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Heart Rate Variability: A Possible Machine Learning Biomarker for Mechanical Circulatory Device Complications and Heart Recovery

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Abstract

Cardiovascular disease continues to be the number one cause of death in the United States, with heart failure patients expected to increase to >8 million by 2030. Mechanical circulatory support (MCS) devices are now better able to manage acute and chronic heart failure refractory to medical therapy, both as bridge to transplant or as bridge to destination. Despite significant advances in MCS device design and surgical implantation technique, it remains difficult to predict response to device therapy. Heart rate variability (HRV), measuring the variation in time interval between adjacent heartbeats, is an objective device diagnostic regularly recorded by various MCS devices that has been shown to have significant prognostic value for both sudden cardiac death as well as all-cause mortality in congestive heart failure (CHF) patients. Limited studies have examined HRV indices as promising risk factors and predictors of complication and recovery from left ventricular assist device therapy in end-stage CHF patients. If paired with new advances in machine learning utilization in medicine, HRV represents a potential dynamic biomarker for monitoring and predicting patient

status as more patients enter the mechanotrope era of MCS devices for destination therapy.

Keywords: heart failure, heart rate variability, machine learning, artificial intelligence, neurolinguistic programming, neural networks, ventricular assist device, biomarker

Introduction

Advanced heart failure (HF) is a growing epidemic with high morbidity and mortality, with patients in HF in the United States expected to increase to >8 million by 2030 [1]. The gold standard for the treatment of end stage HF remains orthotopic heart transplantation. With the ongoing shortage of available organs for heart transplantation and new UNOS criteria for allocation, utilization of mechanical circulatory support (MCS) device, especially the left ventricular assist device (LVAD), has increased greatly for managing acute and chronic HF, the latter of which is refractory to medical treatment. MCS devices are now utilized both as a bridge to transplant or as a bridge to alternate destination therapy. The application of continuous-flow LVADs demonstrates 1-year survival of up to 80% as compared to that of heart transplantation at 86% (1). Although the durability of MCS devices allows long-term beneficial effects of mechanical unloading, this strategy is not free of complications and device-related issues, which makes this therapy a challenge to apply to a broader population. The main complications can be grouped into five categories, including bleeding (gastrointestinal bleeding 18-40%), pump thrombosis (8.4% at 3 months after LVAD implantation), driveline infection (17-30%), stroke (up to 17%), and right-sided HF (10-30%) (1). Despite significant advances in MCS device design and surgical implantation technique, it remains difficult to predict recovery response to device therapy.

There is a need for a consistent, reproducible, and cost-effective method of determining cardiac recovery in patients who receive emerging novel therapeutics for advanced and end-stage HF. It has been proposed that a major contributor to deteriorating severe end-stage HF is a prominent inappropriately elevated sympathetic activation outflow to the heart, in conjunction with a concurrent vagal outflow withdrawal (2). Various mechanisms of disease propagation secondary to this autonomic dysregulation have been proposed, including abnormal transduction of beta-adrenergic signals, induced tachyarrhythmias, renin-angiotensin-aldosterone-system (RAAS) activation, myocardial remodeling, and accelerated myocardial cell death (2). With the increasing use of ventricular assist devices (VADs) in end-stage HF, objective device diagnostics are available for analysis.

Heart rate variability (HRV), an accessible diagnostic measure, defines the variation in time interval between adjacent heartbeats. It is most commonly

measured utilizing R-R intervals from patients' electrocardiograms, i.e. via 24-hour Holter monitoring. Previous literature has shown that a reduction in various HRV indices has been both associated with and an independent predictor of higher risk for all-cause mortality in healthy patients, CHF patients, and post-AMI patients (2,3). HRV can be defined in different ways, including time-domain indices, frequency-domain indices, and non-linear indices (3).

Time-domain analyses utilize the normal R-R intervals of ventricular contractions, with various measurements calculated from these intervals to quantify the variability of each interbeat interval (IBI). The monitoring periods over which time-domain indices may be measured can range from as short as <1 min to as long as >24 hrs. SDNN is the standard deviation of all normal R-R intervals in a 24-hour time period. SDANN is the standard deviation of 5-minute averages of normal R-R intervals. ASDNN is the average of SDNN's over 5 minutes. rMSSD is the root-mean square of the difference between successive R-R intervals. pNN50 is the number of instances in 1 hour in which 2 consecutive R-R intervals differs by more than 50ms over 24 hours.

