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Review Article

Contributions of the heart rate turbulence method to risk stratification in patients after myocardial infarction: a review

Rafael Alessandro Ferreira Gomes*, Michel Pompeu Barros de Oliveira Sá*, Dario Celestino Sobral Filho*

*PROCAPE, Pernambuco University, Rua dos Palmares, s/n, Santo Amaro, Recife-Pernambuco, Brazil. *Equal contributors.*

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Abstract: Coronary artery disease remains an important cause of morbidity and mortality worldwide. The impact of ventricular arrhythmias and impaired cardiac vagal activity on coronary events is one of the most relevant prognostic factors, despite little research being conducted in clinical practice. A simple and cost-effective way to analyze cardiac autonomic regulation is through the heart rate turbulence (HRT) method. Studies have shown that altered HRT, which indicates reduction in the vagal cardiac activity, can identify patients who are at a higher risk of sudden death. Thus, aspects related to the definition, pathophysiological mechanism, conditions that alter the HRT behavior, and the main studies that analyzed the prognostic importance of HRT in patients with ischemic disease were discussed in this review. HRT analysis was proven to be a simple and cost-effective way to assess cardiac autonomic dysfunction by providing complementary information to classic parameters, such as the assessment of ventricular function.

Keywords: Cardiac arrhythmia, sudden cardiac death, myocardial infarction

Introduction

Coronary artery disease (CAD) is a highly prevalent condition characterized by the build-up of atherosclerotic plaques in the epicardial arteries [1, 2]. CAD has a high mortality, particularly due to to the development of cardiac arrhythmias and the unexpected characteristics associated with its clinical decompensation [3]. It is estimated that >15 million Americans have CAD, with ~357,000 deaths per year in the US owing to its complications [4]. The cost of diagnosis and treatment is high, with figures exceeding $200 billion per year [3].

Strategies to reduce the high morbidity and mortality involve identifying prognostic risk markers that can identify patients with the worst cardiovascular outcome. One of the most promising markers, which still has no widespread use in clinical practice, is heart rate turbulence (HRT), an important parameter for assessing cardiac dysautonomia [5].

This review aims to describe some aspects related to the definition, pathophysiological mechanisms, and conditions that alter HRT behavior, and the main studies that have analyzed the prognostic importance of HRT in patients with ischemic disease.

Discussion

Definition

HRT is defined as a fluctuation in sinus frequency that occurs after a premature ventricular beat (PVB). This phenomenon was described in 1999 by Schmidt et al. [5], who observed that cardiovascular risk in patients with coronary disease was associated with a different ventriculophasic sinus arrhythmia. They reported that patients with a lower risk of cardiovascular events had a brief sinus frequency acceleration with subsequent deceleration after an isolated PVB (**Figure 1**).

Pathophysiological mechanisms

The integrity of the autonomic nervous system (ANS) is fundamental for transient variation in heart rate. A cardiac cycle interrupted by a PVB

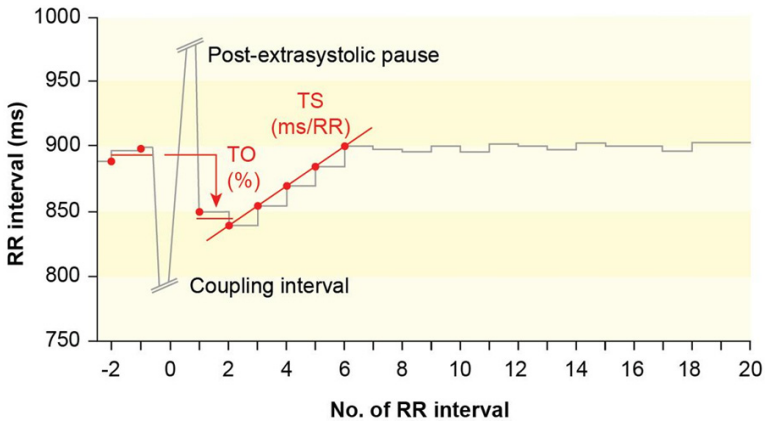

Figure 1. Tachogram of heart rate turbulence demonstrating the two main parameters of analysis. TO calculated based on the last two sinus RR intervals immediately before the PVB-coupling interval, and the two sinus RR intervals immediately after the compensatory pause; TS calculated using the slope of the line formed by five RR intervals after the PVB, which are obtained from among the first 15 sinus RR intervals that follow the PVB. TO, turbulence onset; TS, turbulence slope.

