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Targeting heart rate variability in heart failure: An expert opinion review on Ivabradine

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Abstract
Heart rate variability (HRV) in patients with chronic heart failure (CHF) predicts mortality outcomes. Assessed in time-domain and frequency-domain measures, HRV can be used to risk stratify patients with CHF. Among various interventions, lifestyle measures and various medications used to treat CHF can improve HRV. Here, we reviewed current evidence with ivabradine and its effect on HRV in patients with CHF. Besides reducing the resting and 24-hour mean heart rate (HR), ivabradine improves the HRV in patients with CHF. The improved HRV is evident in awake phase as well as during sleep. The improved HRV is seen on top of guideline-directed optimal medical therapy inclusive of beta-blockers. In our opinion, HRV should be assessed routinely in patients with CHF. Further research is required to understand the impact of improved HRV in altering the outcomes in patients with CHF. In conclusion, for CHF patients with reduced HRV, addition of ivabradine improves HRV on top of exiting therapy.

Keywords: Heart rate, heart rate variability, chronic heart failure, ivabradine, beta-blockers

Introduction
Beat-to-beat variation in either heart rate (HR) or the duration of the R-R interval represents heart rate variability (HRV) [1]. HRV reflects the changes in autonomic regulation but exact contributions from sympathetic and parasympathetic systems are unclear [2]. In 1977, Wolf *et al*. demonstrated the prognostic utility of reduced HRV with higher risk of post-infarction mortality [3]. With introduction of power spectral analysis of HR fluctuations to determine beat-to-beat cardiovascular control, clinical importance of HRV began to be appreciated [4]. Investigations from late 1980s confirmed that HRV was a strong and independent predictor of mortality after an acute myocardial infarction (MI) [5, 6]. Further understanding of HRV led to emergence of its measures. HRV is described as 24-hour, short-term (ST, ~5 min), and ultra-short-term (UST, <5 min) HRV using time-domain, frequency-domain, and non-linear measurements [1, 7]. Various measures of HRV have been found to be prognostically important in cardiovascular conditions. In chronic heart failure (CHF), reduced HRV is associated with increased risk of mortality [8, 9]. Further, different HRV measurements predict different modes of death in CHF. Short-term oscillations and sympathovagal interaction are predictors for sudden cardiac death, whereas global and slow oscillatory measures are predictors of all-cause mortality or cardiac events [10].
The Heart Failure Association of the European Society of Cardiology identifies that normalization of autonomic imbalance can be a therapeutic strategy for patients with HF. Approaches to target autonomic nervous system (ANS) reflexes include stimulation of cervical vagus nerve, renal sympathetic nerves, carotid body and baroreceptor, exercise training, and drugs [11]. Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) proved that pharmacological modulation of HR with ivabradine significantly reduces the risk of cardiovascular (CV) deaths and hospitalization related to HF as well as death from HF [12]. The SHIFT Holter sub study demonstrated improved HRV with addition of ivabradine to the guideline-based optimized HF therapy [13]. Further, ivabradine improves HRV among patients with non-ischemic dilated cardiomyopathy [14]. Thus, it is important to understand the role of HRV in HF and its modulation with pharmacological approaches such as ivabradine. In this article, we briefly discuss measures of HRV and review the evidence on its impact on HF outcomes as well as provide current opinions about modulation of HRV with ivabradine in HF.

An online advisory board meeting was conducted with eminent cardiologists from across India to obtain their perspectives on the importance of targeting heart rate variability in heart failure. Based on the meeting, a consensus document was developed to provide a framework for clinicians and healthcare providers on the role of heart rate variability in the management of heart failure in patients.

