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Correlation Properties and Complexity of Perioperative RR-Interval Dynamics in Coronary Artery Bypass Surgery Patients

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Background: **Dynamic measures of heart rate variability (HRV) may uncover abnormalities that are not easily detectable with traditional time and frequency domain measures. The purpose of this study was to characterize changes in RR-interval dynamics in the immediate postoperative phase of coronary artery bypass graft (CABG) surgery using traditional and selected newer dynamic measures of HRV.**

Methods: **Continuous 24-h electrocardiograph recordings were performed in 40 elective CABG surgery patients up to 72 h postoperatively. In one half of the patients, Holter recordings were initiated 12–40 h before the surgery. Time and frequency domain measures of HRV were assessed. The dynamic measures included a quantitative and visual analysis of Poincaré plots, measurement of short- and intermediate-term fractal-like scaling exponents (α_1 and α_2), the slope (β) of the power-law regression line of RR-interval dynamics, and approximate entropy.**

Results: **The SD of RR intervals ($P < 0.001$) and the ultra-low-, very-low-, low-, and high-frequency power ($P < 0.01$, $P < 0.001$, $P < 0.001$, $P < 0.01$, respectively) measures in the first postoperative 24 h decreased from the preoperative values. Analysis of Poincaré plots revealed increased randomness in beat-to-beat heart rate behavior demonstrated by an increase in the ratio between short-term and long-term HRV ($P < 0.001$) after CABG. Average scaling exponent α_1 of the 3 postoperative days decreased significantly after CABG (from 1.22 ± 0.15 to 0.85 ± 0.20, $P < 0.001$), indicating increased randomness of short-term heart rate dynamics (*i.e.*, loss of fractal-like heart rate dynamics). Reduced scaling exponent α_1 of the first postoperative 24 h was the best HRV measure in differentiating between the patients that had normal (≤ 48 h, n = 33) or prolonged (> 48 h, n = 7) intensive care unit stay (0.85 ± 0.17 *vs.* 0.68 ± 0.18; $P < 0.05$). In stepwise multivariate logistic regression analysis including typical clinical predictors, α_1 was the most significant independent predictor ($P < 0.05$) of long intensive care unit stay. None of the preoperative HRV measures were able to predict prolonged intensive care unit stays.**

Conclusions: **In the selected group of patients studied, a decrease in overall HRV was associated with altered nonlinear heart rate dynamics after CABG surgery. Current results suggest that a more random short-term heart rate behavior may be associated with a complicated clinical course. Analysis of fractal-like dynamics of heart rate may provide new perspectives in detecting abnormal cardiovascular function after CABG. (Key words: Fractals; heart rate dynamics; holter recordings; risk stratification.)**

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EARLIER studies have shown that overall heart rate variability (HRV) is reduced after coronary artery bypass graft (CABG) surgery (see Appendix).[1,2] Generally, reduced HRV seems to be an independent predictor of mortality in patients with coronary artery disease and after myocardial infarction (MI).[3,4] Recent studies suggest that newer measures of HRV, such as fractal analysis methods, can complement the traditional time and frequency domain HRV measures in risk stratification of patients with heart disease.[5-11] These new dynamic analysis methods describe qualitative rather than quantitative properties of HRV.

The basic physiologic dynamics of normal sinus rhythm have been shown to have fractal-like features.[12-14] Fractal-like heart rate (HR) dynamics exhibit long-range correlations between RR intervals (*i.e.*, interbeat interval at every time point is partially dependent on the intervals at all previous time points).[15] There are several analysis methods that are able to describe and quantify the fractal characteristics and complexity of HRV from standard ambulatory electrocardiograph (ECG) recordings.[5,8,15-17] However, there are only few studies that have explored the capability of these new fractal and complexity measures in risk stratification of patients undergoing CABG surgery.[9] The purpose of this study was to explore the characteristics of fractal-like HR dynamics in CABG patients before surgery and for 3 days postoperatively, to examine whether patients with prolonged intensive care unit (ICU) stay (> 48 h) have altered fractal-like HR dynamics, and to determine the possible predictive value of the different HRV measures for prolonged ICU stay.

Materials and Methods

Patients and Study Design

Forty-six consecutive adult patients scheduled for elective CABG surgery underwent continuous postoperative ECG monitoring. The postoperative ECG recording was initiated immediately after surgery and continued for 48 h in 46 patients, of whom 14 had an additional 24 h of recording. Preoperative recordings were initiated 12--40 h before surgery (mean ± SD, 26.8 ± 11.5 h) in 20 patients. Exclusion criteria included diabetes or other illnesses likely to be associated with autonomic neuropathy or MI less than 1 month preoperatively. The patients were retrospectively classified according to normal (≤ 48 h, group A) and long (> 48 h) postoperative ICU stay (group B), as previously described.[18,19] The study protocol was approved by the local ethics committee, and all patients gave written informed consent.

Anesthetic and Surgical Management

The patients received their regular antianginal medication (β-blockers, calcium channel blockers, or nitrates) until the time of surgery. Patients were premedicated with scopolamine 6 μg/kg and morphine 0.2 mg/kg intramuscularly. Anesthesia was induced with 20 μg/kg fentanyl and 70 μg/kg midazolam. Pancuronium 0.1 mg/kg was given for muscle relaxation. Anesthesia was maintained with isoflurane as needed in oxygen-air (40/60%) and with continuous infusion of fentanyl (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and midazolam (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Moderate systemic hypothermia (core temperature 30–33°C), α-stat pH management, and pump flow rate 2.4 l/min/m^2 were used. Antegrade cold cardioplegia with topical iced "slush" or antegrade intermittent cold-blood (+10°C) cardioplegia was used during cardiopulmonary bypass. Hemoglobin concentration was kept above 7 g/dl during cardiopulmonary bypass and above 9 g/dl after the operation.