has a short diastolic period, and the cycle containing the PVB has lesser ventricular synchrony in a scenario of greater afterload, which is not preceded by an atrial contraction. Thus, the ejected stroke volume is expected to be lower, which results in a quick response from the baroreceptors in the ANS to prevent a drop in pressure levels [6].

The immediate ANS reaction is vagal inhibition, which promotes initial heart rate acceleration and sympathetic stimulation, thereby increasing peripheral vascular resistance. These combined effects increase systemic blood pressure levels. However, non-repetition of the PVB in subsequent cycles makes this new hemodynamic scenario of tachycardia and hypertension inadequate. In turn, the vagal stimulus slows the heart rate and returns it to pre-PVB baseline levels [6].

Thus, HRT can indirectly assess vagal autonomy through the vagal inhibition effect and stimulation of heart rate. Turbulence onset (TO) analyzes the initial heart rate acceleration, while the turbulence slope (TS) analyzes the late heart rate deceleration. Based on the study by Schmidt et al., it was agreed that the HRT behavior is normal when the TO levels are <0% and the TS levels are >2.5 ms/RR [5]; i.e., patients who are unable to react quickly to hemodynamic changes caused by PVB-associated cardiac dysautonomia are at a higher risk of death and future cardiovascular events (**Figure 2**). It is still possible that there is also a direct effect of PVB and the baroreceptor reflex on HRT, however, autonomic dysfunction seems to be the main one.

HRT analysis parameters

The two main parameters for analyzing the HRT are TO and TS. Although there are other assessments for HRT behavior, they need to be further validated before their incorporation into the cardiovascular risk analysis, since they require longer electrocardiographic records in addition to their complex measurement. These parameters include turbulence timing, turbulence jump, TS correction coefficient, turbulence dynamics, and turbulence frequency decrease [7].

TO is calculated based on the last two sinus RR intervals immediately before the PVB-coupling interval, and the two sinus RR intervals immediately after the compensatory pause. TO (in percentage) has negative values for patients with low cardiovascular risk since there is immediate heart rate acceleration after PVB.

Turbulence Onset

$$= \frac{(RR_1 + RR_2) - (RR_{-1} + RR_{-2})}{(RR_1 + RR_2)} \times 100\,(\%)$$

The TS is calculated using the slope of the line formed by five RR intervals after the PVB, which are obtained from among the first 15 sinus RR intervals that follow the PVB. The TS is given in milliseconds per RR interval, and the heart rate of patients with a low cardiovascular risk is decreased by up to 8 beats/min following the initial acceleration caused by the PVB; thus, the reference values are >2.5 ms/RR, which translates to the maximum variation in sinus RR intervals (ms) among the five sinus RR intervals to be analyzed.

