HRT assessment reviewed: a systematic review of heart rate turbulence methodology

Valeria Blesius, Christopher Schölzel, Gernot Ernst and Andreas Dominik

1 THM University of Applied Sciences, Giessen, Germany
2 Vestre Viken Hospital Trust, Kongsberg, Norway
3 University of Oslo, Norway

Keywords: heart rate turbulence, ventricular premature contraction, methodology, systematic review

Abstract

Heart rate turbulence (HRT) is a biphasic reaction to a ventricular premature contraction (VPC) mainly mediated by the baroreflex. It can be used for risk stratification in different disease patterns. Despite existing standards there is a lot of variation in terms of measuring and calculating HRT, which complicates research and application. Objective: This systematic review outlines and evaluates the methodological spectrum of HRT research, especially filtering criteria, parameter calculation and thresholds. Approach: The analysis includes all research papers written in English that have been published before 12.10.2018, are listed on PubMed and involve calculation of HRT parameter values. Main results: HRT assessment is still being performed in various ways and important specifications of the methodology are not given in many articles. Nevertheless, some suggestions regarding HRT methodology can be made: a normalised turbulence slope should be used to uncouple the parameter from heart rate and frequency of extrasystoles. Filtering criteria as formerly reviewed in the guidelines should be met and mentioned. The minimal number of VPC snippets (VPCSs) as well as new cut-off values for different risks need to be further evaluated. Most importantly, the exact and complete methodology must be described to ensure reproducibility and comparability. Significance: Methodical variation hinders comparability of research and medical application. Our continuing questions help to further standardise the measurement and calculation of HRT and increase its value for medical risk stratification.

Acronyms

ACS Acute coronary syndrome
AF Atrial fibrillation
AMI Acute myocardial infarction
APC Atrial premature contraction
CAD Coronary artery disease
CHF Congestive heart failure
compl Compensatory interval
coupl Coupling interval
DCM Dilated cardiomyopathy
ECG Electrocardiogram
HF Heart failure
HiF High frequency power
HR Heart rate
HRT Heart rate turbulence
HRV Heart rate variability
LoF Low frequency power
LVEF Left ventricular ejection fraction
MI Myocardial infarction
#minVPCS Minimal number of suitable VPCS needed for HRT analysis
OSAS Obstructive sleep apnea syndrome
postRR Regular interval in a VPCS after the compl
preRR Regular interval in a VPCS before the coupl
1. Introduction

1.1. Rationale
Heart rate turbulence is the naturally occurring fluctuation of heart rate (HR) after a ventricular premature contraction (VPC) (see figure 1) (Schmidt et al 1999). While re-establishing the former blood pressure, which fluctuates due to a VPC, a characteristic heart rate pattern occurs (see figure 2): as the VPC is a premature beat, it leads to a shortened interval, called the coupling interval (couplI). This interval is followed by a compensatory interval (compI) that is much longer than a normal cycle duration, because the ectopic beat suppresses one contraction that would regularly have been triggered by the sinus signal. After these two irregular intervals, a characteristic pattern can be observed which consists of an initial fast increase of HR followed by a smooth HR decrease and a latter return to the baseline. The term heart rate turbulence (HRT) refers to this fluctuation of the HR after the compI.

The turbulence depends mainly on the baroreflex and thus is an indirect marker of the condition of the autonomic nervous system (Cygankiewicz et al 2013). Two HRT parameters, turbulence onset (TO) and turbulence slope (TS), were developed to define HRT.

TO quantifies the initial increase of the heart rate after the compI and is suggested to reflect vagal inhibition (Lombardi et al 2011). The VPC is hemodynamically inefficient compared to a normal sinus beat: It has lower contractility strength due to the missing atrial contraction, incomplete electrical recovery, and thus less synchronization and it moves less blood volume due to less diastolic filling and higher afterload. Hence, the systolic blood pressure drops. This lack of afferent baroreflex input results in vagal inhibition (Bauer et al 2008). To quantify this fast reaction, the relative difference between the arithmetic mean of the two beats after compI ($RR_1 + RR_2$) and the arithmetic mean of the last two beats before couplI ($RR_{-1} + RR_{-2}$) is calculated. TO is given as a percentage:

$$\frac{(RR_1 + RR_2) - (RR_{-1} + RR_{-2})}{(RR_{-1} + RR_{-2})} \times 100\%.$$  \hspace{1cm} (1)

It is first calculated for each VPC and averaged afterwards to get a subject’s overall TO value.

TS is the steepest slope of the increase of interval length following the compI and reflects vagal activation (Lombardi et al 2011): after the initial inhibition vagal activity recovers with increasing interval lengths (Bauer et al 2007). The slope is measured as the steepest regression line over any 5 succeeding intervals within the first 20 intervals after the compI and is given as ms/RR interval. In contrast to TO, an averaged tachogram of all suitable extrasystoles is calculated first, before TS is assessed once for a subject.

The workflow of HRT assessment begins with a 24-h Holter electrocardiogram (ECG)-recording. The record has to be cleaned from erratic data, meaning artefacts and noise. Afterwards, all VPC snippets (VPCs) have to be singled out. A VPC contains several intervals: the couplI between a sinus beat and the early occurring VPC, the long compI between the VPC and the following sinus beat, and a number of regular intervals preceding (preRRs) and following (postRRs) these two VPC intervals (VPCIs). The intervals of the VPCs are filtered based on a set of established criteria (Grimm et al 2003). These criteria regard the length of the intervals to discard ectopy within the regular intervals and ensure a sufficient prematurity of the VPC. Afterwards, HRT can be calculated from these suitable VPCs as mentioned before. In healthy volunteers TO ranges from $-2.7\%$ to $-2.3\%$, TS ranges from 11.0 to 19.2 ms/RR interval (Diaz et al 2002, Grimm et al...
Figure 1. Example of a ventricular premature contraction (VPC): A stimulus originating from the ventricles leads to a broad QRS complex with an abnormal morphology, here shaped like a right bundle branch block pattern. The extrasystole appears prematurely, superimposes the naturally occurring sinus signal and causes two specific intervals: The coupling interval (couplI) and the compensatory interval (complI) are separated by the VPC. The length of these two intervals is equivalent to the length of two of the surrounding sinus RR intervals. The intervals before (preRR) and after (postRR) the VPC interval are framed by regular sinus beats.

In many studies the two HRT parameters have been identified as feasible markers for all-cause mortality after myocardial infarction or chronic heart failure as reviewed by Cygankiewicz et al. (2013). In recent studies HRT has been shown to significantly contribute as predictive factor in different clinical settings. HRT combined with traditional heart rate variability improves the sensitivity of the diagnosis of early cardiac autonomic neuropathy in diabetic patients to 98% (Lin et al. 2017). Including HRT to a predictive model of death associated with chronic heart failure improved the accuracy of the model Ramirez et al. (2017). HRT increased the predictive sensitivity and specificity in life-threatening ventricular tachyarrhythmias (VTA) (Frolov et al. 2017). The predictive value of HRT has also been shown in subjects with Marfan syndrome (Schaeffer et al. 2015), chronic obstructive pulmonary disease (Gunduz et al. 2009), metabolic syndrome (Erdem et al. 2012) or obstructive sleep apnea syndrome (D’Addio et al. 2013).

In contrast to heart rate variability (HRV) that shows autonomic activity during sinus rhythm, HRT reflects autonomic responses to endogenous interference. Cardiac diseases can significantly depress autonomic functions and thus attenuate HRV (Malik et al. 1996). Since they can also increase VPC occurrence (Gorenek et al. 2020), HRT may be able to detect residual autonomic activity that cannot be detected by HRV. Therefore, it can be a valuable addition to risk prediction, that usually incorporates many different indicators.

In 2008 the International Society for Holter and Noninvasive Electrophysiology Consensus was published (Bauer et al. 2008). Though it is referred to as a standard for HRT calculation, it did not define norms but rather summarised commonly used methods. Despite the common ground established in this paper, HRT methodology varies widely regarding data recording, filtering of measurements and calculation itself. Different methodologies lead to different results. This lack of comparability hinder the understanding of HRT, e.g. the intensity of influences on this phenomenon. It also complicates finding suitable standards for HRT application in the medical field.

1.2. Objectives
We systematically assess the methodology of determining HRT parameter values in research since its original description. The scope of the study is not to review the clinical use of HRT but the assessment itself. The aim is to outline the different types of HRT assessment as well as their usefulness in order to create a basis for determining precise guidelines that will lead to higher comparability between studies.

When defining guidelines the aim of ECG recording and HRT assessment have to be considered: Recording ECGs in order to assess HRT is rare and limited to scientific research. In most cases HRT is
Figure 2. Schematic visualisation of heart rate turbulence (HRT): the ventricular premature contraction (VPC) creates a short coupling interval (couplI) between a sinus beat and the VPC and a long compensatory interval (complI) between the VPC and the following sinus beat, while an intermediate sinus signal is skipped. The actual HRT occurs afterwards, beginning with the first interval after complI, when the interval lengths show an initial drop off, a steep increase and a following decline. Turbulence onset (TO) represents this first drop-off in HR, while turbulence slope (TS) represents the subsequent increase.

calculated from records made during clinical practice and without focus on HRT. Therefore, guidelines have to take into account what is possible to implement in the daily clinical routine.

1.3. Reviewing details
Our approach followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Liberati et al 2009) wherever possible. The PRISMA statement provides guidelines for systematic reviews and meta-studies in the medical field (Liberati et al 2009). Since the scope of our study differs from common reviews not all guidelines were applicable.

In a PubMed search made on 12.10.2018 we gathered all articles containing the term ‘heart rate turbulence’. After checking for HRT assessment and language we examined the remaining 240 articles regarding the exact methodology of HRT that was used in the respective study. As baseline methods we used the filtering criteria of Grimm et al (2003), the calculation rules by Schmidt et al (1999) and the minimum number of needed VPCS as reviewed by Bauer et al (2008). A detailed description of our methods with all examined aspects, baseline methods and resulting number of articles can be found in the appendix Methodological details.

We want to give an overview about the most common practices regarding HRT assessment as well as a critical evaluation to provide the reader with guidelines. Therefore we structured our findings into chapters following a customary data assessment:

- Section 2 ‘Data collection’ summarises the variety of the length of the ECG measurement, different approaches to assess HRT after other arrhythmias and the technique of inducing VPCs to circumvent the difficulty of getting enough suitable VPCSs. It also includes the approach to adapt TS to address several biasing influences due to different recording lengths.
Section 3 ‘Data preparation’ assesses the application of filtering criteria for VPCs by Grimm et al (2003). Furthermore, it covers the number of VPCs needed to calculate HRT and the different approaches to handle measurements with lesser VPCs.

Section 4 ‘Data analysis’ covers variations of the calculation techniques by Schmidt et al (1999) and a third established HRT parameter.

Section 5 ‘Classification’ discusses cut-off values for risk stratification and classification systems.

Section 6 ‘Description of HRT assessment’ covers the methodological details that need to be given in publications.

2. Data collection

The ECG recording duration is very important for HRT calculation for three reasons: First, there must be enough suitable VPCs available for HRT calculation. This can be a challenge since the occurrence of VPCs in healthy hearts can be very low (Kostis et al 1981). Secondly, TS is correlated with the number of VPCs used for calculation and therefore correlated with the length of the measurement (Cygankiewicz et al 2004, Hallstrom et al 2004). And finally, since HRT is based on the baroreflex and therefore the autonomic nervous system, it depends on the circadian rhythm (Chen 2011, Cygankiewicz et al 2004, Hallstrom et al 2005).

2.1. Common recording durations

Although most inspected articles state the planned recording duration (i.e. given as mean of the population) is mostly missing: in 198 articles either Holter monitoring or 24 h are reported as the planned recording duration. Some studies used short recordings with a planned duration of less than 1 h (Raj et al 2005, Berkowitch et al 2004, Davos et al 2009, Malberg et al 2004, Voss et al 2006, Davies et al 2001, Jeron et al 2003, Wichterle et al 2006, Goernig et al 2006, Segerston et al 2007, Watanabe et al 2006, Tekelioglu et al 2013) or between 2 and 8 h (Solem et al 2008, Rich et al 2012, Gil et al 2013, Tekelioglu et al 2013, Solem et al 2006, D’Addio et al 2013, D’Addio et al 2014, Yang et al 2005, Watanabe et al 2008, Tuomainen et al 2005). In several studies 24-h Holter recordings were cut into 1, 2, 4 or 6 h snippets (Cygankiewicz et al 2004, Hallstrom et al 2004, Hallstrom et al 2005, Lewis et al 2011, Watanabe et al 2007). In contrast, two studies used longer recordings, namely 28 h (Ovreiu et al 2008) and 7 days (Manzano-Fernández et al 2011).

2.2. Methods to enable HRT assessment

Naturally, HRT can only be calculated when recordings contain VPCs. Based on the researched population, obtaining a sufficient number of suitable VPCs can be challenging, since the prevalence of VPCs is positively correlated with increasing age (Kostis et al 1981) and higher cardiovascular risk (Latchamsetty et al 2015, Lown et al 1971). The amount of VPCs is likely to decrease even more after filtering. Options to address the problem of having a low incidence of VPCs for HRT assessment are: extending the recording time, inducing VPCs or using other heart beats to calculate HRT.

2.2.1. Extending the recording duration

The HRT guidelines (Bauer et al 2008) and the vast majority of studies analysed in this systematic review, use a recording duration of 24 h. As mentioned, this duration can be too short to measure enough VPCs for HRT assessment. With extended recording duration the probability to measure a suitable amount of VPCs rises considerably (Kostis et al 1981). Accordingly, Manzano-Fernández et al suggested a 3-day recording duration for HRT assessment: They found subjects to change from unmeasurable into abnormal HRT categories (group HRT1 or HRT2) after measurements of 72 h compared to just 24 h (Manzano-Fernández et al 2011). This approach is only feasible if HRT assessment is the main focus of the recording. Elongating the recording time in clinical routine during patient admission is not viable.

2.2.2. Induced VPCs

Inducing VPCs is a way to bypass the difficulty of obtaining the needed number of VPCs based on naturally occurring extrasystoles. In many studies HRT has been shown to be present after electrical stimuli of the ventricles (Marine et al 2002, Lin et al 2002, Watanabe et al 2002, Roach et al 2002, Savelieva et al 2003, Wichterle et al 2003, Raj et al 2005, Iwasa et al 2005, Vukajlovic et al 2006, Makai et al 2008, Rojo et al 2009, Havranek et al 2007). Instead of VPCs some authors use ventricular pacing trains as HRT triggers (Raj et al 2005, Havranek et al 2007).

There seems to be no significant difference between HRT after spontaneous and induced VPCs during programmed ventricular stimulation (PVS) sessions (Raj et al 2005, Iwasa et al 2005). However, HRT after
induced VPCs and during Holter monitoring differs (Iwasa et al. 2005). This is to be expected due to different measurement conditions and lengths:

First, the number of VPCs used for calculation is correlated with TS as mentioned before (Cygankiewicz et al. 2013). Depending on the incidence of spontaneous VPCs in subjects, TS may differ significantly. Secondly, hemodynamic changes depend on the subject’s position and movement: it can be assumed that values differ between Holter ECG (with varying, but mostly upright position and movement) and induced HRTs (with supine position and rest). Makai et al. showed that TS differed significantly from supine to upright position and correlated significantly with baroreceptor sensitivity in both positions. However, it should be mentioned that HR, which is negatively correlated with TS, also differed significantly, but was not taken into account as covariate in this study (Makai et al. 2008). Thirdly, sedation can have an affect on the cardiovascular system depending on the sedative and its dose (Lau et al. 1993, Kanaya et al. 2003, Frölich et al. 2011). Unfortunately, the article by Iwasa et al. does not specify the sedative or differences of other cardiovascular parameters (Iwasa et al. 2005). To sum up, although HRT can be triggered by electrical stimuli, the validity of HRT from induced VPCs at rest in contrast to HRT from VPCs in Holter ECG remains to be investigated. Again, this approach is unfitting for the clinical practice, because it entails additional stress and effort for both patient and medical staff.

2.2.3. HRT based on other arrhythmias

The turbulence following a VPC is mainly mediated by the baroreflex responding to blood pressure turbulence (Wichterle et al. 2006, Davies et al. 2001, Lin et al. 2002). It can be assumed that the baroreflex reacts similarly to other arrhythmic events and, thus, HRT is also present. This has been studied for APCs, premature sinus beats and ventricular tachyarrhythmia (VT). To prevent ambiguity, HRT and its parameters are marked in this section as ventricular (V), atrial (A), sino-atrial (S) or tachycardial (T).

Atrial premature complexes: Heddle et al. analysed the HR dynamics after an atrial premature contraction (APC) and found no turbulence but continuously decreasing interval lengths. The first interval after the APC was lengthened and the interval lengths decreased for about five intervals (Heddle et al. 1985). In contrast, Lindgren et al. compared HRT after APCs and VPCs and found a one-beat-delayed HRTA: The first interval after compl was relatively long and was followed by a shortened second interval (Lindgren et al. 2003). A similar pattern of a one-beat-delay followed by a HR acceleration and deceleration was shown by Wichterle et al. (2007).

HRTA was milder, meaning TSA was lower and TOA higher, but still negative (Lindgren et al. 2003, Schwab et al. 2004). Similar results, but with a positive TOA were found by Savelieva et al., Wichterle et al and Ovreiu et al. (Savelieva et al. 2003, Wichterle et al. 2007, Ovreiu et al. 2008). The abnormal TOA may depend on the study populations, consisting of patients referred to VT evaluation (Savelieva et al. 2003, Wichterle et al. 2007) or after cardiac surgery (Ovreiu et al. 2008). However, about half of the patients examined by Schwab et al. had sudden cardiac death (SCD) but a negative median for TOA anyway (Schwab et al. 2004). This effect should impact both TO and TS, but Savelieva et al. described a strong correlation for TSS and TSV, but not for TOA and TOV (Savelieva et al. 2003). An explanation is the one beat delay existing in HRTA (Wichterle et al. 2007, Lindgren et al. 2003). Thus, an adjustment of the TOA calculation using the second and third interval after the APC compl should be more suitable and may better reflect TOA.

