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Heart rate turbulence as risk-predictor after myocardial infarction

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Heart rate turbulence (HRT) is the baroreflex-mediated short-term oscillation of cardiac cycle lengths after spontaneous ventricular premature complexes. HRT is composed of a brief heart rate acceleration followed by a gradual heart rate deceleration. In high risk patients after myocardial infarction (MI) HRT is blunted or diminished. Since its first description in 1999 HRT emerged as one of the most potent risk factors after MI. Predictive power of HRT has been studied in more than 10,000 post-infarction patients. This review is intended to provide an overview of HRT as risk-predictor after MI.

Keywords: autonomic function, heart rate turbulence, myocardial infarction, risk stratification, sudden death

INTRODUCTION

Despite significant advances in interventional and medical therapy late mortality after myocardial infarction (MI) is still high. A substantial number of these late deaths occur suddenly, potentially preventable by an implantable cardioverter-defibrillator (ICD). Randomized multicenter trials have shown that mortality can be reduced in post-infarction patients at high risk for death by 20–54% (Moss et al., 1996, 2002; Buxton et al., 1999; Bristow et al., 2004; Bardy et al., 2005). Current guidelines recommend ICD implantation in patients characterized by a compromised left ventricular ejection fraction (LVEF 30–35%) which is considered to be the gold standard in risk prediction (Gregoratos et al., 2002; Zipes et al., 2006).

However, clinical studies have consistently shown that the criterion of a reduced LVEF is neither sensitive nor specific. It lacks of sensitivity as approximately 2/3 of deaths in post-infarction patients occur in patients with LVEF >35% who are not covered by the criterion of reduced LVEF (Myerburg et al., 1997, 1998; Huikuri et al., 2001; Buxton, 2003). It also lacks of specificity as 11 ICDs have to be implanted to save one life (Camm et al., 2007). The majority of ICD recipients will never receive an adequate shock. Therefore, development of additional risk stratification strategies is urgently needed.

Twelve years ago, an electrocardiographic phenomenon later on termed "heart rate turbulence (HRT)" has been described (Schmidt et al., 1999). At that time, it has been firstly recognized that in healthy persons spontaneous ventricular premature complexes (VPC) are followed by a characteristic short-term oscillation of heart rate. The oscillation is composed of a brief heart rate acceleration followed by a gradual heart rate deceleration before returning to baseline. As post-ectopic changes of cycle lengths are in the range of milliseconds and masked by heart rate variability of other origin it can only be visualized by signal averaging.

Very early it became clear that post-infarction patients at increased risk for adverse events showed different post-extrasystolic patterns of heart rate. In high risk patients the typical HRT response is blunted or entirely missing. Within the last decade, HRT emerged as one of the most potent ECG based risk predictors. Several large-scale studies have demonstrated its strong prognostic power in post-infarction patients. This review is intended to provide a review of HRT as risk-predictor in post-infarction patients.

MEASUREMENT OF HEART RATE TURBULENCE

Heart rate turbulence is obtained from standard 24-h Holter recordings with a minimum temporal resolution of 128 Hz which allow for accurate determinations of RR intervals and beat classifications. In contrast to other techniques such as T-wave alternans no specific electrodes or other equipments are needed. The technical assessment of HRT has been described in details elsewhere (Bauer et al., 2008). Briefly, the RR intervals surrounding spontaneous VPCs are averaged in order to obtain a so-called local tachogram demasking the average pattern of sinus RR intervals surrounding VPCs (**Figure 1**). VPCs used for HRT computation need to fulfill certain criteria with respect to prematurity and compensatory pause. Details regarding these filter criteria have been described elsewhere (Bauer et al., 2008).

The two phases of HRT are quantified by the two parameters turbulence onset (TO) and turbulence slope (TS).

