Heart Rate Variability (HRV) Signal Analysis

CLINICAL APPLICATIONS

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Heart Rate Variability in Congestive Heart Failure

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16.1 Cardiac Autonomic Derangements in Heart Failure

The incidence and progression of heart failure are associated with an increasing severity of autonomic derangements, specifically a compensatory increase in activity of the sympathetic nervous system and a decrease in activity of the parasympathetic nervous system (Floras, 2009; Binkley et al., 1991). In this simplistic model, left ventricular (LV) systolic dysfunction elicits an increase in sympathetic outflow directed at the entire vascular system. From this perspective, increasing sympathetic activity is mediated by reflexes associated with arterial baroreceptors, which respond to decreased systolic and pulse pressures and decreased functioning of cardiopulmonary baroreceptors due to prior myocardial infarction (MI), receptor down-regulation or ventricular dilatation. If this simplistic description were sufficient, more severe heart failure should always be associated with a decrease in both global measures of heart rate variability (HRV) and in those that specifically reflect parasympathetic activity. In reality, abnormalities in HRV among patients with heart failure have heterogeneous characteristics despite similar degrees of cardiac dysfunction, indicating that changes in the autonomic function of such patients are complex.

In his excellent review of the topic, Floras (2009) presents a far more nuanced picture of autonomic changes in heart failure. In this review, he makes the following important

points: (1) Changes in sympathetic activation, both time course and magnitude, are not a sole function of ventricular systolic function but rather are target-organ specific and (2) human heart failure is characterized by a rapidly responsive regulation of muscle sympathetic nerve activity (MSNA) by the arterial baroreflex, a reduction in cardiopulmonary reflex modulation of MSNA, a sympathoexcitatory cardiac reflex due to increased cardiopulmonary filling pressure and by variation between patients in other non-baroreflex-mediated sympathoexcitatory mechanisms, which might include comorbid sleep apnea, myocardial ischemia, obesity and sympathetic reflexes from exercising muscles. Other factors that can modify the relationship between heart failure and autonomic function include: age, possibly gender, diabetes, ischemic versus non-ischemic etiology, diastolic function and, of course, concomitant medical therapy. A detailed discussion of this complex phenomenon is beyond the scope of this review, but this perspective points to the exciting possibility that a detailed analysis of different aspects of HRV, coupled with a clearer picture of the exact nature of individual physiological changes associated with heart failure, could point to a way to obtain far more meaningful information from HRV and the progression of HRV.

Further, as will be seen in this chapter, the ability to compare findings of different studies is limited by differences in the length of ECG records used for HRV measurement as well as in the HRV measures selected. More subtle are differences that arise from precision of ECG scanning software used, or the care with which interbeat intervals are characterized (cleaned up). It is worth mentioning here, that among heart failure patients there is a tendency for disorganization in HR due to a high degree of sinus arrhythmia that does not track respiration, a phenomenon which we have termed erratic rhythm (Stein et al., 2005a,b). This phenomenon is not limited to heart failure patients and strongly affects the magnitude of HRV variables that represent beat-to-beat changes in HRV including rMSSD, pNN50, high-frequency (HF) power, normalized low-frequency (LF) and HF powers and the LF/HF ratio, making them look "better" than they really are. Graphical analyses of HR patterns, including tachograms of instantaneous HR, power spectral plots and Poincaré plots are useful in identifying erratic rhythm and should be considered whenever any analysis involving beat-to-beat HRV in heart failure patients is considered. Fortunately, novel HRV measures such as the short-term fractal scaling exponent do represent changes brought about by increased erratic rhythm, and that may help explain why they are better at predicting outcomes than many traditional HRV measures (Stein et al., 2005a,b).

16.2 Predictors of Incident Heart Failure

One population at high risk of incident heart failure is the group with acute MI (AMI). Perkiömäki et al. (2010) recently compared the ability of brain naturietic peptide (BNP), HRV and baroreflex sensitivity (BRS) assessed by the phenylephrine method to predict acute heart failure hospitalizations in 569 patients initially hospitalized for AMI who were followed for up to 8 years. Of these, 79 patients reached the study endpoint. After adjustment for covariates, increased BNP, decreased values for short-term fractal scaling exponent and decreased HR turbulence slope (TS), all identified patients at increased risk of heart failure hospitalization after their MI. To our knowledge this is the only study to have tested the ability of abnormal HRV to identify post-MI patients at risk for congestive heart failure (CHF) hospitalization.

16.3 Association of HRV with Heart Failure Severity

Various clinical measures are used to quantify heart failure severity, including: New York Heart Association (NYHA) Class I–IV, left ventricular ejection fraction (LVEF), echocardiographic measures of ventricular function, pulmonary capillary wedge pressure and markers of diastolic function. The relationship of these markers with HRV has been explored in several studies. Lucreziotti et al. (2000) collected 5 min ECG recordings in 75 ambulatory CHF patients being evaluated for transplant. No correlation was found between NYHA functional class and HRV (although it must be recognized that most patients were class III or IV), but significant relationships were found between HRV (especially decreased LF power) and other hemodynamic parameters including LVEF. Also, interestingly, decreased HRV (specifically LF power) was highly related to *right ventricular* dysfunction. In another study, Soejima et al. (2000) evaluated 24 h HRV as a marker for severity of heart failure in 90 patients (51 ischemic, 39 with idiopathic dilated cardiomyopathy [DCM]) with LV dysfunction defined as LVEF <40%. Severity of heart failure was also assessed by LVEF, LV end-systolic diameter and left atrial diameter. Normal controls ($n = 52$, aged >50) were selected from a prior study. None of the measures of heart failure severity correlated with NYHA. HF power declined in heart failure patients but reached its nadir in NYHA class II patients, whereas LF power continued to decline with increasing NYHA class. Normal versus abnormal HRV was determined by the lower limit of LF or HF among normal controls. With the exception of NYHA class IV patients (100% abnormal), subjects with HRV within normal limits could be found in each functional class, although the proportion with normal HRV declined to 58% in class III. An interesting corollary to these observations was an investigation of differences between patients with LVEF ≤40% who did or did not have symptomatic heart failure (Kocaman et al., 2010). They reported that although BNP and NT-pro-BNP levels were significantly higher in symptomatic patients, only markedly decreased HRV in these patients independently predicted whether patients were symptomatic.

