, sympathetically mediated overshoot of SBP in the late phase of HRT is not significantly affected, and consequently, late deceleration of heart rate due to preserved vagal response remains unchanged in comparison to no-drug conditions.

Indeed, blood pressure dynamics did not change significantly after vagal blockade (Güttler et al. 2001), but were significantly blunted in patients with sympathetic neurocirculatory failure and abolished in healthy subjects during trimethaphan-induced ganglion blockade (Goldstein et al. 2000).

The effect of premature ventricular paced beats on HRT parameters was recently investigated (Raj et al. 2005). HRT was very similar whether it followed a spontaneous VPC or a paced beat. Moreover, not only the magnitude but mainly the duration of hypotension during short ventricular train drives was highly correlated with HRT tachycardia, thus confirming the critical role of sympathetic activation and vagal withdrawal in determining HRT initial tachycardia. This also underscores an importance of full compensatory pause after isolated VPCs in HRT initiation. In agreement, another study (Havranek et al. 2007) found that HRT after ventricular pacing trains reflects a combination of vagal withdrawal due to transient hypotension (dependent on train cycle length) and suppression of sinus node automaticity in case of preserved VA conduction.

Early heart rate acceleration and late deceleration after a single VPC parallel corresponding changes of SBP with a rather constant delay and a pattern of change that is fully compatible with baroreflex physiology (Davies et al. 2001; Lin et al. 2002; Voss 2002a; Roach et al 2002; Roach at al. 2003; Wichterle et al. 2006). The pattern of change of SBP appears, instead, repetitive; thus heart rate slope rather than blood pressure slope after VPC seems to convey the information relevant to baroreflex sensitivity (Davies et al. 2001). Another evidence of baroreflex involvement in HRT comes from the retrospective analysis the ATRAMI study in which both Turbulence Onset (TO) and Turbulence Slope (TS) correlated with baroreflex sensitivity assessed by the phenylephrine method (Ghuran et al. 2002).

Also, post-VPC heart rate patterns simulated by mathematical model of hemodynamics with baroreceptor feedback (with preserved and blunted baroreflex sensitivity) were similar to those often found in low and high risk subjects (Mrowka et al. 2000).

IX. Speculative non-autonomic mechanisms of HRT

The late post-VPC increase in SBP could be alternatively attributed to a transient increase of cardiac output due to purely non-autonomic mechanism. This possibility, however, is unlikely because post-extrasystolic potentiation of contractility has a rapid exponential decay (Seed et al. 1984; Sung et al. 1980; Shimizu et al. 2000) and no substantial dynamics of stroke volume in the late phase of HRT were observed when beat-by-beat stroke volume and peripheral vascular resistance were computed by a non-linear, self-

adaptive model of aortic input impedance (Wichterle et al. 2006). On the contrary, peripheral vascular resistance increased significantly in the late phase of HRT.

Like in the case of ventriculophasic sinus arrhythmia, other non-autonomic mechanisms might be suggested to be involved in 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 (Brooks et al. 1966) or sinus node (Lange et al. 1966), an increase of atrial pressure in isolated denervated hearts (Blinks et al. 1956; Pathak et al. 1958), and a reduction of perfusion pressure of the sinus nodal artery (Hashimoto et al. 1967). Similarly, it was demonstrated that the positive chronotropic effect produced by traction on the sinus nodal region as well as on atrial appendages is purely sympathetically mediated (Kappagoda et al. 1972a; Kappagoda et al. 1972b). However, presently available data do not support any other "backward" hemodynamic and/or mechanical effects of VPCs on the atria unrelated to the autonomic reflex arch.

X. Gender and age dependency of HRT

Gender has not been found to influence HRT in healthy controls (Grim et al. 2003) or in postinfarction patients (Jeron et al. 2003). An increasing age was associated with a decrease in HRT (Schwab et al. 2005), as it has been reported for most measures of autonomic control.

XI. HRT and heart rate / heart rate variability

All studies that investigated the relationship between HRT and heart rate found that HRT is reduced by high heart rate (Schmidt et al. 2000; Watanabe et al. 2002; Schwab at al. 2004a; Cygankiewicz et al. 2004a; Bauer et al. 2005). The mechanisms responsible for heart rate modulation of HRT (likewise of heart rate variability and baroreflex sensitivity) are not completely understood. Two possible and non-exclusive explanations have been proposed (Melenovsky at al. 2005). 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 be given by intrinsic properties of sinus node, specifically by the non-linear relationship between vagal neural activity and the rate of diastolic depolarization of pacemaker cells (Zaza et al. 2001). This phenomenon generates the question if HRT indices should be corrected for heart rate (Cygankiewicz et al. 2004a). On the other hand, it remains to be established if such correction could increase the predictive power of HRT based on the fact that intraindividually assessed steepness of the regression line between

Turbulence Slope and prevailing heart rate appears to have already an independent predictive value for mortality (Bauer et al. 2005).