While Savelieva et al. and Schwab et al. found no correlation between the prematurity (namely the couplI length) and HRTA (Savelieva et al. 2003, Schwab et al. 2004), except for TOA induced in the sinus node (Schwab et al. 2004), in another study TSA and TSV have been shown to both inversely and significantly correlate with couplI (Wichterle et al. 2004). Wichterle et al. later found a correlation between APC prematurity and TOA, but not TSA (Wichterle et al. 2007).

In three studies the usefulness of HRTA was investigated: TSA could be used as a risk stratifier for all-cause mortality after myocardial infarction (MI), although it was a weaker predictor than TSV. In their study Wichterle et al. found a dichotomy optimum of 0.8 ms/RR as cut-off for TSA (Wichterle et al. 2004). In another case, patients with atrial fibrillation (AF) after cardiac surgery had significantly higher TSA, while there was no difference in TOA (Ovreiu et al. 2008). Finally, while no other measurements showed significant differences between non-AF and AF episodes, TOA was impaired within one hour before atrial fibrillation (Vikman et al. 2005).

Sinus beats: Voss et al. first proposed HRT after sinus beats using ‘most premature normal beats’ defined as having a couplI length <80% and compl length >120% compared to the mean4 of all intervals in the measurement. No significant difference was found in all HRT parameters (TOA, TSV, CI/COMPP5) between dilated cardiomyopathy (DCM) patients and controls. TOA was positive and TSV attenuated in comparison to

---

4 The exact type of mean is not specified in the article.
5 CI/COMPP is the ratio between the length of couplI and compl (Voss et al. 2006).

HRT$_{V}$ (Voss et al 2006). The same approach was used by Jochum et al to find differences in patients before and during clomethiazole therapy. Except from a significant change of TS$_{V}$ before and after 2 h of medication, no changes in HRT after ventricular or sinus beats were found. Again, TO$_{V}$ was negative while TO$_{T}$ was positive while TO$_{T}$ was negative (Flevari et al 2007, Havranek et al 2005, Sestito et al 2004). In conclusion, a sinus beat with suitable prematurity can trigger a turbulence, but HRT$_{S}$ lacks the typical initial HR decrease. This is similar to HRT$_{A}$, but neither Jochum et al nor Voss et al describe a one beat delay (Jochum et al 2012, Voss et al 2006).

**Ventricular tachycardia:** The third approach was to calculate HRT after spontaneous or induced VT (Flevari et al 2007, Raj et al 2005, Havranek et al 2007). TO$_{T}$ (Raj et al 2005, Flevari et al 2007) as well as TS$_{T}$ (Havranek et al 2007, Raj et al 2005, Flevari et al 2007) were present after VT. Flevari et al report, that HRT$_{V}$ and HRT$_{T}$ correlated significantly, although TO$_{T}$ was significantly higher than TO$_{V}$ (but still marginally negative) (Flevari et al 2007). Additionally, both HRT$_{T}$ parameters correlated significantly with HRV parameters: TO$_{T}$ correlated with SDNN (Flevari et al 2007). Analogously, TO$_{T}$ has been shown to correlate with SDNN (Koyama et al 2002, Sestito et al 2004, Ghuran et al 2002, Lindgren et al 2003). TS$_{T}$ correlated with SDNN, left ventricular ejection fraction (LVEF), SDNNI, VLoF and HiF (Flevari et al 2007). Similarly, TS$_{V}$ correlated with LVEF (Koyama et al 2002), SDNN (Cygankiewicz et al 2004, Sestito et al 2004, Ghuran et al 2002, Koyama et al 2002), SDNNI (Cygankiewicz et al 2004, Sestito et al 2004), LoF (Cygankiewicz et al 2004, Sestito et al 2004) and HiF (Cygankiewicz et al 2004, Koyama et al 2002) (further information about HRV parameters can be found in the standards of measurement, physiological interpretation, and clinical use of HRV (Malik et al 1996)).

A turbulence pattern exists after VT, but results of HRT$_{T}$ are ambiguous: Different results can be found regarding the correlation of HRT with the mean interval length of VT (Flevari et al 2007, Havranek et al 2007) and the number of tachycardiac beats (Flevari et al 2007, Raj et al 2005).

In conclusion, ventricular tachycardia triggers HRT$_{T}$ and may be usable for HRT analysis. Like TS$_{V}$, TS$_{T}$ is diminished in subjects with reduced LVEF (Havranek et al 2007, Flevari et al 2007), while TO$_{T}$ is not (Flevari et al 2007). However, the studies used subjects with cardiomyopathies (VT, heart failure (HF)) and no control groups, so a prognostic value of HRT$_{T}$ remains to be analysed. Furthermore, the ambiguous results inhibit a sound deduction whether the number and interval lengths of beats of the VT influence HRT$_{T}$ (see 2.2.3) (Raj et al 2005, Flevari et al 2007, Havranek et al 2007).

### 2.3. Methods to reduce bias on parameter values

HRT can be influenced by various factors. Apart from diseases associated with the impairment of the autonomic nervous system, HRT is biased by age, HR and the number of VPCSs used for the calculation as reviewed by Bauer et al (2008) and Cygankiewicz et al Cygankiewicz et al (2013). The latter two influences have to be taken into account during data collection, because they can have implications on the desired ECGs recording time.

#### 2.3.1. Influences related to recording duration

**Heart rate:** The baroreflex correlates with HR (Melenovsky et al 2005); consequently HRT correlates with HR as well: TS has been shown to be decreased with higher HR (Watanabe et al 2002, Cygankiewicz et al 2004, Kowalewski et al 2007, Bauer et al 2006). Zaza et al reason that the non-linear neural modulation of the HR leads to a rate-dependency of all autonomic markers (Zaza et al 2001). However, TO does not seem to be influenced by HR (Watanabe et al 2002, Cygankiewicz et al 2004). Contrastingly, Schwab et al report a correlation of TO and HR as well as a correlation of TS and HR in men, but not in women (Schwab et al 2004). The authors speculate that this sex-dependent variation is based on a higher sympathetic tone in men as described by Ramaekers et al (1998). Regarding TO an affect of HR is less likely, since TO characterises sudden changes while TS is based on a slow change in HR (Cygankiewicz et al 2004).

**Circadian rhythm:** Since HR shows a circadian rhythm and HRT is dependent on HR, the circadian rhythm can bias HRT parameter values when recording durations shorter or longer than 24 h are used (Hallstrom et al 2004). Even with normalisation with respect to HR, TS has been shown to keep a weaker circadian pattern (Watanabe et al 2007). In this article, even TO showed this rhythm (Watanabe et al 2007), that has not been shown before in studies analysing circadian pattern in HRT (Hallstrom et al 2005, Hallstrom et al 2004, Cygankiewicz et al 2004). A circadian rhythm that is not only based on the HR can be assumed since the incidence of VPCs is higher at day time than night time (Lown et al 1973, Chen 2011).

**Number of VPCS:** With increasing number of VPCSs HRT is attenuated (Chen 2009). Some studies show only a correlation between TS and VPCSs (Cygankiewicz et al 2004, Hallstrom et al 2005) or no correlation at all (Kowalewski et al 2007, Lindgren et al 2003). Three reasons have been proposed for a relationship between the number of VPCSs and HRT: Firstly, Cygankiewicz et al reason that a low incidence of VPCSs indicates a preserved baroreflex sensitivity and consequently a distinctive HRT (Cygankiewicz et al 2004).
Secondly, Chen proposed a baroreflex fatigue caused by a high VPC burden and suggested that longer pauses between VPCSs should be used for HRT calculation (Chen et al 2009). Last, the relationship of TS and the number of VPCSs is mathematically induced (Hallstrom et al 2004). Even for a sequence of 15 normal beats with random variation, the maximising step will find a slope proportional to the standard deviation. This standard deviation in turn depends on the number of VPCSs, because the averaging of the tachogram reduces the standard deviation by a factor of \(1/\sqrt{\#\text{VPCSs}}\).

### 2.3.2. Adjustment of turbulence slope

An approach to bypass these biases on TS is to normalise it with regard to HR and the number of VPCSs used. This parameter would be independent of the circadian pattern and the length of the recording. Several adaptations have been proposed that are discussed below. To reduce confusion we adopted the nomenclature used in the respective original papers.

Cygankiewicz et al adapt TS to HR (Cygankiewicz et al 2004, Cygankiewicz et al 2004) by assuming a relationship of the form:

\[
TS = TS_c \cdot RR^x
\]

where \(TS_c\) is the ‘corrected’ TS, that is the part of TS that is independent of HR. The parameter \(x\) is population-specific. It can be determined by a linear regression of \(\log RR\) against \(\log TS\), since

\[
\log TS = x\log RR + \log TS_c.
\]

For their population, Cygankiewicz et al find a value of \(x = 3.4\). With this, \(TS_c\) becomes

\[
TS_c = \frac{TS}{RR^{3.4}}.
\]

Hallstrom et al used two normalisation steps for HR and the number of VPCSs. First, they rescaled the tachogram to an average HR of 75 bpm before calculation which yields \(nTS\). In a second step, they also address the fact that TS (and also \(nTS\)) is biased towards higher values for a low number of VPCSs. For a set of intervals that should yield a TS of zero, the maximising step in the calculation actually introduces a slope proportional to the standard deviation of the local variation in the intervals. The averaging step before the calculation of this slope reduces this standard deviation, which can be assumed to be equal to RMSSD\(^6\), by a factor of \(1/\sqrt{\#\text{VPCSs}}\). This yields the following formula:

\[
TS_c = 0.02475 \cdot (k - 2)^{0.9449} \frac{\text{RMSSD}}{\sqrt{\#\text{VPCSs}}}.
\]

Here \(k\) is equal to the number of intervals in which TS is calculated (\#TSRR). The numerical parameters were determined by Hallstrom et al by a fit of the formula to simulated data. The new unbiased estimator \(n\)TS is then defined as

\[
nTS = TS - TS_c.
\]

This approach was reused by Yang et al (2005) and D’Addio et al (2014).

The adjustments of TS to HR and the number of VPCSs abolished the dependency on circadian patterns for both parameters as well as the dependency on recording duration for \(n\)TS Hallstrom et al (2004). Like TS the new parameter \(n\)TS is correlated with age Hallstrom et al (2004).

Hallstrom’s \(n\)TS showed the same clinical value as the standard TS: D’Addio et al found a significant difference of TS as well as \(n\)TS‘ in obstructive sleep apnea syndrome (OSAS) patients during normal and obstructive apnea breathing (D’Addio et al 2014). Similarly, Yang et al used \(n\)TS (only adapted to the number of VPCSs) and found a significant decrease of both TS and \(n\)TS in patients with moderate or severe OSAS compared to patients with mild OSAS with both parameters identically inversely correlating with apnea-hypnea index (Yang et al 2005). But the positive and negative predictive value of TS was higher than of \(n\)TS (Yang et al 2005). Still, TS as well as \(n\)TS were both univariate predictors of survival after MI (Hallstrom et al 2005). Cygankiewicz’ adjusted TS\(_c\), too, showed the same results as TS and significantly decreased after CABG surgery (Cygankiewicz et al 2004).

\(\text{RMSSD}\) is the square root of the mean of the squared successive differences between adjacent intervals Malik et al (1996).

\(\text{RMSSD}\) is the square root of the mean of the squared successive differences between adjacent intervals Malik et al (1996).

\(\text{RMSSD}\) is the square root of the mean of the squared successive differences between adjacent intervals Malik et al (1996).
Lin et al also normalised TS to HR, but used 1000 ms as normalisation interval length (Lin et al 2004). Malberg et al introduced a number of other variations of TS (Malberg et al 2004). It was adjusted to the length of the couplI and compI and several blood pressure indices. Both Malberg et al and Lin et al did not compare their adapted TS to standard TS (Malberg et al 2004, Lin et al 2004).

Almost all comparisons between the standard TS and the respective adjusted TS show equal results regarding their usability (D’Addio et al 2014, Yang et al 2005, Hallstrom et al 2005, Cygankiewicz et al 2004). However, an TS adjusted to the HR as well as the number of VPCSs used is less variable and therefore much more comparable.

2.4. Conclusion: data collection
Most articles use 24-h recordings for HRT assessment. However, a minimal number of VPCSs has to be recorded for parameter calculation, which may be a challenge in different populations. Therefore, longer recordings could increase the amount of suitable data similarly to HRT induced by electrical stimuli and HRT calculated from other types of contractions. While extending the recording duration and induced VPCs are not feasible for clinical routine, calculating HRT based on other contractions might increase the accessible data. Best studied is HRT after APCs, but further research is needed to determine the prognostic value of these types of HRT. Particularly, we suggest whether a shifted onset of HRT after a APC in comparison to VPCs can be verified and eventually adapt TS calculation to this shifted onset into account. For HRT assessment, where longer recordings are possible, the extent of HRT variability between days remains to be studied and should be taken into account when determining the optimal recording duration.

Furthermore, HR and the number of VPCSs bias TS. This leads to a dependency of this parameter on the recording duration as well as on circadian rhythm. To cancel this influence we suggest to use a TS adjusted to HR and the number of VPCSs. Nevertheless, to improve comparability we suggest to give the arithmetic mean of the ECG measurement duration and the time of day if the recording durations are no multiple of 24 h as well as the mean of VPCSs used for HRT calculation per patient.

Research questions:

- Can HRT after other arrhythmias be used with a similar prognostic value?
- Is there a day-to-day variability of HRT?
- How long is the optimal recording duration to calculate valid HRT parameter values?

3. Data preparation
As a first step after data collection, the recorded data has to be filtered for suitability. Apart from checking the quality (e.g. noise), data is scanned for two aspects: Firstly, VPCSs have to be suitable for HRT calculation meaning that enough sinus beats have to be present before and after the VPCI and all intervals have a suitable length. Secondly, records must contain a minimal number of suitable VPCSs.

3.1. Filtering criteria
Only snippets that are as free as possible of bias, e.g. other arrhythmias, and which contain effective VPCs with a sufficient prematurity should be included in HRT calculation. Therefore, filtering of the VPCs and their surrounding intervals is necessary. Since filtering criteria of the ECG data determine the input for the calculation, the exact procedure is crucial. In the original publication of HRT no criteria for filtering were suggested (Schmidt et al 1999). The first set of criteria was introduced by Grimm et al (2003) (see the filtering criteria summarised in the section 2.1 or detailed in the appendix). These criteria were repeated almost identically in the HRT guidelines (Bauer et al 2008). Nevertheless, there are many different approaches to filter the interval series before parameter calculation. Some studies report excluding VPCSs containing abnormal beats (arrhythmia or ectopy) or erratic data (artefacts and noise). Commonly, a quantitative filtering is made regarding the length and the range of the inspected intervals.

Length of intervals in a VPCS: The minimal prematurity as well as the minimal length of compI varies in different studies and is sometimes not explicitly stated. The surrounding preRRs and the regular intervals in a VPCS after the compI (postRRs) are either filtered via absolute values or proportionally in comparison to preceding intervals or a calculated reference interval (refI) (see table 1).

Range of checked intervals: The first range in which intervals were checked was introduced by Davies et al consisting of 20 intervals before and after the VPCIs, respectively (Davies et al 2001). The range of 2 preRRs and 15 postRRs, which was proposed by Bauer et al, was first defined by Grimm et al (2003) and propagated.
Table 1. Filtering criteria that differ from the Grimm et al criteria Grimm et al (2003) regarding the length of all intervals in a VPC snippet (VPCS). How many intervals are included as surrounding intervals varies (see paragraph Range of checked intervals). NS: not specified in article.

| Criterion | Refl | References |
|-----------|------|-------------|
| Length of couplI | | |
| 20–80% | Preceding interval | Fazio et al (2010) |
| 88% | NS | Lindgren et al (2003) |
| 100 ms shorter | Preceding interval | Watanabe et al (2007) |
| 'Less' | Preceding interval | Bauer et al (2006) |
| Not 'too long' | - | Manzano-Fernández et al (2011), Casella et al (2006) |
| 'Distinct' | - | Vikman et al (2005) |
| Length of complI | | |
| 110% Mean of five intervals preceding the couplI | Tuomainen et al (2005), Tuomainen et al (2005) |
| 100 ms longer | Preceding interval | Watanabe et al (2007) |
| Not 'too short' | - | Manzano-Fernández et al (2011), Casella et al (2006) |
| 'Distinct' | - | Lindgren et al (2003) |
| 'Full' | - | Goernig et al (2006) |
| Length of surrounding intervals | | |
| 110% Mean of five intervals preceding the couplI | Tuomainen et al (2005), Tuomainen et al (2005) |
| < 2000 ms | - | Watanabe et al (2007) |
| 200–2000 ms | - | Park et al (2014), Malberg et al (2004), Kowalewski et al (2007) |
| 200–2500 ms | - | Kossaify et al (2014) |
| 80–120% | Preceding interval | Bauer et al (2006) |
| 80–120% '5 consecutive sinus intervals' | - | Golukhova et al (2016) |
| 80–120% Mean of all intervals in recording | - | Yoshihisa et al (2014), Walker et al (2016), Moore et al (2006) |
| Not 'very short or long' | - | Cano et al (2008) |

a Notice: The phrasing in the papers is ‘mean’, which probably refers to the arithmetic mean.
b Notice: The phrasing in the papers is ‘mean’, which probably refers to the arithmetic mean.
c The exact type of mean is not specified in the articles.

Most authors do not explicitly specify the checked range before and/or after the VPCIs (176 articles), though some cite Bauer’s guidelines (Bauer et al 2008) or use the algorithm from www.h-r-t.org/.com. Most authors that state the range explicitly use the ranges of 2 preRRs and 15 postRRs, 5 preRRs and 15 postRRs, or 20 intervals before and after, respectively (see table 2).