Postoperative Treatment

After surgery, all patients were transferred to the ICU. They were mechanically ventilated until they had stable hemodynamics (systolic arterial pressure > 80 mmHg or diastolic arterial pressure–pulmonary capillary wedge pressure > 40 mmHg with or without a cardiac index > 2.0 l/min/m^2), and had recovered from the anesthesia. Oxycodone was administered intravenously in 3- to 5-mg increments for pain control. Midazolam (3 mg intravenously) was given if needed for postoperative sedation. β-Blockers were not continued after surgery until discharge from the ICU. Criteria for discharge from ICU were stable hemodynamics and no need for inotropic drugs, intravenous nitroglycerin, or sodium nitroprusside.

Perioperative Electrocardiogram Recordings and Biochemical Assessments

Two-channel (bipolar leads CC5 and modified CM5) 24-h Holter ECG values were recorded in 34 patients using a digital Holter (Oxford Medilog, Oxford Medical, Ltd., Woking, UK) device with a temporal resolution of 1024 Hz and in 12 patients with an analog Holter device with temporal resolution of 128 Hz (8500 series, Marquette Electronics, Milwaukee, WI). The intraoperative periods were excluded. A blood sample for determination of creatine kinase MB isoenzyme (CK-MB) was obtained on arrival at the ICU, in the morning and evening of first postoperative 2 days, and at discharge from the hospital or 7 days postoperatively, whichever occurred first. An elevation of CK-MB activity to > 100 μg/l at any time postoperatively or to > 70 μg/l at any time after the first postoperative 12 h indicated perioperative MI.[20] A 12-lead ECG was obtained preoperatively, after arrival to the ICU, in the first and second postoperative mornings, and at discharge from hospital. Each ECG was analyzed using Minnesota code criteria.[21] All new Q-waves were identified. The occurrence of Q-wave was determined in one or more of the three lead groups: anterolateral (I, AVL, V_6), posteroinferior (II, III, AVF), and anterior (V_1 - V_5). A non-Q-wave MI was defined as the absence of a Q-wave but an elevation of CK-MB activity to the above level. An additional ECG was obtained if perioperative MI was suspected or if there was an elevation of CK-MB activity. The clinical data were analyzed by an experienced cardiologist who was blinded to the Holter data.

Measurement of Heart Rate Variability

The ECG data of both analog and digital Holter recorders were sampled digitally and transferred from the Oxford Medilog scanner (Oxford Medical Ltd.) to a microcomputer for further analysis of HRV (Hearts5 software program, Heart Signal Co., Kempele, Finland). Details of this analysis technique have been described elsewhere.[22,23] Careful manual editing of the RR-interval series with inspection of the ECG data by deleting premature beats and noise was performed. All RR intervals of suspected portions were printed out on a two-channel ECG at a paper speed of 25 mm/s to confirm the sinus origin of the RR-interval data.[10] The same edited data were used for all HRV measures used in this study. The data of low-frequency (LF) and high-frequency (HF) power spectral densities, approximate entropy (ApEn), and quantitative analysis of Poincaré plot were analyzed in segments of 1,000 beats. In visual analysis of Poincaré plots, however, segments of 3,000 beats were used. A detrended fluctuation analysis was analyzed in segments of 8000 beats. Very-low-frequency (VLF) and ultra-low-frequency (ULF) bands and the β-slope of a power-law relation were analyzed as a whole epoch of 24 h, as previously described.[5,7,8,9,15-17] Whenever segments of 1,000 and 8,000 beats were used, the average of 24-h epochs were calculated. All segments with > 85% of qualified sinus beats were included.[7]

Frequency and Time Domain Analysis of Heart Rate Variability

After editing the RR-interval tachograms, the RR-interval spectrum was computed according to a previously described method.[13] Briefly, a fast Fourier transformation was used to estimate the power spectral densities of RR-interval variability. Frequency domain measures of RR-interval variability were computed by integrating the power spectrum over the frequency intervals. The power spectra were quantified by measuring the areas in the following frequency bands: ULF power < 0.0033 Hz, VLF power 0.0033-0.04 Hz, LF power 0.04-0.15 Hz, and HF power 0.15-0.4 Hz, as recently suggested.[24] Mean length of RR intervals (HR) and SD of all RR intervals were used as time domain measures of HRV.

Poincaré Plot Analysis

The Poincaré plot is a diagram in which each RR interval is plotted as a function of the previous one. Both visual analysis of the graphic display and quantitative analysis of the plots can be used for describing the RR-interval dynamics. The quantitative two-dimensional analysis of these plots has been described in detail elsewhere.[16,25] Briefly, the markings of the plot are gathered around a line of unitary slope passing through the origin. The center point of the markings is at (RR_{aver}, RR_{aver}), where RR_{aver} is the average RR-interval length for the tachogram. Quantitative analysis entails fitting an ellipse to the plot, with its center coinciding with the center point of the markings, and comparing points from two lines traversing through the center point of the data, longitudinal and transverse. The longitudinal line starts from the origin and has a slope of 1.0. The transverse line is perpendicular to longitudinal line. The length of the longitudinal line, which is defined as the SD of the plot data in this direction, describes continuous, long-term variability of the data (SD2). The length of the transverse line is defined as the SD of the plot data in perpendicular direction. This measure describes the instantaneous beat-to-beat variability of the data (SD1). The SD1-SD2 ratio was also calculated. In visual analysis, the graphic display of the 24-h and all 3,000-beat segment scattergrams were analyzed in a blinded fashion by one investigator. We used previously presented criteria for the patterns of the plots (fig. 1).[16,26] A normal configuration of the plot was defined as a fan or comet shape. Abnormal forms were a random pattern characterized by asymmetrical RR-interval clusters, a ball-shaped pattern with symmetrical clusters around the center, and a torpedo-shaped pattern with narrow configuration that lacked RR-interval dispersion at slower HRs.[16] The random pattern may have many forms which can resemble a butterfly or a horseshoe (parabola shape).