There is a modest correlation between HRT descriptors and indices of heart rate variability suggesting that other intrinsic modulators or different facets of the autonomic pathways may be important in regulating HRT physiology (Ghuran et al. 2002; Sestito et al. 2004; Cygankiewicz et al. 2004a). Circadian variability of HRT is blunted in coronary artery disease patients and parallels circadian variability of mean RR interval and heart rate variability parameters (Cygankiewicz et al. 2004b).

XII. HRT and character of ventricular premature complexes

The baroreflex-related basis of HRT is also supported by the greatest HRT response to more premature (and less hemodynamically efficient) VPCs with longer compensatory pauses. Both TO and TS depended on coupling interval of preceding VPC when analyzed from Holter recordings in EMIAT trial (Schmidt et al. 2000). The effects of VPC coupling interval on HRT was directly addressed in two pacing studies (Watanabe et al. 2002; Savelieva et al. 2003) with rather conflicting results. Surprisingly, the former study failed to find any relationship between VPC coupling interval and HRT parameters when patient data were pooled. Even reverse relationship was observed in individual cases. In the latter study, instead, the correlation between TS, TO and normalized coupling interval was, respectively, negative and positive, in agreement with the physiological interpretation of HRT.

The site of origin of the ventricular premature beat exhibits no influence on HRT (Schwab et al. 2004b), whereas retrograde atrial depolarization, which may reset the sinus node, has a rather opposite effect to the autonomic modulation of heart rate after VPC and may change the dynamics of subsequent sinus RR intervals (Lee at al. 2004). It is unclear, whether the retrograde ventriculoatrial (VA) conduction, whose presence cannot be assessed from Holter data, could adversely interfere with the predictive value of this methodology. It must be recalled, however, that most of the patients with structural heart disease have poor or absent VA conduction. Moreover, in large post-infarction databases, mean coupling interval of VPCs is between 60-65%, so that even in the presence of VA conduction only limited number of retrogradely conducted VPCs may effectively reset sinus node function. It is believed that late retrograde atrial depolarization (in the case of late VPCs) and missing or decremental VA conduction (in the case of short-coupled VPCs) might also prevent a significant effect of VA conduction on HRT indices.

XIII. HRT and AV nodal turbulence

The biphasic profile of AV intervals consisting of early shortening and later prolongation of AV intervals after a single VPC was observed in the pacing study (Wichterle et al. 2003). The major observation was that AV interval dynamics significantly precedes the change of RR intervals, which is in conflict with near to zero phase of transfer function between RR and AV intervals in previous studies (Leffler et al. 1994; Chen et al. 1999). Again, the early dynamics of AV intervals after a VPC may be more influenced by purely electrophysiological mechanisms rather than by vagal withdrawal. However, in the late phase, where non-autonomic effects are less likely to occur, the temporal dissociation between RR and AV interval response was even more pronounced and no plausible explanation has been given. In absolute values, the response of AV conduction to a VPC was drastically weaker in both early and late phase than that of RR intervals. Therefore, the dynamics of AV delay has a little impact on accuracy of HRT assessment using the surface ECG. This is in agreement with the findings of the study of Marine et al. (2002) which indicated that almost all post-VPC variation in VV intervals was due to corresponding variation in AA and not in AH and HV intervals. It is probable that ventriculophasic modulation of AV nodal conduction is masked by opposing effects of ventriculophasic modulation of the sinus rate (Skanes et al. 1998).

XIV. HRT and dynamics of ventricular repolarization

Dynamics of QT interval in sinus beats after VPCs was characterised by an abrupt prolongation immediately after VPC suggesting non-neural mechanism and by a slow return to baseline values (Savelieva et al. 2005). There was not any dynamics in QT interval corresponding to vagal activation in late phase of HRT. Initial QT interval prolongation was significantly more prominent in patients with preserved LV function.

XV. HRT physiology in heart disease

The analysis of Holter data from EMIAT trial shown that TO and TS were significantly influenced by left ventricular ejection fraction (Yap et al. 2001). The direct comparison of patients with congestive heart failure and controls revealed that HRT indices are significantly depressed in patients with congestive heart failure compared to healthy controls (Koyama et al. 2002). It was also shown that even the presence of organic heart disease with preserved left ventricular function, may affect HRT indices to a similar extent (Sestito et al. 2002).