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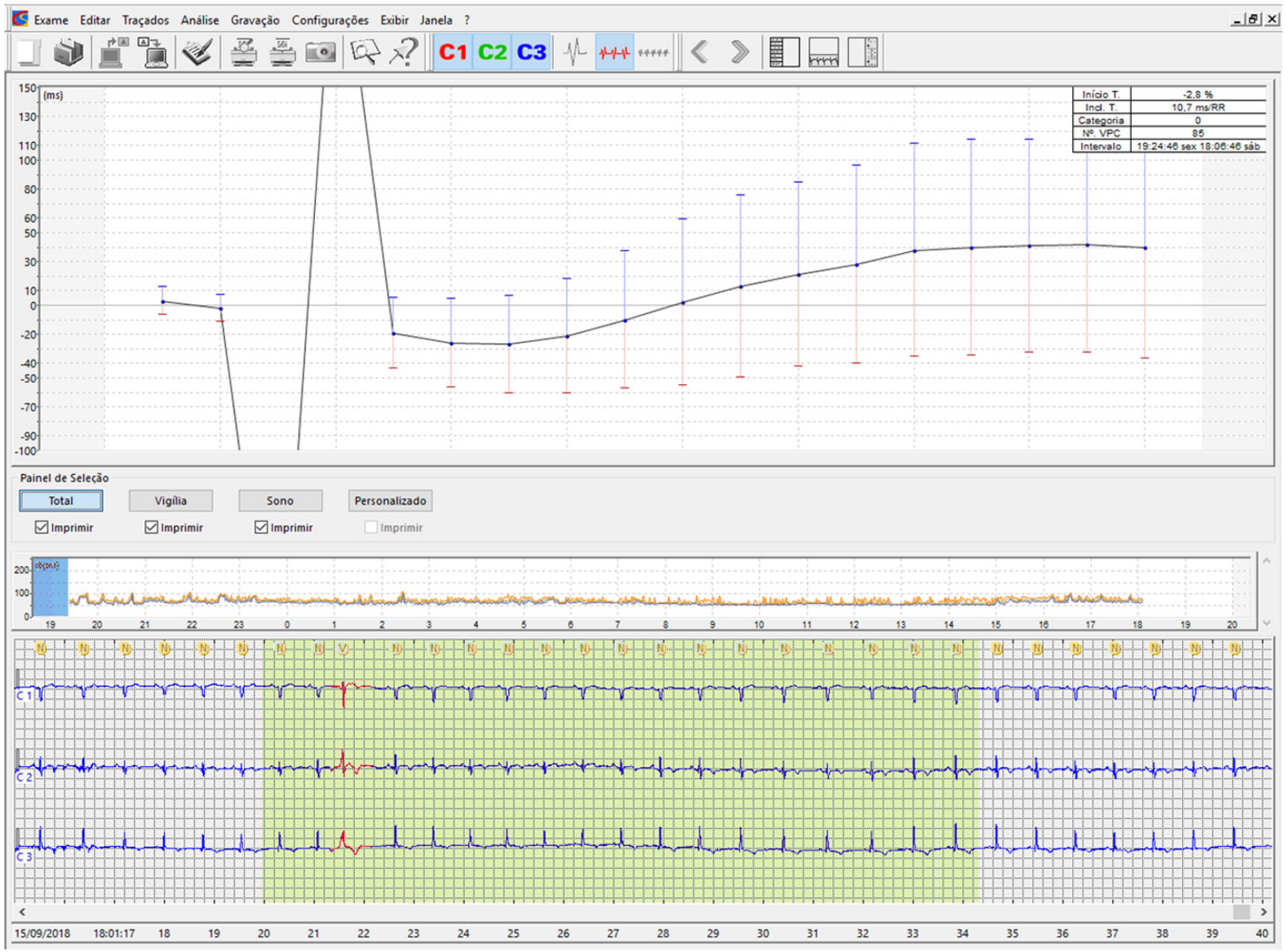
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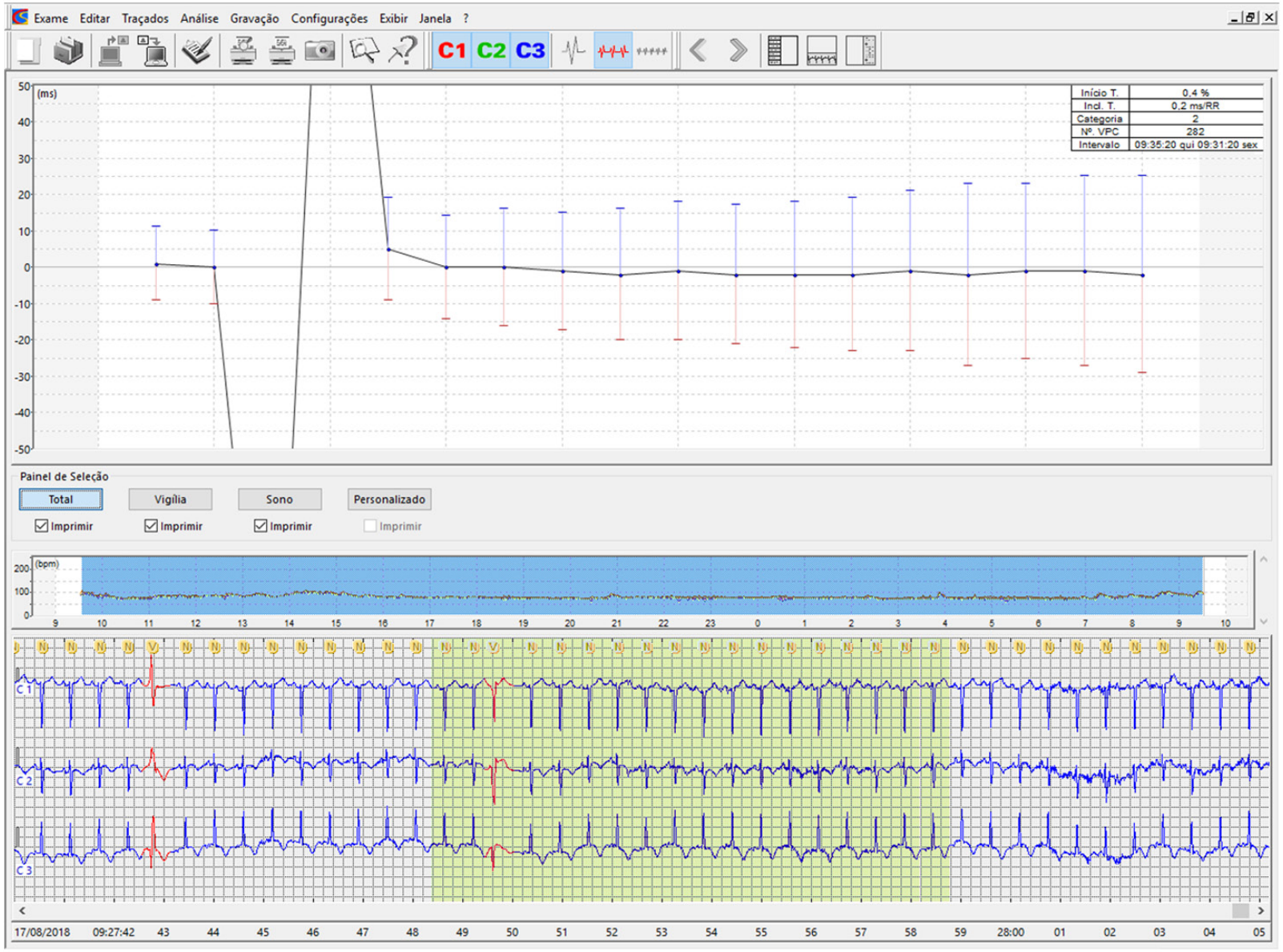
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Figure 2. Comparison of the HRT behavior in patients with low and high cardiovascular risk. A. HRT in low cardiovascular risk. There is an initial acceleration and subsequent deceleration following the PVB, showing that the sympathetic nerve activity is intact. B. The PVB is unable to alter the chronotropic response. HRT, heart rate turbulence; PVB, premature ventricular beat.

