

Effects of Beating- versus Arrested-Heart Revascularization on Cardiac Autonomic Regulation and Arrhythmias

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ABSTRACT

Background. Altered autonomic regulation after cardiac operations precipitates cardiac arrhythmias, affects repolarization, and increases the risk of sudden cardiac death. We sought to clarify how the 2 different techniques of coronary artery bypass grafting (CABG), namely conventional CABG using cardiopulmonary bypass (on-pump) and beating-heart CABG without cardiopulmonary bypass (off-pump), affect cardiac autonomic regulation and arrhythmic disturbances postoperatively.

Methods. We included 57 consecutive patients, 28 in the on-pump group and 29 in the off-pump group. The electrocardiographic recordings were performed on the preoperative day and the fourth, seventh, and twenty-eighth day after operation. Fifteen-minute digital recordings were taken; one channel was used to record electrocardiogram and the other breathing. Detailed analyses of arrhythmia, heart rate, and heart rate variability indices were performed on respective days to assess sympathetic and parasympathetic modulation of the heart and relate it to detected arrhythmic disturbances.

Results. Total power, low-frequency power, which indicates baroreceptor-mediated sympathetic modulation, and high-frequency power, indicating parasympathetic vagal modulation, declined significantly in both groups after CABG ($P < .001$); however, 7 days after CABG, total and high-frequency power were better preserved in the off-pump group. Mean RR interval was longer in the off-pump group at 7 ($P = .006$) and 28 days ($P = .008$) after surgery. The total incidence of arrhythmic events was higher in the on-pump group on the seventh day ($P = .017$, adjusted odds ratio = 8.6, 95% confidence interval 1.4-80.3).

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Conclusions. The results show profound impairment of cardiac autonomic regulation after CABG, showing better preserved cardiac autonomic modulation 7 days after beating-heart revascularization. Evidence suggests that slower restoration of heart rate and increased incidence of arrhythmic events after CABG using cardiopulmonary bypass are the result not only of impaired cardiac autonomic regulation but also of the involvement of additional factors of nonautonomic origin.

INTRODUCTION

Despite the implementation of revascularization techniques, which constantly improve outcomes by lowering the mortality and morbidity after coronary artery bypass procedures [Edwards 1997; Dewey 2004], a substantial number of patients after coronary artery bypass grafting (CABG) experience cardiac arrhythmias [Scharf 2001; Budeus 2006]. The risk of potentially fatal arrhythmia is higher in patients with poor ventricular function and even increases in the early postoperative period after surgical revascularization [Kaul 1998]. Factors already known to contribute to the onset of perioperative or postoperative arrhythmia include acute atrial changes, ischemia and perioperative myocardial infarction (MI), electrolyte disturbances, or cardiopulmonary bypass (CPB). Recent studies extended the list by adding altered catecholamine states, systemic inflammation, differential gene expression, and sympathovagal interaction [Kalman 1995; Chung 2000; Bittar 2005]. While cardiac electrical properties and structural remodeling have been thoroughly studied as critical pro-arrhythmic factors, much less emphasis has been put on the role and mode of cardiac autonomic regulation after cardiac operations.

Autonomic derangement has been proven to pose deleterious effects on the heart [Armour 1999]. By applying noninvasive advanced computer analyses on high-quality electrocardiographic recordings (ECG) it has been possible to infer information on the functional state of cardiac autonomic modulation and control of heart rate [Special Report 1996; Furlan 2001]. Heart rate variability (HRV) parameters such as total power, high-frequency power, low-frequency power, and their normalized counterparts quantify cardiac autonomic neural regulation and determine the levels of sympathetic and

parasympathetic modulation of the heart [Malliani 1991; Special Report 1996; Goldberger 2001; Zaza 2001; Verrier 2004]. Depressed HRV indicates cardiac autonomic dysfunction and independently predicts arrhythmic events and cardiac mortality [Lombardi 2001; Carpeggiani 2004].

Substantial depression of HRV has been shown to occur after CABG using CPB (on-pump) [Niemela 1992; Kuo 1999]. Moreover, the early postoperative profile of HRV changes and mode of cardiac autonomic modulation after beating-heart CABG without CPB (off-pump) has been described [Kalisnik 2006]. There has yet been no prospective comparative study conducted to evaluate cardiac autonomic modulation up to 4 weeks after off- and on-pump CABG. The autonomic derangement was not related to the occurrence of arrhythmic disturbances after each of the 2 different techniques of myocardial revascularization.

MATERIALS AND METHODS

The study was approved by the Slovenian State Medical Ethics Committee, based on the principles of the Declaration of Helsinki, Finland, and Oviedo Convention, Asturia, Spain.

