The Role of Heart Rate Variability in Risk Stratification for Adverse Postoperative Cardiac Events

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There is growing evidence of a strong association between the compromised autonomic nervous system and sudden cardiac death. Heart rate variability (HRV) measures are widely used to measure alterations in the autonomic nervous system. Several studies with cardiac patients show that decreased HRV as well as baroreceptor dysfunction are more powerful predictors for sudden cardiac death than established clinical predictors such as left ventricular ejection fraction. One-third of all postoperative complications and more than half of the deaths are due to cardiac complications. Several risk indices are useful for immediate perioperative short-term, but not for long-term outcome risk stratification of an individual patient. Currently, there are no clinically assimilated methods for long-term postoperative risk assessment. Recently, few studies have shown that preoperatively decreased HRV can independently predict postoperative long-term mortality. Further studies with surgical patients are needed to establish a possible predictive value of preoperative baroreceptor dysfunction, alone and combined with HRV, for short- and long-term postoperative outcome.

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About 30 million patients undergo noncardiac surgery in the United States each year, and more than 1 million of them will have a severe cardiovascular complication (e.g., perioperative myocardial infarction (MI), cardiac death) (1,2). One-third of all postoperative complications and more than half of the deaths are due to cardiac complications. In the aging population worldwide, the number of complex comorbid patients will increase. Although the problem of perioperative MI has been recognized over the past 50 yr, it remains a major perioperative threat (1,2).

Recommendations of American College of Cardiology/American Heart Association, Revised Cardiac Risk Index, and several other risk indices have been validated and are useful for immediate perioperative short-term risk stratification. These indices have also been successfully used to identify patients who can be recommended to undergo more detailed cardiac testing. However, the risk indices cannot be used to predict the long-term outcome of an individual patient (i.e., patients who survive the first 30 days after surgery) although mortality peaks during the following months and years (3–11). Currently, there are no clinically assimilated methods for long-term postoperative risk assessment.

Evidence from numerous studies indicates a strong association between compromised autonomic nervous system (ANS) (e.g., decreased vagal activity or increased sympathetic activity), sudden cardiac death (SCD) and non-SCD (12–24). In addition, increased sympathetic activity elicited by acute MI may play a pivotal triggering role leading to SCD (12,18,25). Various measures of heart rate variability (HRV) are widely used to measure alterations in ANS. Several studies with cardiac patients suggest that decreased HRV as well as baroreceptor dysfunction are more powerful predictors for cardiovascular mortality, including SCD, than established clinical predictors, such as left ventricular ejection fraction (LVEF) and ventricular premature complexes (VPC) (15–21,26,27). Several studies have shown that perioperative HRV is a powerful predictor for postoperative morbidity and for long-term mortality as well (28–32). In addition, nonlinear measures capable of calculating short-term correlation properties seem to have superior predictive value over time- and frequency-domain measures of HRV (19–21,28–31). The purpose of this article is to overview HRV measures and to discuss their incremental value in perioperative risk stratification, especially for long-term outcome.

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TIME AND FREQUENCY DOMAIN MEASURES OF HRV

Time Domain

HRV has been traditionally analyzed by time-domain measures. The simplest and most often used are the instantaneous heart rate (HR), intervals between normal successive sinus beats (i.e., intervals between normal-to-normal QRS complexes, usually referred with the abbreviation NN), average HR, mean NN interval, and the difference between the longest and shortest NN interval.

Other time domain calculations include variables derived from direct measurements of the NN intervals or instantaneous HR, such as the standard deviation of the NN intervals (SDNN), and variables derived from the differences between NN intervals, such as the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the number of pairs of adjacent NN intervals differing by more than 50 ms in the recording period (NN50), and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50) (33).

Frequency Domain

Akselrod et al. (34) applied spectral analysis by calculating the frequency domain of power spectral analysis. All rhythmic HR oscillations can be viewed with the total power of spectral analysis, which is often divided into four spectral components by integration over the corresponding frequency intervals. The power spectrum is quantified by measuring the areas in the following frequency bands: ultra-low frequency (ULF) power <0.0033 Hz (i.e., >5 h cycle length), very low frequency (VLF) power from 0.0033 to 0.04 Hz (i.e., >25 s cycle length), low frequency (LF) power from 0.04 to 0.15 Hz (i.e., >6 s cycle length), and high frequency (HF) power from 0.15 to 0.4 Hz (i.e., 2.5–6 s cycle length) as has been suggested by the Task Force (33). Typical examples of spectral analyses can be seen in Figures 1–3.

The two main methods used for computation of power spectrum are nonparametric fast Fourier transformation and parametric autoregressive modeling (35). The spectral estimate provided by fast Fourier transformation and autoregressive modeling, especially with the fixed model order, is similar in practice (36).

The spectrum of normal RR-interval time series is inversely related to frequency over a wide frequency range of 0.00003 to 0.1 Hz (from 10 h to 10 s) (37,38). This spectral power-law relationship of RR-interval variability differs from the conventional frequency domain measures in that it characterizes the shape of the RR-interval spectrum, whereas the conventional measures reflect the magnitude of HRV on various frequency bands. The spectral power-law relationship of RR-interval variability is calculated for slow HR fluctuations from the frequency range of 10^{-4} to 10^{-2} Hz. A robust line-fitting algorithm of log (spectral power) on log (frequency) is applied to the power spectrum between 10^{-4} and 10^{-2} and the slope of this line (β-exponent) is calculated (39) (bottom panel of Fig. 3).