$$Turbulence\ slope = \frac{Y5 - Y1}{X5 - X1}$$

In 1999, Schmidt et al. analyzed the ventriculophasic behavior after a PVB in 100 patients following myocardial infarction [5]; this study was validated with the Multicenter Post-Infarction Program (MPIP) database and the placebo arm of the European Myocardial Infarction Amiodarone Trial (EMIAT), totaling 1.200 patients in multicenter studies with independent populations. Approximately 577 patients in the MPIP study were evaluated with Holter recordings that was performed 2 weeks after their myocardial infarction episode, and the follow-up was continued for 22 months. Approximately 614 patients in the EMIAT study were evaluated between the second and third week after their infarction episode; each patient had a left ventricular ejection fraction (LVEF) of ≤40%. It was concluded that patients with altered HRT following an infarction episode had a higher risk of death within 2 years. The hazard ratio (HR) in the MPIP study was 3.2 (95% confidence interval (CI) 1.7-6.0, P=0.0002), while the HR in the EMIAT study was 3.2 (95% CI 1.8-5.6, P<0.0001). Both TO and TS were independent predictors of mortality in this study, with information complementary to each other. The combination of TO and TS was the strongest risk predictor in the MPIP trial patients and in the EMIAT study placebo group, even when adjusted for other mortality predictors such as LVEF, arrhythmia count, heart rate variability, heart rate, and history of infarction. For this reason, the authors suggested categorizing HRT behavior into 0, 1, and 2, depending on whether the individual had two normal parameters, one altered parameter, or two altered parameters, respectively.