It is well known that diabetes is associated with decreased HRV, and is prevalent in patients with heart failure (Burger and Aronson, 2001). Aronson and Burger (2001) compared HRV among diabetic and non-diabetic patients with heart failure and concluded that diabetes had no additional effect on HRV among heart failure patients. HRV was extremely depressed in this study, however, and all patients were in NYHA functional class III and IV. This question was revisited by Stein et al. (2010). They analyzed the effect of diabetes on HRV in NYHA class II and III heart failure patients via a *post hoc* analysis of pre-treatment HRV in 80 diabetic and 74 non-diabetic systolic heart failure patients entered into a heart failure drug evaluation study. Results indicated that diabetes was associated with further decreases in age-adjusted HRV among NYHA class II patients, but had little further impact on the more depressed HRV of class III patients.

Finally, systolic dysfunction might not be the only factor influencing HRV, because patients with systolic dysfunction also have varying degrees of diastolic dysfunction, and some patients present primarily diastolic impairment. Arora et al. (2004) reported in a study involving 19 patients with diastolic heart failure, 9 patients with systolic heart failure and 9 healthy volunteers, that time and frequency domain HRV was reduced in both heart failure groups compared to healthy controls, and that patients with diastolic heart failure had higher HRV than those with systolic heart failure. Reduced HRV in patients with restrictive filling was also reported by Poulsen et al. (2001) who studied 64 consecutive patients with first AMI. Furthermore, the presence of a restrictive filling pattern and

reduced ejection fraction (EF) were independent predictors of cardiac death and readmission to the hospital with heart failure. Stein et al. (2007) explored the impact of concomitant and more severe diastolic dysfunction, categorized as impaired relaxation time versus a restrictive filling pattern on HRV in the same cohort as that analyzed by Stein et al. (2010). Consistent with other reports, the presence of a restrictive pattern was associated with further reductions in HRV, even after adjustment for clinical covariates including NYHA.

16.4 Effect of Interventions on HRV in Heart Failure

16.4.1 Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is delivered via a small implantable device (called a CRT or biventricular pacing device), which is prescribed to heart failure patients who, in general, meet the following criteria: NYHA III/IV with QRS duration ≥120 ms and LVEF ≤35%. By sensing the patient's natural sinus rhythm, the device delivers pacing pulses to both left and right ventricles to resynchronize the dyssynchronized contractions (between left and right) of the ventricles in order to improve cardiac hemodynamic function and heart failure symptoms. The CRT device is a proven therapy that significantly reduces morbidity and mortality among select CHF patients (Feldman et al., 2005). That is, CRT works well for many patients, but studies have also demonstrated that CRT therapy has a non-responder (lack of therapeutic efficacy) rate ranging from 18% to 52% (Auricchio et al., 2011). To our knowledge, there are no tests that can help predict beforehand which patients will respond and which patients will not respond to CRT but, as described in the next section, patients who are responders are more likely to show improvements in HRV.

In a 3-month follow-up study (Livanis et al., 2003) on 13 CRT patients, HRV (mean 24 h RR, SDNN, SDNN-I, rMSSD, total, ultralow-frequency [ULF] and very-low-frequency [VLF] power) measured via 24 h Holters, improved significantly after 3 months of CRT therapy. Improvements were also seen in NYHA functional class, quality of life, 6 min walk distance and exercise duration. Cha et al. (2008) conducted a study of 16 consecutive CRT recipients compared with 10 controls. Twenty-four hour ambulatory ECG-based HRV (measured by SDNN) increased significantly (from 82 ± 30 ms to 111 ± 32 ms) after 6 months of CRT. There were also improvements in NYHA class and LVEF while at the same time cardiac sympathetic activity measured by iodine-123-metaiodobenzylguanidine (I-MIBG123) decreased significantly, also indicating improvement in cardiac autonomic control.

In another test of the effect of CRT on HRV, Adamson (2003) randomized 25 patients who were on CRT therapy to CRT-ON and 25 to CRT-OFF. HRV, measured as the standard deviation (SD) of the atrial cycles sensed by the CRT device, was monitored. After 2 months, HRV was higher in the CRT-ON group than in the CRT-OFF group, despite a similar mean atrial cycle length between these two groups (844 ± 129 vs. 851 ± 110 ms). However, changes in plasma catecholamines from baseline to follow-up were not different between these two groups. Hence, these authors conclude the "improvement in ventricular performance by CRT shifts cardiac autonomic balance toward a favorable profile that is less dependent on sympathetic activation." However, it must be noted that SDANN is primarily a marker of circadian rhythm. Thus, if patients feel better and are more active, this is likely to be reflected in SDANN.

Finally, Gademan et al. (2008) studied 32 CRT patients to determine the acute effect of CRT on arterial baroreflex function the day after they received device implantation. HRV (SDNN during 10 min of supine paced breathing) and non-invasive BRS were measured during a randomized order of CRT on/off for each patient. CRT ON resulted in a significant immediate increase in SDNN (18.5–24.0 ms) and a significant BRS increase as well, with the latter correlating significantly ($r = 0.44$) with the change in LVEF.

Today, many CRT devices offer HR and HRV-based diagnostic features, such as HRV Footprint/Heart Rate trend/HRV Trend (Boston Scientific) or Heart Rate Trend or HRV Trend (Medtronic), in order to capture baseline HRV and trends in the HRV status of heart failure patients. These HRV features are mostly time domain indices based on SD over a window of approximately 5 min. Unlike HRV calculated from a single 24 h Holter ECG, CRT device–based HRV enables follow-up in a large number of patients at multiple follow-up time points.