Frequency-domain indices involve computing the beat-to-beat timing (R-R intervals) with a Fast Fourier Transformation, to determine the amount of component HRV signal that exists within four varied frequency bands (ULF, VLF, LF, HF) similar to the component wavelengths of light. The ULF-band is defined as 0.003 Hz, with no current understanding of the mechanism from which it is generated physiologically. The VLF-band is defined as 0.003-0.04 Hz and is proposed to be related to thermoregulation of vasomotor tone. The LF-band is defined as 0.04-0.15Hz and is proposed to represent the body's natural baroreflex mechanism, reflecting both SNS and PNS tone. The HF-band is defined as 0.15-0.40Hz and is proposed to be influenced by the parasympathetic nervous system outflow to the heart as well as respiratory frequency. The LF/HF ratio is intended to estimate the ratio of SNS to PNS activity (sympathovagal balance). Total power is defined as the estimated sum of the frequencies. There are also several non-linear HRV indices. Triangular index (TI) is calculated by geometric analysis, analyzing ECG recordings to create histograms of intervals sorted into 7.8 ms bins.

There are several new non-linear indices being examined that go beyond time and frequency domains. These forms of HRV indices essentially allow one to attempt to quantify the unpredictability and natural randomness of a time series measurement. Dyx, a non-linear HRV measure utilizing density analysis, derives HRV information from both time and frequency domains, reflecting the increasing randomness in RR interval series (4). There are various other non-linear measures of HRV that are calculated by extracting correlations of different RR intervals over various time scales, such as detrended fluctuation analysis (DFA) alpha1 or alpha2, approximate and sample entropy (ApEn, SampEn), and D2 (3). Poincaré plots, a scatter plot of each RR interval against its previous interval, allow for discovery of patterns within various time series. Analysis of such plots yields the non-linear measurements of S, SD1, and SD2. These indices, derived from base concepts rooted in chaos theory and fractals, may demonstrate more accurate

insights into the autonomic health of the heart, supported by evidence that the cardiovascular system may function in a non-linear manner (4).

As availability of hearts for transplant plateaus with everchanging UNOS allocation criteria, MCS, and, specifically LVADs, provide an effective strategy for patients with HF whether used as a bridge to transplant or as a destination therapy. A mechanically unloaded heart following LVAD implantation demonstrates reverse remodeling and a signature of myocardial recovery. Following implantation of the VAD, HeartWare's HVAD® (Medtronic) records HRV regularly, suggesting that it is a valuable parameter for the assessment of cardiac recovery in patients. There have been various studies investigating the prognostic information HRV can provide about patients with CHF, as well as more broadly the relationship between HRV and the health of the body's cardiac autonomic nervous system (ANS) (2). Therefore, HRV measurement could be utilized as a metric for stratifying end-stage CHF patients, predicting acute decompensation or ventricular tachyarrhythmias (VTA) development vs. recovery, and determining patient response to various therapeutics (LVAD vs. temporary VAD, i.e. Impella [Abiomed]) (Figure. 1).
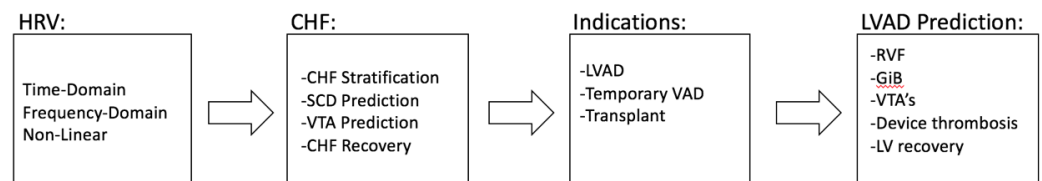
HRV:	CHF:	Indications:	LVAD Prediction:
Time-Domain Frequency-Domain Non-Linear	-CHF Stratification -SCD Prediction -VTA Prediction -CHF Recovery	-LVAD -Temporary VAD -Transplant	-RVF -GiB -VTA's -Device thrombosis -LV recovery