Measures of HRV

HRV is assessed over 24 hours as short-term (~5 min), and ultra-short-term (<5 min). The measurements are done using time-domain, frequency-domain, and non-linear measurements. A detailed discussion of the measures has been reviewed in detail elsewhere [7]. Time-domain analysis measures variation in HR over time, whereas frequency domain provides both frequency and amplitude information on the specific rhythms that exist in the HRV waveform. Non-linear measurements allow us to quantify the unpredictability of a time series. Table 1 enlists the HRV measures in three domains [1, 7]. A 24-hour recording of the standard deviation of NN intervals (SDNN) is considered as the gold standard for stratification of cardiac risk. Individuals with SDNN <50 ms, 50-100 ms and >100 ms are categorized as unhealthy, compromised health, and healthy, respectively [15]. Beat-to-beat variance in hear rate is indicated by the root mean square of successive differences between normal heartbeats (RMSSD). It is used to determine the vagal influences on HRV. Ultra low frequency (ULF) band is measured over a period of at least 24 h and circadian rhythms might be the primary driver for it [16]. Very low frequency (VLF) band is recorded as short as 5 min to 24 hours. It is a better predictor of all-cause mortality than low frequency (LF) and high frequency (HF) bands. Low VLF is associated with heightened inflammation and arrhythmic deaths [7]. Cardiac sympathetic nervous system influences the amplitude and frequency of oscillations of VLF rhythm [16]. Additionally, parasympathetic activity might also affect VLF rhythm as blocking parasympathetic stimuli obliterated VLF power [17]. HF band (measured over 1 min) affected by parasympathetic activity indicating HRV related to the respiratory cycle [18]. LF/HF ratio of 24-hour recordings is indicative of both sympathetic and parasympathetic influences. Low LF/HF ratio indicates dominance of parasympathetic activity and vice-a-versa [7]. However, some reports indicate controversial role of LF/HF ratio.

Table 1: Select HRV domains with their description

Domain and parameters (units)	Description
Time domain	
SDNN (ms)	SD of NN intervals (i.e., interbeat intervals from which artefacts have been removed)
SDANN (ms)	SD of the average NN intervals for each 5 min segment of a 24 h HRV recording
SDNN index (ms)	Mean of the SD of all NN intervals for each 5 min segment of a 24 h HRV recording
SDRR (ms)	SD of RR intervals (i.e., time interval between successive heart beats)
RMSSD (ms)	Root mean square of successive RR interval differences
pNN50 (%)	Percentage of successive RR intervals that differ by more than 50 ms
HR Max – HR Min (bpm)	Average difference between the highest and lowest HRs during each respiratory cycle
TINN (ms)	Baseline width of the RR interval histograms
HRV triangular index	Integral of the density of the RR interval histogram divided by its height
Frequency domain	
5-min total power (ms^2)	NN interval variance over temporal segment (~ ≤0.4 Hz)
ULF power (ms^2)	ULF band absolute power (≤0.003 Hz)
VLF power (ms^2)	VLF band absolute power (0.0033 – 0.04 Hz)
LF power (ms^2)	LF band absolute power (0.04 – 0.15 Hz)
LF power (nu)	LF band relative power (normal units) (0.04 – 0.15 Hz)
LF power (%)	LF band relative power (0.04 – 0.15 Hz)
LF peak (Hz)	LF band peak frequency (0.04 – 0.15 Hz)
HF power (ms^2)	HF band absolute power (0.15-0.4 Hz)
HF power (nu)	HF band relative power (normal units) (0.15-0.4 Hz)
HF power (%)	HF band relative power (0.15-0.4 Hz)
HF peak (Hz)	HF band peak frequency (0.15-0.4 Hz)
LF/HF (%)	LF: HF power ratio

HF, high frequency; HRV: heart rate variability; SD: standard deviation; ULF: ultra-low-frequency, VLF: very-low-frequency, LF: low-frequency