Detrended Fluctuation Analysis

Detrended fluctuation analysis quantifies fractal-like correlation properties of the time-series data.[15,27,28] The mathematical details of this method have been described elsewhere.[6,7,15,27-29] Briefly, the deviations of each RR interval from the average RR interval are integrated over the selected window (8,000 beats). This produces an integrated time series. Then the window is divided into

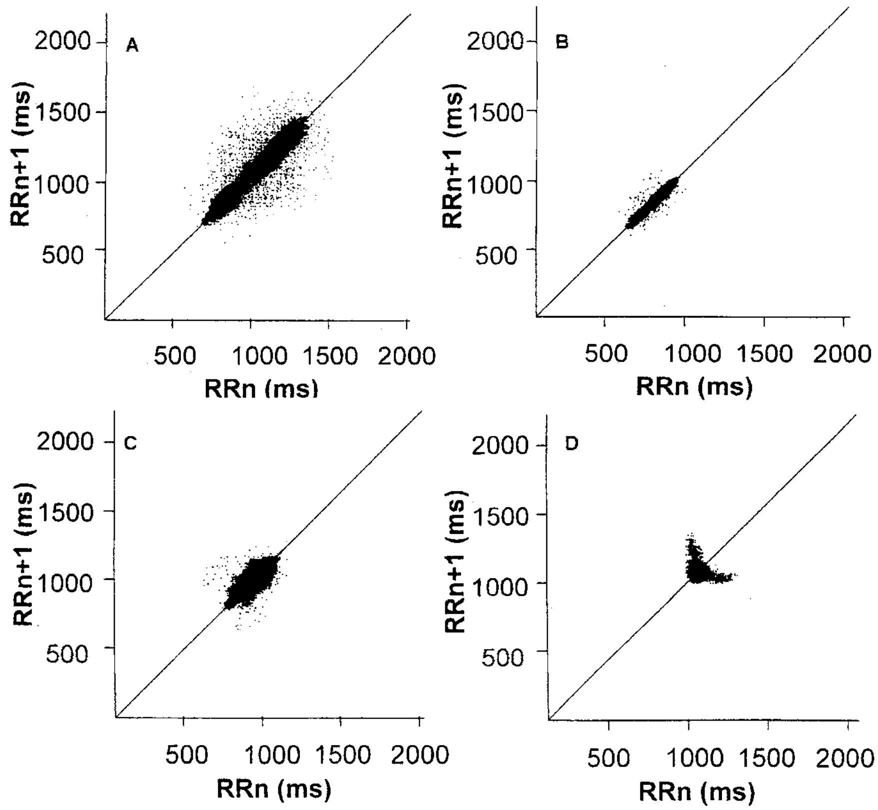

Fig. 1. Examples of Poincaré plots analyzed from (*A–C*) more than 100,000 and from (*D*) 3,000 consecutive sinus beats. (*A*) A comet-shaped pattern in a patient before coronary artery bypass graft (SD1–SD2 ratio = 0.22). (*B*) A torpedo-shaped pattern in a postoperative patient (SD1–SD2 ratio = 0.34). (*C*) A complex ball pattern in a postoperative patient (SD1–SD2 ratio = 0.46). (*D*) A random-shaped pattern in a postoperative patient prior to a sepsis-like high cardiac output syndrome (SD1–SD2 ratio = 1.35).

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. A root mean square fluctuation is then calculated from this integrated and detrended time series. This procedure is repeated using different time scales. Typically, there is a linear relation between the logarithm of the fluctuation and the logarithm of the size of the time scale. However, the slope of this line is usually different with very small ($<$ 10–15 beats) time-scale windows compared with larger time-scale ($>$ 15 beats) windows. The scaling exponent represents the slope of this line, which relates (log)fluctuation to (log)window size. The present HR correlation was defined for short-term fractal-like correlation α_1 (window size $\leq$ 11 beats) and intermediate-term fractal-like correlation α_2 ($>$ 11 beats) of RR-interval data, based on a previous finding of altered short-term HR behavior among patients with arrhythmias. Figure 2 shows two examples of the plots generated by the detrended fluctuation analysis method. An exponent value of 1.5 (*i.e.*, Brownian noise-type HR dynamics) indicates high interbeat correlations. An exponent value of 0.5 indicates that there are no correlations between the RR intervals as a result of random HR dynamics. In this case, the frequency spectrum is flat, without discrete spectral peaks, because all the frequencies are represented at an equal density. An exponent value of 1.0 contains both random and highly correlated characteristics in RR-interval time series and has been interpreted to indicate fractality in the HR dynamics. This type of fractal behavior with an exponent value of 1.0 has been documented for normal HR dynamics.[8,12,13,15,29]

Power-Law Relation Analysis of Heart Rate Variability

Power-law relation of RR-interval variability was calculated for slow HR fluctuation from a frequency range of 10^{-4} to 10^{-2} Hz using a previously described method.[8,13] Briefly, regularly spaced time series were derived by sampling the irregularly spaced RR-intervals at 2^{18} time points. A power spectrum was then computed using these points. The resulting point power spectrum was logarithmically smoothed in the frequency domain