Although only two intervals are needed for HRT calculation, many studies filter more intervals before the VPC. This is in accordance with the results of Chen showing a negative and positive correlation of TO and TS, respectively, with the number of VPCs within the 2 minutes before the VPC used for HRT calculation (Chen 2009). However, the results may be biased for several reasons: different sample sizes of HRTs with or without preceding VPCs in the study (Chen 2009), the incidence of VPCs due to circadian rhythm (Lown et al 1973, Chen 2011) and the correlation of diminished HRT with a high incidence of VPCs (Cygankiewicz et al 2004).

3.2. Minimal number of VPCs

Number of VPCs needed for HRT analysis: The minimal number of suitable VPCs needed for HRT analysis (#minVPCs) is not explicitly stated in most articles (173). Sometimes a minimal number of VPCs is given as a criterion for a patient’s inclusion in the study; however, these VPCs are not explicitly defined to be part of VPCs suitable for analysis. While Bauer et al suggested 5 VPCs for HRT calculation (Bauer et al 2008), various numbers between 1 and 100 have been used, mostly 5, 1 and 2 (in descending order of the frequency of usage, see table 3).

8 Unfortunately the websites have been offline for some months now, but some snapshots can be found via the Wayback Machine of the Internet Archive: web.archive.org.
Only two articles used a maximal number of VPCs, namely 2400 (Szydlo et al 2011) and 200 (Chen 2009). All numbers used for #minVPCS are merely suggestions, because the optimal #minVPCS has yet to be systematically identified. By now there have only been two studies focusing on #minVPCS: Both did not find any difference of the predictive value of HRT when comparing the whole dataset or just patients with a minimum of 2 (Osman et al 2004) or 4 (Berkowitz et al 2004) VPCs. However, their approach compares two groups where one is the subset of another, which inherently makes finding a difference less probable. Cygankiewicz et al found that TS may be only correlated to the number of VPCs for low absolute numbers of VPCs, while the dependency of HRT on the number of VPCs vanished in patients with more than 10 VPCs (Cygankiewicz et al 2004). A systematic study to find #minVPCS for reliable risk stratification should not only focus on significant differences of HRT parameters between study groups, but on their variances and should be done with a larger range of numbers of VPCs.

Data with insufficient number of VPCs: Most authors do not specify the procedure regarding measurements not meeting the #minVPCS criterion. In most cases it can only be assumed that the subjects were excluded from analysis. The second most common approach is categorising subjects with too few VPCs in a low-risk group. Some studies use the category (HRT0 (Kop et al 2010, Harris et al 2013, Maeda et al 2009, Erdem et al 2013, Marynissen et al 2014, Exner et al 2007, Poliwczak et al 2014) or define these subjects as having ‘normal’ (HRT Stein et al 2011, Hayano et al 2011, Stein et al 2008, Stein et al 2009, Bauer et al 2009, Zuern et al 2012, Huikuri et al 2010, Stein et al 2009, Rizas et al 2017) or being HRT ‘negative’ (Kawasaki et al 2012, Maeda et al 2004, Kai et al 2013, Park et al 2014, La Rovere et al 2012, La Rovere et al 2011, Carton et al 2012). The data situation however is insufficient and contradictory:

Table 2. Number of preRRs and postRRs, that are used for filtering given explicitly in specified references. NS: not specified in article.

| #preRRs | #postRRs | Number of articles | References |
|---------|----------|--------------------|------------|
| 2       | 15       | 9                  | Park et al (2014), La Rovere et al (2012), La Rovere et al (2011), Berkowitz et al (2004), Grimm et al (2003), Kawasaki et al (2015), Stein et al (2011), Secemensky et al (2011), Bissinger et al (2014) |
| 2       | 16       | 1                  | Wustmann et al (2009) |
| 2       | 20       | 3                  | Chen (2011), Casella et al (2006), Schwab et al (2004) |
| 3       | 15       | 1                  | Bauer et al (2006) |
| 3       | 21       | 1                  | Jansen et al (2018) |
| 3-5     | 15-20    | 1                  | Golukhova et al (2016) |
| 3 or 5  | NS       | 1                  | Soquero-Ruiz et al (2018) |
| 5       | 15       | 11                 | Schaeffer et al (2015), Dursun et al (2015), Lenis et al (2013), Lewis et al (2011), Celik et al (2011), Celik et al (2012), Schwab et al (2011a), Tuomainen et al (2005), Tuomainen et al (2005), Kossaify et al (2014), Celik et al (2011b) |
| 5       | 18       | 1                  | Malberg et al (2004) |
| 5       | 20       | 4                  | Pinnacchio et al (2015), Chen et al (2011), Chen (2009), Gil et al (2013) |
| 10      | 20       | 5                  | Martinez et al (2010), Martinez et al (2008), Lindgren et al (2003), Lanza et al (2009), Sestito et al (2004) |
| 12      | 12       | 1                  | Watanabe et al (2007) |
| 12      | 20       | 3                  | Moore et al (2006), Walker et al (2016), Yoshihisa et al (2014) |
| 15      | 10       | 1                  | Wichterle et al (2003) |
| 15      | 15       | 5                  | Wichterle et al (2006), Wichterle et al (2004), Wichterle et al (2004), Flevari et al (2007), Solm et al (2008) |
| 20      | 20       | 12                 | Kawasaki et al (2003), Davies et al (2001), Iwasaki et al (2005), Bonnaemeier et al (2005), Davos et al (2009), Vikman et al (2005), Karakurt et al (2007), Zhong et al (2007), Aytemir et al (2007), Kowalewska et al (2007), Iwasa et al (2005), Yorgun et al (2012) |
| 20      | 20       | 12                 | Kawasaki et al (2003), Davies et al (2001), Iwasaki et al (2005), Bonnaemeier et al (2005), Davos et al (2009), Vikman et al (2005), Karakurt et al (2007), Zhong et al (2007), Aytemir et al (2007), Kowalewska et al (2007), Iwasa et al (2005), Yorgun et al (2012) |
| 20      | 20       | 15                 | Oertel et al (2005) |
| 20      | 20       | 2                  | Rojo et al (2009) |
| NS      | 20       | 1                  | Sahiner et al (2012), Goernig et al (2006) |
| 15 sec  | 20       | 1                  | Raj et al (2005) |
| 15 sec  | 15 sec   | 2                  | Roach et al (2002), Savelieva et al (2003) |
What is the minimal and optimal number of VPCSs to calculate valid HRT parameter values?

What is the optimal handling of subjects with too few VPCSs?

How many preRRs are needed to avoid bias by preceding arrhythmias?

Barthel et al. found no difference between postinfarction patients in groups HRT0 (low risk) and HRT (noncalculable) (Barthel et al. 2003), while Manzano-Fernández et al. show that 5 of 12 subjects classified as HRTx (noncalculable) moved to HRT1 (intermediate risk) or HRT2 (high risk) within 6 days of recording (Manzano-Fernández et al. 2011). However, in contrast to Barthel et al., Manzano-Fernández et al. made no survival analysis so that patients moving to higher risk groups may be false positives (Manzano-Fernández et al. 2011). Additionally, since TS decreases with increasing number of VPCs, ‘worse’ values should be expected with longer measurements. For more information about this influences see section 2.3.3.

For risk stratification in the clinical practice a standardised workflow needs to be established. It must be investigated whether an unsuitable number of VPCSs displays a low risk regarding HRT or whether HRT should be removed from the risk model in that case.

**Table 3. Minimal number of suitable ventricular premature contractions (VPCs) used for heart rate turbulence (HRT) calculation.**

| #minVPCS | Number of articles | References |
|----------|-------------------|------------|
| 1        | 11                | Jeron et al (2003), Aysar et al (2007), Dursun et al (2015), Roach et al (2002), Watanabe et al (2006), Cygankiewicz et al (2008), Kilic et al (2008), Çağırıcı et al (2009), Osman et al (2004), Berkowitsch et al (2004), Wichterle et al (2004) |
| 2        | 6                 | Iwasa et al (2005), Bienias et al (2017), Bienias et al (2015), Wustmann et al (2009), Bonnemeier et al (2003), Moore et al (2006) |
| 3        | 3                 | Wichterle et al (2006), Iwasaki et al (2005), Osman et al (2004) |
| 4        | 1                 | Berkowitsch et al (2004) |
| 5        | 26                | Patel et al (2017), Kop et al (2010), Harris et al (2013), Manzano-Fernández et al (2011), Poliwczak et al (2014), Pinnacchio et al (2015), Carney et al (2007), Wongcharoen et al (2013), Szymanowska et al (2008), Kilit et al (2015), Park et al (2014), Hayano et al (2011), Stein et al (2009), Stein et al (2011), Stein et al (2009), Stein et al (2008), Lenis et al (2013), Stein et al (2010), Stein et al (2010), Ortak et al (2005), Wichterle et al (2004), Casella et al (2006), Savelieva et al (2003), Flevari et al (2007), Watanabe et al (2007), Wichterle et al (2004) |
| 6        | 4                 | Yin et al (2014), La et al (2012), Suzuki et al (2012), D’Addio et al (2013) |
| 9        | 1                 | Ikeda et al (2011) |
| 10       | 1                 | Bonnemeier et al (2005) |
| 15       | 4                 | Martinez et al (2008), Hallstrom et al (2004), Hallstrom et al (2005), Smith et al (2010) |
| 16       | 1                 | Martinez et al (2010) |
| 20       | 1                 | Gil et al (2013) |
| 21       | 1                 | Chen et al (2011) |
| 25       | 1                 | Schaeffer et al (2015) |
| 40       | 1                 | Smith et al (2010) |
| 100      | 1                 | Cygankiewicz et al (2004) |

Barthel et al. investigated whether an unsuitable number of VPCSs displays a low risk regarding HRT or whether HRT should be removed from the risk model in that case.

### 3.3. Conclusion: data preparation

After the common step of ensuring the quality of a recording, the VPCSs need to be sorted out. Therefore, filtering criteria specify the length of the intervals and the range that has to be checked. These criteria are mostly not mentioned in the literature and if mentioned vary widely. We suggest the usage of Grimm’s filtering criteria for the time being (Grimm et al. 2003). One exception from these criteria should be the number of preRRs being 5 intervals instead of just 2, because these intervals are used as reference for other filtering criteria. It should be analysed how many intervals before the couplI are suitable to exclude VPCSs that are directly preceded by a VPC and are therefore biased. It is noteworthy, that the number of postRRs should be longer or equal to #TSRR.

The #minVPCS mostly used is 1, 2 or 5. The optimal #minVPCS still needs to be determined systematically in a large sample considering the difficulty of low incidence of VPCs on one hand and statistical validity of a sufficient amount of data points on the other. Subjects with less VPCSs are either excluded from the studies or classified as having low risk. It must be investigated which procedure is optimal for risk stratification in the clinical setting.

**Research questions:**
- What is the minimal and optimal number of VPCSs to calculate valid HRT parameter values?
- How many preRRs are needed to avoid bias by preceding arrhythmias?
- What is the optimal handling of subjects with too few VPCSs?
4. Data analysis

After collecting a minimal amount of suitable VPCSs, HRT parameters can be calculated. The most common parameters are TO and TS as defined by Schmidt et al (1999) and the new parameter turbulence timing (TT). Although these parameters are equally calculated in most of the inspected articles, the number of intervals in which TS is calculated varies as well as the calculation order of all parameters.

4.1. Turbulence onset

Most studies (203) follow the calculation process suggested by Schmidt et al (1999). In 136 articles the method is explicitly stated, in 67 a calculation reference is given. In 31 studies TO is used, but no calculation or reference is described. TO is consistently calculated with the two intervals before and after the VPCIs, respectively, and is hardly calculated with a different approach.

4.2. Turbulence slope

In most studies #TSRR is either 15 as first suggested by Barthel et al (2003) or 20 intervals as suggested by Schmidt et al (1999). In 129 articles the range is explicitly stated; 77 provide only a calculation reference. Apart from this the calculation process remains the same. Some studies examine the use of TS that was adjusted to several biases, which we describe in 2.3.2. For higher comparability we suggest to use this adjusted TS as defined by Hallstrom et al (2004) instead of the original TS.

4.3. Turbulence timing

The most commonly calculated HRT parameter apart from Schmidt’s originals is turbulence timing (TT). It was first defined by Watanabe et al as the index of the first interval in the interval series, whose regression line has the steepest slope and is therefore used for the TS calculation (Watanabe et al 2002). It has been used since then in nine of the studies inspected here (Schwab et al 2004, Schwab et al 2005, Bonnemeier et al 2005, Ortak et al 2005, Schwab et al 2005, Watanabe et al 2006, Średniawa et al 2010, Cebula et al 2012, Bonnemeier et al 2003). Its value ranges from 1 to #TSRR-4.

TT was positively correlated with HR (Watanabe et al 2002, Średniawa et al 2010). While Schwab et al found no gender-dependent difference of TT (Schwab et al 2004), Średniawa et al found TT to be significantly higher in women than in men (Średniawa et al 2016). No conclusion is possible, since women have significantly higher HR in the study population of Schwab et al and Średniawa et al do not mention HR as a covariate (Schwab et al 2004, Średniawa et al 2016). While no differences of TT could be found between postinfarction patients 10 days and 1 year after MI (Ortak et al 2005), TT was an independent risk stratifier for major adverse cardiac event (Cebula et al 2012) and all-cause mortality (Średniawa et al 2016) after MI as well as in patients before and after percutaneous coronary intervention (Bonnemeier et al 2003) or carvedilol and metoprolol treatment of acute myocardial infarction (AMI) (Bonnemeier et al 2005). Additionally, TT was identified as the most powerful risk predictor for development of end-stage heart failure in patients with stable congestive heart failure (CHF) (Średniawa et al 2010).

The only cut-off for TT used by now is 10. It was determined by Średniawa et al, because it was the ninth decile in another study. Unfortunately, this result could not be found in any of the references given for TT (Średniawa et al 2010). Nevertheless, with this cut-off abnormal values were found in 30% of investigated patients with stable CHF (n = 110) (Średniawa et al 2010), in 28.6% MI patients (n = 500) (Cebula et al 2012) and 28.6% MI patients (n = 489) (Średniawa et al 2016). To this day, no study used this cut-off on a healthy study group to evaluate its specificity.

4.4. Numbers of intervals used for TS calculation

Until now the optimal #TSRR has not been studied. One standardised range is crucial for comparability, because differing #TSRR can lead to different filters and therefore different VPCS sets as well as diverging TS values for the same VPCs. The optimal range can possibly be deducted from TT, since it describes the first interval of the sequence used to calculate TS. An analysis of the statistical keypoints of this parameter might indicate the optimal value of #TSRR.

Table 4 shows values for TT that have been obtained by articles covered in this work.

The arithmetic mean TT ranges from 3.6 ± 1.0 (Watanabe et al 2006) to 7.3 ± 3.0 (Średniawa et al 2010), meaning that in most cases 15 intervals seem to be suitable as #TSRR. It must be noticed that the choice of #TSRR limits the maximal value of TT and can thus bias the results. Apart from that, a short #TSRR is favourable to increase the number of available VPCSs. Since a turbulence appears in proximity to the VPC, we hypothesise that TS with a TT of 7 or more, meaning a #TSRR of more than 10, just presents random fluctuation rather than HRT. Watanabe et al found 6 to be the maximum TT of all subjects, so 10 was defined to be the minimum number of intervals needed after a VPC to calculate HRT (Watanabe et al 2006). In
The intra-subject variability in TT could also be used to distinguish between TS occurring randomly and based on autonomic regulation. For this, TT must be calculated before the tachogram is averaged. If the turbulence is based on a regulated mechanism, it is likely to be similar for each VPCS, thus having little intra-subject variance. If autonomic regulation is failing, however, and TT is calculated from random fluctuations, the variance should be considerably higher, while the TS can still lie in the normal range. However, no results of correlation analysis between TT and TS have been published by now apart from Cebula et al, who found no correlation between all HRT parameters (Cebula et al 2012). Thus, the optimal #TSRR remains to be determined.

### 4.5. Calculation order

TO as well as TS are influenced by the order of their calculation: Schmidt et al propose to first calculate TO in each VPCS and average the results afterwards while TS should be calculated from the averaged tachogram (Schmidt et al 1999). In a few studies TO was calculated from the averaged tachogram instead (Solem et al 2008, Wichterle et al 2006, D’Addio et al 2013, Huikuri et al 2010, Schwab et al 2004, Lin et al 2002, Yang et al 2005, Wichterle et al 2007). More commonly the calculation order of TS is reversed, calculating individual values for each VPCS which are then averaged (Wichterle et al 2003, Chen et al 2011, Savelieva et al 2003, D’Addio et al 2010, Davies et al 2001, Davos et al 2009, Yalta et al 2007, Erdem et al 2015, Golukhova et al 2016, Chen et al 2009, Chen et al 2010, Roach et al 2002, Erdem et al 2012, Erdem et al 2012, Lin et al 2004, Watanabe et al 2006, Erdem et al 2013).

Chen et al showed, that the order of the workflow has an impact on the parameter values: Though the results from both methods were significantly correlated for both parameters, the arithmetic mean of TS after Schmidt’s method was considerably lower than TS with averaging afterwards. Since averaging smooths the slope due to different TT, it decreases the overall slope in the tachogram and therefore decreases TS. This difference is most notable when TS values are very low (Chen et al 2011). Thus, averaging the TS results afterwards leads to classification in lower risk groups compared to Schmidt’s method as shown by Chen et al (2011), Soguero et al (2013). Notice, that Soguero et al used a different approach to assess HRT categories, thus results may change when the data were assessed as usual (Soguero et al 2013). Nevertheless, the order of calculating and averaging of the HRT parameters affects the results and should therefore be performed uniformly. While averaging the tachogram first reduces noise, assessing TS from the separate tachograms takes into account the variable onset of the HR acceleration.

### 4.6. Mean vs. median

In the original article by Schmidt et al, the method description uses the general term ‘average’, but the numbers given in the article fit the definition of the arithmetic mean (Schmidt et al 1999). Accordingly, the arithmetic mean is mostly used as descriptor for HRT. Few studies use the median (Savelieva et al 2003, Witham et al 2012) or a trimmed mean (Marine et al 2002) instead.

