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INSIGHTS FROM THE STUDY OF HEART RATE VARIABILITY

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ABSTRACT

Indices of heart rate variability (HRV) provide a window onto autonomic modulation of the heart. HRV indices, determined in either the time or frequency domain, are closely related and reflect parasympathetic, mixed sympathetic, and parasympathetic and circadian rhythms. In population studies, decreased HRV has had predictive value for mortality among healthy adults. It is a well-established risk factor for arrhythmic events and mortality among post-myocardial-infarction patients but has only moderate sensitivity and specificity. Decreased HRV has had mixed predictive success in congestive heart failure. Reduced HRV identifies diabetic patients with autonomic neuropathy. HRV in combination with other risk stratifiers, e.g. ejection fraction, can identify cardiac patients at especially high risk of mortality. Many but not all interventions associated with increased HRV are also associated with better survival rates.

INTRODUCTION

Analysis of heart rate variability (HRV) provides insights into autonomic function and has broad applications in both human and animal physiology. A Medline search in April 1998 yielded 2150 citations. This brief review focuses on clinical insights, mainly cardiology-related, obtained from analysis of HRV determined from 24-h Holter recordings.

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HEART RATE VARIABILITY REFLECTS CARDIAC AUTONOMIC MODULATION

Fluctuations in the interval between normal heartbeats, because they are mediated by autonomic inputs to the sinus node, provide information about cardiac autonomic modulation. These fluctuations are quantified by HRV analysis. Usually, increased HRV reflects increased autonomic modulation of the heart rate, and the converse is also true. It must be emphasized, however, that although "cardiac autonomic modulation" and "cardiac autonomic tone" are often used interchangeably, HRV reflects only phasic modulation of heart rate. Thus, low HRV values could reflect a lack of central modulation of heart rate or a lack of response of the sinus node; the latter could even be caused by saturation from highly *elevated* levels of autonomic tone (1).

In most clinical applications, HRV is analyzed by time, frequency domain, or nonlinear methods. Time and frequency domain indices of HRV, which are closely related (2), are based on normal-to-normal (N–N) interbeat intervals only. Nonlinear methods, which are currently under investigation, are not discussed in this review.

Time Domain Indices

Time domain indices are simplest to calculate. There are two kinds of time domain variables: statistics derived directly from the N–N interbeat intervals and statistics calculated from the differences between successive N–N intervals. Interbeat interval-based measures are influenced by both short-term (e.g. respiratory) and long-term (e.g. circadian) factors (3). Time domain measures based on interbeat intervals include SDNN (the standard deviation of all N–N intervals) and SDANN (the standard deviation of the average of N–N intervals for each 5-min period over 24 h), both of which primarily reflect circadian rhythms. Another time domain index of HRV, SDNNIDX, is the average of the standard deviations of N–N intervals for each 5-min period. SDNNIDX reflects both sympathetic and parasympathetic modulation of heart rate and may be thought of as the variance not included in SDANN. The second class of time domain variables, based on comparisons of lengths of adjacent cycles, includes pNN50 (the percentage of adjacent cycles that are >50 ms apart) and rMSSD (the root mean square successive differences in milliseconds). Under normal circumstances, these indices reflect vagal modulation of the SA node (3). But while SDNN and SDANN reflect 24-h HRV, the other indices (SDNNIDX, pNN50, rMSSD) reflect the average over 24 h of indices that are influenced by circadian rhythms. Another quasi-time-domain index, HRV index, is the baseline width of a triangle superimposed over the histogram of all interbeat intervals in milliseconds divided by ~7.8 ms; this reflects total HRV

(4). HRV index is computed in the many studies published by the prominent group at St. George's Hospital in London.

Frequency Domain Indices

HRV analysis in the frequency domain is mathematically more complex and requires a Holter system with a calibrated timing signal. Moreover, since ectopic beats are replaced using a splining technique, a large number of such beats (>20% in a given segment of the recording) will render frequency domain HRV from that segment uninterpretable. Frequency domain analysis yields information about the amount of the variance (power) in the heart's rhythm explained by periodic oscillations of heart rate at various frequencies. These frequencies, when grouped together in bands, provide a detailed view of cardiac autonomic modulation. A standard approach is to calculate power in four bands (5).

