

# Cardiovascular Clinical Implications of Heart Rate Variability

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## Abstract

Heart rate variability (HRV) is one of the promising emerging noninvasive modalities that are extensively used nowadays in research and risk stratification of several diseases. Reduced HRV has been linked to several cardiovascular risk factors such as hypertension (HTN) and diabetes mellitus (DM) also; it has been linked and used for years now in the risk stratification of congestive heart failure, coronary artery disease (CAD), and acute myocardial infarction (AMI). Controversial data are present about the effect of coronary artery bypass graft (CABG) on HRV and the use of HRV for risk stratification in post-CABG patients while percutaneous coronary intervention was linked to a dramatic improvement in HRV and improved survival of CAD patients. Although experimental data are present correlating reduced HRV with increased risk for cardiovascular morbidity and mortality, extensive research is required for further implementation in daily clinical use. In this review, we will discuss the current cardiovascular clinical implications and highlight the limitations of usage and future perspective of HRV.

**Keywords:** Acute myocardial infarction, autonomic nervous system, coronary artery disease, diabetes mellitus, heart rate variability, hypertension, percutaneous coronary intervention, risk stratification

## INTRODUCTION

Heart rate variability (HRV) is the spontaneous fluctuations in the normal sinus rhythm; it can be measured as the standard or the average deviation from the mean R-R intervals of all cardiac cycle length (R-R intervals for normal sinus beats) over a given period.<sup>[1,2]</sup>

HRV is considered a reflection of natural sympathovagal balance on the heart or the normal activity of the autonomic nervous system (ANS).

Several methods have been proposed by the Task Force of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) to define and to establish the standards of measurement, physiological interpretation, and clinical use of HRV.<sup>[3]</sup> Time domain indices, nonlinear geometric measures, and frequency domain indices are considered the standard clinically used parameters.<sup>[4]</sup> The analysis of HRV data should meet the defined standards of measurement by the Task Force of ESC and NASPE either through the short-term recordings of

5 min made under physiologically stable conditions and/or long 24-h recordings (Holters).<sup>[3]</sup> Over the past years, HRV has been correlated with most cardiovascular diseases and risk factors.<sup>[2]</sup>

### Clinical perspective:

To review the current clinical trials that linked heart rate variability to different cardiovascular risk factors and diseases and to determine usage limitations and future perspectives of heart rate variability as a noninvasive diagnostic modality in risk stratification of several cardiovascular diseases.

## CLINICAL IMPLICATIONS OF HEART RATE VARIABILITY

### Hypertension

One of the most important risk factors for coronary artery disease (CAD) is hypertension (HTN). Numerous studies

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Submission: 16-Aug-18 Revision: 03-Oct-18 Accepted: 04-Oct-18

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**Website:**  
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**DOI:**  
10.4103/IJCA.IJCA\_36\_18

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**How to cite this article:** Abdelnabi MH. Cardiovascular clinical implications of heart rate variability. *Int J Cardiovasc Acad* 2019;5:37-41.

have documented the association between cardiac autonomic dysfunction and HTN.<sup>[5]</sup>

Huikuri *et al.* studied the correlation between HRV and long-standing systemic HTN comparing patients with long-standing HTN with the age-matched normotensive population. The data showed that long-standing HTN results in reduced overall HRV suggesting that low HRV may contribute to increased cardiac mortality in patients with long-standing HTN.<sup>[6]</sup>

Liao *et al.* examined the association between 2 min of supine HRV and HTN in a random sample derived from the biracial Atherosclerosis Risk in Communities (ARIC) study with a 3-year follow-up. The results suggested a positive correlation between decreased HRV and HTN and furthermore suggest that decreased HRV was associated with increased risk for HTN.<sup>[7]</sup>

Singh *et al.* conducted a study aiming to compare the measures of HRV between hypertensive and normotensive subjects and to examine the role of HRV as a predictor of new-onset HTN using data derived from the Framingham Heart Study (FHS). HRV was significantly lower in hypertensive men and women while among normotensive men, lower HRV was associated with greater risk of developing HTN. These findings are consistent with the hypothesis that autonomic dysregulation is present in the early stages of HTN.<sup>[8]</sup>