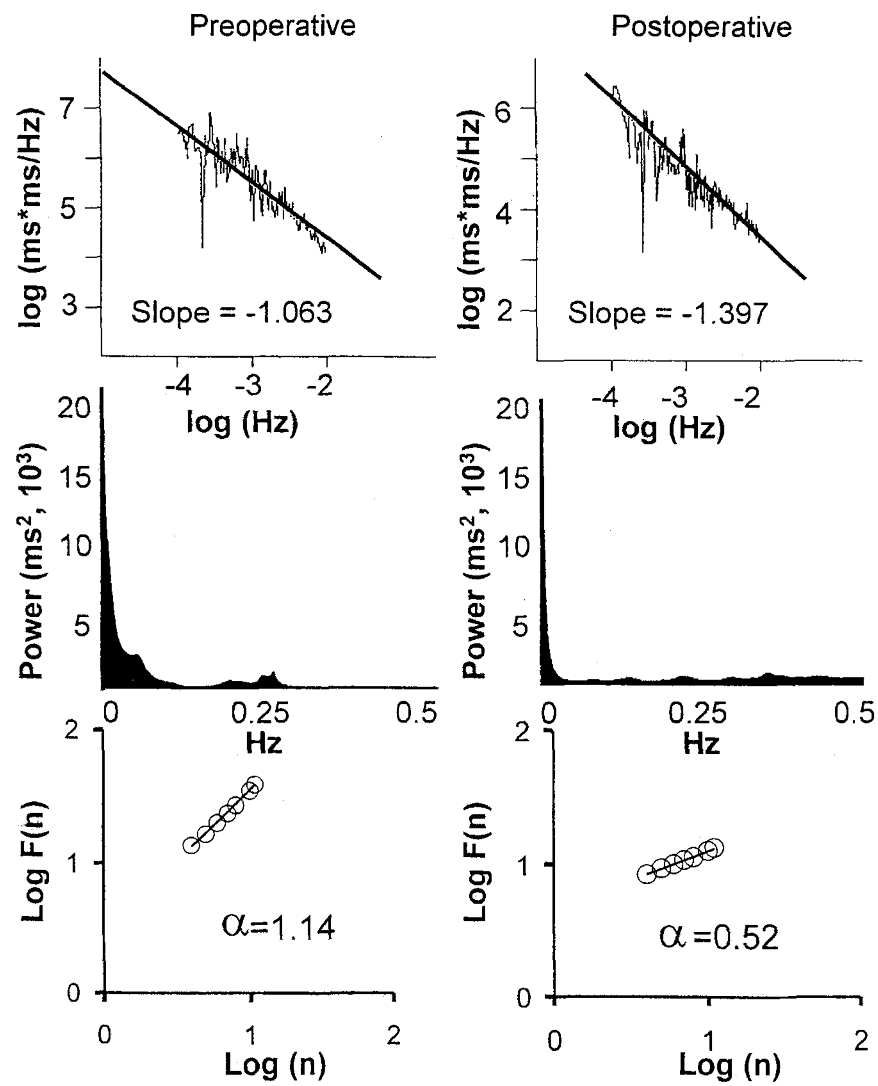

Fig. 2. Examples of power-law slopes (*top*) before (*left*) and after (*right*) CABG, power spectral analyses (*middle*), and the short-term correlation property (α_1) (*bottom*) before (*left*) and after (*right*) coronary artery bypass graft in the same patient. The postoperative power spectra show no respiratory peaks, and the scaling exponent α_1 shows completely random heart rate dynamics postoperatively. In the figure of scaling exponent α_1 (*bottom*), the x-axis represents the log of window size (n) $\le$ 11 beats. The y-axis represents the average root mean square fluctuation of integrated and detrended time series as a function of window size n. The data was analyzed from 24-h epochs.

by first calculating the common log of frequency and then integrating power into bins ("boxes") spaced 60 per decade (*i.e.*, 0.0167 log [Hz] wide). Bins at higher frequencies contain more points than those at lower frequencies, because in the log scale, each decade has 10 times the number of points as the previous decade. A robust line-fitting algorithm of log (power) on log (frequency) was then applied to the power spectrum between 10^{-4} to 10^{-2}, and the slope of this line (β) was calculated (fig. 2). This frequency band was chosen on the basis of previous observations regarding the linear relation between log (power) and log (frequency) in this range.[8,13]

Approximate Entropy

Approximate entropy is a measure and parameter that quantifies the regularity or predictability of time series data. It measures the logarithmic likelihood that runs of patterns that 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, and conversely, random data produce higher values. Two input variables, number of observations (m) and filter level (r), were fixed to compute ApEn, and m = 2 and r = 20% of the SD of the data sets were used for time series, as have been recommended based on previous findings of good statistical validity.[17,30] The details of this method have been discussed by Pincus and Goldberger.[30]

Statistical Analysis

Because the skewed and nonnormal shape of distributions, the data were analyzed using nonparametric methods. The comparisons among data from the preoperative period and the postoperative 2 days were analyzed using the Wilcoxon matched pairs test with Bonferroni correction corresponding all three pairwise comparisons of the three (preoperative, first postoperative day, and second postoperative day) time points. Comparison between groups of categorical variables was done using the Fisher exact test. The first, second, and third postoperative days were compared with the preoperative values of 20 patients. Significance of associations between potential predictors and long ICU stay were analyzed using logistic models. Univariate logistic regression analysis was performed, first applying maximum likelihood methods with SAS statistical software (SAS System for Windows, release 6.12/1996, SAS Inc., Cary, NC). For significant or marginally significant ($P < 0.10$) predictors, the results were confirmed by calculating the exact P values and confidence intervals (CI) using the LogXact package (LogXact-turbo 1993, Cytel Software Corporation; Cambridge, MA). A stepwise multivariate logistic regression analysis was also applied to estimate the independent predictive associations of various postoperative HRV measures and clinical variables to predict the length of ICU stay. For significant associations, odds ratios (OR) and their 95% CIs were calculated for increases corresponding to the magnitude of interquartile range.

The variables included were HRV measures, age, gender, body mass index, duration of angina pectoris symptoms, recent MI, New York Heart Association class, cigarette smoking, use of β-blockers preoperatively and postoperatively, use of vasoactive and inotropic sympathomimetic medication intraoperatively and postoperatively during the first 24 h, use of angiotensin converting enzyme inhibitors preoperatively, number of vessels involved, number of coronary bypasses performed, preoperative left ventricular ejection fraction assessed by angiography (grade 1, > 50%; grade 2, 35–50%; grade 3, 20–34%; grade 4, < 20%),[18,19] duration of anesthesia, duration of cardiopulmonary bypass and aortic cross clamping, duration of surgery, type of cardioplegia used, highest value of postoperative CK-MB, amount of bleeding during the first postoperative 24 h, Acute Physiologic and Chronic Health Evaluation (APACHE II),[31] cardiac index, cardiac output at arrival to the ICU, and the average cardiac output during the first 24 h.[18,19] In addition, the impact of various categorical factors including the use of vasoactive and inotropic support (epinephrine or norepinephrine with or without dopamine or dobutamine), New York Heart Association class, and type of cardioplegia was analyzed using the Mann-Whitney U test, and β-blocker use was analyzed using the Wilcoxon matched pairs test. Correlations between HRV measures were performed using the Spearman correlation test. $P < 0.05$ was considered statistically significant.