High-frequency (HF) power, which is parasympathetically mediated and abolished by atropine infusion (6), is the highest frequency band quantified. It reflects, primarily, respiration-mediated HRV at 0.15–0.4 Hz. The adjacent group of frequencies is the low-frequency (LF) band, which is modulated by both the sympathetic and parasympathetic nervous systems. LF power is virtually abolished by total autonomic blockade (6), is strongly affected by the oscillatory rhythm of the baroreceptor system (7), and is measured at 0.04–0.15 Hz. A 0.5-Hz oscillation in the LF band reflecting thermoregulation has been described (8). The very-low–frequency (VLF) band, at 0.0033–0.04 Hz, reflects even slower modulations of heart rate. The VLF band may represent the influence of the peripheral vasomotor and renin-angiotensin systems (9). The ultra-low–frequency (ULF) band contains most of the power in a 24-h recording. It reflects all variance below 0.0033 Hz, encompasses all variations in heart rate with a period of >5 min, and reflects primarily circadian but also neuroendocrine and other poorly understood rhythms (10). Total power (TP) represents all of the variance over 24 h.

As mentioned above, there is a consensus that, under normal circumstances, HF power reflects vagal modulation of the heart rate. In addition, it has been claimed that LF power—especially normalized LF power, which is LF/LF+HF—reflects primarily sympathetic modulation of heart rate (11), and that the LF/HF ratio reflects "sympathovagal balance" (12). This claim has found its way into numerous papers that assume LF power reflects sympathetic tone. Although proponents cite experimental evidence of the association between maneuvers that increase sympathetic tone and increased LF power (11, 12), a large body of contradictory evidence exists as well. For example, if LF power reflects sympathetic modulation of the heart rate, then beta blockade should consistently reduce or even abolish it. In fact, beta blockade can actually increase LF power (13). Direct cardiac sympathetic blockade via epidural

anesthesia, which should abolish LF power, has no effect on it (14). In addition, atropine, which blocks the vagal component of HRV, reduces LF power, showing that vagal tone contributes to LF (9). Thus, the majority consensus is that LF power reflects a complex mixture of sympathetic and parasympathetic modulation of heart rate, which can, under certain circumstances, reflect sympathetic tone (15). Similar considerations apply to the LF/HF ratio as a marker of sympathovagal balance.

Because of the difficulty of calculating frequency domain HRV, or the lack of a calibrated timing signal, sometimes only time domain indices of HRV are available. Fortunately, every time domain index of HRV has at least one frequency domain index that correlates with it sufficiently ($r \geq 0.90$) to be used as a surrogate (16). Thus, SDNN correlates with TP, SDANN with ULF, SDNNIDX with both VLF and LF, and both rMSSD and pNN50 correlate with HF.

For HRV to be useful in assessing changes of cardiac autonomic modulation, it must be stable over time when clinical condition is unchanged. The stability of Holter measures of HRV has been assessed in younger normal subjects, where intraclass correlation coefficients for recordings 3 to 65 days apart ranged from 0.88 for rMSSD to 0.92 for mean daytime SDNN (1). Similar results were obtained in stable patients with congestive heart failure (CHF) measured at 2-week intervals (17), and over a 1-year period in healthy older adults (PK Stein et al, submitted for publication). These results support HRV as a tool for the assessment of changes in cardiac autonomic modulation.