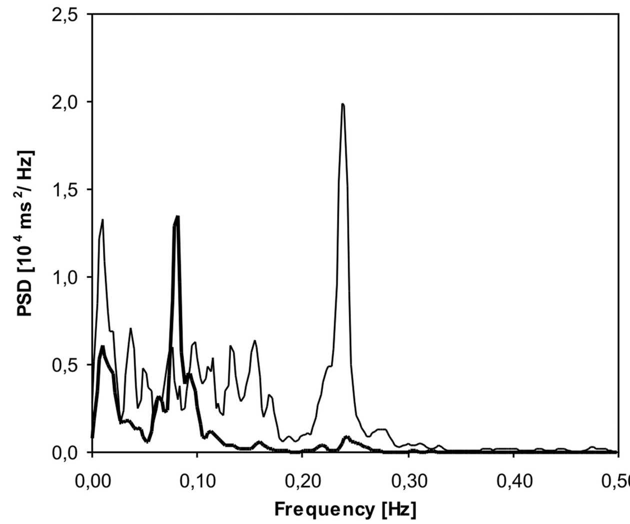

Figure 1. An example of RR-interval spectral analysis during supine—head-up tilt test in a healthy volunteer. The normal and thick lines represent the spectrum during supine and during head-up position, respectively. The power spectrum during supine position demonstrates a typical peak in the high frequency range reflecting respiration-driven vagal modulation of sinus arrhythmia (respiratory sinus arrhythmia). The low frequency power (i.e., 0.1 Hz oscillation) during head-up position is accentuated reflecting an acute sympathetic drive.

DYNAMIC MEASURES OF HRV

The sinus rhythm seems to exhibit fractal properties, which is especially characteristic in complex systems (40–47). In fractal system, a subunit of the RR-interval time series resembles the larger time scale. The degradation of this multiscale nonlinear complexity toward behavior resembling either random fluctuations with no correlation between interbeat intervals (i.e., white noise), or toward less random behavior (i.e., Brownian noise) appear in disease and with aging, and may lead to a reduced adaptive capacity. It has been suggested that self-similarity (i.e., fractal) may be a central organizing principle of physiologic structure and function, and that the breakdown of this organization may be physiologically deleterious (40,43,48).

HRV is modulated by multiple factors, both endogenous and exogenous, forming a complex and fractal system, which is not detectable with traditional time- and frequency-domain measures. Goldberger et al. (42,49) introduced analysis methods of HRV, which are based on statistical physics and fractal mathematics. These nonlinear HRV methods (i.e., dynamical measures) have been intensively developed to detect and quantify the correlation properties of physiological time series, as well as the presence of chaos, and to deal with the ubiquity of nonstationarity (i.e., statistical properties change with time).

Poincaré Plot

The Poincaré plot is a return map in which each RR-interval is plotted as a function of the previous one. The Poincaré plot belongs to a category of geometric HRV methods (33). Both visual analysis of the graphic

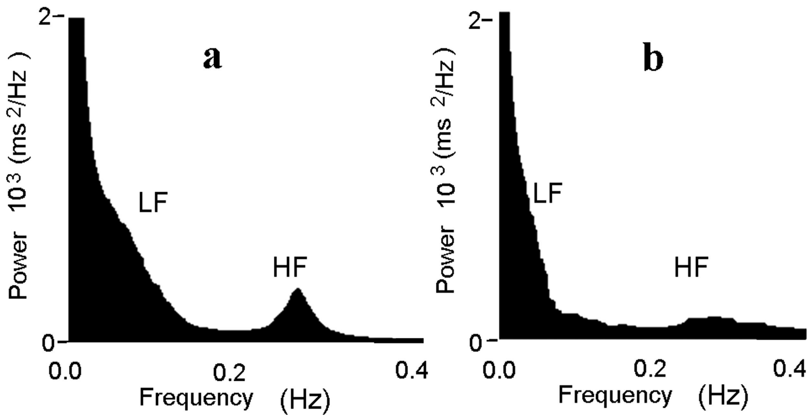

Figure 2. A typical 24-h power spectrum in a healthy volunteer (a) compared with a spectrum in a heart failure patient (b) with a left ventricular ejection fraction <35% showing reduced low frequency power despite of a chronic sympathetic stimulation.