Turbulence onset is calculated as follows:

$$\mathrm{TO} = \frac{(\mathrm{RR}_1 + \mathrm{RR}_2) - (\mathrm{RR}_{-2} + \mathrm{RR}_{-1})}{(\mathrm{RR}_{-2} + \mathrm{RR}_{-1})} \times 100[\%]$$

whereas RR_{-2} and RR_{-1} are the two RR intervals immediately before the VPC coupling interval. RR_1 and RR_2 are the

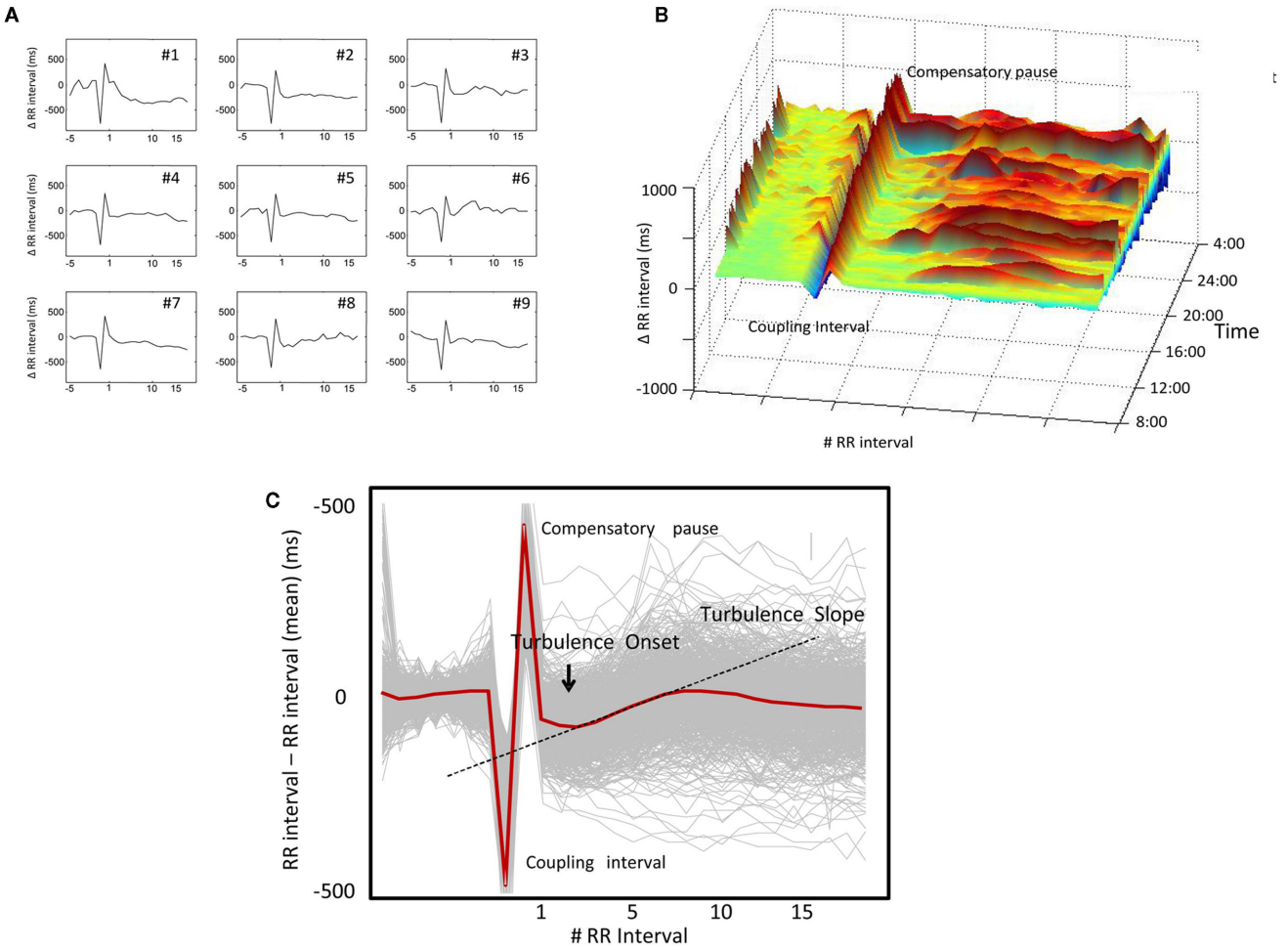

FIGURE 1 | Assessment of heart rate turbulence (HRT) from 24-h Holter recordings: (A) high variability in single "local tachograms" surrounding randomly selected ventricular premature complexes (VPCs); (B) high circadian variability in single local tachograms observed over 24 h; although typical HRT response can be suggested from this graph; (C) smooth HRT pattern (red curve) after signal averaging of single tachograms (gray curves). Quantification of HRT by turbulence onset and turbulence slope (see text for explanation).

two RR intervals which immediately follow the compensatory pause. TS is defined as the maximum positive regression slope assessed over any five consecutive sinus RR intervals within the first 15 RR intervals following the VPC. Hence, in normal subjects, the initial acceleration of sinus rate after the VPC is characterized by negative TO and the following heart rate deceleration is characterized by positive TS. TO $<0\%$ and TS >2.5 ms/RR interval are considered normal (Bauer et al., 2008).

For use of risk stratification in different patient populations, HRT is usually divided into three categories: (1) HRT category 0 is defined as normal TO *and* normal TS, (2) HRT category 1 means that either TO *or* TS are abnormal, and (3) HRT category 2 is characterized by *both* abnormal TO and TS. If no sufficient VPC tachograms are recorded and patients are otherwise in sinus rhythm, HRT is classified as category 0 since those patients were shown to have equally good prognosis as patients with normal HRT (Barthel et al., 2003). As this was only shown for post-infarction patients, this approach might not be valid if other pathologies (e.g., heart failure) are considered.

The HRT software is commercially available on GE and Getemed Holter systems. However, as the algorithms have been published in detail (www.h-r-t.com) HRT can also be obtained from the series of RR intervals by a custom-made software.