Using this technology, Gilliam et al. (2007) conducted an analysis based on 1421 patients in the Heart Failure HRV registry for patients who received CRT devices capable of HRV measurement. Measures included HRV footprint, SDANN, mean, minimum and maximum of HR at four visits over a year (2 weeks, 3 months, 6 months and 12 months after implantation). Significant ($p < .001$) improvements were found in SDANN and HRV footprint, along with significant improvements in clinical status such as quality of life, activity and NYHA. The greatest change was observed between the 2-week and 3-month visits.

In another 12-month follow-up study on 509 consecutive CRT patients, device-computed HRV (SDANN) increased after 4 weeks of CRT (from 69 ± 22 to 82 ± 27 ms, $p < .001$) with a further increase observed after 6 months (Landolina et al., 2008). In a randomized 12-month follow-up study (Piepoli et al., 2008), both control ($n = 45$) and CRT groups ($n = 44$) underwent cardiopulmonary exercise testing, 2D-Echo, HRV measurements, carotid baroreflex and BNP assessments at baseline, 6-month and 12-month follow-up. It was observed that both cardiac indices and BNP concentration improved after 6 months and such improvement persisted at 12-month follow-up. CRT "responders" as defined by changes in LVEF and LV diameters, had greater improvements in the above assessments. Less depressed functional status at baseline was the strongest predictor of being a responder to CRT therapy.

Although it is a proven therapy for CHF patients with qualified indications, CRT (device + surgery) is associated with a high non-responder rate as well as potential patient complications due to the invasiveness of the therapy. Even though considerable evidence exists for restoration of HRV along with overall improvement in heart failure status by CRT, whether HRV can add to functional status parameters in predicting who will respond to therapy is still an open question. Further discussion of the relationship of HRV measured by implantable devices and outcomes will be found in Section 16.5.4.

16.4.2 Pharmacological Interventions

The effect of pharmacological interventions on HRV in heart failure patients has been examined in numerous studies, although many of them involve relatively small numbers of patients. This topic has recently been reviewed by Desai et al. (2011). Use of ACE inhibitors (ACE-I) has been clearly associated with symptomatic improvement and better survival in heart failure, but whether this is mediated by changes in the autonomic nervous system is not completely clear. The effect of different ACE-I on HRV in heart failure yielded inconsistent results. No effect on HRV was found in association with treatment with Lisinopril in a study of 16 patients with mild-to-moderate heart failure (Inkoko et al.,

2001), but Zhang et al. (1995) reported a positive effect of treatment with Enalapril in 12 similar patients. Two early studies, one using Zofenopril ($n = 13$) (Binkley et al., 1993) and the other using Captopril ($n = 32$) (Flapan et al., 1992), reported an increased in parasympathetically mediated HRV in heart failure, but Kamen et al. (1997) suggested that this effect was dose-dependent with increased parasympathetic control of HR only with low doses of Captopril. However, their sample size consisted of only nine patients.

Angiotensin receptor blockers (ARBs) are also common therapy in heart failure patients. De Tommasi et al. (2003) compared HRV effects of Valsartan (an ARB) and Lisinopril (an ACE-I) in 80 mild-to-moderate heart failure patients randomized to one or the other therapy over 16 weeks. No difference was observed between therapies in the effect on HRV, but plasma norepinephrine (NE) levels showed greater reductions with Valsartan. Vaile et al. (2001) failed to find any effects of the acute and chronic administration of another ARB, candesartan, on the HRV in 21 patients, despite its beneficial effects on baroreceptor sensitivity.

β-Blockers and Carvedilol (a combined α–β blocker) have had considerable success in improving both EF and survival in heart failure patients. Since these drugs act directly on the autonomic nervous system, it is not surprising that they have uniformly been associated with improved HRV in most heart failure patients. Lin et al. (1999) studied the effect of β-blocker therapy with Atenolol before and after 1, 3, 6 and 9 months in 15 patients with advanced heart failure. Although 2 patients died within a month, the 13 survivors showed marked improvements in cardiac function and increased HRV after at least 3 months of therapy. In another study of Atenolol treatment in 10 patients with advanced heart failure, Lin et al. (2004) reported that 3 months of treatment also improved heart rate turbulence (HRT) slope and that this improvement was strongly correlated with improvements of vagally modulated HRV indices. Aronson et al. (2001) tested the effect of β-blocker therapy on HRV in 199 patients with decompensated heart failure. Of these patients, 46 received a β-Blocker (Carvedilol, Atenolol, Metoprolol or Labetalol depending on what was prescribed by their physician). Patients on a β-blocker, despite being more likely to have coronary artery disease, had significantly higher HRV than those who were not, suggesting the potential benefit of β-blockers even during this time of high stress.

Multiple studies with small-sample sizes have reported a generally beneficial effect of Carvedilol therapy on HRV in heart failure patients. In perhaps the largest such study, Nessler et al. (2007) followed 86 patients in class II or III heart failure over a year of treatment. Patients were already receiving an ACE-I and diuretics. The focus of the study was on risk factors for sudden cardiac death, including HRV. After 1 year of treatment, the number of risk factors per patient including HR >75 bpm or SDNN <100 ms declined significantly (from 50 to 16 for HR and from 19 to 9 for SDNN). Akdeniz et al. (2006) studied the effects of Carvedilol therapy in heart failure from the perspective of ventricular repolarization characteristics. They studied 31 patients over 6 months. Unlike Nessler et al. (2007), they found little change in HRV, although SDANN did increase, but they reported a significant improvement in various QT-based ventricular repolarization parameters. Mortara et al. (2000) performed a case-control study to investigate the effect of 6 months of Carvedilol on HRV and BRS in 19 consecutive patients in stable class II or III heart failure. Controls were matched based on age and heart failure characteristics from an existing database. In addition to symptomatic improvement, which was found in all studies, significant decreases in HR and improvements in SDNN and rMSSD and improvements in BRS were reported while no change was seen in controls. Also, during 19 months of follow-up, fewer Carvedilol-treated patients than controls reached an endpoint of death or transplantation (31% vs. 58%). Bullinga et al. (2005) performed a randomized study of 4 months of Carvedilol ($n = 17$) versus placebo ($n = 12$) in symptomatic heart failure patients. The group

treated with Carvedilol had significant increases in total power, VLF power, HF power, SDNN, rMSSD and pNN50, and those changes corresponded with improved hemodynamics. Finally, Ridha et al. (2002) included the short-term fractal scaling exponent (DFA1), one of the strongest predictors of mortality among cardiac patients (Stein et al., 2005b), as well as other HRV measures in a study of 15 heart failure patients (class II–III) treated for 12 weeks with Carvedilol. The average HR decreased significantly while parameters such as LF and HF as well as rMSSD and pNN50 increased. DFA1 increased significantly especially for those with the most depressed values of the parameter. Also, the change in DFA1 correlated strongly ($r = 0.63$) with the change in LVEF.