Figure 1. *Heart rate variability (HRV) as a dynamic biomarker for end-stage congestive heart failure (CHF) stratification, CHF prognosis, Left Ventricular Assist Device (LVAD) complication prediction, and left ventricular (LV) recovery. Additional abbreviations: sudden cardiac death (SCD); ventricular tacharrhythmia (VTA); gastrointestinal bleeding (GiB); right ventricular failure (RVF)*

Methods

Search Strategy

PubMed, Ovid, and Google Scholar databases were searched using the terms "heart rate variability," "HRV," "VAD," and "heart failure." Full text articles were then obtained. Each article's bibliography was searched for further studies and references that were not initially generated electronically.

Selection Criteria and Review Process

Only English language publications involving adults of at least 18 years examining HRV were included. Due to the low volume of published research available, publications were not filtered or excluded based on type of HRV index studied.

Data Synthesis

122 total articles were identified. Data are presented as the time, frequency, and non-linear domains of HRV as reported within the literature.

Results

HRV: CHF Stratification, Prognosis, and Recovery

HRV is frequently deranged in CHF patients secondary to chronic, inappropriate sympathetic activation with withdrawal of parasympathetic tone. However, even amongst "healthy" patients without heart disease, each person's baseline HRV values vary person to person (5). It is well established that HRV values are severely attenuated in CHF patients compared with normal controls (2). There have been a select number of studies aiming to establish means of differentiating and stratifying CHF patients from healthy patients without cardiac disease, citing significant differences in predominantly frequency-domain indices including HF/VLF, LF, VLF, LF/HF (6, 7).

Depressed HRV is an independent predictor for all-cause mortality, cardiac decompensation, and sudden cardiac death (SCD) in end-stage HF patients (2). Significantly decreased SDNN has demonstrated utility in contributing to a dynamic risk score for evaluating 30-day HF hospitalization, as an independent predictor for cardiac death, all-cause death, transplant, or worsening CHF in reduced LVEF patients, and a prognostic marker for all-cause mortality or SCD in CHF patients (8-15). As SDNN reflects the overall autonomic health of the cardiac system, CHF patients with attenuated cardiac ANS are expected to present with lower SDNN values as compared to healthy controls (3). The varying levels of SDNN cutoffs reflect both the person-to-person differences in baseline HRV values, as well as the possibility for a gradient of worsening clinical presentation correlated to severity of affected SDNN. Diminished daytime LF(ln) values, night LF, night HF, and LF/HF ratios were independent predictors for all-cause mortality and cardiac events (12, 14-17). LF, representative of the baroreflex activity at rest, largely demonstrates similar prognostic power compared with time-domain indices such as SDNN and SDANN (3). Limited studies demonstrate low utility in HF, reflective of the PNS activity and HR variations as related to respiration, for prediction of all-cause mortality or SCD (10). However, the finding of nocturnal HF ≤60 as predictive of SCD by Guzzetti et al. perhaps sheds insight into the influence of circadian cycle and changes in respiration on HRV (17). LF/HF is a calculated ratio derived to observe the balance between the SNS and PNS. Despite its controversial nature regarding what it actually measures, it has been repeatedly

demonstrated as an independent predictor for SCD and cardiac events (12, 18). Non-linear HRV measures of alpha1, IMAI2, and IVP, which may serve as more accurate representations of the cardiac ANS, have also been shown to have predictive value in CHF patients (19-20).

There is limited data with regards to HRV as a predictor for LV recovery in CHF patients. A study by Landolina et al. found that in CHF patients undergoing CRT device implantation, SDANN was a significant predictor for all-cause mortality or urgent transplantation (21). While the number of studies is limited, this demonstrates the ability to utilize HRV as a predictor for not just clinical decline, but as a monitor for patient recovery in end-stage CHF as well.