PHYSIOLOGY OF HEART RATE TURBULENCE

When the first clinical studies of HRT in risk prediction have been published the exact physiological mechanisms behind HRT were largely unknown (Schmidt et al., 1999; Bauer and Schmidt, 2007). The (patho)physiological mechanisms behind HRT are complex and involve both branches of the autonomic nervous system. In their work, Wichterle et al. (2006) provide an excellent review of HRT physiology. The VPC induces a transient drop of arterial blood pressure which leads to an activation of the baroreceptors. Vagal activity is abruptly withdrawn resulting in an almost

immediate shortening of RR interval cycle lengths (as measured by TO). However, also the sympathetic system reacts (Segerson et al., 2007). Increased sympathetic activity results in a gradual increase of vascular resistance and systolic arterial blood pressure. As consequence, vagal activity reestablishes and cycle lengths prolong (as measured by TS). Importantly, HRT requires an intact interplay of both, vagal and sympathetic systems. Absence of normal HRT can be caused by an alteration in one of the systems (Wichterle et al., 2006).

HRT STUDY POPULATIONS

Evidence of HRT as risk-predictor in post-infarction patients is based on five retrospective and five prospective studies including a total of more than 10,000 patients. Study characteristics are summarized in **Tables 1** and **2**.

Heart rate turbulence was originally developed in a small dataset comprising of 100 patients suffering from coronary artery disease and subsequently validated in a blinded fashion in the cohorts of the MPIP study ($n = 577$) and the placebo arm of the EMIAT study ($n = 614$; Schmidt et al., 1999). Two years later, Ghuran et al. (2002) tested the predictive power of HRT in the dataset of the ATRAMI study ($n = 1{,}212$) which was originally designed to assess the prognostic power of baroreflex sensitivity. Another 3 years later, predictive power of HRT was also tested in the dataset of the CAST study ($n = 744$; Hallstrom et al., 2005). The FINGER study combined a Finish and German post-infarction population (Barthel et al., 2003; Huikuri et al., 2003) to specifically address the question whether HRT predicts sudden death (Makikallio et al., 2005).