Results

Clinical Data

Forty-six patients entered the study. Five patients were excluded after surgery due to excessive arrhythmia or ectopy, and one patient was excluded because of a need for continuous pacing after surgery. There were 33 patients in group A (ICU stay $\leq$ 48 h) and seven patients in group B (ICU stay > 48 h). The angiographic, clinical, and operative data of these patients are summarized in table 1. Twenty patients had preoperative Holter recordings. Four patients had a perioperative MI, two of whom were in group A. In addition, one patient had postoperative MI 1 month later. Three patients in group A and two in group B had attacks of atrial fibrillation; all of these occurred during the second postoperative day. There were no perioperative deaths. Twenty-seven patients needed vasoactive medication during the postoperative follow-up. Vasoactive medications included inotropic and antianginal medications including dopamine, dobutamine, norepinephrine, epinephrine, sodium nitroprusside, and nitroglycerin. Fourteen patients in group A required inotropic support (table 1). All group B patients required inotropic support after 48 h, but two of these did not need it during the first 24 h. The patient with the longest ICU stay (8 days) did not need vasoactive medication during the first postoperative 24 h.

Time and Frequency Domain Analysis of Heart Rate Variability

SD of all RR intervals on each of the two postoperative days was significantly lower than that obtained preoperatively ($P < 0.001$). All frequency domain measures (ULF, VLF, LF, and HF) were significantly lower during each of the two postoperative days than values obtained preoperatively. The results are summarized in table 2.

Table 1. Clinical and Operative Data of Patients Undergoing Coronary Artery Bypass Surgery (n = 40)

	Group A ICU Stay ≤ 48 h (n = 33)	Group B ICU Stay > 48 h (n = 7)	
Clinical data			
Age	65 (45–74)	66 (57–74)	$P = 0.231$
Sex (F/M)	6/27	1/6	$P = 1.000$
BMI (kg/m^2)	26 (22–35)	27 (21–32)	$P = 0.708$
Symptomatic CAD (yr)	2.5 (0.5–25)	1.3 (0.5–19)	$P = 0.532$
Patients with previous MI	15	1	$P = 0.210$
Smoking (n)	8	4	$P = 0.168$
Patients with β-blockers (n)	30	6	$P = 0.552$
Patients with ACE inhibitors (n)	9	0	$P = 0.175$
EF %			
Grade 1 (> 50%)–2 (35–50%)	29	6	
Grade 3 (20–34%)–4 (< 20%)	3	1	$P = 0.563$
Operative data			
Duration of anesthesia (min)	230 (185–300)	255 (210–308)	$P = 0.310$
Duration of surgery (min)	172 (118–240)	187 (140–290)	$P = 0.309$
Duration of CPB (min)	92 (45–155)	106 (65–140)	$P = 0.170$
Cross clamp time (min)	71 (18–120)	84 (38–90)	$P = 0.631$
Type of cardioplegia			
Cold (n)	23	4	
Cold blood (+10°C) (n)	10	3	$P = 0.662$
Postoperative inotropics (n)			
Dopamine and/or dobutamine (n)	16	7	$P = 0.014$
Epinephrine and/or norepinephrine (n)	5	2	$P = 0.584$
Perioperative MI (n)	2	2	$P = 0.134$
Duration of mechanical ventilation (h)	18 (7–32)	66 (24–200)	$P = 0.00005$
ICU stay (h)	22.5 (20–48)	94 (49–195)	
Loss of blood (ml)	950 (460–3,195)	1320 (750–4,005)	$P = 0.052$
CI at arrival to ICU (l/min)	2.3 (1.6–3.1)	3.1 (2.5–4.7)	$P = 0.011$
CO (l/min)	5.7 (3.4–7.6)	5.3 (4.5–7.9)	$P = 0.942$
APACHE II of the first postoperative 24 h	12 (3–19)	15 (10–16)	$P = 0.014$

Group A: intensive care unit (ICU) stay ≤ 48 h; group B: ICU stay > 48 h. Statistical significance was tested with Mann–Whitney U test and Fisher exact test. Values are median and range or number of patients presented.

BMI = body mass index; CAD = coronary artery disease; MI = myocardial infarction; ACE = angiotensin-converting enzyme; EF % = left ventricular ejection fraction; CPB = cardiopulmonary bypass; CI = cardiac index; CO = average cardiac output measures of the first postoperative 24 h; APACHE = Acute Physiologic and Chronic Health Evaluation scoring.

Poincaré Plots

Preoperatively, 17 patients exhibited comet-shaped plots, one had a fan-shaped plot, one had a torpedo-shaped plot, and one had a random-shaped plot. Postoperatively, visual analysis revealed that none of the patients exhibited normal comet-shaped plots during any of the postoperative days. Thirteen patients had a torpedo-shaped pattern, six had a complex ball pattern, and one had a complex pattern (fig. 2) during the follow-up period.

The SD1 variability of all postoperative days was significantly lower than preoperative values ($P < 0.01$, table 2). The SD2 variability also reduced significantly postoperatively compared with the preoperative level ($P < 0.001$). The SD1-SD2 ratio during the postoperative follow-up increased significantly from the preoperative level ($P < 0.001$) due to a greater relative decrease of SD2 than SD1.