Spironolactone, an aldosterone blocker has also been shown to improve symptoms and survival in heart failure as well. Korkmaz et al. (2000) studied the effects of Spironolactone on a group of 126 patients with heart failure and angiographically documented coronary artery disease. HRV was measured on three occasions, at baseline, and at 1 and 12 months of therapy. After 1 month of therapy, the triangular index of HRV and pNN50 increased significantly and this effect persisted for 12 months. Changes in echocardiographic parameters and symptomatic improvement were noted. However, changes in normalized LF or HF power were not seen. Shehab et al. (2008) investigated the effect of Spironolactone versus the ARB Losartan versus both on HRV in eight patients with class III–IV heart failure. They reported that each treatment resulted in increased HRV (triangular index, SDANN, rMSSD), with no differences between treatments. However, there does not seem to have been a washout period between treatments, so these results have to be interpreted with caution.

16.4.3 Exercise Training

It was once believed that patients who developed heart failure needed to rest in order to avoid putting additional stress on their already compromised cardiovascular systems. This advice has been proven to be incorrect, and now, exercise is recognized as an important component of managing patients with heart failure. In addition, several studies with relatively small enrollments of class II–III heart failure patients have suggested that the benefit of exercise in heart failure is mediated by favorable changes in autonomic function. In the first of these studies, Kiilavuori et al. (1995) randomized 8 heart failure patients to a training group and 12 to a usual care control group. The training consisted of 3 months of exercise on a bicycle ergometer (30 min, 3×/week, 50%–60% of VO_2 peak). A significant "training effect" was seen for exercise duration with a trend to increased VO_2 peak and these were unchanged among controls. Daytime HF power increased in the training group and the LF/HF ratio decreased as well. The LF/HF ratio also decreased in the control group.

Malfatto et al. (2002) studied the effect of 3 months of low-intensity rehabilitation compared with conventional therapy in only 45 patients (30 receiving rehabilitation, 15 not) and further studied the effect of an additional 6 months of at home exercise in 11 of those in the rehabilitation group. LF/HF was tested during supine rest with free breathing, supine rest with paced breathing, and during standing. After 3 months, resting HRV was unchanged, but LF/HF during paced breathing and during standing increased significantly, as did VO_2 peak. This favorable trend was more pronounced after 6 months of exercise at home, while no changes were seen in those randomized to conventional care.

Selig et al. (2004) randomized 19 heart failure patients to 3 months of resistance training using hydraulic ergometers. There were 20 patients in the control group. Both strength and endurance increased in the exercise group but were unchanged in the control group. VO_2 peak increased in the exercise group and actually decreased in the control group.

The LF/HF ratio decreased in the exercise group and was unchanged in the control group suggesting improved autonomic balance and supporting the beneficial effect of this form of exercise training in heart failure patients.

Recently, Piotrowicz et al. (2009) studied the effect of 8 weeks of physical therapy on HRV, HRT and HR recovery after exercise in 41 patients with heart failure. All patients demonstrated improved physical fitness. Training was associated with a significant increase in SDNN, HF power and a decrease in the LF/HF ratio, but there was no change in HRT or HR recovery.

16.5 HRV and Risk Stratification in Heart Failure

16.5.1 HRV and Outcomes in Heart Failure of Mixed Origins

Although there is limited evidence that HRV may be higher in patients with DCM compared to patients with ischemic cardiomyopathy, many studies of HRV and outcomes have included heart failure patients of both etiologies. Most studies have focused on stable patients, usually in NYHA class II–III heart failure. However, patients in acute heart failure have been studied. Other investigators have focused on heart failure after AMI; still others on patients with advanced heart failure (class III–IV) and at least one included patients described as having mild-to-moderate heart failure. Usually, HRV has contributed risk stratification as an independent variable, but results have not been consistent as to the specific HRV measure that best predicts outcomes. This could be due to differences in the study design and algorithms used to compute HRV measures or the specific etiology or degree of heart failure. In general, as can be seen from the studies cited below, traditional time and frequency domain HRV have had a strong association with mortality due to pump (i.e., mechanical) failure and a less clear, but sometimes significant, association with sudden death (typically due to arrhythmia).

Ponikowski et al. (1997) explored the prognostic value of HRV in NYHA class II–IV patients of whom 24 had heart failure due to idiopathic DCM and 78 had heart failure due to ischemic disease. During a mean follow-up of 584 days, 19 patients died. SDNN <100 ms identified patients more likely to die. Also, the combination of decreased SDNN and VO_2 peak <10 mL/kg/min identified a subgroup with a 1-year survival of 68% compared to 94% for the remaining patients.

Guzzetti et al. (2000) examined the prognostic power of both spectral and non-linear HRV measures from 24 h Holters in 30 stable heart failure patients followed for 2 years. In a model that also included HR and SDNN, they found that decreased values for normalized LF power were an independent predictor of mortality. Bonaduce et al. (1999) also examined the predictive value of HRV to beyond that of clinical data and measures of LV dysfunction in 97 patients with moderate heart failure (LVEF ≤40%) of mixed origin. Mean follow-up was for 39 months during which period 32 patients died. Decreased LF/HF ratio and decreased pNN50 entered the model which also included age and LV end-diastolic volume.