In 2003, the results of the first prospective study ISAR-HRT ($n = 1{,}455$) were published which was designed to validate the prognostic value of HRT in a large cohort of post-infarction patients receiving contemporary treatment (Barthel et al., 2003). The REFINE study ($n = 322$) published 2007 was designed to assess the predictive value of a combination of several risk predictors including HRT as well as the time of their assessment after acute MI (Exner et al., 2007). In 2009, the results of the largest prospective HRT study were published. ISAR-RISK tested the prognostic value of a combination of HRT and deceleration capacity (Bauer et al., 2006a) in post-infarction patients with preserved LVEF (Bauer et al., 2009a). Deceleration capacity is an integral measure of all deceleration related modulations of heart rate observed over 24 h and thus, most presumably, a measure of tonic vagal activity. The CARISMA study ($n = 312$) deserves special attention as loop recorders have been implanted in all patients to specifically address the endpoint of severe arrhythmic events (Huikuri et al., 2009). Very recently, the results of ISAR-SWEET have been published

Table 1 | Retrospective studies (or sub-studies) investigating heart rate turbulence as a post-infarction risk-predictor.

	MPIP (Schmidt et al., 1999)	EMIAT (Schmidt et al., 1999)	ATRAMI (Ghuran et al., 2002)	CAST (Hallstrom et al., 2005)	FINGER (Makikallio et al., 2005)
Number of patients	577	614	1,212	744	2,130
Year of publication of original study	1983	1997	1998	1991	2003
Inclusion criteria*	MI ≤4 weeks, age ≤70 years	MI ≤4 weeks, age ≤75 years, LVEF ≤40%	MI ≤4 weeks, age ≤80 years	MI ≥6 VPC/h	MI ≤4 weeks, age ≤75 years
Follow-up (months)	22	21	20	55	33
Endpoint	Mortality	Mortality	Cardiac mortality†	Mortality	Sudden death
Endpoints reached (%)	13	14	4	29‡	2
Time of HRT assessment after MI	2nd week	2nd to 3rd week	2nd to 4th week	10 weeks	2nd week
Treatment of acute MI	None	60% Lysis	63% Lysis	28% Lysis	70% PCI, 14% lysis
Mean LVEF (%)	45	30	49	37	Not specified
Betablockers (%)	55	32	20	30	94
UNIVARIATE ANALYSIS					
HRT category 2	5.0 (2.8–8.8)	4.4 (2.6–7.5)	6.9 (3.1–15.5)	Not specified	4.6 (2.6–8.1)‖
LVEF ≤30%	4.0 (2.5–6.4)	2.2 (1.4–3.5)	4.7 (2.6–8.3)	Not specified	4.5 (2.5–8.0)#
MULTIVARIATE ANALYSIS					
HRT category 2	3.2 (1.7–6.0)	3.2 (1.8–5.6)	4.1 (1.7–9.8)	20.4 (10.2–30.6)**	2.9 (1.6–5.5)
LVEF ≤30%	2.9 (1.8–4.9)	1.7 (1.1–2.7)	3.5 (1.8–7.1)	Not specified	Not specified

Sinus rhythm was inclusion criterion in all studies.

†*Cardiac Mortality included fatal and non-fatal cardiac arrest.*

‡*Cumulative mortality rate only presented for total study population of CAST after 5 years.*

‖*Relative risks presented for turbulence slope ≤2.5 ms/RR interval.*

#*LVEF was dichotomized at 35%.*

***Log of Turbulence Slope corrected for heart rate and VPC count (optimized in CAST data).*

Table 2 | Prospective studies (or sub-studies) investigating heart rate turbulence as a post-infarction risk-predictor.