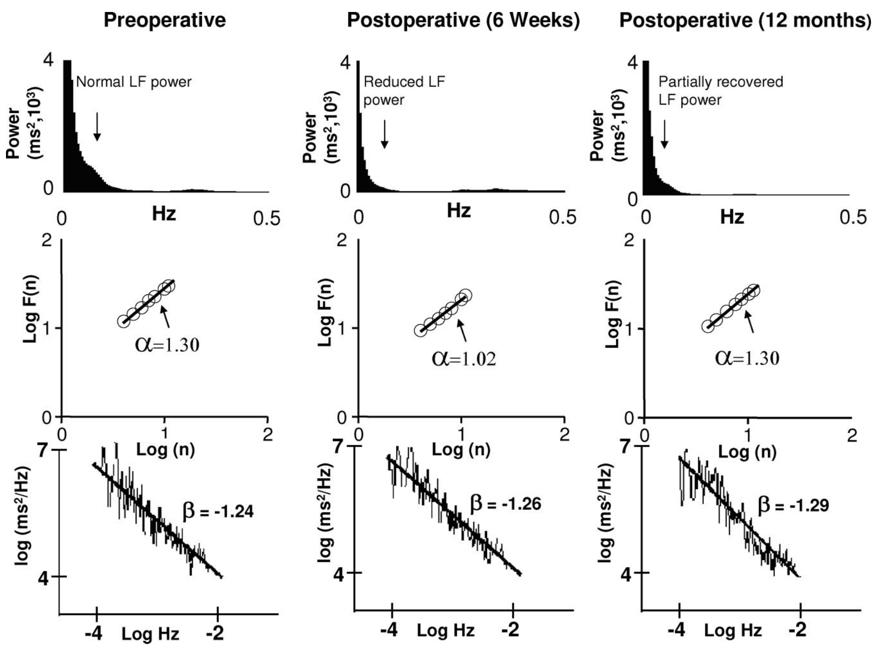

Figure 3. Examples of power spectral analyses (top), short-term correlation property (α_1) (middle) and power-law slopes (bottom) in the same patient before coronary artery bypass graft (CABG) surgery (left), and 6 wk (middle) and 1 yr (right) after CABG surgery with uneventful perioperative course. The top panel shows that the least recovery occurred in the range of low frequency power. The fractal scaling exponent α_1 was at significantly lower level 6 wk after CABG than preoperatively, but recovered to the preoperative level 6 mo after the operation (117).

display and quantitative analysis of the plots can be used for describing RR-interval dynamics (Fig. 4).

Approximate Entropy

Approximate entropy (ApEn) is a measure and parameter that quantifies the regularity or predictability of time series data. It measures the logarithmic likelihood that runs of patterns which are close to each other will remain close in the next incremental comparisons. A greater likelihood of remaining close (high regularity) produces smaller ApEn values (approximately 0.7–1.0) and, conversely, random data produces higher values (close to 2) (50–53).

ApEn is heavily dependent on the record length and is uniformly lower than expected for short records. It also lacks relative consistency. That is, if ApEn of one data set is higher than that of another, it should, but does not, remain higher for all conditions tested. Sample entropy is an alternative approach to calculate the entropy (54). In contrast to ApEn, sample entropy is largely independent of record length, and displays relative consistency under circumstances where ApEn does not.

Multiscale Entropy

Unlike the dynamics of healthy systems, diseased systems typically show reduced entropy values. However, some cardiac pathology, e.g., atrial fibrillation, is associated with highly erratic fluctuations, with statistical properties similar to uncorrelated noise. Traditional algorithms, like approximate and sample entropy, will yield an increase in entropy values for such noisy pathologic time series when compared with healthy dynamics, even though the latter represents more physically complex states. This obvious inconsistency may be related to the fact that the entropy measures used are based on single-scale analysis without considering the complex temporal fluctuations of a healthy physiological control system. Instead of computing one single-scale entropy measure for the time series, the signal can be analyzed using a multi-scale approach. The mathematical details have been described elsewhere (55).

Detrended Fluctuation Analysis

Long-range correlations between RR-intervals characterize fractal-like HR time series; i.e., the interbeat interval at every point is partially dependent on the interval