The UK-Heart study (Nolan et al., 1998) focused on the prognostic significance of HRV in 431 outpatients with NYHA class I–III CHF and showed that reduced SDNN predicted mortality better than any conventional or clinical measure. Annual mortality rates for the study population were 5.5% for SDNN >100 ms, 12.7% for SDNN = 50 to 100 ms and 51.4% for SDNN <50 ms. Increased mortality was mainly due to progressive heart failure rather

than sudden death among the CHF patients with reduced SDNN. LaRovere et al. (2003) examined the hypothesis that HRV measured from short-term laboratory recordings during both spontaneous and controlled breathing can predict sudden (presumably arrhythmic) death in 202 consecutive heart failure patients with moderate-to-severe disease (mean LVEF 24%). From these data, they created a risk model which they then validated against 242 subsequent patients. Sudden death was predicted by a model that included decreased LF power during controlled breathing, increased LV end-diastolic diameter and an increased number of ventricular premature beats (VPCs) on 24 h Holter recordings, suggesting that this model might be applied to risk stratification for requiring implantable cardiac defibrillator (ICD) implantation.

In another study, Guzzetti et al. (2005) examined the usefulness of HRV from 24 h Holters to predict whether patients would die suddenly or from pump failure. They tested their hypothesis on 330 consecutive patients in sinus rhythm. They were able to develop two simple multivariate models to identify those at risk for one or the other outcome. Decreased nighttime VLF power, combined with high pulmonary wedge pressure and LVEF $\leq$24% identified those at high risk of progressive pump failure, while decreased LF power and increased LV end-systolic diameter were associated with sudden death.

Poinkowski et al. (1996) examined whether HRV could predict either ventricular tachycardia (VT) or death in 50 patients with advanced heart failure (mean LVEF 19%) of mixed origin during a mean follow-up of 2 years. Half of the patients went on to have at least one episode of VT, but there were no clinical differences between those who did or did not have this outcome. However, those with VT had decreased HRV. Decreased values of HF power were the only independent predictor of this outcome. The 12 patients who died during follow-up did have lower LVEFs. Upon multivariate analysis, either decreased SDNN or SDANN (which are highly correlated) was the best predictor of mortality.

HRV has been studied in stable patients with advanced heart failure. Binder et al. (1992) examined time and frequency domain HRV as a predictor of mortality in patients awaiting cardiac transplantation. SDANN <55 ms was found to have the greatest sensitivity (90%) and specificity (91%) for increased risk of death. Furthermore, HRV was better than any other clinical risk factor.

Lucreziotti et al. (2000) tested the ability of frequency domain HRV from 5 min recording to predict outcome in 75 advanced heart failure patients referred for transplant evaluations. Patients were followed for a median of 11.4 months. Decreased LF/HF ratio was an independent predictor of cardiac events. Decreased HRV, and especially LF power was also highly related to right ventricular dysfunction.

The predictive value of HRV has also been tested on hospital admission for heart failure exacerbation, that is admission for symptomatic worsening of heart failure. Aronson et al. (2004) obtained 24 h HRV during admission for 199 patients with a previous diagnosis of NYHA class III or IV heart failure. During a mean follow-up of 312 days, 40 patients died. Being in the lowest tertile of measures primarily reflecting circadian rhythm, namely, SDNN, SDANN and their frequency domain equivalents total and ULF power, identified those who were at high risk of death. The independence of these predictors was confirmed by a multivariate model.

Hadase et al. (2004) studied a similar population, although HRV was measured after pulmonary congestion had improved. In their study, 54 consecutive patients were recruited, of whom 7 died, 18 experienced cardiovascular events and 11 were re-hospitalized with worsening heart failure, within a mean 20 month follow-up. In a multivariate model, cardiac events were most strongly predicted by LF power, total power, diabetes, BNP and NHYA functional class, and decreased VLF power was also an independent predictor.

Finally, Smilde et al. (2009) tested the usefulness of HRV to risk stratify patients with mild heart failure. They studied 90 patients, 80% in NYHA class II and 20% in NYHA class III, who had been enrolled in the Dutch Ibopamine Multicenter Trial. During follow-up, digoxin, ACE inhibitor and β-blocker treatment were initiated in this unusual population. During 13 years of follow-up, 47 patients died, 39 of cardiovascular causes of which 28 were sudden. Independent risk factors for cardiac and sudden death were LVEF ≤30% and VPCs >20/h. However, decreased total power was also an independent predictor of cardiovascular but not sudden death.

16.5.2 HRV and Outcomes in Ischemic Heart Failure

Blichik et al. (2002) retrospectively examined Holter data from 127 patients in the Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure to determine if SDNN would be useful as a predictor of mortality and sudden death. They found that SDNN <65.3 ms (lowest quartile) was the only independent predictor of survival in a multivariate model, and that patients in this high-risk group also had an increased risk of sudden death.

16.5.3 HRV and Outcomes in DCM Patients

In one of the earlier trials of HRV and mortality in DCM, Yi et al. (1997) analyzed HRV in 64 patients and 19 relatives with LV enlargement and compared it with HRV in 33 healthy controls. HRV was reduced in patients and was similar in both relatives of the patients and in controls. After a mean 24 months of follow-up, those with lower HRV (SDNN <50 ms) were found to develop progressive heart failure, whereas those with higher HRV remained clinically stable. Stepwise multiple regression analysis confirmed that SDNN <50 ms was an independent predictor of heart failure progression. At about the same time, Fauchier et al. (1997) compared 24 h HRV in 93 patients with idiopathic DCM and 63 control subjects. Even patients who never had heart failure had lower HRV than controls. During a mean follow-up of 49.5 months, patients with decreased SDNN had an increased risk of death or cardiac transplantation, which remained significant upon multivariate analysis.

In the DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) trial, SDNN was evaluated by tertiles (Rashba et al., 2006). There were no deaths during a 3-year follow-up among those with SDNN >113 ms (highest tertile). Among those with SDNN 81–113 ms, 7% of the patients died and among those with SDNN <81 ms, 10% of the patients died. Among excluded patients (atrial fibrillation or >25% ectopic beats) 17% patients died.