### Diabetes mellitus

Diabetes mellitus (DM) is another important risk factor for CAD has also been linked to decreased HRV. Autonomic neuropathy is a common complication of DM, and the early subclinical detection of autonomic dysfunction may be important for the risk stratification and subsequent management of diabetics.<sup>[5]</sup>

In the first study to examine the relationship between HRV as an indicator of ANS and DM, Liao *et al.* computed high-frequency power (HF) as index of vagal tone from 2-min recordings of a sample derived from the ARIC and found that DM was associated with a lower HRV than age, race, and gender-matched nondiabetics also, prediabetics were associated with a reduce HRV suggesting that reduced vagal tone may be involved in the pathogenesis of DM.<sup>[9]</sup>

Singh *et al.* examined the relationship between HRV and blood glucose levels from data derived from the FHS. HRV indices were significantly reduced in diabetics and those with impaired fasting glucose compared to those with normal fasting glucose levels.<sup>[10]</sup>

### Heart failure

The ANS regulation plays an important role in the progression of congestive heart failure (CHF).<sup>[11]</sup> It may affect the cardiovascular system in heart failure in several ways including downregulating  $\beta$ -adrenergic receptors, exerting direct toxic effects on the myocardium, and contributing to myocardial remodeling and life-threatening arrhythmias. In this sense, CHF patients are a high-risk group for death.<sup>[4]</sup>

Ventricular tachycardias often occur in patients with compromised left ventricular ejection fraction (LVEF) and

up to 80% of patients may die suddenly with an average 60% survival at 4 years.<sup>[4]</sup>

Sympathetic activation and reduced vagal tone are usually reflected by a significant increase in low-frequency power (LF) and decrease in HF component and this sufficiently intact sympathetic activation at less advanced stages of CHF reflected by increased LF contribute to arrhythmogenesis and sudden death.<sup>[12]</sup>

In the advanced stages of heart failure, there is a loss of rhythmicity in the LF and HF components. A particular finding is the highly reduced or even undetectable LF in spite of the high levels of sympathetic activation. This behavior of the LF component suggests that the integrity of the sympathetic innervation becomes defective with the progression of CHF.<sup>[12]</sup> The highly reduced LF power in the advanced stages of CHF may be secondary to abnormalities in central autonomic regulation and impairment of  $\beta$ -adrenergic receptor sensitivity.<sup>[10,13]</sup>

Patients in very advanced stages of the disease behave as if they had cardiac denervation and loss of neural modulation of cardiac rate, resembling patients with recently transplanted hearts.<sup>[14]</sup> HRV may be used in patients with CHF as a marker for the prediction of mortality due to progressive LV dysfunction and to sudden cardiac death.<sup>[15-19]</sup>

### Coronary artery disease

Autonomic dysfunction in the form of enhanced sympathetic tone and reduced vagal tone and has been suggested in CAD in the early reports.<sup>[20-22]</sup>

Wennerblom *et al.* investigated the correlation between uncomplicated CAD and reduced HRV using frequency domain measures and proved that uncomplicated CAD in patients without previous acute myocardial infarction (AMI) or any other diseases were associated with reduced HF and LF HRV as a marker of reduced vagal tone.<sup>[23]</sup>

Feng *et al.* studied the alteration of HRV time domain measures depending on the characteristics of coronary lesions in stable angina pectoris patients summarizing that compared with a control group, standard deviation of all R-R intervals measured in milliseconds (SDNN) in one-vessel, SDNN, standard deviation of the averages of R-R intervals in all 5-min segments of the entire recording measured in ms (SDANN) in two-vessel disease and in three-vessel disease were lower and compared with two-vessel disease, SDNN, SDANN lower in three-vessel disease. Compared with right CAD, SDNN and SDANN in the left CAD group were lower, while compared with lesions in left circumflex, SDNN in lesions in the left anterior descending artery is lower.<sup>[24]</sup>