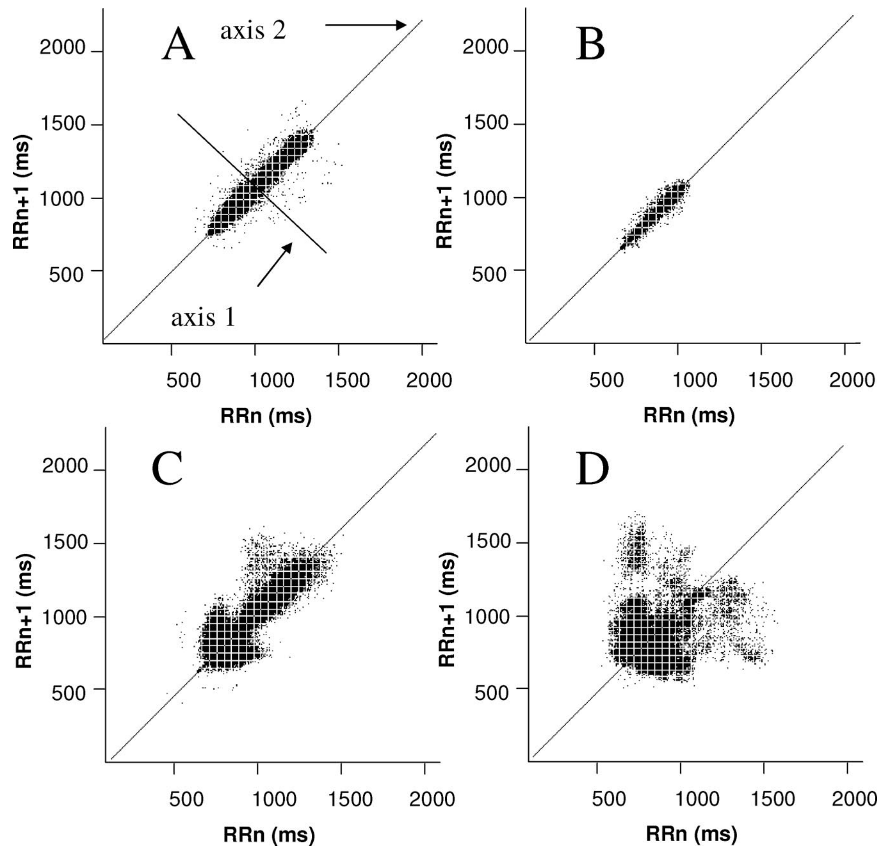

Figure 4. Examples of Poincaré plots (A–D), analyzed from more than 100,000 consecutive beats of 24 h. In quantitative analysis, the length of the longitudinal line (axis 2) describes the continuous long-term variability of the data (SD2). It is defined as the standard deviation (SD) of the plot data in the direction of axis 2. This has a moderate positive correlation with low frequency power of spectrum analysis at rest ($r = 0.70$). The length of the transverse line is defined as the SD of the plot data in a perpendicular direction (axis 1). This measure describes the instantaneous beat-to-beat variability of the data (SD1). This correlates strongly with high frequency power at rest ($r = 0.94$). Also the SD1/SD2 ratio may be calculated. A comet (A) and a torpedo-shaped (B) pattern of Poincaré plot in the same patient before (A) and after (B) coronary artery bypass graft (CABG) surgery with no ischemia pre- or postoperatively. A comet-shaped pattern is also typically seen in healthy subjects. (C) A complex pattern in a patient before CABG surgery with postoperative ischemia, myocardial infarction (MI), and prolonged intensive care unit (ICU) time of 7 days. (D) A complex pattern of the first postoperative day in another CABG patient with postoperative ischemia, MI and prolonged ICU time of 8 days.

at all previous points (40,46,47). Detrended fluctuation analysis (DFA) has been created to quantify such fractal-like correlation properties of time-series data (45,56) (middle panel of Fig. 3). The mathematical details of this method have been described elsewhere (56). Briefly, in DFA, the deviations of each RR-interval from the average RR-interval are integrated. Then the integrated time-series is divided into smaller windows (time scales) and a least squares line fit is applied to the data in each window. This produces a "local" trend, which is subtracted from the overall integrated time series, producing a detrended time series. Then a root mean square fluctuation is calculated from this integrated and detrended time series. This procedure is repeated using different time scales. Typically, there is a linear relationship between the logarithm of the fluctuation and the logarithm of the size of the time scale, indicating the presence of scaling (self-similarity), i.e., fluctuation in smaller time windows is related to fluctuations in larger time windows in a power-law fashion. The fractal scaling exponent α represents the slope of this line, which relates (log) fluctuation (y axis) to (log) window size (x axis) (Fig. 3). Short-term (α_1) and long-term (α_2) fractal correlation properties can be calculated using short and long time scales, respectively. DFA can detect the presence of random, fractal, or Brownian dynamics in HRV. In a normal healthy HR time series, $\alpha = 1$. The scaling exponent α is 0.5 for random and 1.5 for Brownian HR dynamics (40,46,47,56).

Other Measures

HR turbulence characterizes fluctuations of sinus-rhythm cycle length after a single ventricular premature beat. In practice, the turbulence onset variable is defined as a difference between the mean of the first two sinus RR intervals after the premature beat and the last two sinus RR intervals before the premature beat, normalized by the mean of the last two sinus RR intervals (26). Another measure, the turbulence slope, is defined as the maximum positive slope of a regression line assessed over any sequence of five subsequent sinus-rhythm RR intervals within the first 20