Maintaining methodological standardization for measuring this method allows for better comparability between studies and applicability of this technique in different scenarios [8]. From this study, it was agreed that HRT analysis should follow the methodology reported by Schmidt et al., with the use of the following categories: 0 when the TO and TS are normal, 1 when any parameter is changed, and 2 when all parameters are changed [5]. Barthel et al. showed that patients who do not have premature ventricular arrhythmia can be included in category 0, owing to the similar rate of cardiovascular events [9].

Situations that can alter HRT analysis

The International Society for Holter and Non-Invasive Electrophysiology published a consensus that standardizes HRT measurement to improve predictive power and decrease interference [6]. This consensus suggests that only a PVB comprising prematurity >20% and a compensatory pause >120% of the average of the last five RR intervals preceding the PVB should be analyzed, in addition to excluding very short (<300 ms) or very long PVB tachograms (>2,000 ms) [6].

Some clinical factors have been identified as being responsible for interfering with the TO and TS response. Schmidt et al. have shown that increasing age is associated with abnormal HRT behavior [5, 9]. These findings were also reported in other studies, such as the Multicenter Automatic Defibrillator Implantation Trial II study (MADIT II) and the Monitoring of Trends and Determinants in Cardiovascular Disease registry [10, 11]. However, there are no robust data on patients >75 years old, as this is the population in which greater cardiac autonomic dysfunction is expected. As reported by Baydar et al., the individual's sex does not alter the HRT behavior [12]. Barthel et al. confirmed these findings in a study with almost 1500 post-infarction patients [9].

The use of beta-blockers improves the TS behavior, as observed in patients in the MADIT II study [10], and the increase in the heart rate can cause abnormal HRT behavior [13, 14]; however, this mechanism is not fully understood. One possibility for this association with the heart rate might be due to a specific property of the sinus node, which results in a nonlinear relationship between the vagal activity and depolarization frequency [15].

It was also observed that other interventions used in the treatment of heart failure, such as

angiotensin-converting enzyme inhibitors and cardiac resynchronization therapy, seem to have the ability to improve HRT parameters [16].

Yagcioglu et al. found no difference in cardiac autonomic function when comparing the use of ticagrelor or clopidogrel in patients undergoing percutaneous coronary intervention [17].

New therapies in the care of post-myocardial infarction patients, such as empaglifozin, also appear to improve cardiac autonomic parameters due to reduced preload, better blood pressure control, and optimization of oxygen delivery to the myocardium. In the Embody trial, the use of SGLT2 inhibitors decreased the occurrence of HRT category 2 significantly after 24 weeks of follow-up (25.6% to 9.3%, P<0.01) [18].

Prognostic importance

Study conducted by Selvaraj et al. in Indian population evaluated 58 individuals with a history of myocardial infarction and ventricular dysfunction during a mean follow-up of 22.3 months. Their data found no significant association between HRT parameters and cardiac death or resuscitated cardiac arrest. Since it has a small sample size and unicentric study, the data must be compared with other scenarios and populations in order to reach a precise conclusion [19].

In the MADIT II study [10], which evaluated 900 post-infarction patients with severe ventricular dysfunction, a statistically significant association was observed between frequent PVB (>3/10 mins) and mortality. The median TS measured was lower in the patients who died than in the survivors (2.3 ms/RR vs. 4.5 ms/RR; P<0.05); however, this parameter lost statistical significance in the multivariate analysis in patients with severe ventricular dysfunction when adjusted for clinical and laboratory variables (age, LVEF, use of beta-blockers, and urea levels). The HRT data in this study may not have reached significance due to the method of obtaining the HRT, which was in a short electrocardiographic screening of up to 10 mins, as opposed to 24 hours idealized by Schmidt et al. [5].

