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Ventricular Repolarization Dynamicity and Arrhythmic Disturbances after Beating-Heart and Arrested-Heart Revascularization

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ABSTRACT

Background: Arrhythmias attributable to altered autonomic modulation of the heart, with elevated sympathetic and depressed vagal modulation, occur to a similar extent after surgery performed on beating or arrested hearts. Coronary artery bypass grafting (CABG) with cardiopulmonary bypass has been associated with more frequent occurrence of arrhythmic events than surgery performed without CABG, even with comparable levels of postoperative cardiac autonomic (dis) regulation after arrested- and beating-heart revascularization. We explored the effects of arrested- and beating-heart revascularization procedures on the dynamics of ventricular repolarization and on increased postoperative arrhythmic events.

Methods: Study participants included 57 CABG patients; 28 underwent on-pump and 29 underwent off-pump procedures. The 2 groups were comparable regarding clinical and postoperative characteristics. With high-quality 15-minute digital electrocardiograms, we assessed ventricular repolarization dynamics using RR and QT intervals and analyzed QT variability (QTV) and QT-RR interdependence. RR and QT intervals were determined from stationary 5-minute segments. QT-interval variability was determined by a T-wave template-matching algorithm. We used linear regression to compute the slope/correlation of the QT/RR interval. The Fisher exact test, nonpaired *t*-test, and ANOVA were applied to test the results; $P < .05$ was considered significant.

Results: Postoperative arrhythmic events were significantly more frequent in both groups. One week postoperatively these events were significantly more frequent in the on-pump group. In both groups, the RR interval was shorter after CABG ($P < .001$). The QT variability index increased from -1.2 ± 0.6 to -0.8 ± 0.4 after off-pump CABG and from -1.3 ± 0.5 to -0.5 ± 0.6 on day 4 after surgery ($P < .05$), further deteriorating to -0.2 ± 0.6 one week after CABG in the on-pump group only ($P < .05$). QT-RR correlations decreased from 0.39 to 0.24 in the off-pump vs 0.34 to 0.17 in the on-pump group ($P < .05$), and in both groups they remained significantly reduced for as long as 4 weeks after CABG.

Conclusions: For both on- and off-pump CABG, beat-to-beat heart-rate changes and rate-dependent ventricular repolarization adaptation showed disparities that worsened after surgery. The observed repolarization lability after CABG procedures seems to be transient but more pronounced after on-pump CABG. The association of arrhythmic events with ventricular repolarization lability changes in the setting of faster heart rates offers novel insights into the mechanisms of perioperative proarrhythmia after beating- and arrested-heart revascularization.

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INTRODUCTION

Arrhythmia occurs in up to 65% of patients undergoing cardiac surgery. The occurrence of arrhythmia varies according to patient profile, type of surgery, and arrhythmia surveillance and definition, but further investigation is needed to elucidate the underlying mechanisms of arrhythmia and to increase the effectiveness of prevention and treatment. Cardiac arrhythmias in the early postoperative period contribute significantly to perioperative mortality and morbidity, and various factors such as cardiac autonomic modulation, systemic humoral activation, inflammation, and genetic predisposition may play a role in triggering, sustaining, terminating, or preventing arrhythmias after cardiac surgery. Exact mechanisms and proarrhythmic factors, however, have not been fully recognized or explained [Kalman 1995; Chung 2000; Maisel 2001; Crystal 2002; Taylor 2002].

Cardiac autonomic derangement has deleterious effects on the heart, including impaired sympathovagal interaction reflecting sympathoadrenergic predominance in the early postoperative period after coronary artery bypass grafting (CABG) [Niemela 1992; Kalman 1995; Kalisnik 2007]. Development of arrhythmias is favored by increased inhomogeneity of ventricular repolarization, which may be associated with sudden cardiac death in coronary heart disease, myocardial infarction, congestive heart failure, and hypertrophic cardiomyopathy [Verrier 2004; Zareba 2005]. Recent studies of QT interval variability and dynamic assessment of the QT/RR relationship have revealed less tight coupling between the QT and RR interval in diseased hearts. The resulting decreased electrical integrity has been proposed to play a role in enhancing arrhythmic risk in patients with severe chronic heart failure, coronary artery disease, dilated myocardiopathy, or unstable angina pectoris [Berger 1997; Faber 2003].

We have shown that apart from significant impairment of cardiac autonomic regulation after CABG, regardless of the technique used [Kalisnik 2007], altered repolarization and increased uncoupling between RR and QT intervals occurs after off-pump CABG [Kalisnik 2006]. In the present study we investigated ventricular repolarization and the QT/RR relationship after beating- and arrested-heart 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 the Oviedo Convention, Asturia, Spain.