### 4.7. Conclusion: data analysis

TO is almost consistently calculated as described by Schmidt et al. TS is calculated differently with either 15 or 20 intervals in which the slope is measured. The new parameter TT might help to determine the optimal range for #TSRR. It is defined as the index of the first interval from which TS is calculated and therefore provides information about the occurrence on TS after the VPC. A first analysis leads to #TSRR of 10, but this needs in-depth investigation. However, TT is a new parameter that is easy to assess without additional

### Table 4. TT values determined in research, SD = Standard deviation, n = number of subjects, Ref [x] = number for #TSRR given in reference, when it was not explicitly stated in the article.

| Arithmetic mean ± | n   | Disease pattern | #TSRR | Source |
|-------------------|-----|-----------------|-------|--------|
| 5.6 ± 3.5         | 8   | various         | 20    | Segerson et al (2007) |
| 7.1 ± 3.1         | 489 | AMI             | 15-20 | Šredniawa et al (2016) |
| 7.3 ± 3.0         | 110 | CHF             | 20    | Šredniawa et al (2010) |
| 7.1 ± 3.1         | 500 | AMI             | Ref [15] | Cebula et al (2012) |
| 6.1 ± 2.6         | 92  | MI              | Ref [20] | Ortak et al (2005) |
| 6.2 ± 2.3         | 92  | MI              | Ref [20] | Ortak et al (2005) |
| 5.8 ± 2.4         | 40  | AMI             | Ref [20] | Bonnemeier et al (2005) |
| 6.1 ± 2.1         | 39  | AMI             | Ref [20] | Bonnemeier et al (2005) |
| 3.6 ± 1.0         | 52  | VT              | 10-20 | Watanabe et al (2006) |
| 3.7 ± 1.1         | 52  | various         | 10-20 | Watanabe et al (2006) |
| 4.8 ± 1.8         | 28  | various         | Ref [20] | Watanabe et al (2002) |
cost and has been shown to be a feasible risk stratifier. Therefore, we suggest to further investigate its usefulness and possible cut-offs. Another variation of TO and TS calculation is the order of the calculation steps. In some studies they are reversed to Schmidt’s original approach. Whether the tachogram itself or the parameter values from single VPCSs should be averaged is not comprehensively studied yet. If parameters are calculated from single VPCSs, they should be given as arithmetic mean.

Research questions:

• How many intervals are sufficient for #TSRR?
• In which order should TO and TS be calculated?

5. Classification

The main usage of HRT is risk stratification. For this purpose, every HRT parameter is dichotomised on the basis of given cut-off values. As supposed by Schmidt et al many studies used the cut-offs 0% for TO (138 articles) and 2.5 ms/RR for TS (136 articles). Other articles proposed alternative cut-offs. Depending on the dichotomisation of each parameter, the record can be classified into risk or non-risk categories. Different classification systems have been established from two to five categories.

5.1. Cut-off values

Alternative Cut-off Values: Some authors suggest other cut-off values (see tables 5 and 6). These values are either statistical descriptors like the median or determined with receiver operating characteristics (ROC) analysis. Accordingly, Cygankiewicz et al used the quartiles of their coronary artery disease (CAD) population –0.37% for TO and 4.25 ms/RR for TS, because Schmidt’s cut-offs were determined for postinfarctional patients (Cygankiewicz et al 2004, Cygankiewicz et al 2004, Cygankiewicz et al 2003, Cygankiewicz et al 2003). Likewise, quartiles were used in stable CAD patients by Sestito et al (2004). Medians were also used as cut-offs, namely 0.1% (TO) and 2.0 ms/RR (TS), for patients with cardiomyopathy after implantable cardioverter defibrillator implantation (Seegers et al 2016) and 0.005% (TO) for risk-stratification of disease deterioration in patients with liver cirrhosis (Jansen et al 2018).

The following studies performed ROC analysis to determine optimal cutoffs: Schaeffer et al identified 3.95 ms/RR to be the optimal cut-off to stratify risk of cardiac events in patients with Marfan syndrome (Schaeffer et al 2015). Perki et al reported TS to predict HF hospitalization in postinfarctional patients with the cut-off 1.29 ms/RR (Perki et al 2010), while TS failed to predict cardiac events in the same population with the cut-off 1.3 ms/RR (Perki et al 2008). Huikuri et al found 2.0 ms/RR as cut-off, with which TS was predictive for arrhythmic events in postinfarctional patients (Huikuri et al 2010). Balcioğlu et al suggested 3.32 ms/RR to detect cardiac autonomic neuropathy in patients with diabetes mellitus (Balcioğlu et al 2007). Karakurt et al used 1.2 ms/RR for TS and found a significant correlation between TS and mortality rate in children with DCM (Karakurt et al 2007). In patients with acute decompensated HF TS with a cut-off of 1.695 ms/RR was predictive for cardiac events (Yamada et al 2018). Yuan et al did not find any prognostic power of TO and TS with the cut-off values -1.17% and 12.1 ms/RR, respectively, in patients with acute coronary syndrome (ACS) (Yuan et al 2015).

Some studies compared their suggested cut-offs with the original values and showed a similar performance of both cut-off types: Schmidt’s cut-off values as well as quartiles (0.025% and 1.27 ms/RR) and continuous values were all useful to predict all-cause mortality in patients with CHF caused by ischemic cardiomyopathy (Cygankiewicz et al 2006). The quartiles 0.22% for TO and 1.42 ms/RR for TS were used for CHF patients, but no difference was found compared to the results using Schmidt’s cut-off values (Cygankiewicz et al 2008). Quartiles 0.31% and 1.5 ms/RR were used for risk stratification in MI patients, but showed no significant results (Berkowitsch et al 2004). A cut-off of 3.2 ms/RR for TS was proposed in postinfarctional patients with malignant ventricular arrhythmias, though its performance was similar to Schmidt’s cut-off regarding sensitivity and specificity (Szydło et al 2011).

Some new cut-off values yielded better results than Schmidt’s values. In the Cardiovascular Health Study, investigating cardiovascular disease in older adults, the cut-off 3.0 ms/RR for TS was used (Patel et al 2017, Kop et al 2010, Stein et al 2011, Stein et al 2010, Stein et al 2008). In contrast to Schmidt’s settings, this value showed a significant correlation between cardiac death and TS (Stein et al 2011). The predictive capability of TS with the new cut-off has also been shown in other studies as well, but without comparison to the traditional values (Stein et al 2010, Koyama et al 2002). A comparison of the cut-off values by Stein et al and Schmidt et al with data from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study showed that Stein’s TS cut-off had a slightly higher sensitivity but slightly lower specificity than Schmidt’s value (Stein et al 2009). Other cut-offs showing improved performance were -1.52% (4th decile) and 4.9 ms/RR (6th decile). In contrast to Schmidt’s cut-offs, these values allowed HRT parameters to
Table 5. Cut-off values for TO in %. New cut-offs were determined in different populations on the basis of statistical descriptors or ROC analysis. The performance was tested in comparison to the traditional cut-off value 0%. +: better performance. =: no difference in performance. ∗: no comparison described.

| Cut-off | Derivation | Subjects | Performance | References                      |
|---------|------------|----------|-------------|---------------------------------|
| -1.52   | Decile     | Unstable angina pectoris | +           | Lanza et al (2009)              |
| -1.17   | ROC        | ACS      | *           | Yuan et al (2015)               |
| -0.37   | Quartile   | CAD      | *           | Cygankiewicz et al (2004), Cygankiewicz et al (2004), Cygankiewicz et al (2003), Cygankiewicz et al (2003) |
| -0.26   | Quartile   | CAD      | *           | Sestito et al (2004)            |
| 0.005   | Median     | Liver cirrhosis | *           | Jansen et al (2018)             |
| 0.022   | Quartile   | CHF      | =           | Cygankiewicz et al (2008)       |
| 0.025   | Quartile   | CHF      | =           | Cygankiewicz et al (2006)       |
| 0.1     | Median     | Cardiomyopathy | *           | Seegers et al (2016)            |
| 0.31    | Quartile   | MI       | =           | Berkowitsch et al (2004)        |
| NS      | ROC        | Myocardial ischemia | *           | Solem et al (2008)              |
Table 6. Cut-off values for TS in ms/RR. New cut-offs were determined in different populations on the basis of statistical descriptors or ROC analysis. The performance was tested in comparison to the traditional cut-off value 2.5 ms/RR. +: better performance. =: no difference in performance. *: no comparison described. **: in Stein et al (2010) and Koyama et al (2002) no comparison was described.

| Cut-off | Derivation | Subjects | Performance | References |
|---------|------------|----------|-------------|------------|
| 1.2     | ROC        | DCM, children | *           | Karakurt et al (2007) |
| 1.27    | Quartile   | CHF      | =           | Cygankiewicz et al (2006) |
| 1.29    | ROC        | MI       | *           | Perki et al (2010) |
| 1.3     | ROC        | MI       | *           | Perki et al (2008) |
| 1.42    | Quartile   | CHF      | =           | Cygankiewicz et al (2008) |
| 1.5     | Quartile   | MI       | =           | Berkowitsch et al (2004) |
| 1.695   | ROC        | Acute decompensated HF | * | Yamada et al (2018) |
| 2.0     | Median     | Cardiomyopathy | * | Segers et al (2016) |
| 2.0     | ROC        | MI       | *           | Huikuri et al (2010) |
| 2.12    | Quartile   | CAD      | *           | Sestito et al (2004) |
| 3.0     | Cox regression | Cardiovascular Disease | + | Stein et al (2008), Stein et al (2010), Patel et al (2017), Stein et al (2009), Stein et al (2011)** |
| 3.0     | NS         | Cardiovascular Disease | + | Koyama et al (2002), Kop et al (2010)** |
| 3.2     | ROC        | MI       | =           | Szydlo et al (2011) |
| 3.32    | ROC        | Diabetes mellitus | = | Balcioglu et al (2007) |
| 3.95    | ROC        | Marfan syndrome | * | Schaeffer et al (2015) |
| 4.25    | Quartile   | CAD      | *           | Cygankiewicz et al (2004), Cygankiewicz et al (2004), Cygankiewicz et al (2003), Cygankiewicz et al (2003) |
| 4.9     | Decile     | Unstable angina pectoris | + | Lanza et al (2009) |
| 12.1    | ROC        | ACS      | *           | Yuan et al (2015) |
| NS      | ROC        | Myocardial ischemia | * | Solem et al (2008) |
be independent predictors for all cause and cardiac mortality in patients with unstable angina pectoris (Lanza et al. 2009).

It is difficult to find a single cut-off value which is suitable for different datasets, even with the same patient background. Only three new cut-off values have been used in more than one study (see tables 5 and 6). However, most of these studies are either based on the same dataset (Stein et al. 2008, Patel et al. 2017, Stein et al. 2011, Kop et al. 2010) or do not compare the new cut-off with Schmidt's original values (Cygankiewicz et al. 2004, Cygankiewicz et al. 2004, Cygankiewicz et al. 2003, Cygankiewicz et al. 2003).

**Different populations:** It is important to notice that cut-off values have first been set for postinfarction patients (Schmidt et al. 1999). In the following, HRT has been used for patients with other pathological background without setting new cut-off values. For example, the standard cut-offs were used in chronic obstructive pulmonary disease (Gunduz et al. 2009), diabetes mellitus (Lin et al. 2017, Balcioglu et al. 2007) or metabolic syndrome (Erdem et al. 2014, Yilmaz et al. 2006, Balcioglu et al. 2016), even apparently healthy subjects (Schwab et al. 2004, Poręba et al. 2011, Grimm et al. 2003).

Additionally, Yilmaz et al. analysed children, while Schmidt et al. analysed elderly patients (Yilmaz et al. 2006, Schmidt et al. 1999). Due to the age-dependency of HRT, however, it can be expected that other values should be used for different age groups (Schwab et al. 2005). This is done by Stein et al., because the population's age was higher than the population used for Schmidt's cut-offs. A new cut-off 3.0 ms/RR for TS was determined (Stein et al. 2008). This is interesting, since heart rate turbulence is decreased with increasing age (Schwab et al. 2005), thus a lower cut-off would have been expected in elderly people.

The cut-off values are also used in the context of medical treatments, e.g. to show an effect of elective gynecologic surgery on autonomic functions (Tekieloglu et al. 2013) or compare different types of hemodialysis (Kaplan et al. 2016). Since HRT is a feasible marker for autonomic functionality, it might be used for these purposes, but specialised cut-offs should be determined for every population.

**Number of false-positives:** Although the standard cut-off values for high-risk patients after infarction were established on the basis of a large population, there are indications that these values still need optimisation. Some studies have reported false-positives, when examining patients indicated for assessment of supraventricular arrhythmias (Vukajlovic et al. 2006) or apparently healthy subjects (Grimm et al. 2003, Schwab et al. 2004). This especially relates to TO. Therefore, Grimm et al. even recommended that only TS is to be used, because TO is not specific enough (Grimm et al. 2003).

**Customised cut-offs:** Instead of using a fixed value, a formula could determine an adaptive cut-off value. This would adjust the cut-off value to the background of the given dataset, avoiding the necessity to determine a great amount of cut-off values for different populations and use cases. However, this approach has not been implemented in the literature and is impractical for risk stratification in the medical routine.

### 5.2. Classification systems

Based on the cut-offs, subjects are categorised as having distinctive HRT (with low risk of adverse outcome) or having impaired HRT (with high risk). The most common categorisation system is defined by Ghuran et al. composed of the three categories: (1) TO and TS normal, (2) either parameter abnormal, and (3) both parameters abnormal (Ghuran et al. 2002). The categories are generally called HRT0-2 and are used for dichotomisation in 23 inspected articles (Maeda et al. 2009, Li et al. 2012, Yin et al. 2014, Kaplan et al. 2016, Soguero et al. 2018, Uzna et al. 2018, Lewek et al. 2009, Balcioglu et al. 2015, Schaeffer et al. 2015, Yoshihisa et al. 2014, Cygankiewicz et al. 2008, Cygankiewicz et al. 2013, Park et al. 2014, Trzos et al. 2008, Bauer et al. 2006, Poręba et al. 2014, Gać et al. 2014, Suzuki et al. 2012, Bauer et al. 2005, Berkowitsch et al. 2004, Secemsky et al. 2011, Stein et al. 2009, Erdem et al. 2012).

Simpler classifications are: 'HRT positive' (both parameters abnormal) or 'HRT negative' (one or both normal) (Miwa et al. 2009, Miwa et al. 2011, Miwa et al. 2012, Ikeda et al. 2011, Kawasaki et al. 2015); 'HRT' (both parameters normal) and 'non-HRT' (one or both abnormal) (Roach et al. 2002); 'HRT abnormal' and 'HRT normal' with either the same definition (Hayano et al. 2011) or already classifying subjects with one abnormal parameter as 'HRT abnormal' (Cetin et al. 2014, Park et al. 2014).

Stein et al. and D’Addio et al. used categories HRT0-2, but differentiated HRT1 into ‘TO abnormal’ and ‘TS abnormal’ (Stein et al. 2011) or HRT1a (TO abnormal) and HRT1b (TS abnormal) (D’Addio et al. 2013), respectively. One system was introduced that considers the number of VPCs: Carney et al. suggested the two new classes ‘a’ with less than 5 VPCs and ‘b’ with a sufficient number of VPCs but not calculable because of artifacts etc. The standard classes HRT0-2 are called c-c, respectively (Carney et al. 2007). It should be investigated, whether a simplification of the classification system yields sufficient results or a differentiation provides added value. Only Barthel et al. reported analysing the discriminative power of the used categories, resulting in combining HRT0 and HRT2 (Barthel et al. 2003).

When not only TO and TS but also TT are analysed, the three categories A (all normal), B (at least one abnormal) and C (all abnormal) have been used (Sredniawa et al. 2016, Cebula et al. 2012). The classification...
into HRT0-2 displays HRT at one point in time. To show HRT changes, Kurpesa et al grouped patients into the categories type I (improvement of both parameters), II (worsening of both) and III (improvement and worsening of one, respectively) (Kurpesa et al 2007).

5.3. Conclusion: classification
If subjects are dichotomised, Schmidt’s cut-off values are mostly used. Different cut-offs for several populations have been proposed with equal or better results than the original cut-offs, but none can clearly be recommended. The cut-off 0% of TO leads to more values being classified abnormal and therefore a higher false-positive rate than the cut-off 2.5 ms/RR of TS. Cut-off values should be reviewed with the result of either new cut-off values for different population backgrounds like medical condition and age or mathematical formulas for adaptive cut-off calculations.

On the basis of these cut-offs subjects can be categorised into different risk classification systems. The most common is a classification into the three groups HRT0 (both parameters normal, low risk), HRT1 (one parameter normal, intermediate risk) and HRT2 (both parameters abnormal, high risk.) Other systems consider subjects that fall short of suitable VPCs, the new parameter TT or HRT development between two points in time. The usefulness of these classification systems with more or less groups than HRT0-2 should be studied. If subjects are categorised into groups, the handling of subjects with an insufficient number of VPCs should be described.

Research questions:

• Which cut-off values are optimal for which population and question?
• Is there an alternative for hard cut-off values?
• Are other classification systems more suitable than the standard HRT0-2?
• Are the prognoses of subjects in categories HRT0 and HRT2 comparable?

6. Description of HRT assessment

When reviewing the methodology used in the 240 inspected articles we encountered missing, unspecific or conflicting descriptions. Transparency and reproducibility depend on full disclosure of the used methodology of a study. Therefore, we summarise the steps of HRT assessment that most commonly have not been sufficiently described.