Patients with structural heart disease have intrinsically depressed vagal and sympathetic modulation. HRT (if not completely missing) is mainly characterized by attenuated early acceleration of heart rate and by subsequent gradual return of SBP and heart rate back to pre-extrasystolic values (Davies et al. 2001). Moreover, in comparison to healthy subjects, the first sinus beat after VPC is potentiated to a greater extent exceeding the set point (baseline SBP) of the baroreflex (Voss at al. 2002a). Prominent post-extrasystolic potentiation interrupts the smooth physiological post-VPC pattern of SBP and interferes indirectly with the magnitude of HRT dynamics (Voss 2002b). Initial vagal inhibition is promptly upturned and subsequent sympathetic activation (and the dynamics of peripheral vascular resistance) is attenuated (Wichterle at al. 2006). For all these reasons, the late overshoot of SBP and RR intervals after VPC is frequently missing. Thus, in patients with structural heart disease, both depressed vagal and sympathetic modulations and, indirectly, enhanced postextrasystolic potentiation account for attenuated HRT.

The potentiation of the first postectopic beat is a potent trigger initiating the mechanical and associated electrical alternans with a rapid time decay which is caused by a combination of alternation in hemodynamics variables (enddiastolic pressure and volume) and inotropic state due to alternation of calcium turnover (Voss et al. 2002b). Post-VPC alternans phenomenon was reported in one third of patients with congestive heart failure (Davies et al. 2001).

XVI. HRT after atrial premature complexes

Dynamics of heart rate after atrial premature complexes (APCs) is different from that after VPCs. While early acceleration and later deceleration is present after VPCs, there is an abrupt deceleration of heart rate immediately after APCs with a prompt return to baseline, which is followed by a second and delayed transitory heart rate deceleration. It is plausible to speculate that initial abrupt deceleration is caused by sinus nodal resetting by APCs with a subsequent recovery of sinus node automaticity (Heddle et al. 1985). This electrophysiological mechanism overwhelms the autonomic component of early acceleration phase of HRT. The late deceleration of heart rate after APCs has the same mechanism as that after VPCs and it is believed to result from a baroreflex response to blood pressure dynamics following the premature contraction. This is supported by the significant intraindividual correlation between TS after APCs and VPCs in pacing (Savelieva et al. 2003) and Holter studies (Lindgren et al. 2003; Wichterle 2004a; Wichterle at al. 2005), by the inverse relationship between TS and APCs coupling intervals, and by the correlation between TS after APCs and phenylephrine baroreflex sensitivity.

The magnitude of TS after APCs is, however, significantly lower than that after VPCs. 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, APC leads to a less pronounced blood pressure perturbation and baroreflex response. Second, the magnitude of TS after VPCs is determined not only by the intensity of late vagal activation but also by the extent of initial heart rate acceleration. Therefore, discordant behaviour of heart rate in both phases augments the TS after VPCs. On the other hand, concordant early and delayed response of heart rate after APC, i.e. early and late deceleration, may artificially reduce TS after APCs (Wichterle et al. 2004a).

Finally, more positive TO (i.e. marked early deceleration of heart rate) after APCs was found temporarily associated with spontaneous episodes of atrial fibrillation (Vikman et al. 2005). Because an early phase of HRT is strongly influenced by APC coupling interval independently of prematurity of conducted ventricular contractions, the most likely explanation is that this observation might be an epiphenomenon of incidental short-coupled APCs with delayed atrioventricular conduction likely triggering atrial fibrillation (Wichterle et al. 2007).

XVII. Summary

Our papers on HRT physiology covered several electrophysiological phenomena associated with turbulent behaviour of sinus nodal discharge after isolated premature beat. Some observations were fairly novel (AV nodal turbulence, QT-turbulence, and HRT after atrial premature complexes), others were confirmative or complementary to the findings of other authors (impact of left ventricular ejection fraction and coupling interval). All of them were helpful for even deeper understanding the fundamental principles involved in HRT that, consequently, may offer an explanation of why HRT is such a potent postinfarction risk stratifier.

From the very beginning we tried to suggest that late deceleration phase of HRT does not simply reflect the vagal function but originates from a complex interplay of both sympathetic and parasympathetic systems. Our paper on HRT hemodynamics (Wichterle et al. 2006) together with the article by Segersen et al. (2007) added perhaps “the last piece to the heart turbulence puzzle”, as appreciated in Heart Rhythm editorial by Munich working group (Bauer et al. 2007).

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XIX. Relevant authors publications related to PhD thesis

Original articles in journals with impact factor

1. Malik M, Wichterle D, Schmidt G. Heart rate turbulence. G Ital Cardiol 1999;29(Suppl.5):65-9.
2. Wichterle D, Savelieva I, Meara M, Camm AJ, Malik M. Paradoxical autonomic modulation of atrioventricular nodal conduction during heart rate turbulence. Pacing Clin Electrophysiol 2003; 26(Pt.II):440-3.
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XX. Appendix: Selected full-text publications in chronological order

1. Malik M, Wichterle D, Schmidt G. Heart rate turbulence. G Ital Cardiol 1999;29(Suppl.5):65-9.
2. Wichterle D, Melenovsky V, Malik M. Mechanisms involved in heart rate turbulence. Card Electrophysiol Rev 2002; 6:262-6.
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