Li *et al.* correlated HRV measures with angiographic CAD in patients with stable angina, independently from other traditional risk factors, comorbidities, medications, or Framingham risk. In addition proved that in patients with high risk of CAD, HRV was even more predictive. Measures of HRV may provide specific advantages in clinical practice

to improve the risk reclassification of the angiographic CAD.<sup>[25]</sup>

Kotecha *et al.* highlighted that low HRV particularly LF power in a 5-min analysis of HRV is strongly predictive of angiographic CAD regardless of other comorbidities and is clinically useful as an independent risk predictor in obstructive CAD patients with sinus rhythm.<sup>[26]</sup>

### Myocardial infarction

The significance of HRV and its prognostic value in AMI survivors has been extensively studied over the years. Wolff *et al.* were the first to assume that HRV measured on the admission of AMI patients can be a predictor of mortality, HRV was measured in 60-s electrocardiogram strips. Patients with a decreased HRV tended to be older, more likely to have an anterior infarct, and more likely to have heart failure. The study concluded that decreased HRV can be used as an independent predictor of adverse outcome and may predict long-term risk after AMI.<sup>[27]</sup>

Kleiger *et al.* described the first study that clearly documents the independent and long-term predictive value of HRV analysis of survivors of AMI through the multicenter postinfarction program (MPIP). 24-h Holter of AMI survivors was evaluated; HRV was proven to be the strongest predictor of mortality.<sup>[28]</sup>

Lombardi *et al.* studied the sympathovagal interaction in AMI patients using analysis of spectral components of HRV over 1 year. At 2 weeks after AMI, the LF component was significantly increased, the HF component was significantly reduced compared to age-matched control subjects. While at 6 and 12 months after AMI, a progressive decrease in the LF and increase in the HF components was observed.<sup>[29]</sup>

Cripps *et al.* conducted a study measuring HRV index in 24-h Holter of AMI survivors aiming to assess this novel measurement of HRV and to relate the prognostic significance of decreased HRV using to other well-recognized prognostic variables such as late potentials, reduced LVEF, in-hospital complication, and KILLIP class.<sup>[30]</sup> Other studies (including a reanalysis of MPIP) have shown that spectral measures of HRV are reduced in survivors of AMI and that decreased values were associated with an increased risk of all-cause mortality.<sup>[31]</sup>

The autonomic tone and reflexes after myocardial infarction trial was a multicenter observational study performed about 10 years after MPIP. The data confirmed that reduced SDNN was associated with an increased mortality during 21 months of follow-up. Furthermore, the combination of low SDNN and LVEF <35% carried a higher risk of mortality.<sup>[32]</sup> HRV is decreased early after AMI and begins to recover within a few weeks. It is maximally but not fully recovered by 6–12 months after AMI.<sup>[33,34]</sup> The assessment of HRV at both the early stage of MI (2–3 days after AMI)<sup>[35]</sup> and pre-discharge from the hospital (1–3 weeks after acute MI) offers important prognostic information. HRV measured 12-month after AMI also predicts further mortality.<sup>[34]</sup>

## EFFECT OF REVASCULARIZATION ON HEART RATE VARIABILITY

### Heart rate variability and coronary artery bypass graft

Previous studies have shown decreased HRV after coronary artery bypass graft (CABG) even more significantly than in patients with AMI<sup>[36]</sup> with a gradual recovery in a few months following the operation.<sup>[37,38]</sup> Possible reasons for a decreased HRV after CABG is a combination of surgical manipulation on the heart and other anatomic structures around the heart, anesthesiological procedures, duration of cardioplegia also, extracorporeal circulation, etc.<sup>[39-41]</sup> According to some reports, unlike decreased HRV in patients after AMI, decreased post-operative HRV do not have any significant prognostic value in CABG patients.<sup>[42,43]</sup> Contrary to those previous reports, recent studies showed that the CABG patients with post-operative decreased HRV have a higher mortality rate than patients with normal HRV with furthermore research is required for further assessment of the prognostic impact of HRV in CABG patients.<sup>[44]</sup>