Patients and Study Design

Fifty-seven consecutive patients with documented 3-vessel stable coronary artery disease (significant disease of all 3 arteries, stenosis $\geq 70\%$) who were referred for elective CABG were assigned alternatively to off- or on-pump CABG. Twenty-eight and 29 patients were entered into the study to form the on- and off-pump groups, respectively. All patients gave written informed consent prior to inclusion. Exclusion criteria were diabetes mellitus with late neurological impairment, coexisting valvular disease, permanent pacemaker, abnormal levels of creatinine preoperatively, atrial fibrillation/undulation or any rhythm other than sinus confirmed by ECG recordings, thyroid or systemic disease, malignancies, new MI within 6 months or postoperative MI, and the need for inotropic support, intra-aortic balloon pump, or endotracheal intubation lasting more than 24 hours after operation. Preoperative β -blocker and calcium channel blocker medication was continued postoperatively.

After CABG, we excluded 2 patients from the on-pump and 3 from the off-pump group because of sustained atrial fibrillation and/or other arrhythmia or ECG technical failure at the time of the recording. Two patients, one from each group, refused further cooperation on the fourth postoperative day; one (from the on-pump group) was excluded because of mental deterioration; 2 were excluded because of changed course of operation (one from the on-pump group because of iatrogenic aortic dissection at cannulation, and one from the off-pump group was converted to on-pump surgery because of intraoperatively reported massive mitral regurgitation); one patient from the on-pump group could not be managed without delayed inotropic and respiratory support; and one from the off-pump group suffered acute stroke, acute respiratory failure, and subsequent lethal pneumonia. Hence, ECG recordings from 45 patients were considered for arrhythmia and HRV analyses, 23 from the off- and 22 from the on-pump group (Figure 1).

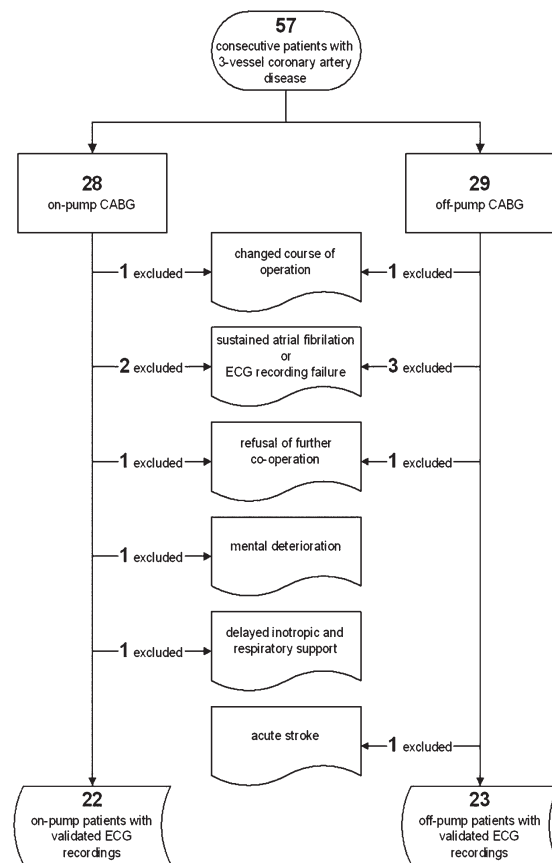


Figure 1. The diagram showing the path from all the included patients to the final sample.

Anesthetic Technique

The anesthetic technique has been standardized and was identical in both groups and has been described previously [Kalisnik 2006]. In both groups, induction was performed with remifentanyl and midazolam. For maintaining narcosis, propofol infusion was given at 3 mg/kg per hour. Neuromuscular blockade was achieved by pancuronium/vecuronium. Heparin was administered at a dose of 300 IU/kg in the on-pump group (target activated clotting time of ≥ 480 seconds) and 100 IU/kg (target activated clotting time between 250-350 seconds) in the off-pump group and antagonized with protamine sulphate to return activated clotting time to preoperative levels on completion of the procedures.

Operative Technique

On-pump operations were carried out using CPB (routine ascending aortic cannulation and double stage venous cannula into the right atrium) in mild hypothermia (34°C-36°C) and nonpulsatile perfusion mode (50-60 mmHg perfusion pressure and a flow rate of 2.4 L/m² per minute). Myocardial protection was achieved by using intermittent antegrade and

retrograde hyperkalemic cold blood (4°C) cardioplegia. After declamping, 5 patients required one countershock to terminate ventricular fibrillation, the remaining 23 in the on-pump group restored sinus rhythm spontaneously. Weaning from CPB was uneventful in all patients.