HRV for LVAD Complication Prediction

There is no established published literature to date discussing HRV indices as prognostic markers for development of new-onset MCS device complications in VAD-dependent end-stage CHF patients. The most common complications secondary to MCS devices include device thrombosis, gastrointestinal bleeding (GiB), aberrant VTA, and RV failure (RVF) (1). While there is a lack of studies comparing HRV with onset of GiB or RVF, there are a handful of preliminary studies examining the prognostic value of frequency-domain (LF, VLF) and non-linear (Dyx, DFA) HRV indices in predicting new onset malignant VTA in CHF patients (2, 22-24). While studies do not directly target device thrombosis events, there are publications that broadly encompass various biomarkers playing key roles in the pathogenesis of thrombus formation (inflammation, hemostasis, thrombosis), and these HRV markers could potentially be extrapolated as starting values to test HRV changes with new onset device thrombosis complications in LVAD patients. Cardiac ANS tone has been shown to be related to platelet-induced thrombosis via alpha-2 receptor mediation (25). In a study by Hamaad et al., reduced mean RR interval (853) was weakly associated with increased P-selectin and D-dimer, two markers of thrombosis, in patients admitted for acute coronary syndrome requiring PCI intervention and thrombolysis (25). In a similar, earlier study by the same group, there was a modest association between reduced RR interval and HRV indices (mean SDNN 42, mean SDNNi 34, mean triangular index 10.0, mean VLF 674) with increased inflammatory markers (white cell count, IL-6, CRP) in acute coronary syndromes patients (26). It is important to note that both of these studies had exclusion criteria of LVEF <40%, Killip class III/IV symptoms, atrial fibrillation or other arrhythmia, and severe valvular disease. While these studies examined HRV in acute MI patients without history of CHF, reduced HRV has been similarly shown to predict cardiovascular morbidity and mortality in this patient population (2).

With no clinical studies having been performed to date that generate specific HRV cutoff target values that would precisely suggest negative outcomes to date, these are data that must be uniquely identified and rigorously tested in order to eventually be utilized to improve patient outcomes.

HRV for LV Recovery in LVAD Therapy

HRV has been sparingly studied as a biomarker for CHF reverse remodeling secondary to LVAD therapy. As the left ventricle is unloaded, reverse remodeling may occur with restoration of the cardiac ANS and improved HRV indices. There are a few studies examining the LV off-loading effects of LVAD therapy in end-stage CHF patients, as monitored by HRV indices. A study by Kim et al. evaluating LVAD therapy in 3 patients demonstrated improved HRV indices (RR 587 to 677, RRSD 8.1 to 27.2, LF increased by 5.2, HF increased by 2.1, LF/HF increased to 2.3 from 1.07) at time of transplant compared with values the day before LVAD implantation, suggestive of improved ANS activity and SNS/PNS balance secondary to the device therapy (27). A study by Cooley et al demonstrated restoration of LF oscillations of RR-intervals in 2 patients as early as 1-month status-post LVAD therapy, previously absent on ECG pre-implant (28). A study by Gardiwal et al demonstrated significantly improved HRV measures in patients with LVAD therapy compared with CHF patients with medical optimization (29). SDNN improved to 108 from 67, SDANN improved to 103 from 56, and triangular index improved to 29 from 18. A study by Imamura et al. demonstrated that in continuous-flow LVAD's, high rotational speeds were correlated with lower LF(normalized unit) ratios (LF/[LF+HF]), increased HF values, improved cardiac index, and lower PCWP (30). Studying LF(NU) as a way to measure the proportion of SNS to PNS activity, data stratification with a LF(NU) cutoff of 55% demonstrated statistically significant improved LVEF in stage D, CHF patients at 6-months post-LVAD implantation, suggesting the importance of high-speed settings in MCS patients with baseline elevated HRV indices and high risk for induced ventricular tachyarrhythmias. A study by Nunan et al indicated lower LF(ln) and LF(NU), and LF/HF values for CHF patients when compared with healthy controls, explanted patients after LVAD therapy, and patients currently on LVAD therapy (2). LF is an independent predictors of mortality in CHF patients, with LF values ranging from <3.3 (LF(ln)) to <13-20 (LF(NU)) as statistically significant markers as compared to estimated normal values of 5.0 and 519, respectively. Furthermore, they demonstrated that the mean LF of explanted patients was similar to controls, which held LF values within the normal range. LF/HF, reflecting the balance of SNS and PNS, is another independent predictor of mortality, with various studies suggesting cutoffs of <0.37 and <0.43. These values among explanted, implanted, and control patients were also nearly identical. The significantly elevated LF and LF/HF values when compared to CHF patients suggests an improvement in cardiac ANS regulation secondary to device therapy that is noticeable during ongoing therapy and remains post-explantation.