### Heart rate variability and percutaneous coronary intervention

Patients with CAD and exercise-induced angina pectoris have a state of sympathetic hyperactivity,<sup>[45]</sup> and it seems that the myocardial ischemia is the trigger of this sympathetic hyperactivity; hence, theoretically, revascularization by percutaneous coronary intervention (PCI) can restore the normal autonomic balance.<sup>[46]</sup>

Sedziwy *et al.* studied HRV time domains before PCI and during a 1-year follow-up using serial 24-h Holter monitoring in all patients (before PCI, 14 days, 3, 6, and 12 months after PCI). A significant increase of HRV parameters was noted with statistically significant increase of HRV parameters occurred during the first 3-month follow-up while the results of the next serial recordings (6 and 12 months after PCI) demonstrated no additional changes in HRV values; however, they were still significantly higher than before procedure concluding that successful revascularization using PCI leads to an improvement in the autonomic balance of HRV.<sup>[47]</sup> Aydinlar *et al.* investigated the effect of PCI on QT dispersion and HRV time and frequency domain parameters and concluded that HRV parameters such as HF component, the square root of the mean of the sum of the squares of differences between adjacent NN intervals measured in ms (rMSSD) and SDNN were significantly increased while LF, LF/HF were significantly reduced. In addition, QT dispersion was significantly decreased with a negative correlation to LF component and LF/HF ratio.<sup>[48]</sup> Abrootan *et al.* studied the changes in HRV parameters after elective PCI in patients with stable angina pectoris. Short-term HRV measurement using time domain parameters was done before PCI and 24-h post-PCI. The data indicated that among different time-domain HRV parameters, only SDNN increased significantly, with a considerable yet statistically insignificant increase in rMSSD after PCI.<sup>[46]</sup>



### Limitations and future perspectives of heart rate variability

In spite of the large number of the currently published experimental and clinical trials concerned with HRV measurements and several clinical implications. Yet still, the use of HRV is limited to research and not routinely used in daily clinical practice.<sup>[49]</sup> Several reasons have been proposed to explain this issue: First, the pathophysiological mechanism of HRV confirming the direct relation between mortality and reduced HRV is still not fully understood. Second, the clinical application of HRV assessment is limited by the lack of standard methods due to variations of the parameters according to gender, age, drug interferences, and concomitant diseases. Third, so far, there is no consensus about the most accurate HRV parameter for clinical use. Fourth, the sensitivity, specificity, and positive predictive accuracy of HRV are still limited. Particularly, its positive predictive accuracy is modest, ranging from 14% to 40%. Yet, it has a higher negative predictive value ranging from 77% to 98%. Fifth, conflicting data<sup>[50]</sup> have been noted regarding HRV measured after MI, suggesting that it may be insufficient by itself for proper risk stratification in high-risk patients. A combination of HRV and other risk stratification methods including LVEF, nonsustained ventricular tachycardia, and baroreceptor sensitivity may improve the overall predictive accuracy.<sup>[32,51,52]</sup> and finally, because HRV measurement depends on R-R interval variations, so the measurement is restricted to sinus rhythm patients and to those with a low number of ectopic beats. Due to this issue, some high-risk patients are excluded from HRV analysis due to frequent ectopy or atrial arrhythmias. Approximately 20–30% of high-risk post-AMI patients and up to 15–30% CHF patients are excluded for HRV analysis due to frequent ectopic beats or more commonly atrial fibrillation that is observed in up to 15%–30% of patients with CHF.<sup>[4]</sup>

### CONCLUSION

HRV is one of the most promising methods for detection and quantification of autonomic dysfunction. Further research is required to define its effectiveness in clinical usage and to validate its usefulness in risk stratification in cardiovascular risk factors and diseases.

### Acknowledgment

The author would like to thank

Professor Dr Moustafa Nawar and Professor Dr Mohammed Ahmed Sadaka

Professors of Cardiology and Angiology, Faculty of Medicine, Alexandria University, Alexandria, Egypt, and

Dr Moataz Ahmed Zaki

Cardiology and Angiology Unit, Clinical and Experimental Internal Medicine Department, Medical Research Institute, Alexandria University, Alexandria, Egypt.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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