HEART RATE VARIABILITY AS PREDICTOR OF OUTCOME IN HEALTHY POPULATIONS

Although this review focuses on applications of results from 24-h Holter monitoring, it interesting to note that, in population studies, decreased HRV from ECG recordings as short as 10 s predicted morbidity and mortality. In the "Men Born in 1913 Study," among randomly selected men aged 50 at baseline and followed for 10 years, decreased HRV from a 10-s strip was significantly associated with increased death from ischemic heart disease (18). The Zutphen study (19) determined HRV using 25–30-s strips from resting 12-lead ECGs. The 5-year, age-adjusted risk of mortality for subjects with low HRV was 2.1 in middle-aged men and 1.4 in elderly men. In addition, a higher HRV was observed in older men, which was associated with increased mortality and did not appear to reflect respiratory modulation of heart rate. There was a consistent association of decreased HRV with sudden death and coronary heart disease mortality but HRV was also predictive of all-cause mortality. The ARIC study (20) obtained 2 min of supine ECG data that indicated an association between altered HRV, especially decreased HF power, and increased risk for develop-

ing coronary heart disease. Two reports from Framingham based on 2-h recordings—one on healthy middle-aged (21) and one on older adults (22)—also confirm the predictive value of HRV in the general population. After 3.5–4 years, HRV remained a significant predictor of outcome (new cardiac events in the middle-aged group and all-cause mortality in the older adults) after adjusting for known risk factors.

HEART RATE VARIABILITY AND MORTALITY FOLLOWING MYOCARDIAL INFARCTION

A relationship between decreased HRV and mortality in post–myocardial-infarction (post-MI) patients was reported by Wolf et al (23) in 1978. However, the relationship between decreased HRV and increased risk of mortality post-MI came to prominence in 1987 with the publication of the results of the Multicenter Post-Infarction Project (MPIP) (24). MPIP found that SDNN 2 ms, measured within 11 days of MI, was associated with a risk of mortality at 1 year 5.3 times higher than SDNN >100 ms. Moreover, decreased HRV remained a risk factor for mortality after adjusting for other risk factors, including ejection fraction. Numerous studies have confirmed that decreased HRV in the time or frequency domain, measured shortly after MI, is associated with increased risk of mortality (25–33). These studies include GISSI-2, which followed post-MI patients treated with streptokinase or TPA (34). In almost every study, HRV was determined in the peri-MI period. However, Bigger et al (35) reported that, even measured 1 year post-MI, power-spectral measures of HRV predict mortality over an average 2-year follow-up. Similarly, Rich et al (36) found that in 100 sequential patients undergoing elective coronary angiography, none of whom had had an MI within the past 4 weeks, decreased HRV and reduced ejection fraction each predicted mortality upon 1-year follow-up, independent of the extent of coronary artery disease.

However, it must be emphasized that decreased HRV, despite having a better predictive value than any other recognized risk factor, lacks the sensitivity and specificity to be clinically meaningful on its own (5). Also, studies have reported cutpoints associated with elevated risk that are not identical (although similar). The clinical utility of HRV is improved by combining it with other risk factors, as is addressed later in this review.

HEART RATE VARIABILITY, SUDDEN DEATH, AND MALIGNANT VENTRICULAR ARRHYTHMIAS

A number of studies have shown that decreased parasympathetic and increased sympathetic tone lower the threshold for ventricular fibrillation and increase

the prevalence of spontaneous ventricular tachycardia in ischemic animals and in humans (37–39). It is not surprising, therefore, that patients at risk of sudden cardiac death have decreased HRV. Investigators have compared HRV in controls with that of outpatients (40), apparently healthy middle-aged adults who had Holter recordings prior to their sudden death (41), patients resuscitated from ventricular fibrillation (42), and patients who died suddenly while wearing a Holter monitor (43). Results have consistently shown a marked decrease in HRV among sudden death patients, independent of disease status. A report of the progressive decrease in HRV in two patients with eventual sudden death within two years of the first recording offers the possibility that serial Holter monitoring can identify patients at especially high risk of sudden death (44). When the outcome variable has included malignant arrhythmias as well as sudden death, results have been similar, with decreased HRV (28, 46, 47) and lack of circadian variation in parasympathetic indices of HRV (48) associated with higher risk.

HEART RATE VARIABILITY AS A PREDICTOR OF OUTCOME IN CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is associated with profound derangements of the autonomic nervous system, which worsen with disease progression (49). Sympathetic tone is markedly increased while parasympathetic modulation of heart rate is markedly decreased (50). Decreased HRV is a consistent finding in CHF patients (51, 52). Moreover, time domain indices of HRV, like SDNN, decline with increasing left ventricular dysfunction (53).