6.1. Recording duration

Some articles provide no recording duration at all (Yang et al 2013, Sandberg et al 2014, Lenis et al 2013, Lenis et al 2013). As mentioned, most articles only state the planned recording duration (see section 2.1), not the actual recording duration that could help estimate the bias on TS. Some authors report the average of the actual recording duration as the arithmetic mean (Tuomainen et al 2005, Balcioğlu et al 2007, Lammers et al 2006, Kowalewski et al 2007, Bienias et al 2015, Liu et al 2014, Secensky et al 2011, Balcioğlu et al 2015, Lindgren et al 2003), others as the median (Balcioğlu et al 2016, Balcioğlu et al 2016, Bienias et al 2010a, Bienias et al 2010b, Wichterle et al 2004, Bienias et al 2010c, Bonnemeier et al 2003, Ortak et al 2005, Zhong et al 2007, Wichterle et al 2004, Bonnemeier et al 2005). Some articles of the same first authors report different types of means (Balcioğlu et al 2015, Balcioğlu et al 2016, Balcioğlu et al 2007, Balcioğlu et al 2016, Bienias et al 2010a, Bienias et al 2010b, Bienias et al 2010c, Bienias et al 2015).

6.2. Number of VPCs

As with recording duration, the arithmetic mean of the number of VPCs actually used for HRT calculation is rarely provided. If a number is mentioned, most of the times it is not transparent whether the number includes different kinds of ectopic beats, all VPCs or just VPCs used for analysis. Additionally, the number may be absolute or extrapolated for 24 h. 46 articles give the mean of VPCs per hour or day, partly even before filtering out patients without suitable VPCs, while 129 articles give no number of VPCs at all. Only in 27 of the 240 articles studied the mean of VPCs in the recording per patient is stated absolutely as either arithmetic mean (17), median (9) or both (1). Again, the majority of these articles report the overall number of VPCs, not the number of VPCs suitable for HRT calculation, or the number is not clearly described. In contrast, Wichterle et al stated the numbers of VPCs and APCs, both recorded and suitable for analysis, respectively, listing four medians (Wichterle et al 2004).

6.3. Filtering criteria

In contrast to the calculation methods, most articles explain their filtering criteria either very briefly or not at all. Examples include vague descriptions such as ‘very short or long cycle lengths’ (Cano et al 2008), no ‘too
long' couplI or 'too short' compl (Mazano-Fernández et al 2011) or no 'inappropriate RR intervals' (Mazano-Fernández et al. 2011). Some articles describe filtering only as 'manual review' (Balcioglu et al 2007, Arslan et al 2008, Ozdemir et al 2007) or 'visual examination' (Stein et al. 2010).

The refI is often defined ambiguously, for example as '5 consecutive sinus intervals' (Golukhova et al 2016), 'normal RR-interval' (Jochum et al. 2012), 'the sinus RR interval' (Jeron et al 2003) or 'normal interval' (La et al 2011, La et al 2012), not giving the range on which basis refI is calculated.

Some articles give as filtering reference the HRT analysis software HRT View or the algorithm from www.h-r-t.org/, but their reported values of the number of intervals used for filtering differ from the default values of the software tools (2 preRRs and 15 postRRs) (Wustmann et al. 2009, Dursun et al. 2015, Celik et al. 2011, Karakurt et al. 2007, Yorgun et al. 2012, Celik et al. 2011b, Schwab et al. 2011a, Celik et al. 2012, Grimm et al. 2003, Iwasa et al. 2005).

6.4. Calculation
As mentioned, #TSRR is often explicitly stated or given with a calculation reference. However, of the articles stating this parameter explicitly, 43 studies use a different range than the respective calculation reference. In three articles the range 15 to 20 intervals is given without further explanation which number is used in which case (Szymanowska et al. 2008, Soguero et al. 2013, Średniawa et al. 2016).

6.5. Conclusion: description of HRT assessment
Mostly the actual recording duration is not provided in the literature, but only the planned recording duration. Descriptions differ between the arithmetic mean and the median. Similarly, the number of VPCs used for calculation is mostly missing. Since TS is correlated with the number of VPCs and therefore the length of the recording, comparability between studies is only given if the mean of the actual recording duration – or better the number of actually used VPCs – is stated.

Filtering criteria are usually not or only partially given. The #TSRR as all calculation steps is usually provided, however, many studies use a different range than the respective reference for the calculation workflow. Unclear definitions and therefore varying filtering criteria lead to a selection of different sets of VPCs out of the same data and consequently to different results. Of course references can be given for the used workflow, which creates the need to accurately carry out HRT assessment as stated there.

7. Conclusion
We studied the methodology assessing HRT parameter values since the original description of HRT (Schmidt et al. 1999) in 240 articles. Since 1999 the methodology has barely changed. The most substantial adjustment was the description of filtering criteria in 2003 (Grimm et al. 2003). Despite the summary of the then present methodology in 2008 (Bauer et al. 2008), many different approaches have been used before and after the publication of these guidelines.

HRT is mostly assessed from 24-h recordings. To increase the number of suitable VPCs, the recording duration can be extended, VPCs can be triggered or HRT can be calculated after other contractions, namely APCs, VT and premature sinus beats. For clinical practice only increasing the data base through other triggers is feasible, for which APCs are most promising. However, more research is needed to determine the usability of HRT after APCs.

The recording duration and the circadian rhythm influences TS, because the parameter is correlated with HR and the number of VPCs. Therefore, we suggest to use a TS adjusted to HR and the number of VPCs (Hallstrom et al. 2004). Several adjusted TS parameters have shown the same prognostic value as TS, but increase comparability between studies.

A step mostly not disclosed in literature and with the most variations is filtering. With minor changes we suggest the usage of Grimm’s filtering criteria (Grimm et al. 2003). Also widely varying is the number of suitable VPCs needed for calculation. The optimal #minVPCs still needs to be determined systematically as well as the handling of subjects with less VPCs.

The calculation workflows vary considerably less than the filtering. Only the optimal range in which the regression line for TS calculation is determined and the calculation order of TO and TS vary. Both need further investigation. A new parameter TT, that is the index of the first interval of the TS regression line, is easy to assess without additional cost and has been shown to be a feasible risk stratifier. Therefore, we suggest to add it to future HRT assessments.

9 Unfortunately the websites have been offline for some months now, but some snapshots can be found via the Wayback Machine of the Internet Archive: web.archive.org.
HRT is mostly used for risk stratification using the cut-off values proposed by Schmidt et al. However, cut-off values are needed for different population backgrounds. The most common classification consists of the three groups HRT0-2. The usefulness of other classification systems with more or less groups than HRT0-2 should be studied.

Many methodological details were not or incompletely given in the literature. This includes the actual recording duration, number of VPCSs used for calculation and the filtering criteria. Regarding the number of intervals used to calculate T5 the descriptions and references given in some articles were contradictory. We recommend to precisely provide the HRT assessment steps (see Suggested methodology as template).

The current state of HRT research is found lacking in comparability, transparency and thus reproducibility as well as control for confounding variables. As it is, this systematic review, although involving all published papers on the topic that are listed on PubMed, cannot constitute conclusive evidence how HRT should be assessed to achieve reliable classification of subjects. There are many contradicting results that may not be due to a limited predictive power, but due to limitations caused by the varying assessment of HRT. We believe that with further research and uniformly used assessment standards HRT can become a more useful and common risk stratifier in clinical practice.

8. Limitations

Our study has a few limitations: There is a risk of bias in the assessment of the frequency of a certain approach in the literature, since there are groups working intensively on the subject and thus particular methodologies of these groups are more frequently used and therefore more common than methodologies of other researchers. Furthermore, we included only original papers that were listed on PubMed.

Acknowledgment

We would like to thank Prof. Dr Alexander Goesmann at the Justus-Liebig-University Giessen for fruitful discussions and for his valuable advice regarding the manuscript.

Author contributions

V B and A D conceived the project, V B performed the literature research and data analysis and drafted the manuscript, and C.S., G.E. and A.D. revised it.

Methodological details

Articles were gathered in a PubMed search with the term ‘heart rate turbulence’ and the setting ‘[All fields]’. No more limitations were set to maximise the retrieval recall. As a first screening step duplicates were removed. Secondly, all records that were no original articles or were not written in English were excluded. For the remaining articles all full-texts were obtained and examined for HRT assessment. The type of the studies as well as participant background, interventions, outcomes and study design were not considered as long as HRT calculation was performed. All articles describing studies without HRT assessment or without applicable full-text were excluded. The articles included in the study were examined for several aspects regarding the filtering and calculation of HRT.

HRT is calculated on the basis of the VPCS, the ECG segments consisting of the VPCs and the surrounding intervals. For more clarity we use the term VPC only for the premature beat itself and VPCS for all intervals that are used for calculation or filtering, including couplI, compI and surrounding intervals. The couplI and compI are combined under the term VPCIs.

Aspects evaluated in the study were as follows:

• $\bar{\phi}$ h: arithmetic mean of the actual recorded hours of ECG measurement per subject
• VPCS filtering criteria: criteria used to filter VPCSs in order to determine if they are suitable for HRT calculation
• $#\text{preRR}$: number of intervals before the couplI that are used for filtering
• $#\text{postRR}$: number of intervals after the compI that are used for filtering
• $#\text{minVPCS}$: minimal number of suitable VPCSs needed for each subject to be eligible for HRT calculation
• VPCSs $<$ $#\text{minVPCS}$: handling of subjects with too few suitable VPCSs

10 https://www.pubmed.de/gateway/nlm-pubmed/.
• COTO: cut-off for TO, if used
• COTS: cut-off for TS, if used
• #TORR: number of intervals used before and after VPC to calculate TO
• #TSRR: number of intervals in which the 5-interval-sequence for TS calculation was assessed (see calculation of HRT below)
• ø VPCSs: arithmetic mean of VPCSs included in calculation for each subject
• Other calculation methods varying from Schmidt’s original methods (Schmidt et al 1999), Grimm’s filtering criteria (Grimm et al 2003) or Bauer’s guidelines (Bauer et al 2008).

The baseline methods, that are accepted as standards, are as follows:

• Filtering of VPCSs (Grimm et al 2003):
  • During filtering the intervals are compared to a refl that is the arithmetic mean\(^{11}\) of the five intervals preceding the couplI.
  • couplI must be no more than 80% of refl
  • compl must be at least 120% of refl
  • normal intervals (intervals before couplI and after compl) used for filtering are two intervals before couplI and 15 intervals after compl
  • normal intervals must be longer than 300 ms and shorter than 2000 ms
  • the difference between succeeding normal intervals must be less than 200 ms
  • the normal intervals must not differ 20% or more from refl
• Calculation (Schmidt et al 1999):
  • TO is the relative difference between the arithmetic mean of the two beats after compl and the arithmetic mean of the last two beats before couplI given as percentage:
    \[
    \frac{(RR_1 + RR_2) - (RR_{-1} + RR_{-2})}{(RR_{-1} + RR_{-2})} \times 100 [%] \tag{A1}
    \]
  • TO is first calculated for each VPC and averaged afterwards to get a subject’s overall TO value
  • TS is the steepest slope of a regression line over any 5 succeeding intervals within the first 20 intervals after the compl
  • First an averaged tachogram of all suitable VPCSs is calculated and then TS is assessed once for a subject
• Other standards are (Bauer et al 2008):
  • all beats (apart from the VPC itself) in the VPCS must be normal sinus contractions
  • to calculate a subject’s overall HRT parameters a minimum of 5 VPCSs is needed

Only explicitly stated data were extracted from the articles. It was only assumed that the calculation methodology of a referenced article was used if it was explicitly mentioned as a calculation resource. Furthermore, if a reference was given for calculation methods, it was only inferred that these exact calculation methods were used but not the filtering criteria of the cited article. If an article was cited for e.g. ‘HRT assessment’, calculation and filtering methods were assumed to be adopted. Other assumptions were, firstly, that filtering was not done if no filtering criteria were mentioned. Secondly, if the algorithm implemented by the TMU working group of Schmidt was used, standard filtering criteria were assumed. The criteria could be assessed on www.h-r-t.org or .com. Unfortunately the websites have been offline for some months now, but some snapshots can be found via the Wayback Machine of the Internet Archive: web.archive.org.

A search in PubMed made on 12.10.2018 resulted in 339 records. After screening of the abstracts 88 records were removed because of duplication (1), language (21), studied organism (8) or article type (comments (18), reviews (37), meta-studies (3)), leaving 251 articles for detailed analysis. The full texts of two articles could not be accessed from databases and after reaching out to the authors. In the remaining articles the aforementioned methods were assessed. Of these articles seven had to be removed because they did not involve HRT calculation. Another two were removed, because no HRT methodology was described and HRT values and units did not fit. Finally, 240 articles were analysed. A list of all articles can be found in the supplement. The numbers can be seen in the PRISMA flow diagram (figure A1).

If not stated otherwise, no reasons were given by the authors for the variations from the standard criteria that are discussed in this analysis.

\(^{11}\) Notice: The phrasing in the paper is ‘average’, which probably refers to the arithmetic mean.
Suggested methodology

We suggest the following methodology, similar to the already established methods, until the questions mentioned in the review are sufficiently analysed:

- **Recording:**
  - The recording duration should be a multiple of 24 h, optimally 72 h

- **Filtering of VPCs:**
  - All beats (apart from the VPC itself) must be normal sinus contractions
  - The length of the refI is the arithmetic mean of the 5 intervals preceding the couplI
  - The couplI must be no more than 80% of refI
  - The complI must be at least 120% of refI
  - Surrounding intervals (intervals before couplI and after complI) used for filtering are 5 intervals before couplI and 15 intervals after complI
  - Surrounding intervals must be at least 300 ms and no more than 2000 ms
  - The difference between succeeding intervals must be no more than 200 ms
  - The intervals must not differ 20% or more from refI
• Calculation:
  • To calculate a subject’s overall HRT parameters a minimum of 5 VPCSs is needed
  • TO
    • is the relative difference between the arithmetic mean of the two beats after compl and the arithmetic mean of the last two beats before coupl given as percentage (see equation (A1))
    • TO is first calculated for each VPC and averaged as arithmetic mean afterwards to get a subject’s overall TO value
  • Adjusted TS: aTS
    • TS is the steepest slope of a regression line over any 5 succeeding intervals within the first 15 intervals after the compl
    • First an averaged tachogram of all suitable VPCSs is calculated with the arithmetic mean of all intervals of one index, respectively, and then adjusted to a HR of 75 bpm (or 800 ms)
    • Then TS is assessed from the averaged, normalised tachogram
    • Finally, TS is adjusted to the number of VPCSs and variance with
      \[ aTS = TS - 0.283 \cdot \text{RMSSD} / \sqrt{\#\text{VPCSs}} \]
  • TT
    • is the index of the interval, from which the TS regression line is calculated, beginning with the first interval after compl being one and so forth
• Description:
  • The actual recording duration
  • The exact filtering criteria for VPCSs
  • The number of VPCSs actually used for the calculation
  • The exact calculation steps in their order

HRT in animals

HRT was not only measured in humans but also in animals. We found ten studies during our literature research, but excluded them because they did not fit the scope of the review. One full-text could not be obtained (Liu et al 2012), but the other nine studies investigate mice, dogs and swines.

As recording duration all studies regarding dogs used 24 h (Harris et al 2017, Noszczyk 2012a, Noszczyk-Nowak 2012b) and the studies regarding mice 24 h (Mersmann et al 2010), 8 h (Stöckigt et al 2015, Stöckigt et al 2014) or 6 h (Petric et al 2012). Three articles with mice (Stöckigt et al 2014, Stöckigt et al 2015, Petric et al 2012) and the article with swines (Wang et al 2011) used induced VPCSs.

The standard HRT methodology is used in studies investigating HRT in animals with the following variations: In the three studies using mice and cut-offs, the HR was normalised to a cycle length of 800 ms (75 bpm) in order to reuse the human standard cut-off values (Stöckigt et al 2015, Stöckigt et al 2014, Mersmann et al 2010). To meet the different characteristics of mice, Stöckigt et al introduced the parameter TS3, that uses 3 intervals instead of 5 to calculate the steepest slope (Stöckigt et al 2015, Stöckigt et al 2014). Additionally, Stöckigt et al calculated TO as the mean of 3 instead of 2 intervals to take a delayed acceleration onset into account (Stöckigt et al 2014). Petric et al calculated TO as the difference of the two intervals before and any two consecutive intervals after the VPCIs (Petric et al 2012).

As in some studies focusing on humans, two of three studies regarding dogs calculated individual TS values before averaging (Harris et al 2017, Noszczyk-Nowak 2012b), while the third article does not describe the exact methodology (Noszczyk 2012a). Harris et al used the HRT View program and adapted it to dogs, but without further explanation on the nature of the adaption (Harris et al 2017).

The usage of HRT in animals is similar to HRT in humans. HRT was used as a cardiac marker for the description of implantable cardioverter defibrillator therapy (Wang et al 2011), for comparison between healthy dogs and dogs with DCM (Harris et al 2017, Noszczyk-Nowak 2012b) or subaortic stenosis (Noszczyk 2012a). Furthermore, it was used for comparison between healthy mice and mice with heart disease, precisely transverse aortic constriction or myocardial cryoinfarction (Stöckigt et al 2015), and for comparison of wildtypes and mutants (Mersmann et al 2010, Petric et al 2012).

Analogously to the findings of Iwasa et al, that HRT measured during PVS and Holter monitoring differed significantly (Iwasa et al 2005), Petric et al described a difference in TO between HRTs measured in 24 h and induced ones in mice (Petric et al 2012).
New HRT parameters

Since the first description of the two HRT parameters TS and TO, many enhancements and new parameters have been developed. Adjustments of TS and TT are discussed in the review. Another parameter, Turbulence dynamics (TD), is measured in a sliding window over a coordinate system with TS on the y-axis and the HR of the three intervals before the couplI on the x-axis. The exact averaging method is not stated on the paper. Supposedly, the arithmetic mean of the three intervals is calculated. It is defined as the steepest slope of the regression line over the part of the plot with the most negative correlation. The width of the sliding window is 10 bpm, for the calculation of a regression line five data points are needed and TD is measured in ms/RRI bpm. TD reflects the relationship between TS and HR. It was found to be an independent predictor of late mortality in patients after myocardial infarction and with low LVEF (< 40%) (Bauer et al 2006).