Analysis of Heart Rate Dynamics

The short-term fractal-like correlation α_1 decreased significantly after the operation and stayed low during the follow-up period (1.22 ± 0.15 *vs.* postoperative mean 0.85 ± 0.2; $P < 0.001$). The intermediate-term correlation property α_2 did not change postoperatively (1.10 ± 0.06 *vs.* 1.05 ± 0.17, not significant). There were no significant differences between preoperative and postoperative values in power-law slopes (β). The mean of postoperative ApEn measures (postoperative 72 h) was higher compared with the preoperative value ($P < 0.05$), but after Bonferroni correction, there was only a marginally significant difference ($P = 0.05$; table

Table 2. Effects of CABG on Heart Rate Variability (HRV) and Heart Rate (HR) Dynamics

	Preoperative Period (n = 20)	Postoperative First Day (n = 20)	Postoperative Second Day (n = 20)
ApEn	1.05 (1.04) ± 0.06 (0.94–1.2)	1.12 (1.15) ± 0.15 (0.77–1.32)	1.15 (1.18) ± 0.15 (0.8–1.37)*
Poincaré plot			
SD1 (ms)	21.4 (20.9) ± 7.0 (9.6–41.0)	12.5 (8.9) ± 8.8 (4.4–44)†	13.5 (9.8) ± 8.4 (4.87–39)†
SD2 (ms)	86.0 (83.1) ± 17.6 (49–104)	27.2 (25.7) ± 13.8 (11–60)‡	30.5 (25.9) ± 16.1 (11.7–73)‡
SD1/SD2	0.28 (0.28) ± 0.06 (0.18–0.45)	0.53 (0.47) ± 0.25 (0.25–1.35)‡	0.5 (0.46) ± 0.28 (0.18–1.56)‡
DFA			
α_1	1.22 (1.23) ± 0.15 (0.96–1.47)	0.85 (0.87) ± 0.20 (0.42–1.19)‡	0.87 (0.86) ± 0.22 (0.42–1.3)‡
α_2	1.10 (1.12) ± 0.06 (0.96–1.21)	1.02 (1.08) ± 0.20 (0.63–1.31)	1.06 (1.09) ± 0.17 (0.63–1.27)
Time domain			
HR (beats/min)	60.9 (60.9) ± 6.2 (49.5–71.7)	89.4 (87.1) ± 13.1 (71–119)‡	85.4 (80.2) ± 13.8 (64.5–112)‡
SDNN (ms)	52.7 (49.1) ± 12.0 (30–74)	19.2 (15.2) ± 10.3 (6.7–50)‡	21.7 (17.5) ± 11.2 (8.7–50.4)‡
Frequency domain			
β-Slope	−1.36 (−1.34) ± 0.15 (−1.63–−1.11)	−1.37 (−1.36) ± 0.33 (−2.25–−0.81)	−1.32 (−1.33) ± 0.33 (−1.98–−0.67)
ULF (ms^2)	9,634 (8,369) ± 5,928 (2,842–23,052)	3,100 (1,589) ± 3,578 (269–15,450)‡	1,785 (1,057) ± 1,868 (281–7,479)†
VLF ($ms^2 \times 10$)	1,198 (974) ± 669 (325–3,312)	272 (108) ± 344 (22–1,379)‡	214 (95) ± 228 (15–750)‡
LF ($ms^2 \times 10$)	588 (469) ± 339 (147–1,288)	103 (38.1) ± 118 (3.6–491)‡	113.5 (40.9) ± 155 (9.1–690)†
HF ($ms^2 \times 10$)	301 (244) ± 209 (62–984)	259 (45.0) ± 645 (7.6–3,008)†	150 (56.7) ± 222 (13.6–922)†

Analyses of standard deviation of all R-R intervals (SDNN), average R-R interval, low frequency (LF), high frequency (HF), approximate entropy (ApEn), and Poincaré plot were performed on 1,000-beat segments, and short-term (α_1) and intermediate-term (α_2) correlation properties (DFA) were performed in segments of 8,000 beats. Very low frequency of spectral power (VLF), ultra low frequency band (ULF), and scaling exponent of the power law relationship (β-slope) were analyzed in epochs of 24 h. Significance levels were tested with Wilcoxon matched pairs test. Values are means (median) ± SD (range).

* $P = 0.05$ *versus* baseline (preoperative value).

† $P < 0.01$ *versus* baseline.

‡ $P < 0.001$ *versus* baseline.

P values are after Bonferroni correction.

SD1 = instantaneous beat-to-beat HRV; SD2 = continuous long-term HRV; CABG = coronary artery bypass graft; DFA = detrended fluctuation analyses.

2). Scaling exponent α_1 correlated significantly only with the SD1-SD2 ratio (r = −0.86; $P < 0.001$), SD2 (r = 0.44; $P < 0.01$), HR (r = −0.42; $P < 0.05$), and VLF (r = 0.38; $P < 0.05$). ApEn did not correlate with any other measure used in this study.

Clinical Course and Heart Rate Variability

Scaling exponent α_1 of the first postoperative 24 h was significantly lower in group B (0.68 ± 0.18) compared with group A (0.85 ± 0.17; $P < 0.05$; table 3). The two patients with longest ICU stay had the lowest α_1 values (0.48 and 0.52, respectively). The patient with the longest ICU stay and postoperative MI was the only one who had a predominantly random pattern of Poincaré plot preoperatively and had the lowest preoperative α_1 value of 0.96. Two patients in group A had random α_1 values of 0.53 and 0.55. One patient in group A and one patient in group B underwent resternotomy 6 and 21 h, respectively, after arrival to the ICU. Their α_1 values were 0.78 and 0.81, respectively. The analyses of different categorical factors showed that ApEn was significantly lower in patients who needed inotropes during the first postoperative 24 h compared with those who did not ($P < 0.05$).

In a univariate logistic model, reduced short-term correlation property α_1 of the first postoperative 24 h (corresponding to change of 0.2 units: OR, 0.29; 95% CI, 0.085–0.85; $P = 0.02$), APACHE II (corresponding to change of 4 units: OR, 3.73; 95% CI, 1.08–17.09; $P = 0.035$) and CK-MB (change of 17 units: OR, 1.2; 95% CI, 1.00–1.5; $P = 0.043$) were the only variables that showed significant prediction of long ICU stay. In stepwise multivariate logistic regression analysis, α_1 and APACHE II were the only statistically significant independent predictors, and scaling exponent α_1 was the most significant predictor (change of 0.2 units: OR, 0.103; 95% CI, 0.007–0.597; $P = 0.039$).