Although decreased HRV would be expected to predict mortality in CHF, results have been mixed. Some studies found no relationship between standard indices of HRV and mortality (54, 55). Others found that HRV had remarkable predictive value, e.g. SDNNIDX <30 ms had a sensitivity of 75% and a specificity of 90% in predicting death in CHF (56). Similarly, Mortara et al (51) reported that patients in whom LF power was nearly absent had a worse prognosis. More recently, Mortara's group (57) reported that HRV did not have prognostic value in patients referred for cardiac transplantation, but among another group of patients awaiting heart transplantation, those with SDANN < 55 ms had a 20-fold relative risk of mortality compared to those with higher values (58).

Although left ventricular ejection fraction (LVEF) was the best predictor of cardiac death among patients with LVEF <40% and CHF associated with ischemic or idiopathic dilated cardiomyopathy, decreased pNN50 and increased LF power were also associated with death from pump failure (59). Another study found that the HRV of patients with idiopathic dilated cardiomyopathy was lower than that of controls, independent of the presence of CHF (60). In this group of patients, decreased SDNN was an independent predictor

of mortality or cardiac transplantation. But in yet another study of patients with idiopathic dilated cardiomyopathy, HRV was not different in patients who sustained events (sudden death, sustained ventricular tachycardia, ventricular fibrillation), although SDNNIDX and pNN50 tended to be lower (61). Further research will determine the circumstances under which decreased HRV identifies high risk among patients with CHF.

PROGNOSTIC VALUE OF HEART RATE VARIABILITY IN OTHER CARDIAC CONDITIONS

Decreased HRV post-MI has been shown to be associated with the development of left ventricular dilatation after the first MI (62). In this study, although patients had similar left ventricular volumes upon discharge, patients with decreased HRV had significantly greater end-systolic and end-diastolic volumes on 12-month follow-up, whereas left ventricular volumes were unchanged in those with higher HRV. Among patients with severe mitral regurgitation, followed for up to 9.2 years, decreased SDANN was the most powerful predictor of subsequent events (progression to valve surgery or mortality) (63). Decreased SDANN was also associated with subsequent development of atrial fibrillation.

RISK STRATIFICATION AFTER MYOCARDIAL INFARCTION, USING HEART RATE VARIABILITY IN COMBINATION WITH OTHER RISK FACTORS

As mentioned above, decreased HRV by itself is insufficient as a single risk stratifier in clinical medicine. For example, in the MPIP study, a single index of HRV (SDNN < 50 ms) identified patients at risk of mortality with a sensitivity of 34% and a positive predictive accuracy (PPA) of 34% (24). Importantly, the negative predictive accuracy (NPA) of SDNN >50 ms was 88%. The addition of other risk factors or multiple indices of HRV to the prediction model greatly improves the clinical utility of decreased HRV (64). In MPIP, when the data were reanalyzed in the frequency domain, the combination of decreased ULF, decreased VLF, and either decreased ejection fraction or a high number of ventricular premature complexes (VPCs) had a PPA of 50% or more for identifying a subgroup of patients at risk of mortality after 2.5 years follow-up (65). The addition of results from signal-averaged ECG can also increase the clinical utility of HRV. Farrell et al (47) reported that the combination of decreased HRV and late potentials has a sensitivity of 58% and a PPA of 33% for identifying post-MI patients at risk for subsequent sudden death or life-threatening arrhythmias during a follow-up of up to 3 years. In another report, based on 6-month follow-up of post-MI patients, decreased rMSSD and prolonged QT from the signal-averaged ECG identified patients at risk for ar-

rhythmic events with a PPA of 14% and a negative predictive accuracy of 100%. Hohnloser et al (67) concluded that HRV was better than LVEF for predicting arrhythmic events and sudden death but the two were comparable for predicting mortality. However, the combined use of HRV and traditional risk factors such as VPCs, signal-averaged ECG, or LVEF improved predictive value, with PPAs in the 30–50% range. Recent results from the ATRAMI study of 1284 post-MI patients showed that either reduced HRV or decreased baroreflex sensitivity (a measure of vagal tone) identified patients at elevated risk of mortality, and that decreased values of both identified a subgroup of patients at 17% risk of mortality over 2 years compared with 2% among those with well-preserved indices (68).