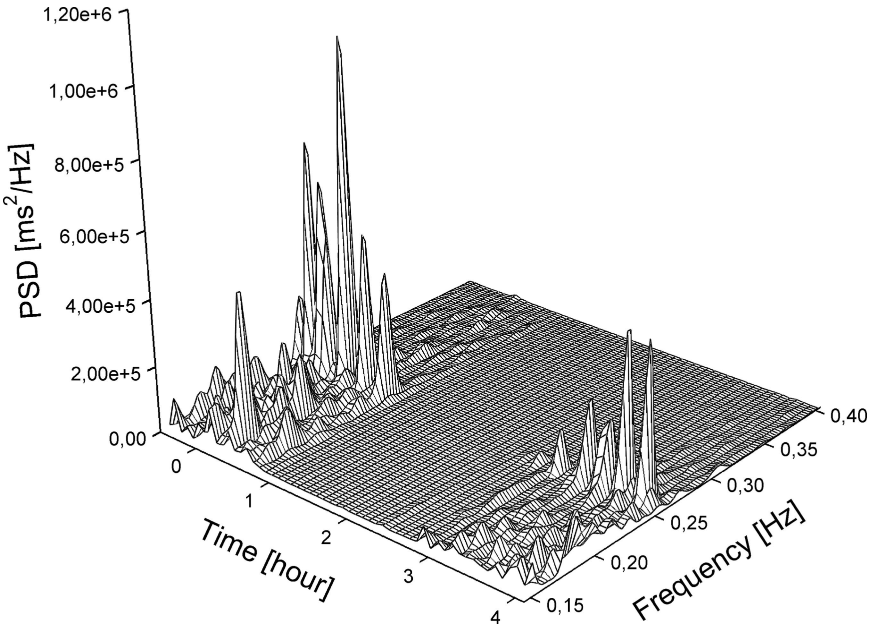

Figure 5. An example of high frequency (HF) variability spectra of a healthy male volunteer (age 28 yr) before, during and after a 2 h infusion of glycopyrrolate (5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ administered between 0 and 2 h). Parasympathetic blockade abolished the HF variability: at baseline, the HF power was 6175 ms^2 and, at the end of the infusion, 5 ms^2. The fast Fourier transformation and 5-min windowing was used for the spectrum analysis. During every third 5-min period, the breathing rate was controlled (15/min), which produced distinct respiratory arrhythmia peaks at 0.25 Hz. PSD = power spectral density. (From Penttilä J, et al. Eur J Clin Pharmacol 2005;61:559–65, © Springer Science and Business Media, reproduced by permission.)

sinus-rhythm intervals after a premature beat. Both variables have been shown to be good predictors of mortality after acute MI (26). Because a premature beat always also generates a sudden decrease in arterial blood pressure, it has been suggested that the turbulence variables are linked to baroreflex function. This method is inapplicable to patients without VPCs (26).

Physiological Background

Alterations in interbeat intervals, i.e., HRV, are mostly under the control of continuously altering and interacting parasympathetic and sympathetic nervous systems. ANS is modulated by the baroreceptors, vasomotor center, respiratory center, arterial blood pressure, and respiratory movements. Thus, HRV reflects an outflow of this system to the heart, resulting in short- and long-term beat-to-beat fluctuations via the sinoatrial node (57–59). Frequency domain measures of HRV provide information on the degree of autonomic modulations rather than of the level of autonomic tone (59).

Generally, time domain measures are highly correlated with the HF component of spectral analysis. The HF component primarily reflects respiration-driven vagal modulation of sinus arrhythmia (respiratory sinus arrhythmia, Figs. 1 and 2), which is believed to be generated by central coupling of the respiratory oscillator with autonomic centers in the brainstem (33,60). This notion is supported by a previous study which showed that the firing of cardiac vagal motoneurons in the nucleus ambiguus was modulated by the central respiratory cycle (61). There is consensus that vagal activity is the major modulator of the HF, e.g., by showing that HF can be abolished by anticholinergic drugs such as atropine or by vagotomy (33,62,63) (Fig. 5).

The physiological correlate of the LF (0.04–0.15 Hz) component of HRV is not as clear. There are studies showing that a normalized value of the LF component is modulated by sympathetic efferent activity (64–67) and some other studies demonstrating that the LF power is modulated by both vagal and sympathetic efferent activity (34,68–70). An acute sympathetic stimulation during head-up tilt test can be demonstrated with spectral analysis (Fig. 1). However, the LF power is paradoxically often reduced or abolished in patients with severe congestive heart failure (Fig. 2). Strong evidence indicates that severe heart failure patients have a chronic resting sympathetic stimulation provided by elevated levels of plasma catecholamines (71). It is widely accepted that the absolute value of LF power does not furnish an index of sympathetic modulation (33,34,64–70). LF oscillation may reflect sympathetic modulation originated from the central nervous system (58,72). Pagani et al. (67) found that LF and HF components of HRV and muscle sympathetic nerve activity alter synchronously during different levels of sympathetic drive. This suggests a common central mechanism governing both parasympathetic and sympathetic cardiovascular modulation. On the other hand, there is evidence that the LF component of HR and arterial blood pressure variability is substantially affected by baroreflex gain (73,74). This is supported by observations that the LF component is consistently reduced after baroreceptor deafferentation (74,75).

A diurnal fluctuation of ANS is a major modulator of the ultra-band. The sympathetic nervous activity especially exhibits a strong circadian rhythm. A paraventricular nucleus of hypothalamus is a pivotal mediator of the diurnal rhythm of ANS activity (60,76–78). The paraventricular nucleus activity depends on circadian input of suprachiasmatic nuclei of hypothalamus, which is a major central oscillator triggering day/night cycle (60). VLF band is suggested to be modulated by temperature regulation and humoral systems (e.g., thyroxine, reproductive hormones, the rennin-angiotensin system, and steroids) (60).

Although the physiological background of the dynamical measures is still not fully established, a previous study by Tulppo et al. (79) provided one plausible explanation for the physiological background of fractal HR dynamics. They used cold hand and cold face immersion tests under controlled conditions. During cold hand immersion, HF decreased significantly, indicating a withdrawal of vagal activity, and muscle sympathetic nervous activity from the peroneus nerve increased, indicating reciprocally enhanced sympathetic outflow. At the same time, the LF/HF ratio increased. These reciprocal alterations in ANS caused increased short-term fractal correlation properties of HR dynamics, expressed as increased scaling exponent α_1. Similar increases in fractal correlation properties, as well as ApEn, have been shown during light-intensity exercise, which can be related to an increase of circulating epinephrine (80–82). The physiology behind entropy measures is not known but they are suggested to be affected by coupling interactions of ANS (80,81). Fractal correlation properties also increase during passive head-up tilt test and vagal blockade by atropine or glycopyrrolate (81,83,84). The cold face test increases both vagal and sympathetic activity simultaneously (85). Tulppo et al. (79) showed that HF power increased, HR decreased, and muscle sympathetic nervous activity increased during the cold face test in all healthy volunteers, indicating increased activity of both parasympathetic and sympathetic activation, respectively. At the same time, the scaling exponent α_1 and LF/HF ratio decreased. The scaling exponent α_1 has also been shown to decrease and the HF component to increase progressively during incremental doses of norepinephrine (83). These results suggest that this breakdown of short-term fractal correlation properties toward more random HR dynamics occur during increased sympathetic activation followed by simultaneous activation of cardiac vagal outflow, also called "accentuated sympathovagal interaction," a concept first introduced by Levy et al. (57,79,83,86). The physiological background of HRV has been discussed in detail in recent reviews, e.g., by Stauss or Penttilä et al. (60,63).