Even without highlighting this important bias, the current guidelines of the American Heart Association and the European Society of Cardiology recommend the prophylactic use of implantable cardio defibrillators (ICD) in post-infarction patients based only on the LVEF [20, 21]. In a quick cost-effectiveness analysis, this device proved to be useful in only one patient for every 11 patients treated with ICD for three years. Nonetheless, it would still be interesting to associate another parameter to optimize the use of the ICD.

Sade et al. reported that HRT parameters had a similar prognostic evaluation to that of the ejection fraction (TS: HR 7.3; 95% CI 1.4-37; P=0.016 vs. LVEF <40%: HR 6.9; 95% CI 1.8-26, P=0.006) in an analysis of 128 post-infarction patients during a mean follow-up of 312 days [22]. When analyzing the total mortality in the multivariate analysis, the combination of TO and TS altered with an LVEF of ≤40% demonstrated a high risk of events (HR 14; 95% CI 3.8-54, P<0.0001), with sensitivity, specificity, positive predictive value, and negative predictive value of 25%, 98%, 60%, and 92%, respectively.

Ghuran et al. retrospectively analyzed data from the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study in 2002 and showed that HRT parameters had a high-risk stratification power for cardiac death and severe cardiac arrhythmia in 1,212 post-infarction patients, who were followed-up for an average of 21 months [23]. When the HRT parameters were analyzed separately, TO was observed to have borderline statistical significance; however, TS presented an HR of 2.47 (95% CI: 1.19-5.12; P=0.015). When the altered parameters were combined, the HR was 4.07 (95% CI: 1.70-9.77; P=0.0017), which was higher than that for an LVEF of <35% (HR 3.53; 95% CI 1.76-7.06; P=0.0004). This indicates that TS and the combination of altered TO and TS added prognostic information in the multivariate analysis to those parameters obtained using other risk predictors, such as the baroreflex sensitivity, standard deviation of normal cardiac intervals, LVEF, mean of normal cardiac intervals, PVB/hour, and age.

The Innovative Stratification of Arrythmic Risk-Heart Rate Turbulence was the first prospective study with the objective of validating the use of HRT [9]. Approximately 1500 survivors of acute myocardial infarction were evaluated for HRT

parameters (TO and TS). The combination of the two altered parameters was the strongest predictor of mortality (odds ratio 5.9; 95% CI, 2.9-12.2), followed by an LVEF of <30%, diabetes mellitus, and age ≥65 years. For the HRT category of 0, 1, and 2, the probability of death was 2.1%, 7.4%, and 21.5% (P<0.0001), respectively. An important finding of this study was that HRT was able to provide information on mortality risk in a more relevant way than that obtained using LVEF.

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability developed by Mäkikallio et al. showed that HRT parameters are useful in stratifying the risk of sudden cardiac death in patients with mild and moderate ventricular dysfunction [24]. The study analyzed 2 130 post-infarction patients who underwent optimal clinical treatment, and who were followed-up in hospitals in Finland and Germany. The change in TS had a sensitivity of 57% and a specificity of 82%, with a negative predictive value of 99% for the risk of sudden cardiac death in patients who presented with an LVEF of >35%. The HR was 4.7 (95% CI 2.3-9.8, P=0.0001). It was also observed that patients who presented with an LVEF of ≤35% had a high risk of sudden death; hence, HRT was not able to improve the prediction of risk of sudden death. The mean follow-up period was 33 months.

In another study conducted in Canadian hospitals (REFINE), 320 patients with acute myocardial infarction and an LVEF of <40% underwent an assessment of HRT parameters between 2-4 weeks and a new assessment between 10-14 weeks after the infarction [25]. During the 47-month follow-up, HRT was a predictor of cardiac death or resuscitated cardiac arrest (HR 2.91; 95% CI 1.13-7.48, P=0.026) when at least one of the HRT parameters was altered.