Discussion

The main finding of this study was that dynamic measures of HRV can detect abnormal HR behavior after CABG surgery. Almost all patients showed normal fractal-like HR dynamics preoperatively (scaling exponent values ≈ 1.0 and comet-shaped Poincaré plots), but more random short-term HR dynamics (reduced short-

Table 3. Linear and Nonlinear Measures of Heart Rate (HR) Dynamics of the First 24 Postoperative Hours

	All (n = 40)	Group A (n = 33)	Group B (n = 7)
ApEn	1.13 (1.15) ± 0.13 (0.77–1.32)	1.13 (1.15) ± 0.12 (0.83–1.31)	1.10 (1.13) ± 0.18 (0.77–1.32)
Poincaré plot			
SD1 (ms)	13 (9) ± 12 (4–73)	13 (8) ± 13 (5–73)	11 (8.7) ± 6 (4.4–18)
SD2 (ms)	26 (22) ± 14 (11–63)	27 (24) ± 13 (11–63)	20 (11) ± 14 (11–44)
SD1/SD2	0.54 (0.47) ± 0.25 (0.24–1.37)	0.50 (0.46) ± 0.22 (0.20–1.36)	0.70 (0.55) ± 0.34 (0.40–1.37)*
DFA			
α_1	0.83 (0.82) ± 0.18 (0.44–1.23)	0.85 (0.82) ± 0.17 (0.54–1.23)	0.69 (0.62) ± 0.18 (0.44–0.9)*
α_2	1.03 (1.1) ± 0.2 (0.52–1.40)	1.05 (1.1) ± 0.19 (0.52–1.41)	0.95 (0.88) ± 0.24 (0.64–1.22)
Time domain			
HR (beats/min)	89 (89) ± 12 (64–119)	87 (89) ± 10 (64–110)	99 (104) ± 15 (78–119)
SDNN (ms)	17 (14) ± 12 (7–69)	19 (14) ± 13 (7–69)	16 (13) ± 11 (7–34)
Frequency domain			
β-Slope	−1.4 (−1.4) ± 0.28 (−2.2–−0.8)	−1.4 (−1.4) ± 0.2 (−2.0–−0.8)	−1.6 (−1.6) ± 0.42 (−2.2–−0.87)
ULF (ms^2)	3,014 (1,765) ± 3,356 (269–15,450)	2,644 (1,888) ± 2,456 (311–10,152)	4,603 (1,419) ± 5,897 (269–15,450)
VLF (ms^2 × 10)	140 (87) ± 138 (7–604)	146 (84) ± 142 (16–604)	114 (96) ± 127 (7–365)
LF (ms^2 × 10)	142 (34) ± 300 (4–1,542)	145 (35) ± 322 (5–1,542)	124 (21) ± 177 (4–491)
HF (ms^2 × 10)	280 (45) ± 668 (8–3,008)	310 (36) ± 730 (10–3,008)	140 (54) ± 171 (8–483)

Results of all the patients and separately of Group A and B patients. Analyses of standard deviation of all R-R intervals (SDNN), R-R interval, low frequency (LF), high frequency (HF), approximate entropy (ApEn), and Poincaré plot were performed on 1,000-beat segments. Short-term (α_1) and intermediate-term (α_2) correlation properties (DFA) were performed in segments of 8,000 beats. Very low frequency of spectral power (VLF), ultra low frequency band (ULF), and scaling exponent of the power law relationship (β-slope) were analyzed in epochs of 24 h. Significance levels were tested with Mann-Whitney U test. Values are means (median) ± SD (range). Group A and B: Intensive care unit stay ≤ 48 h and > 48 h, respectively.

* $P < 0.05$ between groups A and B.

SD1 = instantaneous beat-to-beat heart rate variation; SD2 = continuous long-term heart rate variation.

term fractal-like correlation property α_1 and increased SD1-SD2 ratio) were observed in the majority of the patients after CABG surgery. Furthermore, the current results suggest that a more random and less fractal-like HR behavior is associated with complicated clinical course in this rather small sample size.

HRV has been conventionally analyzed by spectral and time domain measures, and consistent with the current findings, a reduction in overall HRV has been described after CABG.[1,2] However, the time and frequency domain measures did not differ between patients with normal and prolonged ICU stays. Concurrent with previous observations, the time and frequency domain measures did not correlate significantly with the different dynamic HRV measures after CABG surgery.[8,16,25]

Approximate entropy tended to increase after CABG, although this change was only marginally significant after Bonferroni correction. This finding is, however, supported by a previous study showing ApEn of HR dynamics to be increased (*i.e.*, regularity to be decreased) in patients with previous MI.[32] These findings are, however, inconsistent with other studies suggesting that decreased ApEn is related to pathologic conditions.[9,17,30] The normal range of ApEn seems to be quite narrow, and a deviation from normal (*i.e.*, a decrease or an increase) may be observed in various cardiovascular disorders.[32]

Analysis methods derived from nonlinear dynamics including chaos theory and fractals have provided a novel approach for studying and understanding the characteristics of dynamic phenomena.[33,34] The normal HR time series have been shown to be fractal-like because they display scale-invariant fluctuations over a wide range of time scales (*i.e.*, a subunit of RR-interval time series resemble the larger time scale). This indicates a long-range correlation between RR-intervals (*i.e.*, interbeat interval at every point is partially dependent on the intervals at all previous points). Therefore, change from scale-invariant behavior toward behavior resembling either random fluctuations (white noise) or highly predictable less complex Brownian noise-type behavior might be physiologically deleterious.[5,8,12–15,29] In this study, the scaling exponents α_1 and α_2 were chosen to measure short- and intermediate-term correlation properties of RR-interval data, respectively, and power-law slope β was chosen to describe the correlation properties of RR interval over VLF and ULF bands.[5,7,8,15] ApEn provides information on complexity in RR-interval dynamics. All these measures differ from time and frequency domain measures of HRV because they do not reflect the magnitude of variability, but rather the distribution of spectral characteristics and other features of HR behavior. We also used Poincaré plot analysis, which gives both visual and quantitative information on HR behavior. In this study, fractal-like dynamics with higher scaling exponent values (> 0.5) were observed in preoperative recordings of all of our patients. Completely random dynamics with α value of 0.5 were observed in some patients after CABG.