Off-pump operations were performed by insertion of a traction suture in the posterior pericardium [De Carvalho Lima 2002] and was followed by the application of a commercially available mechanical stabilizer. For antegrade blood control, a pledget-armed tourniquet was applied to the target vessel proximal to the anastomotic site. For all anastomoses, 7/0 or 8/0 monofilament sutures were used. During the operation, all patients received aprotinin at a dose of 2 million units. In off-pump patients, blood was conserved using cell saver; in on-pump patients, all the contents of the CPB circuit were retransfused at the end of the operation.

Postoperative Management, Monitoring, and Definitions

After surgery, patients were transferred to the intensive care unit and ventilated with 40% oxygen with volume-controlled ventilation and a tidal volume of 10 mL/kg with 5 cm H₂O of positive end-expiratory pressure. To maintain PaO₂ at 80 to 100 mmHg and PaCO₂ at 35 to 40 mmHg, adjustments were made according to routine blood gas analyses. Patients were extubated as they met the following criteria: hemodynamic stability, no excessive bleeding (<80 mL/h), normothermia, and consciousness with pain control. Fluid management after surgery consisted of 5% glucose or normal saline infused at 1 mL/kg per hour, with additional colloid solution, fresh frozen plasma, or concentrated red blood cell transfusion to maintain normovolemia and hematocrit >24%. Potassium and magnesium deficiency were promptly treated as necessary to maintain electrolyte balance within the normal range.

Heart rate and rhythm were continuously monitored and displayed on a screen with an automated arrhythmia detector (HP 1205A; Hewlett-Packard, Andover, MA, USA). Twelve-lead ECG recordings were performed before operation, daily from the fourth to the seventh postoperative day, and at any other time on the basis of any clinical suspicion of arrhythmia. Arrhythmia was registered positive if any of the above events appeared; supraventricular rhythm disturbances were documented as atrial premature beats, fibrillation, flutter, or tachycardia, whereby we distinguished sinus tachycardia from atrial ectopic tachycardia by P wave morphology analysis [Kalman 1995]. Ventricular arrhythmias were classified either as complex (estimated more than 30 ventricular ectopic beats/hour, multifocal, and/or repetitive ectopic beats) or simple (unifocal ventricular ectopic beats less than 30/hour) [Huikuri 1990]. The criterion for both supraventricular and ventricular tachycardia was at least 3 abnormal complexes in sequence with a rate exceeding 100/minute.

Postoperative diagnosis of MI was based on at least one of the following criteria: new Q waves of >0.04 ms and/or reduction in R waves >25% in ≥2 leads, a ratio of peak creatine kinase (CK)-MB/peak total CK ≥10%, or CK-MB 5-fold upper limit for normal. Arterial hypertension was

diagnosed in patients with concurrent antihypertensive therapy and in patients with systolic arterial pressure >140 mmHg and/or diastolic arterial pressure >90 mmHg at admission.

Digital ECG and Breathing Measurements

Ten-minute simultaneous ECG and breathing were recorded under resting conditions between 3:00 PM and 6:00 PM on the preoperative day and the fourth, seventh, and twenty-eighth day after operation while the patient was in a postprandial state. The subjects were requested not to smoke or drink any caffeinated beverages 24 hours prior to measurements, which were performed each time in a quiet room at the department after 10-minute nondormant supine rest to allow for hemodynamic stabilization. A digital recorder (Intekom, Ljubljana, Slovenia) with the sampling rate of 450 Hz on 2 channels was used. The ECG was recorded by self-adhesive Ag-AgCl disk electrodes in bipolar CM₅ lead with a resolution of 5 μV. Respiratory waveforms were recorded on the second channel using a custom-designed nose temperature probe (thermistor 10K3MCD1; Betatherm, Shrewsbury, MA, USA) with a resolution of 0.03°C.

Analysis of HRV and Respiratory Frequency

Both ECG and respiratory signals were analyzed offline. Noise was reduced from the ECG by a digital low-pass filter with a cut-off frequency of 40 Hz. Baseline wander was removed by linear correction. An automated computer-based R-wave peak detection algorithm was used to find the RR intervals. Data were manually inspected and 5-minute segments stored for computation of HRV parameters. Irregularities in RR intervals resulting from ectopic beats or sinus pause were replaced by the preceding intervals. A measurement was disregarded if percentage of replacements exceeded 5%. RR intervals were resampled (4 Hz) by linear interpolation [Special Report 1996]. Spectral power analysis was performed with discrete Fourier transform on linearly detrended segments comprising 1200 data points. The sum of spectral components within the frequency range from 0.01 to 0.40 Hz was defined as total power. The areas of spectral peaks in the subranges 0.01-0.04 Hz, 0.04-0.15 Hz, and 0.15-0.40 Hz were defined as very low-frequency power, low-frequency power indicating modulated sympathetic activity and high-frequency power indicating vagal modulation [Special Report 1996]. High-frequency power relates to efferent vagus activity and increases in the states of heightened vagal tone, but it can be abolished by atropine administration. Conversely, sympathetic activation results in the increase of the low-frequency component and can be abolished by β-adrenergic blockade [Koh 1994; Eckberg 1997]. Normalized low-frequency power and normalized high-frequency power were defined as power/(total power – very low-frequency power) as previously defined [Special Report 1996]. The average respiratory frequency was determined from the corresponding 5-minute segments.