In a Japanese study by Hoshida et al., 313 patients were analyzed after myocardial infarction with a mean LVEF of 47% during a mean follow-up of 3 years [26]. The study showed that when HRT parameters were altered, they were strong predictors when associated with cardiac mortality and fatal cardiac events (HR 5.7; 95% CI 2.1-15.9, P=0.0008).

In the Cardiac Arrhythmias and Risk Stratification After Myocardial Infarction (CARISMA) study, Huikuri et al. followed-up 310 patients who had a myocardial infarction with an LVEF of ≤40% for 2 years [27]. The patients were evaluated on the first and sixth weeks after the infarction. The primary outcome of documented ventricular fibrillation or ventricular tachycardia was observed in 9% of the patients. The TO did not reach statistical significance, although the TS was associated with the outcome (HR 2.8; 95% CI 1.1-7.2, P=0.038) in the multivariate analysis. An evaluation of HRT parameters based on the categories was not performed. Similar to the REFINE study, the prognostic value of HRT parameters was greater when evaluated after the ischemic event.

Huikuri et al. analyzed the dynamic changes that occur in the HRT parameters following a myocardial infarction [28]. Using data from the CARISMA and REFINE studies, the researchers observed that a slower recovery from cardiac dysautonomia owing to infarction (defined by the variation in TS of <2.0 ms/RR) was associated with an increased risk of fatal and non-fatal arrhythmic events, both in the CARISMA (HR 9.4; 95% CI 1.2-71.6, P<0.05) and REFINE (HR 7.0; 95% CI 1.6-29.6, P<0.05) studies.

Therefore, based on these studies that have been presented, it seems to us that the scenario in which HRT seems to have its greatest usefulness in post myocardial infarction is in cases of preserved or mildly reduced ventricular function. In this situation, reduced cardiac autonomic function translates to a greater risk of severe cardiac arrhythmias and sudden death. This is because patients who have severe ventricular dysfunction after myocardial infarction already have a reserved prognosis regardless of other factors such as whether the autonomic function is preserved or not.

Considering that HRT is a baroreflex sensitivity marker, few PVBs would be sufficient to illustrate this phenomenon well; therefore, studies that evaluated the HRT using short electrocardiographic recordings at rest were not able to obtain statistical significance [10], differing from almost all studies that analyzed the HRT as standardized by Schmidt et al. (**Table 1**) [5].

Other parameters used to analyze the autonomic regulation of the heart

There are other parameters obtained through 24-hour Holter recordings that can help in understanding cardiac autonomic function,

Table 1. Most relevant information regarding the HRT behavior in the main clinical studies

Study	Study design	Number of individuals/ characteristics	Time post-MI	Follow-up period	Outcome analyzed	HRT parameter analyzed	Statistical information
Schmidt et al. [5] (1999)	Retrospective cohort	100 LVEF: 46.4% Previous AMI: 26%	NA	24 months	Mortality	TO + TS	HR 7.4 (95% CI 3.1-17.3; P<0.0001)
Schmidt et al. [5] (1999)	Validation (MPIP)	577 LVEF: 45.4% Previous AMI: 25,4%	NA	22 months	Mortality	TO + TS	HR 3.2 (95% CI 1.7-6.0; P=0.0002)
Schmidt et al. [5] (1999)	Validation (EMIAT)	614 LVEF: 29.9% Previous AMI: 26,2%	NA	21 months	Mortality	TO + TS	HR 3.2 (95% CI 1.0-5.6; P<0.0001)
Ghuran et al. [23] (2002)	Retrospective Cohort	1,212 LVEF: 50%	First 28 days	21 months	Mortality + severe cardiac arrhythmia	TO + TS	HR 4.07 (95% CI 1.70-9.77; P=0.0017)
Barthel et al. [9] (2003)	Prospective cohort	1,455 LVEF: 56%	First 28 days	22 months	Mortality	TO + TS	HR 5.9 (95% CI 2.9-12.2; P<0.0001)
Sade et al. [22] (2003)	Prospective cohort	128 LVEF: 43% (non-survivors) and 56% (survivors)	1 day	10.2 months	Mortality	TS	HR 7.3 (95% CI 1.4-37; P=0.016)
Berkowitsch et al. [10] (2004)	Retrospective cohort	884 LVEF: 23% *Holter 10 mins*	Minimum of 30 days	20 months	Mortality	TO + TS	HR 1.30 (95% CI 1.16-1.43; P=0.53)
Mäkikallio et al. [24] (2005)	Retrospective cohort	2,130	NA	33 months	Sudden cardiac death	TS	HR 4.7 (95% CI 2.3-9.8; P=0.0001); LVEF >35% HR 3.0 (95% CI 1.1-8.3; P=0.035); LVEF ≤35%
Exner et al. [25] (2007)	Prospective cohort	322 LVEF: 40%	2-14 weeks	47 months	Cardiac death or resuscitated cardiac arrest	TO or TS	HR 1.47 (95% CI 0.54-3.75; P=0.47); 2-4 weeks after cardiac arrest HR 2.91 (95% CI 1.13-7.48; P=0.026); 10-14 weeks post cardiac arrest
Huikuri et al. [27] (2009)	Prospective cohort	312 LVEF ≤40%	2-7 days	24 months	Ventricular fibrillation or ventricular tachycardia	TS	HR 2.8 (95% CI 1.1-7.2; P=0.038)
Hoshida et al. [26] (2013)	Prospective cohort	313 LVEF: 47%	NA	36 months	Cardiac death	TO + TS	HR 5.7 (95% CI 2.1-15.9; P=0.0008)