Prognostic implication of HRV in heart failure

In patients with CHF, factors such as low left ventricular ejection fraction, New York Heart Association (NYHA) functional stage, and increased heart rate predict mortality [19]. In patients with CHF, both time-domain measures and frequency-domain measures predict all-cause mortality, cardiac event, and sudden cardiac death (SCD). HRV measures such as VLF, ULF, SDNN, and SD of the average NN intervals (SDANN) that indicate global and/or slow oscillations in RR interval predict all-cause mortality [20]. LF power and LF/HF ratio derived from short-term or 24-hour recordings can independently predict sudden cardiac death (SCD) [20]. In a study of 116 patients with idiopathic dilated cardiomyopathy, Fauchier *et al* found that SDNN ($p = 0.02$) and ventricular tachycardia during 24-h electrocardiogram recording ($p = 0.02$) were predictors of sudden death and/or arrhythmic events [21]. A recent systematic review of 14 studies identified that variables of SDNN, SD derived from time-domain analysis, NN, SDANN, pNN50, rMSSD, HRV index, sNN50, log HRV and RR have limited role in predicting SCD. However, they also observe that HRV parameters used in each study were variable [22]. Markedly reduced HRV, even in short-term, is associated with increased severity of CHF and is an independent marker of

sympatho-excitation [23]. Short-term HRV measures can be employed in ambulatory care, for patient monitoring and in situations necessitating immediate results [24]. Thus, some investigators also suggest short-term HRV should be used routinely in patients with CHF [25].

Modulation of HRV in heart failure

There are multiple factors that affect HRV. Physiological parameters such as gender and circadian rhythm; various diseases involving heart, lungs, kidneys, metabolic diseases, and sepsis; lifestyle factors such as active lifestyle, physical fitness, smoking, alcohol, and obesity; external factors like heat, noise, and night shift work; and medications affect HRV [26]. In patients with CHF, modulating HRV is essential. Reduced LF power is found to be associated with non-sudden cardiac death (NSCD) in CHF. It indicates that increasing vagal tone might protect HF patients against NSCD over and above the slowing of HR using β-blockers [27]. Exercise training is effective in restoring autonomic balance and increasing HRV [28]. Drugs used in management of HF such as renin-angiotensin aldosterone system (RAAS) inhibitors (e.g., ramipril, losartan), beta-blockers (e.g., carvedilol), spironolactone, clonidine, ivabradine, and digoxin have shown to improve HRV [29-33]. Below we discuss the use of ivabradine in management of CHF with its relation to HRV.

Ivabradine: Effect on HRV in CHF

CHF is a state of an autonomic imbalance with increased sympathetic activity and reduced vagal activity. It results in increased HR and reduced HRV [34]. Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker. Pacemaker current (I_f), which controls the spontaneous diastolic depolarization in the sinoatrial (SA) node, is selectively blocked by ivabradine. In turn, there is prolonged diastolic depolarization that results in slowing of HR. The reduction in HR is dose-dependent [35]. Various clinical trials have proven its efficacy in patients with HF.

The Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT) included 6605 adult (≥18 years old) patients with stable symptomatic chronic HF (NYHA class II–IV) having resting HR of ≥70 beats per min and left ventricular ejection fraction (LVEF) of ≤35%. Compared to placebo, treatment with ivabradine was associated with 18% relative risk reduction in composite endpoint of CV death or hospitalization for worsening HF and 26% relative risk reduction in each endpoint of hospitalization for worsening HF and death from HF. Among other endpoints, ivabradine was associated with significant reduction in all-cause hospital admissions, any CV hospital admission as well as endpoint of CV death, hospitalization for HF, or nonfatal MI [12].

SHIFT Holter sub study was a pre-specified study from SHIFT to analyse 24-hour Holter recordings. It included data from 298 patients receiving ivabradine or 304 patients receiving placebo. Majority of the patients received guideline-based optimized heart failure therapy (93% with renin-angiotensin-aldosterone system [RAAS] inhibitors and 93% with beta-blockers in maximally tolerated doses). After 8 months, HR over 24 h reduced significantly with ivabradine but not with placebo treatment (mean change 9.5±10.0 vs. 1.2±8.9 bpm, respectively; $p<0.0001$). Similar significant effects were reported in resting office and in 24-h, awake, and asleep recordings. Also, all the time-domain as well as frequency-domain parameters of HRV increased significantly with ivabradine but there was no change in the placebo group. These findings indicate the beneficial effects of ivabradine on HRV on top of beta-blocker therapy [13].