Statistical analysis. Descriptive statistics were calculated for all the studied parameters (numerical variables are reported as mean ± standard deviation, while categorical variables are reported as frequency and percentage). Because of their

right-skewed distribution, the majority of HRV parameters were log-transformed to allow for parametric statistical analysis. Group differences were tested bivariate using the *t* test for numeric variables and the Fisher exact test for categorical variables. The overall incidence of arrhythmias was compared between days using the exact McNemar test for dependent proportions. The independent influence of CABG technique on postoperative arrhythmia was tested by means of exact logistic regression, controlling for preoperative arrhythmia, use of β -blockers postoperatively, reduced left ventricular ejection fraction (LVEF; <40%), and number of conduits performed. To assess the influence of the technique on individual ECG parameters while adjusting for the number of conduits performed and use of β -blockers, multiple linear regression was used. To analyze the time-course of ECG parameters and possible differences between the 2 operative techniques, 2-way mixed-model analysis of variance was used (with Greenhouse-Geisser correction when needed), whereby simple within-subject contrasts were used to test postoperative means against preoperative values. Statistical analyses were performed using SPSS for Windows 11.0 (Chicago, IL, USA) and LogXact-4 (Cytel Software, Cambridge, MA, USA). Statistical significance was set at $P < .05$.

RESULTS

Patients

Among 57 patients enrolled, 45 (79%) patients fulfilled clinical and technical criteria for subsequent analyses. No differences regarding age, gender, severity of coronary artery disease, previous MI, hypertension, diabetes mellitus, dyslipidemia, LVEF, or estimated risk by EuroSCORE were found between the off- and on-pump groups (Table 1). The mean CPB and aortic cross-clamp times in the on-pump group were 93 ± 20 minutes and 64 ± 19 minutes, respectively, whereby no significant difference in the mean aortic

cross-clamp time for the preoperative arrhythmia/nonarrhythmia on-pump subgroup (60 ± 16 minutes versus 67 ± 21 minutes, respectively) could be observed. The average number of bypasses was significantly higher in the on-pump group (3.8 ± 0.8 versus 3.0 ± 0.6 ; $P < .001$). Somewhat higher use of β -blockers was found postoperatively in the off-pump group (70% versus 41%; $P = .075$). Hence, the number of conduits performed and use of β -blockers were controlled for in the subsequent regression analyses to eliminate potential confounding effects.

Arrhythmia

The arrhythmic events were analyzed postoperatively only in patients who had presented with stable sinus rhythm preoperatively (Table 2). No difference between groups regarding the occurrence of arrhythmias was found before the operation ($P = .823$). Pairwise comparisons of incidence of arrhythmic events with exact McNemar's test indicate that the arrhythmic events occur most frequently between day 4 and 7 and significantly decline 4 weeks after operation.

Significant influence of CABG technique on arrhythmia after adjusting for the number of conduits, use of β -blockers, LVEF, and preoperative arrhythmia was found on day 7 (exact logistic regression, $P = .017$), whereby the odds of a patient from the on-pump group developing an arrhythmic disturbance one week after operation were about 8 times higher than those of a comparable patient from the off-pump group (odds ratio = 8.5, 95% confidence interval 1.4-80.3). Occurrence of arrhythmia on day 4 and day 28 was significantly influenced by preoperative arrhythmia ($P = .036$ and $.022$, respectively).