HRV and Anesthesia

Anesthetic drugs alter HRV significantly. LF and HF powers are decreased significantly by halothane, isoflurane, desflurane, and xenon in healthy subjects, suggesting reduction in efferent cardiac vagal and sympathetic activity (87–96). Ishiguro et al. (95) showed that xenon blunts baroreflex sensitivity and decreases LF and HF more than isoflurane.

Several studies with and without controlled breathing patterns have shown persistent LF power, decreased HF power indicating decreased efferent cardiac vagal activity, and depressed baroreflex sensitivity during propofol infusion in animals and in humans (89,97–101). However, previous studies showed that LF and HF powers decreased significantly but that there were no significant changes in baroreflex function during sevoflurane or propofol anesthesia with or without N_2O (102,103).

HRV and Surgery

Recent studies have shown that high LF/HF ratio can identify patients with risk of developing severe hypotension during spinal anesthesia for cesarean delivery or for prostate gland procedures in ASA I or II patients (104,105). Receiver operator curve analysis revealed 85% sensitivity and 85% specificity of LF/HF >2.5 to predict systolic blood pressure decrease of more than 20% of baseline after spinal anesthesia (105). The studies of the effect of spinal anesthesia on HRV show controversial results, which also depend on the level of the sensory block and on the patient (104–109). Marsch et al. (108) showed decreased absolute HF and LF powers in elderly patients for up to 5 days after elective hip arthroplasty. Tetzlaff et al. (109) showed no change in LF and HF powers during low spinal block for elective lumbar spine surgery. Hanss et al. (105) showed decreased LF and increased HF powers during spinal anesthesia with the sensory block reaching the Th 8–9 ± 2 level in ASA I-II patients. In their studies, patients with significantly higher LF/HF and lower HF at baseline demonstrated severe hypotension during spinal anesthesia (104,105). Earlier studies in patients with ANS dysfunction due to diabetes mellitus scheduled for ophthalmologic surgery, and in patients scheduled for day-surgery have demonstrated that preoperatively impaired parasympathetic activity, reflected by HF power, indicated a high risk of hemodynamic instability during general anesthesia (110,111). It has been suggested that LF/HF ratio could be used as a tool to guide prophylactic therapy of patients at high risk for hypotension during spinal anesthesia (112).

Predictive Value of HRV for Postoperative Outcome

An association between mortality after MI and decreased HRV was first shown by Kleiger et al. (15). Decreased HRV has powerful long-term predictive value in MI patients, and in elderly subjects, for non-SCD and SCD (Table 1) (15–24,26,27). Several studies with MI patients have shown that among various HRV measures, especially short-term fractal scaling exponent α_1 as well as HR turbulence, are better in risk stratification for cardiac mortality than LVEF and VPC (15–21,26,27). This is also true for scaling exponent α_1 in surgical patients. The predictive value of HR turbulence or baroreceptor function alone or combined with HRV for adverse outcome in surgical patients has not been studied. Notably, La Rovere et al. (18) showed, in MI patients, that a combination of low baroreceptor function and HRV improved risk stratification over and beyond that obtained from LVEF and VPC.

Table 1. Predictive Value of Various HRV Measures for Morbidity and Mortality in Patients After Myocardial Infarction

Disease state and study	Primary end points	Studied HRV measures	No. of patients	Main result
MI patients				
Kleiger 1987 (15)	All-cause mortality over 4 yr	SDNN of time domain	808	SDNN < 50 ms; RR 2.7
Bigger 1992 (16)	Cause specific and all-cause mortality	Frequency domain	715	Decrease of ULF and VLF; RR 2.1–2.5 for cause specific and all-cause mortality
Zuanetti 1996 (17)	Cardiac and all-cause mortality over 3 yr	Time domain	567	NN50+ <200, cardiac and all-cause death; RR 4.0
Bigger 1996 (39)	Arrhythmic, cardiac and all-cause mortality >3 yr	Frequency domain and nonlinear	715	β-slope and log(power) at 10–4 Hz for all-cause mortality; RR 6.07
La Rovere 1998 (18)	Cardiac mortality over 2 yr	SDNN and BRS	1284	Combination of SDNN <70 ms and BRS <3.0 ms/mm Hg; RR 7.3
Huikuri 2000 (19)	Arrhythmic, nonarrhythmic and all-cause mortality	Time and frequency and nonlinear	645	α1 <0.75 for primary end points; RR 1.4, 2.6, 2.0, respectively Sensitivity 62%, Specificity 73%, PPA 46%, NPA 84% for all-cause death
Tapanainen 2002 (20)	All-cause mortality	Time and frequency and nonlinear	697	α1 <0.65 RR 3.9 Sensitivity 43%, Specificity 89%, PPA 23%, NPA95%, ROC 0.716
Mäkikallio 2005 (21)	SCD and non-SCD with modern treatment	Turbulence slope (TS), time and frequency domain and nonlinear	2130	TS ≤2.5 ms/RRI; HR 4.7 for SCD α1 <0.75; HR 2.7 for SCD Sensitivity 57%, specificity 82%, PPA 5.5%, NPA 99% for TS ≤2.5 ms/RRI in patients with EF >35%

The relative risk (RR), odds ratio (OR), or hazard ratio (HR) for the best predictor is obtained after multivariate model (if available) with adjustment for other clinical risk factors.