(Lenis et al characterised four parameters: The damping coefficient \(d\) measures the stability of the system. \(\omega_0\) is the ‘resonance frequency’ and measures how rapidly the system responds to an external influence. The two ‘Morphology HRT’ parameters MTO and MTS are calculated analogously to HRT but depend on T-wave morphology, so they compare different morphological features of the T-waves of the beats before and after the VPC (Lenis et al 2013, Lenis et al 2013).

The IPFM model, a model of the cardiac pacemaker, was adapted for HRT (Solem et al 2006, Solem et al 2007, Solem et al 2006, Solem et al 2008). Based on this, a detection statistic was introduced by (Martínez et al that discriminates between HRT and no HRT better than TO and TS (Martínez et al 2008). The parameter \(T_\Sigma\) characterising the HRT shape (Martínez et al 2010) was later used by Gil et al to compare HRT calculated from ECG and photoplethysmography (PPG) (Gil et al 2013). \(T_\Sigma\) and \(T_\mu\) performed better than TO and TS to predict cardiac death in ischemic heart failure patients, needed less VPCSs and could predict mortality very early (within few months) (Martínez et al 2010). \(T_\Sigma\) was used by Gil et al to compare HRT calculated from ECG and PPG and, in contrast, did not show any improvements over TO and TS (Gil et al 2013).

The parameter CI/COMPP was defined by Voss et al as a ratio between the length of couplI and compI. CI/COMPP did not show significant differences between DCM patients and controls (Voss et al 2006).

Other parameters were defined but not used in the inspected articles in this review, namely Turbulence Frequency, Turbulence Jump and Correlation Coefficient as reviewed by (Watanabe 2003).

The performance of the summarised new parameters has either been tested only once (Neyman–Pearson detector, CI/COMPP, \(T_\Sigma\) and \(T_\mu\), TD) or not at all (MHRT, \(\omega_0\), \(d\)). Even though some parameters showed better results than the standard parameters, more studies on different populations are needed to determine their prognostic value.

ORCID iDs

Valeria Blesius  ∘ https://orcid.org/0000-0002-2391-242X
Christopher Schölzel  ∘ https://orcid.org/0000-0001-8627-0594
Gernot Ernst  ∘ https://orcid.org/0000-0001-5224-0338
Andreas Dominik  ∘ https://orcid.org/0000-0002-9368-0812

References

Arslan U, Ozdemir M, Kocaman S A, Balcioğlu S, Cemrî M and Cengel A 2008 Heart rate variability and heart rate turbulence in mild-to-moderate aortic stenosis EP Europace 10 1434–41 2008
Avsar A, Acaturk G, Meleki K, Kilit C, Celik A and Onrat E 2007 Cardiac autonomic function evaluated by the heart rate turbulence method was not changed in obese patients without co-morbidities J. Korean Med. Sci. 22 629–32
Aytémir K et al 2007 Increased myocardial vulnerability and autonomic nervous system imbalance in obstructive sleep apnea syndrome Respir. Med. 101 1277–82
Balcioğlu A S, Akinc S, Cicek D, Coner A, Bal U A and Müderrisoglu H 2016 Cardiac autonomic nervous dysfunction detected by both heart rate variability and heart rate turbulence in prediabetic patients with isolated impaired fasting glucose Anatom. J. Cardiol. 16 762–9
Balcioğlu A S, Akinci S, Cicek D, Eldem H O, Coner A, Bal U A and Müderrisoglu H 2016 Which is responsible for cardiac autonomic dysfunction in non-diabetic patients with metabolic syndrome: Prediabetes or the syndrome itself? Diabetes & Metabolic Syndrome 10 513–20
Balcioğlu A S, Cicek D, Akinci S, Eldem H O, Bal U A, Okyay K and Müderrisoglu H 2015 Arrhythmogenic evidence for epicardial adipose tissue: heart rate variability and turbulence are influenced by epicardial fat thickness Pacing Clin. Electrophysiol. 38 99–106
Balcioğlu S, Arslan U, Türközoğlu S, Ozdemir M and Cengel A 2007 Heart rate variability and heart rate turbulence in patients with type 2 diabetes mellitus with versus without cardiac autonomic neuropathy Am. J. Cardiol 100 890–5
Bartel P, Schneider R, Bauer A, Ulm K, Schmitt C, Schömig A and Schmidt G 2003 Risk stratification after acute myocardial infarction by heart rate turbulence Circulation 108 1221–6
Bauer A, Guzik P, Bartel P, Schneider R, Ulm K, Watanabe M A and Schmidt G 2005 Reduced prognostic power of ventricular late potentials in post-infarction patients of the reperfusion era Eur. Heart J. 26 755–61 2005
Bauer A et al 2008 Heart rate turbulence: standards of measurement, physiological interpretation and clinical use. Int. society for holter and noninvasive electrophysiology consensus I. Am. Coll. Cardiol. 52 1353–65
Bauer A, Malik M, Barthel P, Schneider R, Watanabe M A, Camm A J, Schömig A and Schmidt G 2006 Turbulence dynamics: an independent predictor of late mortality after acute myocardial infarction Int. J. Cardiol. 107 42–7
Bauer A, Mehlli J, Barthel P, Müller A, Kastraü A, Ulm K, Schömig A, Malik M and Schmidt G 2009 Impact of myocardial salvage assessed by (99m)tc-sestamibi scintigraphy on cardiac autonomic function in patients undergoing mechanical reperfusion therapy for acute myocardial infarction JACC: Cardiovascular Imaging 2 449–57
Bauer A and Schmidt G 2007 Last piece of the heart rate turbulence puzzle? Heart Rhythm 4 290–1
Bauer A, Watanabe M A, Barthel P, Schneider R, Ulm K and Schmidt G 2006 QRS duration and late mortality in unselected post-infarction patients of the revascularization era Eur. Heart J. 27 427–33
Berkowitsch A, Zareba W, Neumann T, Erdogan A, Nitt S M, Moss A J and Pitschner H F 2004 Risk stratification using heart rate turbulence and ventricular arrhythmias in MADIT II: usefulness and limitations of a 10-minute holter recording Ann. Noninvas. Electro. 9 270–9
Bienias P et al 2004 Cardiac autonomic function in type 1 and type 2 myotonic dystrophy Am. J. Cardiol. 27 193–202
Bienias P, Ciurzyński M, Glińska-Wielochowska M, Korczak D, Kalińska-Bienias A, Gliński W and Pruszyński P 2010b Heart rate turbulence impairment and ventricular arrhythmias in patients with systemic sclerosis Pacing Clin. Electrophysiol. 33 920–8
Bienias P, Ciurzyński M, Glińska-Wielochowska M, Zwizeczy A, Korczak D, Kaliska-Bienias A, Glinski W and Pruszyński P 2010a Heart rate turbulence assessment in systemic scerosis: the role for the detection of cardiac autonomic nervous system dysfunction Rheumatology 49 355–60
Bienias P, Ciurzyński M, Korczak D, Jankowski K, Glińska-Wielochowska M, Liszewska-Piefer D, Gliński W and Pruszyński P 2010c Pulmonary hypertension in systemic sclerosis determines cardiac autonomic dysfunction assessed by heart rate turbulence Int. J. Cardiol. 141 322–5
Bienias P, Kostrubiec M, Rymarczyk Z, Korczak D, Ciurzyński M, Kurzyna M, Tobicki A, Fijalkowska A and Pruszyński P 2013 Severity of arterial and chronic thromboembolic pulmonary hypertension is associated with impairment of heart rate turbulence Ann. Noninvas. Electro. 20 69–72
Bissing A, Rufer J, Ahmed R B and Lubinski A 2014 Heart rate turbulence in patients with poorly controlled diabetes mellitus type 2 Arch Med. 10 1073–7
Bonmeñé H, Ortak J, Tölg R, Witt M, Schmidt J, Wiegold U K H, Bode F, Schunkert H and Richardt G 2005 Cardedicol versus metoprolol in the acute phase of myocardial infarction Pacing Clin. Electrophysiol. 28 2222–226 Suppl1
Bonmeñé H, Wiegold U K H, Friedlindener J, Schubenhau S, Hartmann F, Bode F, Katus H A and Richardt G 2003 Reflex cardiac activity in ischemia and reperfusion: heart rate turbulence in patients undergoing direct percutaneous coronary intervention for acute myocardial infarction Circulation 108 958–64
Cagiric G et al 2009 Influence of heavy cigarette smoking on heart rate variability and heart rate turbulence parameters Ann. Noninvas. Electro. 14 327–32
Cano O et al 2008 Analysis of heart rate turbulence in advanced heart failure and heart transplantation patients Transplantation Proc. 40 3012–13
Carney R M et al 2007 Heart rate turbulence, depression and survival after acute myocardial infarction Psychosom. Med. 69 4–9
Casella M et al 2006 Heart rate turbulence as a noninvasive risk predictor of ventricular tachyarrhythmias in myotonic dystrophy type 1 J. Cardiovascular Electrophysiol. 17 871–6
Cebula S, Średniwa B, Kowalczyk J, Musialik-Lydka A, Woźniak A, Sedkowska A, Światkowski A and Kalarus Z 2012 The significance of heart rate turbulence in predicting major cardiovascular events in patients after myocardial infarction treated invasively Ann. Noninvas. Electro. 17 239–40
Celik A et al 2011a Heart rate variability and heart rate turbulence in hypothyroidism before and after treatment Ann. Noninvas. Electro. 16 344–50
Celik A, Koç F, Kadi I, Ceyhan K and Erkorkmaz U 2011b Heart rate variability and heart rate turbulence to determine true cardiac autonomic dysfunction in systemic sclerosis: the role for the detection of cardiac autonomic nervous system dysfunction Rheumatology 49 355–60
Celik A, Koç F, Kadi I, Ceyhan K and Erkorkmaz U 2012 Inflammation is related to unbalanced cardiac autonomic functions in hypothyroidism: an observational study Anadolu Kardiyoloji Dergisi/The Anatol. J. Cardiol. 12 233–40
Celik A, Melek M, Yılmaz K, Onrat E and Avsar A 2011 Cardiac autonomic dysfunction in hemodialysis patients: The value of heart rate turbulence Hemodialysis Int. 15 193–9
Celik A, Özturk A, Özbebek K, Kadi I, Koc F, Ceyhan K and Erkorkmaz U 2011b Heart rate variability and turbulence to determine true coronary artery disease in patients with ST segment depression without angina during exercise stress testing Clin Invest Med 34 E349–E357
Cetin M, Kozdag G, Ural D, Kahraman G, Yılmaz I, Akay Y, Onuk R and Dursun N 2014 Could decreased vitamin d levels be related with impaired cardiac autonomic functions in patients with chronic heart failure: an observational study Anadolu Kardiyoloji Dergisi/The Anatol. J. Cardiol. 14 434–11
Chen H Y 2009 Relationship of heart rate turbulence, heart rate variability and the number of ventricular premature beats in patients with mitral valve prolapse and non-significant regurgitation Int. J. Cardiol. 135 269–71
Chen H Y 2009 Impact of preceding ventricular premature beats on heart rate turbulence Ann. Noninvas. Electro. 14 333–9
Chen H Y 2010 Circadian variation of heart rate turbulence and the number of ventricular premature beats in patients with mitral valve prolapse Int. J. Cardiol. 141 99–101
Chen H Y 2011 Circadian patterns of heart rate turbulence, heart rate variability and their relationship Cardiol. Res. 2 112–8
Chen H Y et al 2011 Implications of turbulence slope variations in different approaches Heart Int. 6 21–5
Cyganekiwicz I et al 2006 Relation of heart rate turbulence to severity of heart failure Ann. J. Cardiol. 98 1635–40
Cyganekiwicz I et al 2008 Heart rate turbulence predicts all-cause mortality and sudden death in congestive heart failure patients Heart Rhythm 5 1095–102
Cyganekiwicz I 2013 Heart rate turbulence prediction Prog. Cardiovasc. Dis. 56 169–71
Cyganekiwicz I, Wramnicz J K, Bobinska H, Zaslonka J, Jaszewski R and Zareba W 2003 Prognostic significance of heart rate turbulence in patients undergoing coronary artery bypass grafting Am. J. Cardiol. 91 1471–4
Cyganekiwicz I, Wramnicz J K, Bobinska H, Zaslonka J, Jaszewski R and Zareba W 2004 Influence of coronary artery bypass grafting on heart rate turbulence parameters Ann. J. Cardiol. 94 186–9
Cyganekiwicz I, Wramnicz J K, Bobinska H, Zaslonka J and Zareba W 2004 Circadian changes in heart rate turbulence parameters J. Electrocardiol. 37 297–303
Cyganekiwicz I, Wramnicz J K, Bobinska H, Zaslonka J and Zareba W 2004 Relationship between heart rate turbulence and heart rate, heart rate variability, and number of ventricular premature beats in coronary patients J. Cardiovasc. Electrophysiol. 15 731–7
Cygankiewicz I, Wranicz J K, Zaslonka J, Bolinska H and Zareba W 2003 Clinical covariates of abnormal heart rate turbulence in coronary patients Ann. Noninvas. Electro. 8 289–95

D’Addio G, Cesarelli M, Corbi G, Romano M, Furgi G, Ferrara N and Rengo F 2010 Reproducibility of heart rate turbulence indexes in heart failure patients 2010 Annual Int. Conf. of the IEEE Engineering in Medicine and Biology 2573–6

D’Addio G, De Felice A, Balzano G, Zotti R, Iannotti P, Bifulco P and Cesarelli M 2013 Diagnostic decision support of heart rate turbulence in sleep apnea syndrome Stud Health Technol Inform 186 150–4

D’Addio G, De Felice A, Insalaco G, Romano M and Cesarelli M 2014 Effects of pathological respiratory pattern on heart rate turbulence in sleep apnea Stud Health Technol Inform 205 506–10

Davies L C, Francis D P, Pomikiewski P, Pieplo M F and Coats A J 2001 Relation of heart rate and blood pressure turbulence following premature ventricular complexes to baroreflex sensitivity in chronic congestive heart failure Am. J. Cardio 87 737–42

Davos C H et al 2009 Heart rate turbulence in adults with repaired tetralogy of fallot Int. J. Cardio. 135 308–14

Diaz J O, Castellanos A, Moleiro E, Interian A and Myerburg R J 2002 Relation between sinus rates preceding and following ectopic beats occurring in isolation and as episodes of bigeminy in young healthy subjects Am. J. Cardio 90 332–5

Dursun H, Onar G, Yilmaz A, Cendogan H, Ozkan A, Limon M, Sanli R, Yilmaz S, Basaran O and Arslan K 2015 Heart rate turbulence analysis in female patients with fibromyalgia Clinics 70 296–300

Erdem A et al 2013 The pure effects of obstructive sleep apnea syndrome on cardiac autonomic functions; heart rate turbulence analysis Eur. Rev. Med. Pharmacol. Sci. 17 2778–83

Erdem A et al 2015 Cardiac autonomic function in healthy young smokers Toxicol. Ind. Health 31 67–72

Erdem A, Uenishi M, Küçükdrumaş Z, Matsumoto K, Kato R, Hara M and Yazici M 2012 The effect of metabolic syndrome on heart rate turbulence in non-diabetic patients Cardio. J. 19 507–12

Erdem A, Uenishi M, Matsumoto K, Küçükdrumaş Z, Kato R, Sahin S and Yazici M 2012 Cardiac autonomic function in metabolic syndrome: a comparison of ethnic Turkish and Japanese patients J. Interventional Cardiac Electrophysiolog. 35 253–8

Exner D V et al 2007 Noninvasive risk assessment early after a myocardial infarction the REFINE study J. Am. College Cardio. 50 2275–84

Fazio G, Sarullo F M, D’Angelo L, Lunetta M, Visconti C, Di Gesaro G, Sutera L, Novo G and Novo S 2010 Heart rate turbulence for guiding electric therapy in patients with cardiac failure J. Clin. Monit. Comput. 24 125–9

Eleva P, Georgiadou P, Leftheriotis D, Livianis E, Theodorakis G and Th Kremastinos D 2007 Heart rate turbulence after short runs of nonsustained ventricular tachycardia in chronic heart failure Pacing Clin. Electrophysiolog. 30 787–95

Franche M, Carpentier A, Juni P and Tognoni G 2011 Rethinking the role of heart rate variability in cardiac risk assessment Circulation 124 2440–5

Fröhlich M A, Arabshahi A, Katholi C, Prasain J and Barnes S 2011 Hemodynamic characteristics of midazolam, propofol and dexmedetomidine in healthy volunteers J. Clin. Anesth. 23 218–23

Frolov A V, Vaikanshaya T G, Melnikova O P, Vorobiev A P and Guel L M 2017 Risk stratification personalised model for prediction of life-threatening ventricular tachyarrhythmias in patients with chronic heart failure Kardiol. Pol. 75 682–8

Gać S and Sobieszczańska M 2014 Effects of cigarette smoke on holter ECG records in patients with arterial hypertension. part 2: Parameters of heart rate turbulence Environ. Toxicol. Pharmacol. 37 600–7 2014

Ghuran A, Elzayat E, La Rove M T, Schmidt G, Bigger J T, Camm A J, Schwartz P J, Malik M and ATRAMI Investigators 2002 Heart rate turbulence-based predictors of fatal and nonfatal cardiovascular arrest (the autonomic tone and reflexes after myocardial infarction substudy) Am. J. Cardio 89 184–90

Gil E, Laguna P, Martinez J P, Barquero P, García-Alberola A and Serrano J 2013 Heart rate turbulence analysis based on photoplethysmography IEEE. Trans. Biomed. Eng. 60 5149–55

Goer H, Piano G, Baier V, Figulla H R, Leder U and Voss A 2006 Altered autonomic cardiac control predicts restenosis after percutaneous coronary intervention Pacing Clin. Electrophysiolog. 29 188–91

Golukhova E Z, Gromova O, Grigoryan M, Merzlyakov V, Shumkov K, Bockeria I and Serebruany V L 2016 Noninvasive predictors of malignant arrhythmias Cardiology 135 36–42

Gorenek B et al 2020 Premature ventricular complexes: diagnostic and therapeutic considerations in clinical practice J. Interventional Cardiac Electrophysiolog. 57 5–26