Heart Rate and the Respiration Rate in Off- and On-Pump CABG

The RR interval shortened and the respiration rate increased after CABG in both groups ($P < .001$). Comparing

Table 1. Patient Characteristics*

| | On-Pump CABG (n = 22) | Off-Pump CABG (n = 23) | P Value for Difference between Groups |
|--|-----------------------|------------------------|---------------------------------------|
| Age, y | 62 ± 8 | 63 ± 9 | .656 |
| Male gender | 18 (78%) | 20 (87%) | .699 |
| Previous myocardial infarction | 10 (45%) | 11 (48%) | 1.000 |
| Hypertension | 16 (70%) | 21 (91%) | .135 |
| Diabetes mellitus | 5 (23%) | 4 (17%) | .722 |
| Dyslipidemia | 19 (86%) | 17 (74%) | .698 |
| Left ventricular ejection fraction, % | 53 ± 11 | 57 ± 12 | .359 |
| EuroSCORE | 3.3 ± 2.2 | 3.0 ± 2.0 | .661 |
| Grafts performed | 3.8 ± 0.8 | 3.0 ± 0.6 | <.001 |
| Medication, preoperatively/postoperatively | | | |
| β -blocker | 13 (59%)/9 (41%) | 13 (57%)/16 (70%) | 1.000/.075 |
| Calcium antagonist | 4 (18%)/3 (14%) | 2 (9%)/2 (9%) | .414/.665 |
| Nitrates | 12 (55%)/4 (18%) | 7 (30%)/1 (4%) | .136/.187 |
| ACE inhibitor | 13 (59%)/8 (36%) | 10 (43%)/7 (30%) | .376/.758 |

*Numeric variables are reported as mean ± standard deviation; categorical variables are reported as frequency and percentage; P values are from independent samples *t* test or the Fisher exact test. CABG indicates coronary artery bypass grafting; ACE, angiotensin-converting enzyme.

Table 2. Incidence of Arrhythmias*

| | On-Pump | Off-Pump | CABG | P | | | |
|-----------------------------|----------|----------|-------|-------------------------|--------|-------------------|--------|
| | | | | Preoperative Arrhythmia | Grafts | β -Blockers | EF <40 |
| Before CABG | 5 (23%) | 5 (22%) | .642 | DV | .272 | .102 | .823 |
| After 4 days | 12 (54%) | 8 (35%) | .375 | .036 | 1.000 | 1.000 | 1.000 |
| Atrial tachycardia | 3 (14%) | 2 (9%) | 1.000 | 1.000 | .529 | .656 | .985 |
| Atrial premature beats | 5 (23%) | 6 (26%) | 1.000 | .155 | .882 | 1.000 | 1.000 |
| Ventricular premature beats | 7 (32%) | 3 (13%) | .358 | .115 | .959 | .988 | .630 |
| After 1 week | 12 (54%) | 3 (13%) | .017 | .316 | .904 | .386 | 1.000 |
| Atrial tachycardia | 5 (23%) | 0 (0%) | .086 | 1.000 | 1.000 | 1.000 | 1.000 |
| Atrial premature beats | 5 (23%) | 1 (4%) | .264 | .837 | 1.000 | 1.000 | 1.000 |
| Ventricular premature beats | 6 (27%) | 2 (9%) | .288 | .127 | .679 | .686 | .924 |
| After 4 weeks | 6 (27%) | 1 (4%) | .210 | .022 | 1.000 | .713 | 1.000 |
| Atrial tachycardia | 0 (0%) | 0 (0%) | NA | NA | NA | NA | NA |
| Atrial premature beats | 2 (9%) | 0 (0%) | .800 | .800 | .667 | 1.000 | NA |
| Ventricular premature beats | 4 (18%) | 1 (4%) | .667 | .116 | .945 | .363 | 1.000 |

*P values from exact logistic regression. CABG indicates coronary artery bypass grafting; EF, left ventricular ejection fraction; DV, variable included in the model as outcome rather than as predictor; NA, not applicable since no arrhythmic events were observed.

the off- to on-pump groups, longer mean RR intervals were observed in the off-pump group one and 4 weeks after the operation ($P = .006$ and $.008$, respectively; Figure 2), whereby there was no significant effect of the number of bypasses and the use of β -blockers. Respiration rate remained elevated on the seventh day and normalized with respect to preoperative values 4 weeks after operation in both groups (Table 3); no differences were observed in respiration rates on either day regarding CABG technique.

Time Course of HRV Parameters in Off- and On-Pump CABG

After the operation, HRV declined significantly in all frequency bands in the off- and on-pump groups (Table 3). The spectral indices remained depressed consistently in both groups also on the seventh day and 4 weeks after the operation ($P < .001$; Figure 3). Total power and high-frequency power in the on-pump group on the seventh postoperative day were significantly smaller than in the off-pump group. With regard to the normalized low-frequency power and high-frequency power and the low-frequency power-to-high-frequency power ratio, no significant changes could be observed on each respective day, either comparing with preoperative levels or comparing the off- to on-pump groups (Table 3). Hence, regardless of the type of CABG, there was no restoration of HRV even 4 weeks after the procedure.