	ISAR-HRT (Barthel et al., 2003)	REFINE (Exner et al., 2007)	ISAR-RISK‡‡ (Bauer et al., 2009a)	CARISMA (Huikuri et al., 2009)	ISAR-Sweet‡‡ (Barthel et al., 2011)
Number of patients	1,455	322	2,343	312	481
Inclusion criteria*	MI ≤4 weeks, age ≤75 years	MI, LVEF <50%	MI ≤4 weeks, age ≤75 years	MI <21 days, LVEF ≤40%	MI ≤4 weeks, age ≤80 years, diabetes
Follow-up (months)	22	47	60	24	60
Endpoint	Mortality	Cardiac death†	Mortality	VF/sustained VT on loop recorder	Mortality
Endpoints reached (%)	5	9	8	8	17
Time of HRT assessment after MI	2nd week	2nd to 4th and 10th to 14th week	2nd week	1st and 6th week	2nd week
Treatment of acute MI	90% PCI, 6% lysis	45% PCI, 21% lysis	92% PCI, 3% lysis	14% PCI, 34 lysis	89% PCI
Mean LVEF (%)	56	47	55	31	51
Betablockers (%)	93	92	94	96	94
UNIVARIATE ANALYSIS					
HRT category 2	11.4 (5.7–22.8)	2.9 (1.1–7.5)††	7.5 (5.3–10.7)	2.8 (1.1–7.2)‖	6.6 (3.9–11.0)
LVEF ≤30%	7.1 (4.2–12.1)	3.3 (1.4–7.6)	6.1 (4.2–8.7)	1.3 (0.5–3.0)#	4.7 (2.8–7.8)
MULTIVARIATE ANALYSIS					
HRT category 2	5.9 (2.9–12.2)	Not specified	3.1 (2.1–4.6)	Not specified	4.1 (2.3–7.2)
LVEF ≤30%	4.5 (2.6–7.8)	Not specified	3.0 (2.0–4.4)	Not specified	2.4 (1.4–4.1)

**Sinus rhythm was inclusion criterion in all studies.*

†Cardiac mortality included fatal and non-fatal cardiac arrest.

‖Relative risks presented for turbulence slope ≤2.5 ms/RR interval.

#LVEF was dichotomized at 35%.

††HRT category ≥1 vs. 0 tested; HRT was assessed 10–14 weeks after MI.

‡‡ISAR-RISK primarily tested the combination HRT category 2 and abnormal deceleration capacity (Bauer et al., 2006a).

which tested the combination of abnormal HRT and deceleration capacity in diabetic post-infarction patients (Barthel et al., 2011).

RISK PREDICTIVE POWER OF HRT IN POST-INFARCTION PATIENTS

In all populations, abnormal HRT was a significant and independent predictor of adverse events yielding a relative risk of 2.8–11.4 on univariate and 3.1–5.9 on multivariate analysis.

The single HRT studies substantially differ with respect to study design (retrospective vs. prospective), the primary endpoint investigated (total mortality, cardiac mortality, and sudden death), time of follow-up, time after MI when Holter recordings have been performed, mean LVEF, and treatment of MI.

Heart rate turbulence is generally a very strong predictor in all studies which used total mortality as primary endpoint (which most of the studies did: MPIP, EMIAT, CAST, ISAR-HRT, ISAR-RISK, ISAR-SWEET). HRT was also a very strong predictor in the ATRAMI study which used a combined endpoint of cardiac mortality and fatal and non-fatal cardiac arrest. Two studies investigated sudden death as primary endpoint, namely the FINGER study and the CARISMA study. While in the FINGER study mode of death was determined anamnestically or with the use of medical recordings, CARISMA had a unique study design: all patients of the CARISMA study underwent implantation of a loop recorder which allowed for a definite assessment of the rhythm at time of death. While HRT was a strong predictor of sudden death in the FINGER study, predictive power of HRT in the CARISMA study was somewhat lower although still significant [relative risk of abnormal TS 2.8 (95% CI 1.1–7.2), $p = 0.038$]. It should be noted, however, that in CARISMA only 25 endpoints occurred during a follow-up of 2 years and that only patients with reduced LVEF (≤40%) have been included. Therefore, conclusions drawn from the CARISMA should not be directly extrapolated to unselected post-infarction populations with no restriction of LVEF.