Grimm W, Buddh S, Mühl J, Müller H H and Maisch B 2003 Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: Results of the marburg cardiomyopathy study Circulation 108 2883–91

Grimm W, Shankwa J, Christ M, Schneider R, Schmidt G and Maisch B 2003 Heart rate turbulence following ventricular premature beats in healthy controls Ann. Noninvas. Electro. 8 127–31

Gunduz H, Talay F, Arinic H, Ozyildirim S, Akdemir R, Yolcu M, Kanat M and Uyan C 2009 Heart rate variability and heart rate turbulence in non-diabetic patients Cardiol. J. 16 553–9

Hallstrom A P, Stein P K, Schneider R, Hodges M, Schmidt G, Ulm K and CAST Investigators 2005 Characteristics of heart beat intervals and prediction of death Int. J. Cardio. 100 37–45

Hallstrom A P, Stein P K, Schneider R, Hodges M and Ulm K 2004 Structural relationships between measures based on heart rate beat intervals: potential for improved risk assessment IEEE. Trans. Biomed. Eng. 51 1414–20

Harris J D, Little C J L, Dennis J M and Patteson M W 2017 Heart rate turbulence following ventricular premature beats in healthy doberman pinschers and those with dilated cardiomyopathy J. Vet. Cardio. 19 421–32 2017

Harris P R E, Stein P K, Fung G L and Drew B J 2013 Prognostic value of heart rate turbulence for risk assessment in patients with unstable angina and nonST-elevation myocardial infarction Vase. Health Risk Manag. 9 465–73

Havranková A, Stochick P, Psenicka M, Wichterle D and Linhart A 2007 Heart rate turbulence after ventricular pacing trains during programmed ventricular stimulation Pacing Clin. Electrophysiolog. 30 S170–73

Hayano J, Kiyono K, Struzik Z R, Yamamoto Y, Watanabe E, Stein P K, Watkins L I, Blumenthal J A and Carney R M 2011 Increased non-gaussianity of heart rate variability predicts cardiac mortality after an acute myocardial infarction Front. Physiol. 2 65

Hedele W F, Jones M E and Tonkin A M 1985 Sinus node sequences after atrial stimulation: similarities of effects of different methods Br. Heart J. 54 568–76

Hoshida K, Miwa Y, Miyakoshi M, Tsukada T, Yusu S, Yoshino H and Ikeda T 2013 Simultaneous assessment of t-wave alternans and heart rate turbulence on holter electrocardiograms as predictors for serious cardiac events in patients after myocardial infarction Circ. J. 77 432–8

Hirukawa H, Enser D V, Kavanagh K M, Aagarwal S G, Mitchell L B, Messier M D, Becker D, Sheldon R S, Bloch Thomsen P E and CARISMA and REFINE Investigators 2010 Attenuated recovery of heart rate turbulence early after myocardial infarction identifies patients at high risk for fatal or near-fatal arrhythmic events Heart Rhythm 7 229–35

Ikeda T, Miwa Y, Abe A and Nakazawa K 2011 Usefulness of heart rate turbulence for predicting cardiac events in patients with nonischemic dilated cardiomyopathy J. Electrocardiol. 44 669–72
Iwasa A, Hwa M, Hassankhani A, Liu T and Narayan S M 2005 Abnormal heart rate turbulence predicts the induction of ventricular arrhythmias Pacing Clin. Electrophysiol. 28 1189–97
Iwaski M, Yuasa F, Yuyama R, Mimura J, Kawamura A, Motohiro M, Yo M, Sugitani T and Iwaska T 2005 Correlation of heart rate turbulence with sympathovagal balance in patients with acute myocardial infarction Clin. Exp. Hypertens. 27 251–7
Jansen C et al 2018 Severe abnormal heart rate turbulence onset is associated with deterioration of liver cirrhosis Plos One 13 e0195631
Jeron A, Kaiser T, Hengstenberg C, Löwe H, Rieger G A J and Holmer S 2003 Association of the heart rate turbulence with classic risk stratification parameters in postmyocardial infarction patients Ann. Noninvasive. Electro. 60 296–301
Jochum T, Schulz S, Schein M, Schröder R, Voss A and Bär K 2012 Heart rate turbulence during acute alcohol withdrawal syndrome Drug and Alcohol Dependence 122 253–7
Kanaya N, Hirata N, Kurosawa S, Nakayama M and Namiki A 2003 Differential effects of propofol and sevoflurane on heart rate variability Anesthesiology 98 34–40
Kaplan R M, Herzog C A, Larive B, Subacius H, Nearing B D, Verrier R P and Passman R S 2016 T-wave alternans, heart rate turbulence and ventricular ectopy in standard versus daily hemodialysis: Results from the FHN daily trial Ann. Noninvasive. Electro. 2016 566–71
Karakurt C, Aytemir K, Karademir S, Sungur M, Oguz D, Ocal B and Senocak F 2007 Prognostic value of heart rate turbulence and heart rate variability in children with dilated cardiomyopathy Acta Cardiologica 62 51–7
Kawasaki M et al 2015 Risk stratification for ventricular tachyarrhythmias by ambulatory electrocardiogram-based frequency domain t-wave alternans Pacing Clin. Electrophysiol. 38 1425–33
Kawasaki T, Azuma A, Asada S, Hadase M, Kamitani T, Kawasaki S, Kuribayashi T and Sugihara H 2003 Heart rate turbulence and clinical diagnosis in hypertrophic cardiomyopathy and myocardial infarction Circ. J.: Official Journal of the Japanese Circulation Society 67 601–4
Kilic H, Karakurt O, Akdemir R, Dogan M, Bicer A, Acikel S, Cagirci G and Gunduz H 2008 Heart rate turbulence and heart rate variability in patients with atrial synchronous ventricular pacing Pacing Clin. Electrophysiol. 31 1113–17
Kilic C, Pasali Kilic T and Omrat E 2015 Autonomic modulation in hypertension without hypertrophy Acta Cardiologica 70 721–7
Kop W J, Stein P K, Tracy R P, Barzilay J I, Schulz R and Gottdiener J S 2010 Autonomic nervous system dysfunction and inflammation contribute to the increased cardiovascular mortality risk associated with depression Psychosom. Med. 72 626–35
Kossaify A, Garcia A and Zaida F 2014 Assessment of heart rate turbulence in hypertensive patients: rationale, perspectives and insight into autonomic nervous system dysfunction Heart Views 15 68–73
Kostis J B, McCrone K, Moreya E, Gotzoyannis S, Aglitz N M, Natarajan N and Kuo P T 1981 Premature ventricular complexes in the absence of identifiable heart disease Circulation 63 1351–6
Kowalewski M, Alifir M, Bochen D and Urban M 2007 Heart rate turbulence in children–age and heart rate relationships Pediatr. Res. 62 710–14
Koyama J et al 2002 Evaluation of heart-rate turbulence as a new prognostic marker in patients with chronic heart failure Circ. J.: Official Journal of the Japanese Circulation Society 66 902–7
Kurpesa M, Tzox E, Rechciński T and Kremzińska-Pakula M 2007 The relationship between heart rate variability and heart rate turbulence dynamics after primary coronary angioplasty Ann. Noninvasive. Electro. 12 50–8 2007
La Rovere M T et al 2012 Autonomic markers and cardiovascular and arrhythmic events in heart failure patients: still a place in prognostication? data from the GISSI-HF trial Eur. J. Heart Failure 14 1410–19
La Rovere M T, Maestri R, Pinna G D, Sleght P and Febo O 2011 Clinical and haemodynamic correlates of heart rate turbulence as a non-invasive index of baroreflex sensitivity in chronic heart failure Circ. Sci. 121 279–84
Lammers A et al 2006 Impaired cardiac autonomic nervous activity predicts sudden cardiac death in patients with operated and unoperated congenital cardiac disease J. Thorac. Cardiovasc. Surg. 132 647–55 2006
Lanza G A, Sguagli A G, Angeloni G, Valsecchi S, Settoso A, Rebuatti A G, Crea F, Maseri A, Cianflone D and Stratification Prognostica dell’Angina Instabile Study Investigators 2009 Prognostic value of heart rate turbulence and its relation to inflammation in patients with unstable angina pectoris Ann. J. Cardio. 103 1066–72
Latchamsetty R and Bogun F 2015 Premature ventricular complexes and premature ventricular complex induced cardiomyopathy Pnamuretive Ventricular Complexes and Premature Ventricular Complex Induced Cardiomyopathy 40 379–422
Lau W, Kovoor P and Ross D I 1993 Cardiac electrophysiologic effects of midazolam combined with fentanyl Ann. J. Cardiol. 72 177–82
Lenis G, Baas T and Dössel O 2013 Ectopic beats and their influence on the morphology of subsequent waves in the electrocardiogram Biomedizinische Technik / Biomedical Engineering 58 109–19
Lenis G and Dössel O 2013 T wave morphology during heart rate turbulence in patients with chronic heart failure Biomedizinische Technik / Biomedical Engineering 58 Suppl1
Lewek J, Wranicz J K, Guzik P, Chudzik M, Ruta J and Cygankiewicz I 2009 Clinical and electrocardiographic covariates of deceleration capacity in patients with ST-segment elevation myocardial infarction Cardiol. J. 16 528–34
Lewis M J, Annandale J, D’Silva I A, Davies R E, Reed Z and Lewis K E 2011 Influence of long-term oxygen therapy on cardiac acceleration and deceleration capacity in hypoxic patients with chronic obstructive pulmonary disease Clin. Physiol. Funct. Imaging 31 258–65
Li-na R, Xin-hui F, Li-dong R, Jian G, Yong-quan W and Guo-xian Q 2012 Ambulatory ECG-based t-wave alternans and heart rate turbulence can predict cardiac mortality in patients with myocardial infarction with or without diabetes mellitus Cardiovasc. Diabetol. 11 104
Liberati A et al 2009 The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration J. Clin. Epidemiol. 62 e1–e34
Lin K, Wei L, Huang Z and Zeng Q 2017 Combination of Ewing test, heart rate variability and heart rate turbulence analysis for early diagnosis of diabetic cardiac autonomic neuropathy Medicine 96 e8296
Lin L Y, Hwang J I, Lai L P, Chan H I, Du C C, Tseng Y Z and Lin J I 2004 Restoration of heart rate turbulence by titrated beta-blocker therapy in patients with advanced congestive heart failure: positive correlation with enhanced vагal modulation of heart rate J. Cardiovascular Electrophysiol. 15 752–6
Lin L Y, Lai L P, Lin J L, Du C C, Shau W Y, Chan H L, Tseng Y Z and Huang S K 2002 Tight mechanism correlation between heart rate turbulence and baroreflex sensitivity: sequential autonomic blockade analysis J. Cardiovascular Electrophysiol. 13 427–31
Lindgren S K, Mäkiäiä T H, Seppänen T, Raatikainen M J P, Castellanos A, Myerburg R J and Huiuk H V 2003 Heart rate turbulence after ventricular and atrial premature beats in subjects without structural heart disease J. Cardiovascular Electrophysiol. 14 447–52
Liu J, Wang Y, Shan Z and Guo H 2012 Influence of acute stress on cardiac electrophysiologial stability in male goats Acta Cardiologica 67 325–30
Liu Y, Syed Z, Scircia B M, Morrow D A, Guttag J V and Stultz C M 2014 ECG morphological variability in heartbeat space for risk stratification after acute coronary syndrome J. Am. Heart Assoc. 3 e000981
Lombardi F and Stein P K 2011 Origin of heart rate variability and turbulence: an appraisal of autonomic modulation of cardiovascular function Front. Physiol. 2 95
Lown B, Tykocinski M, Garfein A and Brooks P 1973 Sleep and ventricular premature beats Circulation 48 691–701
Lown B and Wolf M 1971 Approaches to sudden death from coronary heart disease Circulation 44 130–42
Maeda S et al 2009 Ambulatory ECG-based t-wave alternans and heart rate turbulence predict high risk of arrhythmic events in patients with old myocardial infarction Circ. J. 73 2223–8
Makai A, Korsós A, Makra P, Forster T, Abrahámovich G and Rudas L 2008 Spontaneous baroreflex sensitivity and heart rate turbulence parameters: parallel responses to orthostasis Clin. Auton. Res. 18 74–9
Malberg H, Bauerschmidt R, Meyerfeldt U, Schridewax A and Wessel N 2004 Short-term heart rate turbulence analysis versus variability and baroreceptor sensitivity in patients with dilated cardiomyopathy Indian Pacing Electrophysiol. J. 4 162–75
Malik M, Bigger J T, Camm A J, Kleger R E, Malliani A, Moss A J and Schwartz P J 1996 Heart rate variability standards of measurement, physiological interpretation and clinical use Eur. Heart J. 17 354–81
Manzano-Fernández S et al 2011 Short-term variability of heart rate turbulence in chronic heart failure J. Cardiac Failure 17 735–41
Marine J E, Watanabe M A, Smith T W and Monahan K M 2002 Effect of atropine on heart rate turbulence Ann. J. Cardiol. 89 767–9
Martínez J P, Cyganiewicz I, Smith D, Bayés de Luna A, Laguna P and Sornmo L 2010 Detection performance and risk stratification using a model-based shape index characterizing heart rate turbulence Ann. Biomed. Eng. 38 3173–84
Martínez J P, Laguna P, Solém K and Sornmo L 2008 Evaluation of a Neyman–Pearson heart-rate turbulence detector 2008 Int. Conf. of the IEEE Engineering in Medicine and Biology Society. 4407–10
Marynissen T, Floré V, Heidbuchel H, Nuyens D, Ector J and Willems R 2014 Heart rate turbulence predicts ICD-resistant mortality in ischaemic heart disease EP 16 1069–77
Melenovsky V, Simek J, Sperl M, Malik J and Wichterle D 2005 Relation between actual heart rate and autonomic effects of beta-blockade in healthy men Am. J. Cardiol. 95 1009–1002
Mersmann J et al 2010 Toll-like receptor 2 signaling triggers fatal arrhythmias upon myocardial ischemia-reperfusion Crit. Care Med. 38 1927–32
Miwa Y et al 2009 Heart rate turbulence as a predictor of cardiac mortality and arrhythmic events in patients with dilated cardiomyopathy: a prospective study J. Cardiovascular Electrophysiol. 20 788–95 2009
Miwa Y et al 2011 Heart rate turbulence can predict cardiac mortality following myocardial infarction in patients with diabetes mellitus J. Cardiovascular Electrophysiol. 22 1135–40
Miwa Y, Yoshino H, Hoshika K, Miyakoshi M, Tsukada T, Yasu S and Ikeda T 2012 Risk stratification for serious arrhythmic events using nonsustained ventricular tachycardia and heart rate turbulence detected by 24-hour holter electrocardiograms in patients with left ventricular dysfunction Ann. Noninvas. Electro. 17 260–7
Moore R K G, Groves D G, Barlow P E, Fox K A A, Shah A, Nolan J and Kearney M T 2006 Heart rate turbulence and death due to cardiac decompensation in patients with chronic heart failure Eur. J. Heart Failure 8 585–90
Noszczyk-Nowak A 2012 Heart rate turbulence in healthy dogs and dogs with dilated cardiomyopathy Pol. J. Vet. Sci. 15 469–75
Noszczyk-Nowak A 2012 Heart rate turbulence in mild-to-moderate aortic stenosis in boxers Pol. J. Vet. Sci. 15 477–81
Ottar J, Weitz G, Wiegand U K H, Bode F, Eberhardt F, Katus H A, Richardt G, Schunkert H and Bommemeier H 2005 Changes in heart rate, heart rate variability and heart rate turbulence during evolving reperfused myocardial infarction Pacing Clin. Electrophysiol. 28 5227–232 Suppl
Osman F, Franklyn J A, Daykin J, Chowdhary S, Holder R L, Sheppard M C and Gammage M D Heart rate variability and turbulence in hyperthyroidism before, during and after treatment Am. J. Cardiol. 94 465–9
Ovreu M et al 2008 Electrocardiographic activity before onset of postoperative atrial fibrillation in cardiac surgery patients Pacing Clin. Electrophysiol. 31 1371–82
Ozdemir M, Arslan U, Turguloglu S, Balcioğlu S and Cengel A 2007 Losartan improves heart rate variability and heart rate turbulence in heart failure due to ischemic cardiomyopathy J. Cardiac Failure 13 812–17
Park S J, On Y K, Kim J S, Jeong D S, Kim W S and Lee Y T 2014 Heart rate turbulence for predicting new-onset atrial fibrillation in patients undergoing coronary artery bypass grafting Int. J. Cardiol. 174 579–85
Patel Y N, Pierce B R, Bodapati R K, Brown D L, Ives D G and Stein P K 2017 Association of Holter-derived heart rate variability parameters with the development of congestive heart failure in the cardiovastar heart study JACC. Heart failure 5 423–31
Perkiömäki J S, Hämekoski S, Junttila M J, Jokinen V, Tapanainen J and Huikuri H V 2010 Predictors of long-term risk for heart failure hospitalization after acute myocardial infarction Ann. Noninvas. Electro. 15 250–80
Perkiömäki J S, Jokinen V, Tapanainen J, Airaksinen K E J and Huikuri H V 2008 Autonomic markers as predictors of nonfatal acute coronary events after myocardial infarction Ann. Noninvas. Electro. 13 120–9
Petric S et al 2012 In vivo electrophysiologic characterization of Task-1 deficient mice Cell. Physiol. Biochem. 30 523–37
Pinnačchio G, Lanza G A, Stazi A, Caregi G, Coviello I, Mollo R and Creaf F 2015 Determinants of heart rate turbulence in individuals without apparent heart disease and in patients with stable coronary artery disease EP 17 1855–61
Poliwczak A R, Tyliszczak M and Brossel M 2014 Testosterone therapy improves the heart rate turbulence without effect on NT-proBNP level in men with metabolic syndrome Horm. Metab. Res. 46 116–19
Poręba R, Poręba M, Gać P, Steinmetz-Beck A, Beck B, Pilecki W, Andrzejak R and Sobieszczanska M 2011 Electrocardiographic changes in workers occupationally exposed to lead Ann. Noninvas. Electro. 16 33–40
Poręba M et al 2014 Heart rate variability and heart rate turbulence in patients with hematologic malignancies subjected to high-dose chemotherapy in the course of hematopoietic stem cell transplantation Ann. Noninvas. Electro. 19 157–65 2014
Raj S R, Sheldon R S, Koshman M and Roach D E 2005 Role of hypotension in heart rate turbulence physiology Heart Rhythm 2 820–7
Ramirez J, Oriñi M, Mincholé A, Monasterio V, Cyganiewicz I, Bayés de Luna A, Martínez J P, Laguna P and Pueyo E 2017 Sudden cardiac death and pump failure death prediction in chronic heart failure by combining ECG and clinical markers in an integrated risk model Phys. One 12 e018652
Ramaekers D, Ector H, Aubert A E, Rubens A and Van de Werf F 1998 Heart rate variability and heart rate in healthy volunteers is the female autonomic nervous system cardioprotective? Eur. Heart J. 19 1334–41
Rich D Q et al 2012 Are ambient ultraviolet, accumulation mode and fine particles associated with adverse cardiac responses in patients undergoing cardiac rehabilitation? Environ. Health Perspect. 120 1162–9
Rizas K D, Zureni C S and Bauer A 2017 Periodic repolarization dynamics in patients with moderate to severe aortic stenosis J. Electrocardiol. 50 802–7
Roach D, Koszman M L, Duff H and Sheldon R 2002 Induction of heart rate and blood pressure turbulence in the electrophysiology laboratory Am. J. Cardiol. 90 1098–102
Rojo-Alvarez J L, Barquero-Pérez Ó, Mora-Jiménez I, Everss E, Rodriguez-González A B and García-Alberola A 2009 Heart rate turbulence denoising using support vector machines IEEE. Trans. Biomed. Eng. 56 310–19
Sahiner I et al 2012 Assessment of the relationship between non-dipping phenomenon and heart rate turbulence Cardiol. J. 19 140–5
Sandberg F, Balion R, Hernando D, Laguna P, Martinez J P, Solem K and Sörnmo L 2014 Prediction of hypotension in hemodialysis patients Physiol. Meas. 35 1885–98
Savelieva I, Wichterle D, Harries M, Meara M, Camm A J and Malik M 2003 Heart rate turbulence after atrial and ventricular premature beats: relation to left ventricular function and coupling intervals Pacing Clin. Electrophysiol. 26 401–5
Schaeffer B N et al 2015 Heart rate turbulence and deceleration capacity for risk prediction of serious arrhythmic events in marfan syndrome Clin. Res. Cardiol. 104 1054–63
Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rohnitzky L, Camm A J, Bigger J T and Schömig A 1999 Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction The Lancet 353 1390–6
Schwab J O, Eichner G, Bahta O and Lüderitz B 2005 Determinants of heart rate turbulence after ventricular premature beats in healthy volunteers Hell. J. Cardiol. 46 31–4
Schwab J O, Eichner G, Shlevkov N, Schrickel J, Yang A, Bahta O, Lewalter T and Lüderitz B 2005 Impact of age and basic heart rate on heart rate turbulence in healthy persons Pacing Clin. Electrophysiol. 28 Suppl I S198–201
Schwab J O, Eichner G, Veit G, Schmitt H, Lewalter T and Lüderitz B 2004 Influence of basic heart rate and sex on heart rate turbulence in healthy subjects Pacing Clin. Electrophysiol. 27 1625–31
Schwab J O, Shlevkov N, Grunwald K, Schrickel J W, Yang A, Lickfett L, Lewalter T and Lüderitz B 2004 Influence of the point of origin on heart rate turbulence after stimulated ventricular and atrial premature beats Basic Res. Cardiol. 99 56–60
Secemsky E A, Verrier R L, Cooke G, Ghosein C, Subacius H, Manschゅrhy A, Herzog C A and Passman R 2011 High prevalence of cardiac autonomic dysfunction and t-wave alternans in dialysis patients Heart Rhythm 8 592–8
Seegers J, Bergau L, Exposito P M, Bauer A, Fischer T H, Lábbtgh L, Hasenfuß G, Frie de T and Zabel M 2016 Prediction of appropriate shocks using 24-hour holter variables and t-wave alternans after first implantable cardioverter-defibrillator implantation in patients with ischemic or nonischemic cardiomyopathy Am. J. Cardiol. 118 86–94
Segerson N M et al 2007 Heart rate turbulence parameters correlate with post-premature ventricular contraction changes in muscle sympathetic activity Heart Rhythm 4 284–9
Sestito A, Valsecchi S, Infusino F, Sguiglia G A, Bellocchi F, Zecchi P, Crea F and Lanza G A 2004 Differences in heart rate turbulence between patients with coronary artery disease and patients with ventricular arrhythmias but structurally normal hearts Am. J. Cardiol. 93 1114–18
Smith D, Solem K, Laguna P, Martínez J P and Sörnmo L 2010 Model-based detection of heart rate turbulence using mean shape information IEEE. Trans. Biomed. Eng. 57 334–42
Soguero-Ruiz C, Lechuga-Suarez I, Mora-Jiménez I, Ramos-López J, Barquero-Pérez Á, García-Alberola A and Rojo-Alvarez J L 2013 Ontology for heart rate turbulence domain from the conceptual model of SNOMED-CT IEEE. Trans. Biomed. Eng. 60 1823–33
Solem K, Laguna P, Martínez J P and Sörnmo L 2008 Model-based detection of heart rate turbulence IEEE. Trans. Biomed. Eng. 55 2712–22
Solem K, Laguna P, Martínez J and Sörnmo L 2007 Performance evaluation of heart rate turbulence detection using an extended IPFM model 2007 Computers in Cardiology 821–4
Solem K, Laguna P and Sörnmo L 2006 Detection of heart rate turbulence using an extended IPFM model 2006 Computers in Cardiology 905–8
Solem K, Nilsson A and Sörnmo L 2006 An electrocardiogram-based method for early detection of abrupt changes in blood pressure during hemodialysis ASAIO Journal 52 282–90
Średniawa B et al 2010 Heart rate turbulence for prediction of heart transplantion and mortality in chronic heart failure Ann. Noninvasive. Electro. 15 230–7
Średniawa B, Mitrega K A, Cebula S, Morawski S, Kowalczyk J, Musialik-Lydka A and Kalarus Z 2016 Gender-dependent profile of heart rate turbulence parameters in patients after acute myocardial infarction treated invasively Kardiol Pol 74 274–9
Stöckigt F, Jüngst P, Linhart M, Nickenig G, Andrér R, Beiert T and Schrickel J W 2015 Association of heart rate turbulence with arrhythmia susceptibility and heart disease in mice J. Cardiovascular Electrophysiology, 26 1262–8
Stöckigt F, Pohlmann S, Nickenig G, Schwab J O and Schrickel J W 2014 Induced and spontaneous heart rate turbulence in mice: influence of coupling interval EP Europe 16 1092–8
Stein P K and Barzilay J L 2011 Relationship of abnormal heart rate turbulence and elevated CRP to cardiac mortality in low, intermediate and high-risk older adults J. Cardiovascular Electrophysiology, 22 122–7
Stein P K, Barzilay J L, Chaves P H M, Domitrovich P P and Gotttdiener J S 2009 Heart rate variability and its changes over 5 years in older adults Age and Ageing 38 212–18
Stein P K, Barzilay J L, Chaves P H M, Mistretta S Q, Domitrovich P P, Gotttdiener J S, Rich M W and Kleiger R E 2008 Novel measures of heart rate variability predict cardiovascular mortality in older adults independent of traditional cardiovascular risk factors: the cardiovascular health study (CHS) J. Cardiovascular Electrophysiology, 19 1169–74
Stein P K and Deedwania P 2009 Usefulness of abnormal heart rate turbulence to predict cardiovascular mortality in high-risk patients with acute myocardial infarction and left ventricular dysfunction (from the EPHEUS study) Am. J. Cardiol. 103 1495–9
Stein P K, Sanghavi D, Siscovick D S and Gotttdiener J S 2010 Association of holter-based measures including t-wave alternans with risk of sudden cardiac death in the community-dwelling elderly: the cardiovascular health study J. Electrocardiol. 43 251–9
Suzuki M, Hiroshi T, Aoyama T, Tanaka M, Iishii H, Kishohara M, Iizuka N, Murohara T and Hayano J 2012 Nonlinear measures of heart rate variability and mortality risk in hemodialysis patients Clin. J. Am. Soc. Nephrol. 7 1454–60
Szydło K, Orszulak W, Trusz-Glusa M, Tabor Z, Wita K, Orszulak M, Marzec M, Kniewska-Jarzabek K and Grabka M 2011 Heart rate turbulence in postinfarction patients with history of malignant ventricular arrhythmias J. Electrocardiol. 44 142–7
Szymanowska K, Pietkowska A, Nowicka A, Michalski M, Dankowski R, Kandziora M, Biegalski W, Wierczowiecki M and Poprawski K 2008 Clinical significance of heart rate turbulence assessment in patients with chronic heart failure Kardiol. Pol. 66 1289–95
Tikeloglu U Y, Erdem A, Demirhan A, Akkaya A, Ozturk S, Bilgi M, Duran B, Yazici M and Kocoglu H 2013 The prolonged effect of 
peumoperitoneum on cardiac autonomic functions during laparoscopic surgery; are we aware? Eur. Rev. Med. Pharmacol. Sci. 17 
895–902