DISCUSSION

Faster heart rates reflect increased sympathetic tone and/or decreased parasympathetic tone altering the propensity to cardiac arrhythmias. They have been associated with higher

risk for sudden and nonsudden cardiac death [Abildstrom 2003]. Heart rate has been identified as an independent predictor of atrial fibrillation after CABG, whereby elevated norepinephrine levels with concomitant increase in heart rate importantly contribute to the precipitation of arrhythmias after CABG [Kalman 1995; Hogue 1998]. In harmony with these findings, faster heart rates in patients after CABG imply excessive adrenergic activation. Moreover, our data shows

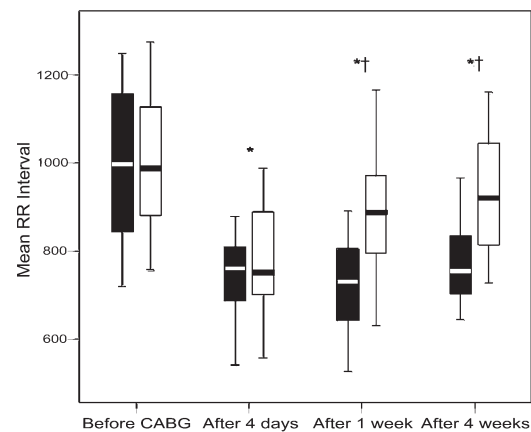


Figure 2. Time course of mean RR interval in on- versus off-pump coronary artery bypass grafting. * $P < .05$ for contrast with baseline. † $P < .05$ for difference between groups. Horizontal line denotes median, box denotes first 1st and 3rd quartile, whiskers denote 1st and 9th decile, filled boxes for on-pump group, empty boxes for off-pump group.

Table 3. Summary of Statistical Analyses for Heart Rate Variability Parameters and Respiration Rate*

| | On-Pump CABG | Off-Pump CABG | P |
|--|---------------|----------------|------|
| Total power, ms ² | | | |
| Before CABG | 797.7 ± 835.9 | 778.9 ± 1228.5 | .634 |
| After 4 days | 158.9 ± 168.7 | 148.0 ± 94.8 | .973 |
| After 1 week | 90.9 ± 123.3 | 191.1 ± 167.6 | .024 |
| After 4 weeks | 184.3 ± 235.7 | 291.0 ± 347.4 | .384 |
| Low-frequency power, ms ² † | | | |
| Before CABG | 217.3 ± 255.8 | 272.1 ± 573.4 | .605 |
| After 4 days‡ | 43.7 ± 56.1 | 42.4 ± 37.5 | .743 |
| After 1 week‡ | 20.9 ± 23.4 | 38.4 ± 37.2 | .138 |
| After 4 weeks‡ | 37.6 ± 41.0 | 92.7 ± 109.6 | .268 |
| High-frequency power, ms ² † | | | |
| Before CABG | 220.7 ± 285.8 | 255.3 ± 529.5 | .458 |
| After 4 days‡ | 40.0 ± 58.8 | 33.0 ± 35.0 | .853 |
| After 1 week‡ | 15.8 ± 19.0 | 49.8 ± 73.6 | .015 |
| After 4 weeks‡ | 69.4 ± 126.4 | 79.3 ± 170.0 | .619 |
| Normalized low-frequency power, nu | | | |
| Before CABG | 50.0 ± 19.6 | 57.3 ± 24.4 | .408 |
| After 4 days | 54.1 ± 22.1 | 60.3 ± 20.9 | .458 |
| After 1 week | 56.9 ± 28.0 | 49.9 ± 27.0 | .267 |
| After 4 weeks | 53.5 ± 22.4 | 58.7 ± 22.4 | .401 |
| Normalized high-frequency power, nu | | | |
| Before CABG | 50.0 ± 19.6 | 42.7 ± 24.4 | .568 |
| After 4 days | 45.9 ± 22.1 | 39.7 ± 20.9 | .476 |
| After 1 week | 43.1 ± 28.0 | 50.1 ± 27.0 | .392 |
| After 4 weeks | 46.5 ± 22.4 | 41.3 ± 22.4 | .500 |
| Low-frequency/high-frequency power ratio, nu | | | |
| Before CABG | 1.5 ± 1.5 | 2.5 ± 2.8 | .698 |
| After 4 days | 2.0 ± 1.8 | 2.4 ± 2.0 | .539 |
| After 1 week | 2.8 ± 2.9 | 2.4 ± 3.9 | .351 |
| After 4 weeks | 1.8 ± 1.7 | 2.2 ± 1.8 | .529 |
| Respiration rate, breaths/min† | | | |
| Before CABG | 16.6 ± 3.5 | 17.0 ± 3.9 | .428 |
| After 4 days‡ | 20.4 ± 3.7 | 22.3 ± 4.0 | .496 |
| After 1 week‡ | 20.5 ± 3.7 | 22.1 ± 2.1 | .107 |
| After 4 weeks | 19.1 ± 4.3 | 18.7 ± 2.3 | .840 |

*Numeric variables are reported as mean ± standard deviation. CABG indicates coronary artery bypass grafting; nu, normalized unit.