including heart rate variability and acceleration and deceleration capacities. Some studies have also identified that these parameters may function as markers of sudden cardiac death in post-infarction patients [29, 30]; however, in isolation, they have a low impact on cardiovascular outcomes [31, 32]. The impossibility of analyzing records with the occurrence of ventricular extrasystoles using these methods is also worth noting since the presence of ventricular arrhythmia makes these analyses difficult.

Perspective

HRT has many clinical advantages, especially as it is a non-invasive method that is easy to obtain and interpret. It is also noteworthy that it can be used as an indicator of response to drug therapy and can better assess ANS function.

Currently, research is evaluating HRT in other clinical scenarios that could refine the screening for sudden cardiac death, such as stimulating the onset of PVB on physical exertion or by electrophysiological study [19]. These evaluations would have a potential advantage of obtaining the prognostic information of HRT in a shorter time.

It is also not yet known when would be the best time to request analysis of cardiac autonomic function in post-myocardial infarction patients. The sympatho-vagal imbalance resulting from the immediate inflammatory context could interfere with the prognostic impact of HRT that is performed less than 2 weeks after the event [25].

Finally, studies indicate that HRT could be used as a follow-up of cardiac autonomic function performance in post-myocardial infarction individuals. Patients who do not improve after behavioral measures and antiarrhythmic medications could be those who need close clinical follow-up and consideration of use of other therapies such as ICDs [18, 33-35]. The ongoing multicenter study "Efficacy of implantable defibrillator therapy after a myocardial infarction (REFINE-ICD)" will answer how to use non-invasive tools, such as HRT, to improve the indication for prophylatic ICD therapy in post myocardial infarction.

Conclusion

Ventricular arrhythmias are common after coronary events [36]. It has been reported that approximately ~30% of patients develop PVB after a myocardial infarction [37], with a higher incidence among those who develop ventricular dysfunction. However, not everyone who develops PVB or ventricular dysfunction after myocardial infarction has an unfavorable cardiac prognosis [38]. Studies have shown that altered HRT, which indicates reduction in the vagal cardiac activity, can identify patients who are at a higher risk of sudden death [5, 16].

In conclusion, HRT analysis was proven to be a simple and cost-effective way to assess cardiac autonomic dysfunction by providing complementary information to classic parameters, such as the assessment of ventricular function.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Rafael Alessandro Ferreira Gomes, Centro De Estudos Do PROCAPE/UPE, Rua dos Palmares, s/n, Santo Amaro, Recife-Pernambuco, Brazil. Tel: +55-81-3183-3510; E-mail: rgomesrecife@gmail.com

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