Patients and Study Design

To further explore the complex mechanisms of arrhythmia and avoid any potentially unrecognized confounding factors, we investigated QT dynamicity properties in a group of patients who had undergone on-pump or off-pump CABG and who had already been assessed for postoperative cardiac autonomic sympathetic and parasympathetic modulation [Kalisnik 2007]. The previous investigation in this group of patients allowed us to better correlate and understand the concomitant changes observed in the present study. Briefly, 57 consecutive patients with documented 3-vessel stable coronary artery disease (significant disease of all 3 arteries with stenosis ≥70%) who underwent elective CABG were assigned alternatively to off- (n = 29) or on-pump (n = 28) CABG. All study patients gave signed informed consent. Special care was taken to adhere to exclusion criteria: diabetes mellitus with late neurological impairment, coexisting valvular disease, permanent pacemaker, abnormal preoperative creatinine levels, atrial fibrillation/undulation or any rhythm other than sinus confirmed by 12-lead electrocardiographic (ECG) recordings, thyroid or systemic disease, malignancies, new myocardial infarction (MI) within 6 months or postoperative MI, or the need for inotropic support, intraaortic balloon pump, or endotracheal intubation lasting more than 24 hours after surgery. Preoperative β-blocker and calcium-channel blocker medication was continued postoperatively. Some patients were later excluded from the study for the following reasons: 2 patients from the on-pump and 3 from the off-pump group were excluded because sustained atrial fibrillation and/or other arrhythmia or technical failure of the ECG recording occurred after CABG; 2 patients refused further cooperation; 1 patient suffered mental deterioration; 2 patients required changes in surgical procedures (in 1 of these patients, from the on-pump group, iatrogenic aortic dissection occurred at cannulation, and in the other patient, from the off-pump group, conversion to on-pump surgery was necessary because massive mitral regurgitation was diagnosed intraoperatively by transesophageal echocardiography); 1 patient, from the on-pump group, required delayed inotropic and respiratory support; and 1 patient, from the off-pump group, suffered acute stroke, acute respiratory failure, and subsequent lethal pneumonia. Hence, ECG recordings from 45 patients were available for subsequent arrhythmia and QT dynamicity analyses, 23 from the off-pump and 22 from on-pump group, as summarized in Figure 1.

Anesthetic Technique

In both groups we used an identical standardized anesthetic technique that has been described in detail previously [Kalisnik 2006; Kalisnik 2007]. In both groups, induction was performed with remifentanyl and midazolam.

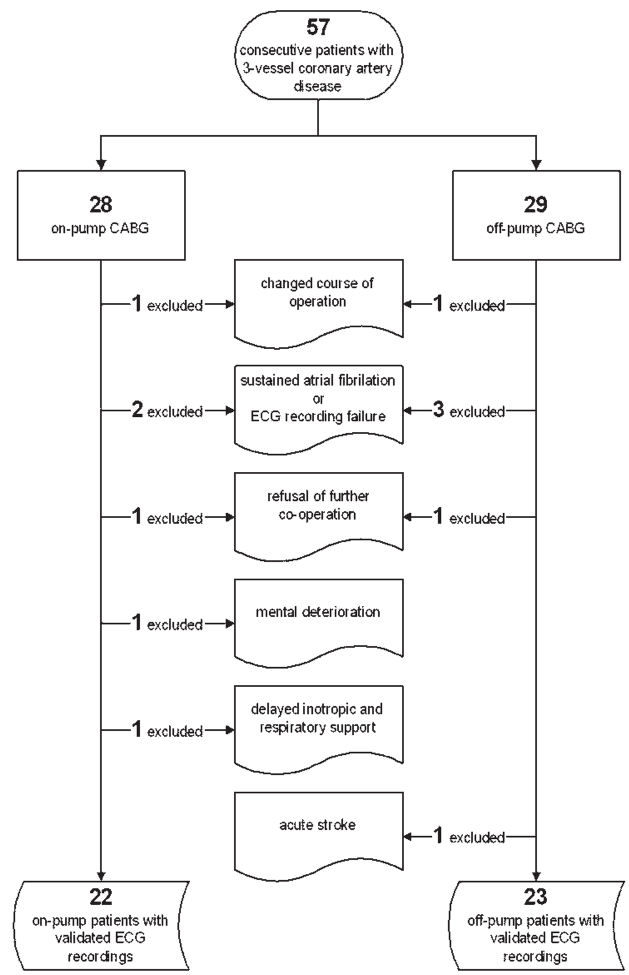

Figure 1. Path from all included patients to the final sample.

For maintaining of narcosis, a 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 of 250-350 seconds) in the off-pump group and antagonized with protamine sulphate to return activated clotting time to preoperative levels after completion of the surgical procedures.