†Statistically significant effect ($P < .001$) of time in 2-way mixed analysis of variance (the time group interaction effect was not significant for any heart rate variability parameter).

‡Statistically significant contrast with preoperative mean (contrasts were tested if the time effect was significant); P value for group comparison is from multiple regression model controlling for the number of bypasses performed and β -blocker use (in both cases where $P < .05$, regression coefficient for off-pump versus on-pump was positive and standardized regression coefficient was about 0.45).

that humoral adrenergic response as assessed from RR dynamics is more pronounced and persists after on-pump CABG longer than after off-pump CABG.

The previous studies of HRV showed reduction of total power, low-frequency, and high-frequency spectral powers after CABG and attributed this to reduced vagal modulation with no or partial restoration of all parameters after CABG [Niemela 1992; Kuo 1999]. Some of the HRV measures have well-defined limitations, the absolute high-frequency and low-frequency powers proved better indicators of sympathovagal modulation than normalized high-frequency

and low-frequency powers in the setting of excessive adrenergic tone [Special Report 1996; Eckberg 1997]. Our data indicating increased adrenergic activation after on- and off-pump CABG again justify the concerns raised when interpreting short-term HRV measures in the clinical setting. Significantly higher values of total power and high-frequency power 7 days after surgery might indicate impaired but still better preserved cardiac autonomic modulation following beating-heart CABG. Nevertheless, after 4 weeks, low-frequency/high-frequency ratio, normalized high-frequency and normalized low-frequency did not differ

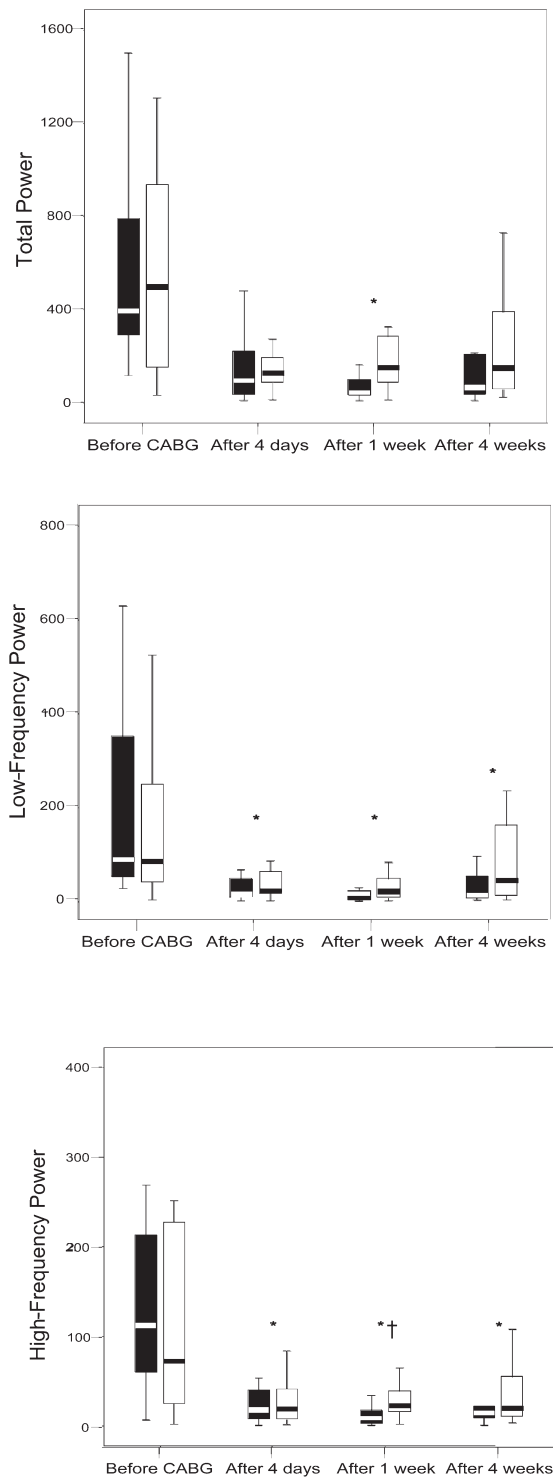


Figure 3. Time course of absolute values of the total frequency power, low-frequency, and high-frequency spectrum component in off- versus on-pump coronary artery bypass grafting. * $P < .05$ for contrast with baseline. † $P < .05$ for difference between groups. Horizontal line denotes median, box denotes 1st and 3rd quartile, whiskers denote 1st and 9th decile, filled boxes for on-pump group, empty boxes for off-pump group.