Trzos E, Krzeminska-Pakula M, Rechciński T, Drozdz J and Kurpesa M 2008 Heart rate turbulence in patients with chronic heart failure 
Kardiol. Pol. 66 1183–90 2008

Tuomainen P, Hartikainen J, Vanninen E and Peuhkurinen K 2003 Warm-up phenomenon and cardiac autonomic control in patients 
with coronary artery disease Life Sciences 76 2147–58

Tuomainen P, Peuhkurinen K, Kettunen R and Rauramaa R 2005 Regular physical exercise, heart rate variability and turbulence in a 
6-year randomized controlled trial in middle-aged men: the DNASCO study Life Sciences 77 3723–34

Uznańska-Loch B, Wiklo K, Trzos E, Wierzbowska-Drahiłk K, Chrzanoski A, Kasprzyk J D and Kurpesa M 2018 Advanced and 
traditional electrocardiographic risk factors in pulmonary lateral arterial hypertension: the significance of ventricular late potentials 
Kardiol. Pol. 76 586–93 2018

Vikman S, Lindgren K, Mákkiallo T H, Yli-Märry S, Airaksinen K E J and Huikuri H V 2005 Heart rate turbulence after atrial 
premature beats before spontaneous onset of atrial fibrillation J. Am. College Cardiol. 45 278–84

Voss A, Schroeder R, Truebner M, Goer nig M, Schir dewan A and Figulla H R 2006 Spontaneous heart rate turbulence in patients with 
dilated cardiomyopathy 2006 Int. Conf. of the IEEE Engineering in Medicine and Biology Society pp 6426–9

Vukajlovic D D, Guettler N, Mircic M and Pitschmer H F 2006 Effects of atropine and pirenzepine on heart rate turbulence Ann. 
Noninvasive. Electro. 11 34–7

Walker A M et al 2016 Diabetes mellitus is associated with adverse structural and functional cardiac remodelling in chronic heart failure 
with reduced ejection fraction Diabetes & Vascular Disease Research 13 331–40

Wang D, Jin Y, Ding C, Zhang F, Chen M, Yang B, Shan Q, Zou J and Cao K 2011 Intracoronalary delivery of mesenchymal stem cells 
reduces proarhythmogenic risks in swine with myocardial infarction Ir. J. Med. Sci. 180 379–85

Watanabe M A 2003 Heart rate turbulence: a review Indian Pacing Electrophysiol. J. 3 10–22

Watanabe M A 2006 Heart rate turbulence slope reduction in imminent ventricular tachyarrhythmias and its implications J. 
Cardiovascular Electrophysiol. 17 373–40

Watanabe M A, Alford M, Schneider R, Bauer A, Barthel P, Stein P K and Schmidt G 2007 Demonstration of circadian rhythm in heart 
rate turbulence using novel application of correlator functions Heart Rhythm 4 292–300

Watanabe M A, Bhalodia R, Lunde quam E J, Domitrović P P, Steimme yer B C, Stein P K, Freedland K E, Dun tley S P and Carney R M 
2008 Increased ventricular premature contraction frequency during rem sleep in patients with coronary artery disease and 
obstructive sleep apnea Indian Pacing Electrophysiol. J. 8 258–67

Watanabe M A, Marine J E, Sheldon R and Josephson M E 2002 Effects of ventricular premature stimulus coupling interval on blood 
pressure and heart rate turbulence Circulation 106 325–30

Wichterle D, Bul kova V, Fikar M, Hav ranek S and Stovic pek P 2007 Heart rate turbulence after atrial premature complexes depends on 
coupling interval and atrioventricular nodal conduction Pacing Clin. Electro physiol. 30 S174–177

Wichterle D, Camm A J and Malik M 2004 Turbulence slope after atrial premature complexes is an independent predictor of mortality 
in survivors of acute myocardial infarction J. Cardiovascular Electrophysiol. 15 1350–6

Wichterle D, Melenovsky V, Simek J, Malik J and Malik M 2006 Hemodynamics and autonomic control of heart rate turbulence J. 
Cardiovascular Electrophysiol. 17 286–91

Wichterle D, Savelieva I, Meara M, Camm A J and Malik M 2003 ParadoXical autonomic modulation of atrioventricular nodal 
conduction during heart rate turbulence Pacing Clin. Electrophysiol. 26 440–3

Wichterle D, Simek M, La Rovere M T, Schwartz P J, Camm A J and Malik M 2004 Prevalent low-frequency oscillation of heart rate: novel 
predictor of mortality after myocardial infarction Circulation 110 1163–90

Witham M D, Dove F J, Sugden J A, Doney A S and Struthers A D 2012 The effect of vitamin D replacement on markers of vascular 
health in stroke patients - a randomised controlled trial Nutr. Metab. Cardiovasc. Dis. 22 604–70

Wongcharoen W, Khienprasit K, Phrommintikul A, Sukonthasarn A and Chattipakorn N 2013 Heart rate variability and heart rate 
turbulence during chronic baroreceptor stimulation on the autonomic cardiovascular regulation in patients with drug-resistant arterial hypertension 
Ir. J. Med. Sci. 180 379–85

Wichmann K, Kucera J P, Schefflers I, Mohaupt M, Kroon A A, de Leeuw P W, Schmidli J, Alleman Y and Delacrétaz E 2009 Effects of 
chronic baroreceptor stimulation on the autonomic cardiovascular regulation in patients with drug-resistant arterial hypertension 
Hypertension 54 530–6

Yalta K, Erdem A, Yilmaz A, Turgut O O, Yilmaz M B, Yontar C and Tandogan J 2007 Heart rate turbulence: an additional parameter in 
determining the need for mechanical relief of mitral stenosis J. Heart. Valve. Dis. 16 255–59

Yamada S et al 2018 Utility of heart rate turbulence and t-wave alternans to assess risk for readmission and cardiac death in hospitalized 
heart failure patients J. Cardiovascular Electrophysiol. 29 1257–64

Yang A, Schäfer H, Manka R, Andrä R, Schwab J O, Lewalter T, Lüderitz B and Tasci S 2005 Influence of obstructive sleep apnea on 
heart rate turbulence Basic Res. Cardiol. 100 439–45

Yang Z, Yu X and Yu M L 2013 Effects of shensongyagin capsule on heart rate turbulence and heart rate variability in chronic heart 
failure Chin. Med. J. 126 4389–91 2013

Yilmaz F, Gunduz H, Karamaslan K, Arinc H, Cosgun M, Sessiz N and Uyan C 2006 Holter analyses in children with adenosinomalous 
hypertrophy Int. Journal of Pediatric Otorhinolaryngology 70 1445–7

Yilmaz M, Akyarici F, Arcan Ozluk O, Peker T and Karaagac K 2013 Heart rate turbulence in patients with metabolic syndrome 
Metabolic Syndrome and Related Disorders 11 132–5

Yin D C, Wang Z J, Guo S, Xie H Y, Sun L, Feng W, Qiu W and Qu X F 2014 Prognostic significance of heart rate turbulence parameters 
in patients with chronic heart failure BMC Cardiovasc. Disord. 14 50

Yorgun H et al 2012 Evaluation of cardiac autonomic function by various indices in patients with primary premature ovarian failure 
Clin. Res. Cardiol. 101 753–9

Yo-shiba A et al 2014 Impact of sleep-disordered breathing on heart rate turbulence in heart failure patients Plos One 9 e10307

Yuan M J, Pan Y S, Hsu W G, Lu Z G, Zhang Q Y, Huang D, Huang X L, Wei M and Li J J 2015 A pilot study of prognostic value of 
non-invasive cardiac parameters for major adverse cardiac events in patients with acute coronary syndrome treated with 
percutaneous coronary intervention Int. J. Clin. Exp. Med. 8 22440–9

Zaza A and Lombardi F 2001 Autonomic indexes based on the analysis of heart rate variability: a view from the sinus node Pacing Clin. 
Electrophysiol. 50 433–42
Zhong J H, Chen X P, Zeng C F, Yun M L, Yang X W, Chen Y F and Yao Z 2007 Effect of benazepril on heart rate turbulence in patients with dilated cardiomyopathy Clin. Exp. Pharmacol. Physiol. 34 612–16
Zuern C S, Eick C, Rizas K D, Stoleriu C, Barthel P, Scherer C, Müller K A L, Gawaz M and Bauer A 2012 Severe autonomic failure in moderate to severe aortic stenosis: prevalence and association with hemodynamics and biomarkers Clin. Res. Cardiol. 101 565–72
Zuern C S, Rizas K, Eick C, Sterz K, Gawaz M and Bauer A 2012 Prevalence and predictors of severe autonomic failure in patients with insulin-dependent type 2 diabetes mellitus and coronary artery disease: pilot study J. Electrocardiol. 45 774–9