Thus, a handful of the cutoff values posited by the aforementioned studies utilizing HRV time indices (SDNN, SDANN, triangular index, RR, RRSD) and frequency indices (LF, HF, LF/HF) may serve as worthwhile starting points for future testing via various diagnostic modalities (4, 27, 29).

Discussion

End-stage CHF is marked by unregulated activation of the cardiac SNS pathways, which further deteriorates myocardial cell recovery and ventricular modeling. As HF therapy progresses toward preferential destination therapy, there needs to be a more frugal understanding of the causes LVAD complications and LV recovery following therapy. With new UNOS allocations for orthotropic cardiac transplantation further limiting available organs based on patient complications (hemolysis, pump thrombosis, RVF, device infection, mucosal bleeding), more patients are entering the mechanotrope era with MCS devices becoming the standard of care both as bridge to transplant as well as destination therapy. Reliable durable LVAD devices (HVAD, Heartmate™ 3 [Abbott]) are currently available on the market that treat dysfunctional end-stage CHF by a mechanism of LV unloading, ameliorating end-organ hypoperfusion, and ultimately promoting improved cardiac ANS innervation. There are also VAD's available for acute cardiogenic shock intervention and bridge to transplant (Impella® [Abiomed], TandemHeart® [LiveNova]). While there continue to be vast improvements with device design and surgical implantation technique, VAD therapy-derived complications continue to pose significant clinical risk to patients. As aforementioned, there are several studies demonstrating HRV as a static variable for risk stratification and clinical prognosis in CHF patients (2, 6, 7). However, there is a significant gap in the field examining utility of HRV in MCS device patients specifically. With variable individual patient response to VAD therapy, there is a need for diagnostics and clinical biomarkers to aid in physician decision making regarding choice of surgical intervention and choice of MCS device.

Machine learning (ML) and neurolinguistic programming (NLP) are a new frontier of research, utilizing artificial intelligence (AI) to further predictive strategies and overall advancements in the field of medicine. Various models have been proposed utilizing AI for more accurate diagnosis methodology and patient complication prediction, such as computer-aided detection of diabetic retinopathy, prediction of cancer evolution, and identification of neck of femur fractures. A study by Zverinski et al. utilized recurrent neural networks to predict mortality, renal failure, and bleeding in the critical care unit after cardiothoracic surgery with PPV's >=0.84 (31). Another study by Iqbal et al. utilized deep deterministic learning that combined predefined ECG-recognizable patterns of ST-T changes and flattened T-waves with fused datasets to derive a 99.97% accurate pattern recognition algorithm to diagnosis myocardial infarction (32). Choi et al. utilized recurrent neural network models with gated recurrent units for detection of new-onset HF, achieving a statistically higher AUC of 0.883 compared with baseline diagnostic methods (33).

HRV and Machine Learning

Studies have examined the potential for HRV in combination with machine learning. Lee et al. demonstrated one of the first uses of HRV, combined with respiratory rate variability (RRV), with an artificial neural network (ANN) utilizing 13

hidden neurons in 1 hidden layer, that was able to predict VTA one hour before occurrence with an accuracy of 85.3%, sensitivity of 73.3%, and specificity of 73.8% (34). Of note, the significant HRV indices demonstrated were SDNN (time-domain) and SD2 (non-linear) with predictive values of 0.073 and 0.098, respectively. As 1 layer represents a rather shallow network, it demonstrates the potential for better accuracy if a deeper network, perhaps with convolutional neural network layers, were constructed. A study by Nagaraj et al. integrated HRV with support vector machine (SVM) machine learning algorithm to create a four-state classifier to classify sedation level of ICU patients (35). Compared with RASS scores, the algorithm achieved 69% accuracy in discriminating between the 4 sedation levels proposed, and 79% accuracy discriminating between sedated and non-sedated states. Another study paired SVM with various combinations of non-standard HRV measures (SUM_TD, SUM_FD, SUM_IE) in an effort to properly detect new-onset CHF in patients (36). At peak performance, the algorithm was able to achieve 100% accuracy, sensitivity, and specificity. In addition, Liu et al. utilized machine learning to improve 1-year prediction of cardiovascular death post-acute coronary syndrome by Beatquency (novel measurement of variation of frequency of heartbeats), increasing the AUC from 0.730 to 0.753 (37).