16.5.4 HRV and Risk Stratification in ICD and CRT Patients

Implantation of ICD and CRT devices enables long-term tracking of SDNN or SDANN of atrial rhythm as an indirect assessment of autonomic function. Adamson et al. (2004) studied CRT device–measured HRV (the SD of 5 min median atrial–atrial intervals or SDAAM) from 370 patients who received CRT implantation. They found that SDAAM <50 ms was associated with an increased mortality risk and was persistently lower among patients who required hospitalization or died. Automated detection of decreases in SDAAM had a 70% sensitivity in identifying cardiovascular hospitalization, with 2.4 false-positives per patient-year during follow-up.

Among 509 patients who received a CRT device for primary or secondary prevention of sudden death or who received a CRT pacemaker, the use of CRT was associated with a significant increase in SDANN as monitored by the device (Landolina et al., 2008). However, SDANN ≤65 ms at baseline or SDANN ≤76 ms 4 weeks after implantation were the strongest predictors of need for transplant or mortality, and there was a significant negative correlation between the reduction in LV end-systolic volume with CRT and SDANN at baseline and at week 4. Thus, HRV measured after implantation might identify CRT patients who are less likely to benefit and who remain at higher risk for adverse events.

Piccirillo et al. (2006) had similar findings in a study of 16 patients. In that study the key HRV parameter used was LF power. They found that a low LF power (defined as ≤13 ms^2) at baseline predicted an increased risk of ventricular arrhythmias during a 1-year follow-up. CRT improved HRV, including LF power as well as systolic blood pressure variability. This study concluded that low baseline LF power may predict an increased risk of malignant ventricular arrhythmias in patients with severe CHF treated with ICD or ICD+CRT.

Molon et al. (2010) measured traditional time domain HRV (mean NN, SDANN) and novel non-linear indices for HR complexity at baseline and 1-year later in 60 CRT recipients. Poor baseline autonomic function, as measured by low HRV and especially by reduced values of complexity-related indices, was associated with adverse clinical outcomes at 1 year following implantation among these patients.

However, the DINAMIT study showed that in patients with recent MI, LVEF ≤35% and signs of impaired cardiac autonomic modulation (SDNN ≤70 ms and mean RR ≤750 ms), there was no difference in overall mortality among those who randomly received an ICD (7.5%) versus controls (6.9%), although arrhythmic death per se was significantly lower in the ICD group (1.5%) than in the control group (3.5%). This led to the speculation that in this population, the ICD resulted in a change in the mode of death but not in overall survival.

Grimm et al. (2003a) studied 70 patients with idiopathic DCM who received ICD implantation due to low LVEF. Mean follow-up was 43 months. SDNN (90 ± 25 ms) in patients who received at least one ICD shock for sustained VT or ventricular fibrillation (VF) was not different from SDNN (94 ± 33 ms) in those who did not, supporting the possibility that at least SDNN is not useful for identifying heart failure patients at increased risk of sudden death.

The mixed results of using HRV for ICD risk stratification may have resulted from heterogeneous patient populations in terms of the etiology of the heart failure and different HRV measures used in various studies. Decreased SDNN, which is strongly associated with overall mortality in the heart failure population primarily reflects a lack of circadian rhythm, and is usually seen as a failure of HR to decrease during the night, and is itself a marker for a specific and severe type of autonomic dysfunction. On the other hand, despite the variety of specific HRV measures, CRT studies do consistently demonstrate increased HRV in the presence of improved cardiac function.

16.6 Novel HRV Measures in Heart Failure

Calculation of traditional frequency domain HRV requires certain mathematical conditions (often ignored), for example signal stationarity and a minimum duration for analysis. Various novel methods to extract further information from HR patterns are under active

development and will be reviewed in this section. One of the most successful is HRT, an alternative, but simple and novel approach to characterizing autonomic function that does not require the same assumptions as traditional frequency domain HRV does. Calculation of HRT generally requires the presence of at least 5 VPCs with at least 2 normal beats before and at least 15 normal beats afterwards (Bauer et al., 2008). HRT quantifies the autonomic response to the circulatory disturbance induced by a VPC and the subsequent return to equilibrium via two metrics: turbulence onset (TO) and TS. TO describes the acceleration of HR (if any) immediately after the VPC (presumably capturing acute vagal withdrawal) and TS represents the magnitude of the oscillation of HR afterwards (believed to represents baroreflex function). In general, TO <0% and TS >2.5 ms/RR are considered lower risk, based on post-MI studies, but higher cut-off points for TS values have been found in other populations (Stein et al., 2008).

HRT was originally applied to risk stratification after MI. Schmidt et al. (1999) first assessed HRT as a predictor of mortality in a study that enrolled 100 AMI patients as the training group, and then analyzed data from two existing studies of AMI patients—MPIP ($n = 715$) and EMIAT ($n = 743$) as the validation group. HRT parameters were obtained from 24 h Holter ECG. Results showed that a combination of abnormal TO and TS was the most powerful risk stratifier for mortality compared with other predictors like low LVEF or high mean HR.

The EPHESUS study enrolled high-risk patients who developed heart failure after an AMI and also post-AMI patients with diabetes and LV dysfunction (Pitt et al., 2001). Patients ($n = 481$) were randomized to Eplerenone or placebo on top of standard therapy and had a 24 h Holter recording before randomization. Over a mean 1-year follow-up, 49 patients died of cardiovascular causes. HRT was the only HRV variable that predicted outcome. In the final multivariate model which also included LVEF $\leq$ 30%, the combination of abnormal TS and TO was associated with a relative risk of 3.6 for cardiovascular death. Notably the optimal cutpoint for TS in this study was 3.0 ms/beat rather than 2.5 (Stein et al., 2009).