HEART RATE VARIABILITY IN DIABETES

One important clinical application of HRV analysis is in the assessment of diabetic autonomic neuropathy (69). Decreased HRV is a far more sensitive indicator of altered autonomic modulation than previously used standard autonomic function tests, and it can identify high-risk patients who require aggressive therapy (70).

INSIGHTS FROM THE EFFECTS OF INTERVENTIONS ON HEART RATE VARIABILITY

Because decreased HRV is strongly associated with an adverse outcome, the obvious question is: Can HRV be increased, and would increased HRV be associated with a better outcome? There is no direct evidence that increasing HRV will improve survival rates. On the other hand, many, though not all, of the interventions associated with decreased mortality are also associated with increased HRV. Pharmacological interventions associated with increased HRV and decreased mortality include beta blockers without intrinsic sympathomimetic activity (ISA) post-MI (71, 72), ACE inhibitors (73, 74) and carvedilol (75) in CHF, sotalol in patients with ventricular arrhythmias (76, 77), and estrogen replacement therapy in post-menopausal women (78). Digoxin, though it increases HRV in stable CHF patients (79), does not reduce mortality.

Successful thrombolysis is an intervention associated with higher HRV and better outcome (80, 81). This increase in HRV may result from the reversal of left ventricular dysfunction, since HRV was unchanged in patients with successful PTCA and normal wall function at baseline (82). On the other hand, there is evidence that coronary artery bypass graft (CABG) surgery, though not associated with increased mortality, results in decreased HRV, at least over a period of weeks to months (83, 84).

It is interesting to note that many of the positive lifestyle changes recommended to cardiac patients may increase HRV. Smoking cessation markedly improves HRV (85). Although there are no data on weight loss and HRV, experimentally induced weight gain results in a decrease in vagally modulated indices of HRV (86). Cardiac patients are advised to exercise, and this may also improve autonomic balance. It is clear in cross-sectional studies that highly fit individuals have increased HRV (87). Also, exercise training increases HRV in healthy older adults (88). The effect of exercise training on HRV in post-MI patients has been less clear, with both positive (89) and negative studies (90, 91). However, even one of the negative studies (77) reported that training altered the flat response of the low- and high-frequency components of HRV to tilt observed at baseline, so that, at post-test, tilting produced the normally seen increase in LF and decrease in HF power. This suggests improvements in cardiac autonomic modulation not reflected by HRV. Exercise training has consistently increased HRV in CHF patients whose baseline HRV is generally low (92–94).

SUMMARY AND CONCLUSION

We conclude that measurement of HRV affords insight into the autonomic modulation of the heart rate. Use of HRV to explore underlying physiology, however, is best accomplished with spectral analysis of data from short-term monitoring periods under controlled conditions, rather than the 24-h Holters appropriate to clinical research.

Many conditions, both cardiac and noncardiac, are associated with alterations of HRV. Among the diverse conditions associated with diminution of HRV are MI, CHF, and diabetes. A reduced HRV has been associated with an increased cardiac mortality, both sudden and non-sudden. This finding has been best documented in patients post-MI. The strongest association has been found for variables measured during 24-h monitoring periods, particularly those measuring long-cycle changes. Although the measurement of HRV alone identifies subgroups with only moderate sensitivity, specificity, and positive predictive accuracy, the combination of HRV measurements and other variables (such as ejection fraction, UPCs, late potentials, baroreceptor sensitivity, etc) identifies groups at particularly high risk for cardiac death and malignant ventricular arrhythmias. This may have important clinical benefits in the era of implantable defibrillators. The effect of cardiovascular drugs on HRV and its possible relationship to survival will undoubtedly also become an area of increasing research activity.

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