Operative Technique

Surgical technique was described in previous studies [Kalisnik 2006; Kalisnik 2007]. In short, on-pump operations were carried out using cardiopulmonary bypass (CPB) (routine ascending aortic cannulation and double-stage venous cannula into the right atrium) with mild hypothermia (34°C-36°C) and nonpulsatile perfusion mode (50-60 mmHg perfusion pressure and flow rate of 2.4 L/m^2 per minute). Myocardial protection was achieved by using intermittent antegrade and retrograde hyperkalemic cold blood (4°C) cardioplegia. After declamping, 5 patients required 1 countershock to terminate ventricular fibrillation; in the remaining 23 patients in the on-pump group sinus rhythm resumed 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 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. In off-pump patients, blood was conserved using a 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 H_2O of positive end-expiratory pressure. To maintain PaO_2 at 80-100 mmHg and $PaCO_2$ at 35-40 mmHg, adjustments were made according to routine blood gas analyses. Patients were extubated when 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 deficiencies 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 surgery, daily from postoperative days 4 to 7, and at the time of any clinical suspicion of arrhythmia. Arrhythmia was registered positive for any of these events: supraventricular rhythm disturbances were documented as atrial premature beats; fibrillation, flutter, or tachycardia, for which 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/min.

Criteria for postoperative diagnosis of MI were: new Q waves of >0.04 milliseconds 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 greater than the upper limit for normal. Diagnosis of arterial hypertension was assigned to patients with concurrent antihypertensive therapy and in patients with systolic arterial pressure >140 mmHg, and/or diastolic arterial pressure >90 mm Hg at admission.

Digital ECG Measurements, QT Dynamicity Assessment

ECG recordings. Simultaneous ECG and breathing were recorded for 10 minutes while patients were resting in a postprandial state between 3:00 and 6:00 PM on preoperative day 1 and postoperative days 4, 7, and 28. The subjects were requested not to smoke or drink any caffeinated beverages 24 hours prior to measurements, which were performed in a quiet room at the cardiac surgery department after 10-minutes of nondormant supine rest to allow for hemodynamic stabilization. A 2-channel digital recorder (Intekom, Ljubljana, Slovenia) with a sampling rate of 450 Hz on both channels was used. The ECG was recorded by self-adhesive Ag-AgCl disk electrodes in bipolar CM_5 lead with a resolution of 5μV.

Analysis of heart rate, QT variability, and QT-RR correlation. Digital ECG signals were analyzed off-line. ECG noise was reduced 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 were stored for computation of QT variability 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. QT intervals were determined from the beginning of the 5-minute segments. A prerequisite for QT analyses was T-wave amplitude exceeding 0.15 mV to avoid misrecognition error. QT-interval variability was determined by a T-wave template-matching algorithm described in detail previously [Avbelj 2003]. A normalized QT variability index (QTVI) has been used to assess QT variability. Normalized QTVI represented the logarithmic ratio between the QT and heart-rate variabilities, each normalized by the squared mean of the respective time series [Berger 1997]. Thus, greater inhomogeneity of repolarization would be reflected by a QTVI shift toward more positive values. To assess the QT/RR relationship, Pearson correlation between the lengths of the RR and QT intervals was computed for each patient's recording. Correlation was chosen apart from slope to make the relationship comparable across subjects and time periods regardless of differences in variability of RR- and/or QT-interval length.

STATISTICAL ANALYSIS

Descriptive statistics were calculated for all the studied parameters. If the distribution was heavily right-tailed, parameters were log-transformed to allow for parametric statistical analysis. For the use of β-blockers and incidence of arrhythmic disturbances, change in proportion of patients between 2 time-points was tested with exact McNemars 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 (<40%), and number of conduits performed. Before statistical testing, we applied Fishers z-transformation to the QT-RR correlations to obtain normal distributions. Repeated-measures ANOVA with post-hoc comparisons was used to test the change in RR, QT, and QTc length and average QT-RR correlation. To analyze the time course of RR and QT dynamicity parameters and possible differences between the 2 operative techniques, 2-way mixed-model ANOVA was used (with Greenhouse-Geisser correction when needed), whereby simple within-subject contrasts were used to test postoperative means against preoperative value. Statistical analyses were performed using SPSS for Windows 12.0 (SPSS Inc, Chicago, IL, USA) and LogXact-4 (Cytel Software, Cambridge, MA, USA). Statistical significance was set at $P < .05$.