In another large, prospective study, Cygankiewicz et al. (2006) assessed HRT as a marker of heart failure advancement and progression. In this study 487 heart failure patients, mostly in NYHA class II, were prospectively enrolled with standard tests performed. Patients in NYHA III had significantly lower TS and greater TO than in NYHA II. HRT parameters correlated significantly with LVEF, LV diameter, as well as with N-terminal-pro-BNP levels. Multivariate analyses showed that abnormal HRT parameters were independent predictors of heart failure severity and associated LV dysfunction indicated by NYHA class III and LVEF <40%.

The association of HRT with outcome was also tested in another prospective study ($n = 553$) of heart failure patients (Moore et al., 2006). HRT was calculated from 24 h Holters at baseline, and patients were followed for 5 years. Abnormal HRT, serum sodium and serum creatinine were independent predictors of death due to decompensated heart failure. The combination of these three variables was able to identify patients at increased risk of dying from decompensated HF, suggesting that these measures might help tailor therapy in this high-risk group.

Sredniawa et al. (2010) also evaluated HRT collected from 24 h Holter recordings for risk stratification among 110 stable CHF patients (NYHA II–IV, LVEF = 30% $\pm$ 10%) followed for an average of 5.8 years. The endpoint was heart transplantation or all-cause mortality. TO, TS or the combination of both, were abnormal in 35%, 50% and 25% of all patients respectively and 31% patients reached an endpoint. There was a 5-year cardiovascular event-free rate of 33% among patients for whom both HRT parameters were abnormal,

while it was 83% among those who had at least one HRT parameter preserved. Although results showed that abnormal HRV measured as SDNN <70 ms was the most powerful predictor of outcome and decreased LVEF was the second most powerful predictor, abnormal TS + TO and also abnormal TO by itself were also independent predictors, suggesting that HRT has a role in risk prediction in CHF.

Cygankiewicz et al. (2008) studied the ability of HRT to predict mortality in 651 CHF patients with NYHA II–III, a cohort with 50% ischemic etiology. Abnormal TS was found to be independently associated with all-cause mortality, sudden death and death due to heart failure progression in a follow-up with a median of 44 months. When the prognostic value of TS for predicting total mortality was explored in various groups dichotomized by age, gender, NYHA class, LVEF and CHF etiology, there was no difference between groups. However, abnormal TS was found to be predictive for total mortality only in patients with QRS >120 ms.

HRT also had predictive value for survival when applied to DCM patients. In a follow-up (41 ± 23 months) study on 242 DCM patients from the Marburg Cardiomyopathy Database (Grimm et al., 2003b), HRT measurements, along with LVEF, LV size and NYHA class III were significantly associated with total mortality or the need for heart transplantation. An abnormal TO identified surviving patients who required heart transplantation, as did LV size and being in NYHA class III. Although abnormal TO, or abnormal TO combined with abnormal TS, were associated with a higher incidence of major arrhythmic events on univariate analysis, only LVEF was a significant independent arrhythmia risk predictor.

A similar lack of association between HRT and incident VT was reported by Koyama et al. (2002) who enrolled 50 heart failure patients (LVEF <50% and/or LV end-diastolic dimension >55 mm; 34 DCM and 16 ischemic) and a control group of 21 patients without known heart disease. Although TS and TO were identical between CHF patients with VT and without VT, both were significantly different ($p < .05$ and $p < .01$, respectively) in heart failure versus control patients.

The CARISMA and REFINE (Huikuri et al., 2009, 2010) studies included post-AMI patients with depressed LV function after AMI (LVEF <40%) and showed that HRV/HRT measured late (i.e., 6 weeks), but not early after AMI, predicted fatal or near fatal arrhythmic events in these patients.

Fractal analysis of HR dynamics has been another promising method to quantify complexity of HR and identify higher-risk heart failure patients. Mäkikallio et al. (1999) studied short-term fractal properties (exponent α-1 [DFA1] and exponent β [power law slope]) along with traditional HRV indices in 159 patients with depressed LV function (LVEF <35%) after an AMI. Reduced scaling exponent α (<0.85) was the best univariate predictor of mortality (relative risk 3.17, 95% confidence interval 1.96–5.15, $p < .0001$), with positive and negative predictive accuracies of 65% and 86%, respectively. In the multivariable Cox proportional hazards analysis, mortality was independently predicted by the reduced exponent α ($p < .001$) after adjustment for several clinical variables and LV function.

Salo et al. (2009) studied the short-term scaling exponent [α (1) or DFA1] and frequency domain measures of HR at the baseline and 5-month follow-up among patients with DCM ($n = 16$), and found that α(1) correlated significantly with LV myocardial efficiency at baseline. They also found improvements in α(1) among a majority of patients after medical intervention. They did not find significant effects on any other indices as a result of the intervention. Hence they concluded that α(1) is an important prognostic marker in heart failure and is related to LV myocardial efficiency.

The DIAMOND-CHF (Danish Investigations of Arrhythmia and Mortality ON Dofetilide) study, which enrolled patients admitted to the coronary care unit with new or worsening heart failure, found that only reduced DFA1 was independently associated with mortality in a population that was followed for a mean of 1.8 years and had a 42% mortality (Mäkikallio et al., 2001). Furthermore, the prognostic value of HRV in this population was stronger in class II than in class III and IV patients.

The Poincaré plot of RR intervals is another non-traditional HRV measure which reflects the non-linear complexity of the HR signal. The Poincaré plot is a graph of each successive RR (or NN) interval versus the next. The Poincaré plot can be analyzed in two ways, either qualitatively by characterizing the plot or quantitatively by calculating the properties of the plot. The simplest and oldest method involves fitting an ellipse to the plot itself and then quantifying the two axes of the ellipse (called SD1 and SD2). SD1, usually the short axis, reflects beat-by-beat changes in HR and correlates almost perfectly with rMSSD. SD2, usually the long axis, reflects the range of HRs and longer-term trends. The plot can be constructed from the entire 24 h beat file or from hourly subsets of the data. The ratio of these measures (SD12) reflects the organization of the plot, with lower values associated with comet-shaped or torpedo-shaped plots and higher values reflected in more abnormal plots.