The pathophysiologic background for the occurrence of more random and complex short-term HR dynamics after CABG is speculative. A potential explanation for the abnormal short-term correlation properties of RR intervals could be the altered sympathovagal interaction after CABG. This concept was recently introduced by Tulppo *et al.*[35] High norepinephrine levels, often reported in patients after CABG,[36] may result in altered beat-to-beat RR-interval dynamics, possibly *via* accentuated sympathovagal interaction.[25,35] High norepinephrine levels have also been reported to be associated with random Poincaré plots in patients with heart failure.[26] Current results suggest that anesthesia itself did not cause the decreased fractal-like dynamics, because the short-term scaling exponent α_1 and the Poincaré plots did not recover during the study period of 2 days or 3 days in 14 patients, suggesting the possibility of a prolonged change of HR dynamics. The data from the third day is not shown because there was no change compared with other postoperative days.

Preoperative and postoperative β-blocker use and use of sympathomimetic inotropic medications were not related to the length of ICU stay. The use of β-blockers or vasoactive medications (inotropes and nitrates) had no influence on different HRV measures. ApEn was the only measure that showed significant difference between patients that had inotropes and those who had not; ApEn was significantly lower in patients who needed inotropes. These observations suggest minimal effects of these drugs on our results; additionally, there are some studies suggesting that β-blockers have no effect on the complexity of RR intervals and fractal-like HR dynamics.[1,9] In any case, the reduced short-term scaling exponent α_1 after CABG implies a temporary change of fractal-like stability of HR behavior in at least some patients after CABG.

It has been proposed that the 1/f system (see Appendix) might be a central organizing principle of normal physiologic function, and that loss of this scale-invariant organization occurs in cardiovascular disorders, which results in a less adaptable system and may be associated with adverse outcome.[11,12,29] This concept is supported by recent findings that altered correlation properties of RR intervals are associated with an increased risk of mortality in heart failure patients and vulnerability to life-threatening arrhythmias.[6,7] This is further supported by our observations that the majority of patients with long ICU stay had more decreased short-term correlation properties of RR intervals in the first postoperative 24 h compared with the patients without such problems.

Limitations

There are several limitations to this study that must be pointed out. First, this study had no control group of comorbid patients undergoing noncardiac major surgery to explore whether the perioperative change of fractal-like HR dynamics is specific for CABG. Second, our sample size was rather small, and the real predictive value, clinical utility, and significance in patient monitoring remains to be explored in larger patient groups. Clear independent predictors were, however, revealed in the multivariate analysis, suggesting strong associations. Third, pathophysiologic background of altered fractal-like HR behavior must be explored to find out if HR dynamics can be restored by any drug intervention in early phase to alter the postoperative course. Silent myocardial or sinus node damage caused by surgery or concomitant medication could explain the alterations in HR behavior. However, as stated previously, the use of inotropes did not seem to have an effect on the different HRV measures except for ApEn, and in the multivariate logistic model including a variety of possible confounding variables, scaling exponent α_1 had the best predictive value for prolonged ICU stay. Finally, the preoperative predictive value remains to be explored in considerably larger patient populations.

Conclusions

These observations suggest that patients with altered fractal-like HR dynamics are more likely to require prolonged ICU care. Furthermore, current results suggest that altered short-term dynamics analyzed by dynamic analysis methods may complement traditional HRV measurements and may help to identify patients who will have a complicated postoperative course.

Appendix

Definitions

Dynamic measures: term used for indices of heart rate variability that do not describe the magnitude of variability but rather the qualitative characteristics and correlation features of heart rate behavior (*e.g.*, approximate entropy [ApEn], short- and intermediate-term fractal-like scaling exponents [α_1 and α_2], the slope [β] of the power-law regression line of RR-interval dynamics, and Poincaré plot). These measures probe temporal or spatial properties not detectable by traditional measures.

Fractal: Initially, the term fractal was used to describe geometrical structures. Fractal structures or processes have a property by which where characteristic forms or fluctuations on a small scale of measurement are similar to those on a larger scale of measurement.

Fractals in heart rate variability: In the field of heart rate variability, the term "fractal-like" has been introduced to emphasize that the normal heart rate time series generated from long successive cardiac interbeat intervals resemble the fractal processes seen in geometric structures.

Linear system: A system in which the relation between input and output varies in a constant (linear) fashion. In a linear system, output equals input. The magnitude of their responses is proportionate to the strength of the stimuli.[33]

Nonlinear system: Any system in which the output is disproportionate to the input.[33]

1/f system or spectrum: In many diverse biologic processes, the power of the spectrum is distributed in an inversely proportional manner over the frequencies, implicating that the current value of the biologic signal (*e.g.*, RR interval of heart rate time series) correlates not only with its most recent value but also with the values at all previous points. This is characteristic of fractal-like HR dynamics. Waves of the ocean, the construction of lungs, and even music from Bach to Beethoven are examples of this 1/f fluctuation pattern. Fractal-like dynamics are a compromise between white (random) and Brownian noise, and contain both random and highly correlated characteristics in an RR-interval time series. Alterations in this construction principle have been shown in various pathologic conditions.

Time series: A series of numbers, each representative of the behavior of a system at particular points in time.[33]

Traditional HRV measures: a group of heart rate variability indices that have been used for decades and mainly reflect the magnitude of heart rate fluctuation (*e.g.*, time and frequency domain measures).[24]

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