Time of HRT assessment after acute MI is an important issue. In most HRT studies Holter recordings have been performed early after MI (usually within the first 4 weeks; MPIP, EMIAT, ATRAMI, FINGER, ISAR-HRT, ISAR-RISK, and ISAR-SWEET). In all of these studies, HRT was a strong and significant predictor of the primary endpoint. However, also in CAST, where risk assessment was performed later after MI, HRT was a strong predictor of death (Hallstrom et al., 2005). In two studies, namely the REFINE and the CARISMA study, risk assessment has been performed at two different time points. In REFINE risk assessment has been performed between the 2nd and the 4th week as well as between the 10th and the 14th week after MI. In CARISMA, risk assessment has been performed during the first week as well as during the sixth week after MI. In both studies, risk assessment later after MI was superior to risk assessment earlier after MI. It might therefore be concluded, that HRT assessed later after MI might be a better predictor than HRT assessed early after MI. These findings are in

agreement with the observation that autonomic dysfunction early after MI might recover, and that patients with sustained blunted autonomic function have the worst prognosis (Huikuri et al., 2010).

The single HRT studies cover the whole spectrum of MI treatment eras. In summary, neither acute treatment of MI (conservative, lysis, PCI) nor concomitant medical treatment including betablockers, ACE-inhibitors, or statins seem to affect risk predictive power of HRT. However, it should be noted that effective reperfusion strategies for acute MI which lead to increased myocardial salvage translate into improved autonomic function and better HRT (Bauer et al., 2009b).

Positive predictive accuracies and sensitivities of abnormal HRT for prediction of adverse events strongly depend on the populations and endpoints investigated. Generally, both positive predictive accuracy and sensitivity is in the range of that yielded by LVEF ≤30%. **Figure 2** exemplarily shows risk stratification by HRT in the largest post-infarction study, the ISAR-RISK study. Of the 2,343 patients studied, HRT category 2 identified a high risk group of 193 patients (8%) out of whom 56 patients died. 2,150 patients (92%) had normal (HRT category 0 and 1) out of whom 125 patients died. Probability of death within 5 years of follow-up of patients with abnormal HRT (HRT category 2) was 34%. In contrast, the 1,652 patients (71%) with completely normal HRT (HRT category 0) had a 5-year mortality of 6%. These figures translate into a positive predictive accuracy of 34% at a sensitivity level of 31%.

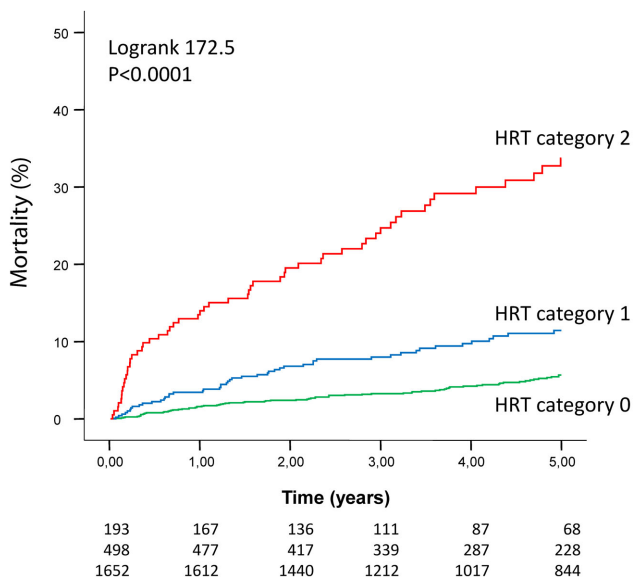

FIGURE 2 | Risk stratification by heart rate turbulence in the ISAR-RISK study (Bauer et al., 2009a). The number of patients of the individual groups involved in the analyses at 0, 1, 2, 3, 4, and 5 years are shown under the graphs. The top and the bottom row corresponds to the upper and bottom Kaplan–Meier curve respectively. For all three comparisons (HRT category 0 vs. HRT category 1, HRT category 0 vs. HRT category 2, and HRT category 1 vs. HRT category 2) the *p*-value was <0.0001. (Adapted by permission from Bauer et al., 2009a).