Woo et al. (1992) performed a qualitative analysis of Poincaré plots from 24 h recordings to compare HR patterns between healthy subjects ($n = 24$) and heart failure patients ($n = 24$). They found that while healthy patients presented a comet-shaped Poincaré plot, none of the heart failure patients had such a pattern but rather had one of three distinctive patterns (a torpedo-shape, a fan-shape, or a complex pattern with clusters.) Woo et al. (1994) also demonstrated that heart failure patients presenting with more complex Poincaré plots had higher serum NE levels and more severe hemodynamic decompensation, despite having similar LVEF, HR and HRV. Kamen et al. (1995) applied qualitative Poincaré plot methodology to the resting HR data (20–40 min) of a group of 23 CHF patients with a control group of age-matched subjects ($n = 20$). Their results demonstrated a significant difference ($p < .0001$) in the Poincare plot pattern types by NYHA class.

Entropy-based methods provide another way to quantify HRV complexity. Truebner et al. (2006) found that compression entropy using beat-to-beat intervals from 24 h Holter ECG, enhanced risk stratification for cardiac death ($p = .005$) and sudden death ($p = .02$) among 300 CHF patients with ischemic heart failure etiology.

Maestri et al. (2007) applied 20 different non-linear HRV indices (symbolic dynamics, entropy, fractality–multifractality, predictability, and Poincaré plot methods, etc.) to 24 h Holter recordings from 200 stable CHF patients, in order to assess the prognostic value of a comprehensive set of non-linear HRV measures. Their results demonstrated that there were correlations >0.80 between several non-linear variables and provided evidence that, despite some redundancies in informative content of non-linear indices and differences in their prognostic power, quantification of non-linear properties of HRV provides independent information in risk stratification of heart failure patients.

16.7 Summary and Conclusions

We emphasize that the measurement of HRV in heart failure patients supports its usefulness in this population. Time domain measurements like SDNN and SDANN that capture

circadian rhythms, when decreased, are clearly associated with higher risk in many studies. However, there have been recent findings which suggest that SDNN has lost its predictive power in post-MI patients, likely due to drastic reductions in the proportion of very sick patients (to <10%) who would be identified by low values for SDNN, thanks to improved modern therapies (Jokinenh et al., 2003; Erdogan et al., 2008). In general, low values for SDNN and SDANN reflect either very low levels of daytime activity or a failure of the HR to decrease at night. The prognostic value of other time domain HRV measures like rMSSD and pNN50 depend on accurate Holter scanning and on a clear distinction between normal sinus and erratic rhythm.

In the frequency domain, measurements of total and ULF power correspond to SDNN and SDANN in the time domain, although sometimes 5 min averaged total power is reported as total power due to a misunderstanding of the Holter scanner HRV software output. However, decreased values for LF power have been associated with higher risk in heart failure patients, and there is evidence that loss of LF power may reflect decreased sympathetic control of HR due to central saturation. Thus, a recent study (Kubo et al., 2011) reporting that treatment with β-blockers restored both LF power and MSNA in the LF band suggests an important mechanism by which decreased LF is associated with higher risk in CHF, and by which β-blocker therapy improves survival. Decreased normalized LF power has also been associated with adverse outcomes in heart failure. However, an important caveat must be added. In general, normalized LF power correlates very closely with the detrended fractal scaling exponent (DFA1). Lower values for DFA1 (i.e., <0.80–0.85) are associated with a higher risk of mortality in patients with heart failure and also with the presence of an erratic rhythm. Because the denominator of normalized LF power includes HF power and erratic rhythm exaggerates HF power (beat-to-beat variability), lower values for normalized LF power might be due to decreased LF power, but could also be due to a relatively increased HF power. Either of these might be associated with higher risk for mortality in heart failure, but the interpretation would be dependent on the patient population being studied.

Finally, there is considerable promise in the newer HRV measures. HRT, especially because it reflects the ability of the autonomic nervous system to adapt to perturbations in cardiac output, has been very successful in identifying heart failure patients with higher risk. There are multiple newer measures and combinations of measures that may prove to be even more closely associated with function and outcomes in these patients (Voss et al., 1998).

In conclusion, there are a large number of existing studies involving Holter recordings of patients with various degrees and types of heart failure and undergoing various types of therapies. At the same time, no *one* HRV measure or group of measures has proven itself to have the greatest value for risk stratification. Thus, the question of which measures are optimal in which patients under which circumstances has not been clearly answered. Although, as has been found in the field of risk stratification post-MI, historic trends in treatment may diminish the usefulness of some of the older datasets, sharing of these resources and testing the efficacy of existing and novel algorithms on these data sets can help optimize the utility of HRV for risk stratification in patients with heart failure. Moreover, as described at the beginning of this chapter, it is possible that specific HRV changes may be associated with individual changes in autonomic function and that tracking changes in specific HRV measures in individual patients, rather than grouping all heart failure patients together, might provide insights into the underlying pathophysiological processes.

Abbreviations

ARB	Angiotensin receptor blocker
BNP	Brain natriuretic peptide
BRS	Baroreflex sensitivity
CHF	Congestive heart failure
CRT	Cardiac resynchronization therapy
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
EF	Ejection fraction
HF	High frequency
HR	Heart rate
HRT	Heart rate turbulence
HRV	Heart rate variability
ICD	Implantable cardiac defibrillator
LF	Low frequency
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MSNA	Muscle sympathetic nerve activity
NE	Norepinephrine
NYHA	New York heart association
pNN50	Percentage differences between normal-to-normal RR intervals greater than 50 ms
rMSSD	Square root of the mean squared standard differences of successive normal–normal RR intervals
SDANN	Standard deviation of sequential 5 min intervals
SDNN	Standard deviation of normal-to-normal intervals
TO	Turbulence onset (heart rate turbulence parameter)
TS	Turbulence slope (heart rate turbulence parameter)
ULF	Ultralow frequency
VLF	Very low frequency
VPC	Ventricular premature beat
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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