AF = atriall fibrillation; BRS = baroreflex sensitivity; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHD = coronary heart disease; ICU = intensive care unit; LF/HF = low frequency/high frequency ratio; MI = myocardial infarction; NPA = negative predictive accuracy; NN50+ = the number of pairs of adjacent NN intervals (i.e. intervals between normal-to-normal QRS complexes) differing by more than 50 ms in the recording period; pNN50 = the proportion derived by dividing NN50 by the total number of NN intervals; POD = postoperative day; PPA = positive predictive accuracy; RCRI = revised cardiac risk index; ROC = receiver operator curve; SCD = sudden cardiac death; SDNN = standard deviation of the NN intervals; SD1/SD2 = SD1/SD2 ratio of Poincaré plot; ULF = ultralow frequency; VLF = very low frequency.

Several studies have shown a significant decrease in the time- and frequency-domain measures, and scaling exponent α_1 immediately after cardiac artery bypass graft (CABG) surgery (30,31,113–115). The follow-up studies of long-term alterations in HRV after CABG surgery showed that the greatest reduction in the immediate postoperative phase and the least recovery occurred in the range of LF power 1 yr after surgery (113,116,117) (Fig. 3). The short-term fractal scaling exponent α_1 recovered to the preoperative level 6 mo after surgery. ApEn tended to decrease during follow-up and it was at a significantly lower level 12 mo after CABG surgery (117). Furthermore, HR turbulence remained low 1 yr after CABG indicating, along with decreased LF power, impaired baroreflex sensitivity (73–75,116). These studies suggest that there are some long-term changes in the ANS after CABG. Unfortunately, the significance of these findings remains unknown.

An association of perioperative HRV for postoperative myocardial ischemia and for prolonged intensive care unit (ICU) stay in CABG patients has been studied (28,30). In these studies, multivariate logistic regression analysis, including multiple confounding variables, revealed that decreased scaling exponent α_1 and increased SD1/SD2 ratio of the Poincaré plot of the first postoperative day were the only independent predictors for prolonged ICU stay (>48 h) and for appearance of ischemia, respectively (Table 2). Pre- and postoperative use of β-blockers, sympathomimetic inotropics and other vasoactive medications were included in the multivariate analysis, and were not found to be related to the length of ICU stay or occurrence of ischemia. Also, the use of these medications had no influence on the HRV measures.

The predictive value of HRV for prolonged ICU stay was later studied in 106 patients who underwent abdominal aortic surgery and in 86 CABG patients (31,32). In the study by Stein et al. (32), VLF was the strongest predictor for prolonged (>7 days) ICU stay but the scaling exponent α_1 was not studied. In the study by Wu et al. (31), ischemic preconditioning was also studied. The short-term fractal organization remained significantly more stable in the ischemic preconditioning group. In addition, preoperative and

Table 2. Predictive Value of Various HRV Measures for Morbidity and Mortality in Surgical Patients

Type of surgery and study	Primary end point(s)	Parameters studied	No. of patients	Main results
Head trauma				
Winchell 1997 (132)	Hospital mortality	Frequency domain	80	Decrease of total power and increase of HF/LF ratio: significant association with increased acute mortality
Abdominal aortic				
Stein 2001 (32)	Prolonged ICU stay >7 d	Time and frequency domain, β-slope	106	VLF: RR 0.59
Peripheral vascular				
Mamode 2001 (131)	MI or cardiac death within 30 d	Time domain (triangular index)	297	Preoperative triangular index ≤25.8; RR 6.0, Thallium scanning; RR 13.62
CABG				
Laitio 2000 (30)	Prolonged ICU stay >48h	Time and frequency and nonlinear	40	Postoperative decrease of α1 of 1st POD; OR 0.103 for a change of 0.2 units
Laitio 2002 (28)	Postoperative ischemia during 2nd POD	Time and frequency and nonlinear	40	Postoperative increase of SD1/SD2 ratio of 1st POD; OR 3.0 for a change of 0.15 units
Wu 2005 (31)	Prolonged ICU stay >24h; postoperative AF	Time and frequency and nonlinear	86	Preoperative decrease of α1
Major noncardiac				
Filipovic 2003 (10)	All-cause mortality 1-yr	Time and frequency domain, Detsky score, AHA clinical predictors, RCRI	173	Preoperative LF/HF <2, OR 16.2, ROC for LF/HF 0.76 Tn-I >2.0, OR 9.8, RCRI, OR 6.2
Hip fracture				
Laitio 2004 (29)	Postoperative prolonged (>10 min) ischemia	Time and frequency domain and nonlinear measures	32	OR 7.7 for an increase of 0.16 units in preoperative night (2–5 AM) to day (7–12 AM) difference of α1 Sensitivity 92%, Specificity 69%, PPA 69%, NPA92%, ROC 0.85 for negative night–day difference of preoperative α1
Major noncardiac				
Filipovic 2005 (11)	Postoperative 1 mo to 2-yr all-cause mortality	Time and frequency domain	167	Preoperative LF/HF ratio <2; OR1 6.4