INDEPENDENCY FROM AND COMBINATION WITH OTHER RISK PREDICTORS

In all studies, predictive value of HRT was independent from that of other risk predictors tested. These included demographic factors and comorbidities (age, gender, presence of diabetes mellitus, and renal insufficiency; Barthel et al., 2011), markers of electrical instability [arrhythmias, T-wave alternans (Exner et al., 2007), late potentials (Bauer et al., 2005), QRS duration (Bauer et al., 2006b)], markers of structural damage (e.g., LVEF), and other markers of autonomic dysfunction (heart rate, heart rate variability, and deceleration capacity; Bauer et al., 2006a, 2009a).

In order to enhance risk predictive power, HRT should be combined with other risk predictors. The ISAR-RISK and the ISAR-SWEET studies investigated the combination of abnormal HRT (HRT category 2) with mildly abnormal deceleration capacity (≤4.5 ms) which is a measure of tonic autonomic activity and bases on the processing of RR interval time series by a new mathematical algorithm (Bauer et al., 2006c). For this combination, the term "severe autonomic failure (SAF)" has been introduced. In both, ISAR-RISK and ISAR-SWEET which included 2,343 and 481 patients respectively, SAF proved to be the strongest predictor of death. These findings were confirmed by the results of a recent metaanalysis which analyzed the combined populations of the MPIP, EMIAT, and MRFAT studies ($n = 2{,}594$; Bauer et al., 2009c). Also the combination of HRT with T-wave alternans is promising as both were independently associated with the primary endpoint in the REFINE study. However, available data do not allow for final conclusions.

Risk stratification by HRT is complementary to risk stratification by LVEF. Only a small proportion of patients with abnormal HRT (category 2) also have LVEF ≤30%. Therefore, the strength of HRT lies in the identification of high risk patients in the large group of patients with preserved LVEF (>30%). **Figure 3** shows complimentary risk stratification by HRT and LVEF in the ISAR-RISK study (Bauer et al., 2009a). The small proportion of patients with both, abnormal HRT and impaired LVEF ($n = 40$; 1.7% of the study population) had the worst prognosis. Patients with either abnormal HRT ($n = 153$; 6.5% of the study population) or impaired LVEF ($n = 80$; 3.4% of the study population) had equally poor prognosis. In contrast, patients with normal HRT (category 0 or 1) and LVEF >30% ($n = 2{,}070$; 88.3% of the study population) had an excellent prognosis. As mentioned above risk stratification by HRT can be further improved by combination with deceleration capacity (Bauer et al., 2009a).

LIMITATIONS OF HEART RATE TURBULENCE

Several limitations need to be recognized when using HRT as risk-predictor. Firstly, assessment of HRT requires the presence of sinus rhythm. Patients with other rhythms than sinus rhythm such as atrial fibrillation have been excluded in all HRT studies but might be at increased risk. In the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO-I) trial, 10.5% of the 41,021 patients had atrial fibrillation during hospitalization (Crenshaw et al., 1997). Further, most HRT studies also excluded elderly patients (age >75 years or age >80 years). It is well known from the ATRAMI study that autonomic function loses some of its predictive value with increasing