between study groups. Consistently, similarly reduced total power, high-frequency, and low-frequency absolute powers after both on- and off-pump CABG after 4 weeks suggest equivalent levels of autonomic derangement, possibly resulting in comparable potency of autonomic triggers after on- and off-pump CABG. Importantly, the latter implies that inadequate intraoperative myocardial protection, mechanical injury to the vagus nerve or sinus node, and central nervous system microembolisms caused by CPB might not be regarded as major determinants of the observed cardiac autonomic derangement after CABG. For the first time, we show that similarly attenuated autonomic modulation of heart rate occurs not only at procedures necessitating atrial incision(s) [Tuinenburg 2005] but also in the absence of any atrial incision, as is the case in beating-heart CABG.

Increased sympathetic activation and surgically induced catecholamine release can cause postoperative supraventricular arrhythmias [Kalman 1996]. Ventricular arrhythmias after CABG similarly occur because of re-entry mechanisms, being enhanced by increased sympathetic tone [Stein 1998]. The similar levels of cardiac autonomous nervous impairment 4 weeks after on- and off-pump CABG in our study indicate that it is not the varying potency of autonomic triggers accounting for higher heart rate and incidence of arrhythmic disturbances observed after on-pump CABG. In particular, higher heart rates in the absence of any significant change of the high-frequency power and low-frequency/high-frequency ratio differences speak in favor of an altered “substrate” in the on-pump group. Interestingly, the differences between on- and off-pump CABG remain significant after controlling for the possible beneficial effects of β -blockers [Aronson 2001; Salamon 2003]. The evidence from this study is in accord with the postoperative re-entrant arrhythmia model of an appropriately timed trigger that interacts with a fixed substrate [Zipes 2003] and with the very recent observation that CPB per se results in direct damage to the heart [Rastan 2005]. Moreover, the data suggest that changing the properties of a “substrate” owing to hyperadrenergic and excessive humoral activation [Bruins 1997] after CABG predominates over the autonomic trigger of vagal withdrawal in the acute phase after CABG. Further supporting this view, the incidence of arrhythmic disturbances 4 weeks after CABG returned to preoperative levels in the lack of any significant restoration of cardiac autonomic modulation. However, it remains unclear whether hyperadrenergic activation alone or serving as a prerequisite followed by subsequent variations of vagal tone [Hogue 1998] precipitates the arrhythmias in posts ischemic myocardium after CABG.

Potential Limitations of the Study

The evidence relating the severity of coronary artery disease to the depression of HRV is inconsistent [Hayano 1990; Huikuri 1994]. Although we did not observe any differences either in patient demographics data or in HRV measures, a greater number of conduits performed could hypothetically be the consequence of more extensive disease in the on-pump group. However, adjustment for the number of bypasses in our statistical design ruled this factor out as a possible underlying cause of the observed differences.

Significant increase of respiration rate after CABG could hypothetically reduce HRV spectra on the fourth and seventh day postoperatively, yet HRV remained depressed despite normalized respiratory rate 4 weeks after CABG, suggesting the HRV dynamics after CABG are not merely a consequence of changing respiratory rates. Moreover, the system gain remains low with increasing respiratory rate in gain-frequency response plots for both low-frequency and high-frequency components in the range between 15 and 25 breaths/minute [Brown 1993]. As shown in Table 3, the respiratory rates varied from 17 to 22 breaths/minute, and did not differ between on- and off-pump groups on any day. Thus, the observed HRV changes cannot be explained by altered breathing.

In our study, more off-pump patients received β -blockers after operation. The latter might influence heart rate and the incidence of arrhythmic disturbances after cardiac surgery [Aronson 2001; Crystal 2002]. Nevertheless, adjusting for postoperative β -blockers did not influence the results obtained, and neither did HRV indices vary among the study groups 4 weeks after the surgery, suggesting that alleging bias due to β -blockers seems unfounded.

Conclusions and Implications

The observations of the present study are confined to the subset of patients with well-preserved left ventricular function, sinus rhythm, and atrial/ventricular ectopy not exceeding 5% of the 10-minute ECG recordings. They support the view of similar cardiac autonomic derangement after CABG but better tolerance of the autonomic disturbances in the off-pump CABG. It is at present not known if the latter also reflects weaker "arrhythmic substrate" after off-pump CABG. Arrhythmic substrate is intensified by left ventricular deterioration [Zipes 2003], so the effects of either CABG technique potentially altering cardiac autonomous regulation and myocardial properties remain to be addressed, particularly in patients with severely depressed LVEF.

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