Future Directions

Current MCS devices continually measure and record various biomarkers, with the ability to derive HRV from device pump waveform analysis without ECG or ICD requirement. Moscato et al. examined continuous pump-derived HRV monitoring in LVAD patients compared to HRV values calculated by traditional ECG measurement demonstrated statistically similar values within 10ms for the time-domain indices of RR, SDNN, RMSSD, and pNN50 (38). With accurate measurements, this sets the stage for HRV as an easily attainable and cost-effective biomarker in LVAD patients for monitoring both complications as well as recovery.

While decreased HRV has been studied as a predictor for mortality and morbidity in general CHF patients, there is no studies discussing HRV indices as prognostic biomarkers for LVAD complications in MCS device patients. Furthermore, current literature extensively examines different HRV indices (i.e. SDNN, LF/HF) for static cutoffs predictive of clinical decline. However, with each patient's unique individualized baseline HRV values, there is a need to study the changes in sequences of HRV data, rather than treating them as independent variables. By using machine-readable HRV data in conjunction with cutting-edge machine learning and neural network algorithms, end-stage CHF patients may be better stratified, with derivation of HRV cutoffs predicting acute decompensation, improvement from LVAD implantation, LVAD complications, and ultimately LV reverse remodeling. Sequence modeling utilizing hidden Markov models, recurrent neural networks, or long-term short-term memory (LSTM) may better stratify CHF with better accuracy. By training each neural network independently for a different complication or clinical status, new HRV trends may be uncovered which predict the next most probably sequence for prediction of complication or recovery. With

the emergence of wearable devices and smart watches measuring heart rate and other diagnostic parameters, HRV continues to be a challenging but solvable index to measure. Individual devices set the stage for a new form of personalized precision healthcare, and predictive algorithms utilizing HRV and other biomarkers loaded on to such devices may provide real-time and dynamic insight into individualized patients' clinical statuses.

Limitations

A major limitation consistent across all studies is the retrospective nature of analysis examining small patient populations at single centers. Furthermore, many studies utilized age and gender-matched controls to compare HRV data to device patients that were studied. However, pre-MCS implantation HRV data was not available for these device patients, making it difficult to compare how HRV values may have changed from pre-device baseline values. Moving forward, longitudinal studies tracking HRV changes pre- and post- LVAD implantation in end-stage CHF patients are necessary to accurately establish predictive cutoffs for decompensation, complications, and recovery.

While deep learning methods can surpass classical rule-based methods on large data sets, their success is hampered by the use of hard to interpret hidden layers. These layers are currently treated as black boxes, making it hard to derive meaningful inferences from them and reason as to why the model works or it does not. This lack of transparency can make it hard to rationalize the success of a model in medical field, where the stakes of mis-classification are much higher compared to other applications of AI. This problem is exasperated with the rising popularity of ResNet based (Residual network) architectures which can have as many as 200 hidden layers. While this is still an active area of research recent work such as Grad-Cam (Gradient-weighted class activation mapping) aims at visualizing parts of what the hidden layers are doing by employing heat maps and pixel-space gradient techniques to visualize various features in deep neural networks (39). Unlike its predecessor model, CAM (Class activation mapping) it does not need the network to confirm to a certain architecture and is able to produce results even in the presence of dense layers which are unable to retain spacial information (40). Grad-Cam has been shown to perform well for CNN with fully connected layers such as VGG, CNN used for structured output such as captioning of describing images (CNN + LSTM) and for multi-modal inputs (41-42). It is interesting to note that not only can we use these methods to rationalize the workings of deep networks but we can also use them to give us insight into new predictive associations which might not have been previously possible for doctors to make.

Conclusion

HRV is a dynamic, inexpensive, and readily measurable biomarker with promising utility in monitoring of end-stage CHF patients on LVAD therapy, as a means of risk stratification, complication prediction, and recovery prediction.

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