For abbreviations see Table 1.

postoperative average value of α_1 of 24 h was significantly lower in patients with prolonged ICU stay (>24 h) (31). Their results suggest and support an earlier study by Laitio et al. (30), which found that less random and more fractal HR behavior in CABG patients resulted in better postoperative outcome (i.e., less inotropic support, shorter respiratory treatment and ICU stay, and less postoperative atrial fibrillation). It seems that certain alterations in HRV caused by compromised ANS occur several hours before adverse events.

A relation between night-time HRV and postoperative prolonged myocardial ischemia has been shown (29). In this study with elderly hip fracture patients, preoperative night-time (from 2 to 5 AM) scaling exponent α_1 was significantly lower than the day-time value (7–12 AM) in patients with prolonged postoperative ischemia. An increased preoperative difference between night-time and day-time values of scaling exponent α_1 (i.e., negative value of night-day difference of α_1) was the best predictor over other clinical factors for postoperative prolonged myocardial (>10 min) ischemia (Table 2). A plausible mechanism for these cardiovascular autonomic changes can be proposed. There is increasing evidence that sleep is not devoid of cardiovascular risk (118–124). It has been hypothesized that compromised dynamics of ANS, especially increased sympathetic activity, during rapid eye movement sleep could be involved in triggering severe cardiovascular events during early morning hours in cardiovascular patients, and in the general population as well (118–120,122,125–130). This is supported by the fact that the risk of sudden death from cardiac causes in the general population peaks during morning hours, and this period of the day is associated with a higher than expected incidence of MI and ischemic stroke (119,120,122–124). The decreased night-time short-term fractal correlation properties may also be a result of sympathoexcitation, because most rapid eye movement sleep appears to be between 2 and 5 AM (118,119).

Previous studies have shown that preoperatively decreased HRV is an independent predictor for postoperative cardiac death or MI in patients after major surgery and in trauma patients (10,11,116,131–133). A prospective study by Filipovic et al. (11) evaluated predictors of long-term outcome in patients with documented or suspected coronary disease who survived major noncardiac surgery. Such patients are still at increased risk of death after discharge from hospital, and they may benefit from further evaluation and optimization of therapy. Notably, they excluded patients who died within 1 mo after surgery. Their results showed that the LF/HF ratio <2 analyzed only 6 min before induction of anesthesia was the best predictor for 2-yr all-cause mortality in 167 patients (odds ratio, 6.4; confidence interval, 1.9–21; $P = 0.002$). Other independent predictors were a history of congestive heart failure and age >70. This study included the risk scores described by Eagle et al. (3), and by Detsky et al. (134) and the Revised Cardiac Risk Index described by Lee et al. (4). These risk scores failed to predict long-term morbidity. The reason for the failure was most probably that the scores have been established and validated to predict short-term outcome or to identify patients with the need for further cardiac testing (11).

As discussed earlier, a baroreceptor dysfunction is characteristic in cardiovascular patients. Although this feature increases the risk for SCD, inadequate compensation of increased sympathetic activity by baroreceptors during sleep as well as during day-time could be a triggering mechanism for acute perturbations in vulnerable patients (18,123,125,130). In such patients, the uncompensated sympathetic hyperactivity may increase platelet aggregability, coronary vasoconstriction, and left ventricular wall stress, predisposing the heart to ischemic episodes and life-threatening arrhythmias, a condition that often precipitates SCD (12,18).

In other words, it is possible that uncompensated sympathetic hyperactivity is a common denominator for altered HRV, for prolonged ICU time, and for postoperative ischemia and mortality as has been suggested for cardiac nonsurgical patients (12,18).

Future Aspects

According to the evidence, low HRV is a major risk factor for adverse cardiovascular events in nonsurgical patients. The low HRV also seems to have similar characteristics in surgical patients. Preliminary results of low HRV in performing as a prognostic test for long-term cardiac morbidity and mortality in surgical patients compare favorably with that of nonsurgical patients (Tables 1 and 2) (10,19–21,29). Also, the study by Filipovic et al. (11) is the only study that compared the predictive value of HRV and other perioperative risk scores. Their study suggests that HRV measures could be used to stratify postoperative long-term cardiac risk. There are two main reasons why HRV has not been assimilated clinically in surgical or nonsurgical patients during the past two decades can be addressed. First, results are mainly achieved from long-term electrocardiogram (ECG) recordings, i.e., 24 h, which is not practical for clinical use. Second, there is no method for automatic editing of the ECG data. Currently, editing is performed manually to ensure the sinus origin of the analyzed ECG data. Therefore, a refinement of existing tools and technology permitting near real-time editing and calculation of the ECG data are needed. Also, the possible predictive value of baroreceptor dysfunction and HR turbulence, alone and combined with HRV, for short- and long-term outcome needs to be studied in surgical patients.

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