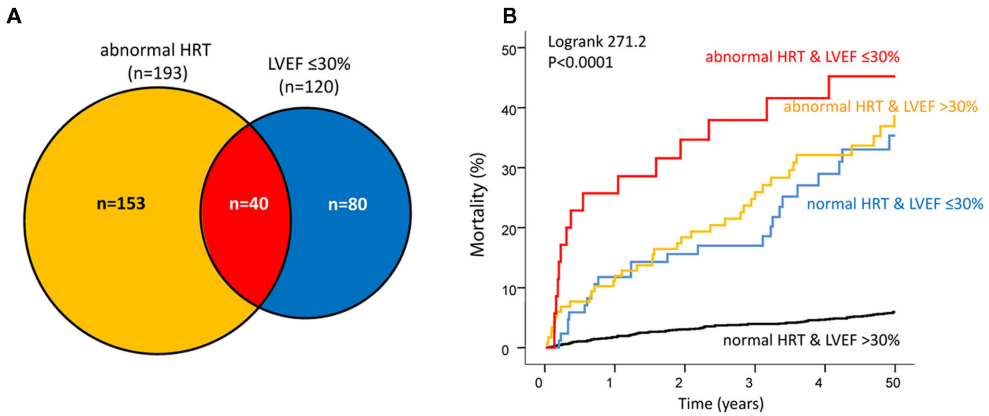

FIGURE 3 | Complimentary risk stratification by HRT and LVEF in the ISAR-RISK study (Bauer et al., 2009a). (A) Distribution of patients with abnormal HRT but LVEF >30% ($n = 153$, orange area), abnormal HRT and LVEF ≤ 30% ($n = 40$, red area), and normal HRT but LVEF ≤30% ($n = 80$, blue area). **(B)** Corresponding 5-year mortality rates of the three groups. Abnormal HRT defined as HRT category 2 (adapted by permission from Bauer et al., 2009a).

age (La Rovere et al., 1998). Similar observations have been made for HRT in the ISAR-HRT study (Barthel et al., 2005). In contrast, HRT was a significant predictor for sudden death in the population based Cardiovascular Health Study which included adults ≥65 years (average 73 years; Stein et al., 2010). Assessment of HRT also requires presence of VPCs. In most studies, patients without VPCs have therefore been excluded from the analysis (e.g., MPIP, EMIAT, ATRAMI). As shown in the ISAR-HRT study post-infarction patients without VPCs have equally good prognosis as patients with normal HRT (Barthel et al., 2003). Therefore, these patients might be treated as having normal HRT (HRT category 0). HRT is usually assessed from full 24-h Holter recordings. Whether HRT derived from shorter recordings provides similar predictive value needs further investigations. A retrospective analysis of HRT in the Multicenter Automatic Defibrillator Implantation Trial 2 that used only 10-min recordings showed the inappropriateness of very short recordings (Berkowitsch et al., 2004). All post-infarction HRT studies included patients early after MI. A large-scale study which investigates the prognostic value of HRT in patients with remote infarction is still missing. This might be of substantial importance as prophylactic ICD implantation in the acute phase of infarction has been generally questioned by the negative results of two randomized ICD trials (Hohnloser et al., 2004; Steinbeck et al., 2009). It should be noted, however, that both studies, the DINAMIT ($n = 674$) and the IRIS study ($n = 898$), used entry criteria that selected only a very small proportion of post-infarction patients at very high risk. For instance, the IRIS study selected 898 patients out of 62,944 patients (1.4%). Conclusions drawn from these two studies should therefore not be generalized and extrapolated to other risk stratification strategies.

CONCLUSION

Heart rate turbulence is easily applicable from routine 24-h Holter recordings. In all post-infarction studies HRT was a strong and independent predictor of adverse events which included death of any cause, cardiac death, and sudden death. In all post-infarction studies, predictive value of HRT was independent from other risk factors tested. For purpose of identifying high risk individuals who might benefit from prophylactic ICD implantation, HRT should be combined with other independent predictors. Potential candidates include impaired LVEF, abnormal deceleration capacity, and/or T-wave alternans. The combination of abnormal HRT and abnormal deceleration capacity termed "SAF" has been tested in the ISAR-RISK study and provides strong prognostic value also in post-infarction patients with preserved LV-function. However, only future interventional trials can finally answer the question whether high risk patients identified by abnormal HRT benefit from prophylactic therapy.

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