Another study by Kurtoglu *et al*. involving 48 patients with compensated HF of non-ischemic origin who underwent 24-hour Holter monitoring found that after 8 weeks of treatment with ivabradine, there was significant improvement in mean RR interval (% change +34.1, $p<0.0001$), SDNN (% change +58.5, $p<0.0001$), SDNN index (% change +55.3, $p<0.0001$), pNN50 (% change +43.3%, $p<0.0001$), and RMSSD (% change +35.2, $p<0.0001$). These improvements remained significant even in awake phase and during sleep. Thus, ivabradine treatment improves HRV even in CHF of non-ischemic origin [14].

Liao *et al* compared ivabradine and beta-blocker combination to beta-blocker alone in 80 patients with CHF. After 3 months of treatment, the combination treatment was associated with significant improvement in HRV. Compared to beta-blockers alone, there was significant improvement in HRV parameters such as SDMN, SDAMN, RMSSD, RR interval, SDNN index and pNN50 with combination treatment [36].

In the Morbidity–Mortality Evaluation of the If Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction (BEAUTIFUL) Holter sub study, ivabradine but not placebo treatment resulted in significant 24-hour HR reduction at 6 months. There were no conduction and rhythm disturbances. Though the study did not report outcomes of HRV, it identified significant HR reduction with ivabradine in patients with coronary artery disease (CAD) receiving beta-blockers without concerns of cardiac safety [37].

Authors' perspectives and expert opinion

Current evidence clearly indicates decreased HRV being a risk factor for adverse outcomes in patients with CHF. Modulation of HRV can be a potential therapeutic target. Exercise, physical activity, and improved lifestyle with avoidance of smoking and alcohol can improve HRV. In patients receiving guideline-directed therapy inclusive of beta-blocker treatment, addition of ivabradine improves HRV on top of existing treatment. Multiple mechanisms underlie improved HRV in HF patients. Improved cardiac circulation and cardiac filling due to prolonged diastole, improvement in left ventricular remodelling, improved sympatho-vagal balance, and reduction of RAAS stimulation due to reduced AT1 receptor expression and angiotensin II level possibly contribute to beneficial effects of ivabradine in improving HRV [38]. Based on current evidence, we provide following expert opinions pertaining to ivabradine effect on HRV in CHF patients.

- Measurement of HRV (at least short-term measures) should be done routinely in patients with CHF
- Ivabradine improves time-domain and frequency-domain measure of HRV in patients with CHF
- Addition of ivabradine on top of guideline-directed therapy of HF provides benefits of improving HRV
- Ivabradine effectively improves sympatho-vagal balance and increases overall HRV as well as during awake phase and while asleep
- Compared to beta-blockers alone, combination of ivabradine and beta-blocker have significantly better improvement in HRV

- Ivabradine can effectively improve HRV in CHF of ischemic as well as non-ischemic origin
- Though there is no direct evidence indicating that improvement in HRV leads to improved outcomes in CHF, indirect evidence from SHIFT and SHIFT Holter sub study possibly indicate implication of HRV in altering HF outcomes

Conclusion

In patients with CHF, reduced HRV is a predictor of mortality. Routine assessment of time-domain and frequency-domain HRV measures is essential to optimally risk stratify patients with CHF. Multiple interventions such as lifestyle measures as well as medications improve HRV. Ivabradine reduces 24-hour heart rate and effectively improves HRV in CHF patients who are being optimally treated with guideline-directed therapy. Addition of ivabradine on top of beta-blocker therapy reduces HR further and improves HRV. Though direct evidence to indicate effectiveness of improved HRV leading to improved outcome is currently not available, improvement in HRV with ivabradine may be associated with potential benefit in HF patients. Further research should incorporate HRV measures in assessing the outcomes of patients with CHF.

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