RESULTS

Patients

The final sample consisted of 45 of 57 initially enrolled patients (79%) who fulfilled clinical and technical criteria for subsequent analyses (Figure 1). To avoid any intergroup bias, we carefully evaluated the numerical data and reason for exclusion of the excluded patients from the initial sample, assuring that the groups remained comparable for analysis of the final sample. The early perioperative mortality of 2% was in this consecutive series of 57 patients relatively higher than the overall mortality because 1 patient presented preoperatively with borderline pulmonary function due to severe chronic pulmonary obstructive disease. Even the a priori decision to include this patient in the off-pump group to potentially avoid the deleterious effects of CPB did not prevent this patient from developing acute pulmonary failure and fulminant pneumonia that eventually resulted in death 10 days postoperatively. The total morbidity (including stroke, aortic dissection, and acute respiratory or renal failure) was 7%; the patient who had a stroke left the hospital without residual deficits, as did the patient who suffered aortic dissection and underwent another procedure in addition to CABG. The off- and on-pump group showed no statistically significant differences in age, sex, severity of coronary artery disease, previous MI, hypertension, diabetes mellitus, dyslipidemia, left ventricular ejection fraction, or estimated EURO-score risk category (Table 1). The mean CPB and aortic cross-clamp times in the on-pump group were 93 ± 20 minutes and 64 ± 19 minutes, respectively. The average number of bypasses was significantly higher in the on-pump group (3.8 ± 0.8 vs 3.0 ± 0.6; $P < .001$). Somewhat higher, although not significant, use of β-blockers was found postoperatively in the off-pump group (70% vs 41%; $P = .075$). Hence, the number of bypasses and β-blocker use were controlled for in the subsequent regression analyses to eliminate potential confounding effects. All the patients

Table 1. Clinical Characteristics of Patients*

	On-pump CABG (n = 22)	Off-pump CABG (n = 23)	*P*
Age, y	62 ± 8	63 ± 9	.656
Male sex	18 (78%)	20 (87%)	.699
Previous MI	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
EURO Score	3.3 ± 2.2	3.0 ± 2.0	.661
Grafts performed	3.8 ± .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
Angiotensin-converting enzyme inhibitor	13 (59%)/8 (36%)	10 (43%)/7 (30%)	.376/.758

*Numeric variables are reported as mean ± SD; categorical variables are reported as n (%); *P*-values for differences between groups were calculated from independent samples *t*-test or Fisher exact test.

Table 2. Incidence of Arrhythmias*

	On-Pump	Off-Pump	*P* for Effect				
			CABG	Preoperative	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

*Preoperative indicates preoperative arrhythmia; Grafts, number of grafts performed; β-blockers, β-blockers (preoperatively for arrhythmia before CABG, postoperatively otherwise); EF < 40, left ventricular ejection fraction <40%; *P* values from exact logistic regression; DV, variable included in the model as outcome rather than as predictor; NA, not applicable because no arrhythmic events were observed.

had documented normal serum electrolytes and thyroid function postoperatively.

Arrhythmia. Only patients who presented with stable sinus rhythm preoperatively were included (Table 2). Before surgery no difference in occurrence of arrhythmic events was found between the on- and off-pump groups (P = .823). Roughly half of the patients experienced arrhythmic events postoperatively; in both groups arrhythmic disturbances occurred with equal frequency until 1 week after CABG. In both on- and off-pump groups increased frequency of arrhythmic events on postoperative day 4 and week 4 after CABG significantly correlated with the presence of preoperative arrhythmia (P = .036 and .022, for 4 days and 4 weeks postoperatively, respectively), whereas arrhythmic disturbances 1 week after CABG, although similar in frequency to day 4 postoperatively, did not correlate with preoperative arrhythmia. In contrast, on-pump CABG was identified as a factor contributing to increased arrhythmia 1 week after surgery (P = .017). Hence, in a multivariate model CABG technique remained the only significant proarrhythmic factor after adjustment for presence of preoperative arrhythmic disturbances, number of bypasses, use of β-blockers, and left ventricular ejection fraction below 40%; thus the odds of a patient from the on-pump group developing an arrhythmic disturbance 1 week after surgery were about 8 times those of a comparable patient from the off-pump group (odds ratio 8.5, 95% confidence interval 1.4-80.3).

Heart rate. Both on- and off-pump CABG group had shortened RR intervals 4 days after CABG ($P < .001$). In both groups 4 weeks after surgery, RR intervals remained shortened with respect to the preoperative baseline. However, consistently shorter mean RR intervals were found at 1 and 4 weeks after on-pump CABG (exact P = .006 and .008 for 1 and 4 weeks, respectively); multivariate regression analysis showed that the length of RR interval after surgery was not affected by the number of bypasses or the use of β-blockers. In contrast, in the off-pump group the RR interval returned more rapidly to the preoperative baseline 1 and 4 weeks after surgery (Figure 2).

QT interval and QTVI after CABG. In both groups the QT interval shortened proportionately to the RR after CABG. No significant change was found in QTc length over time (Table 3). The QTVI significantly increased after CABG and remained elevated through postoperative day 4 to 7 in

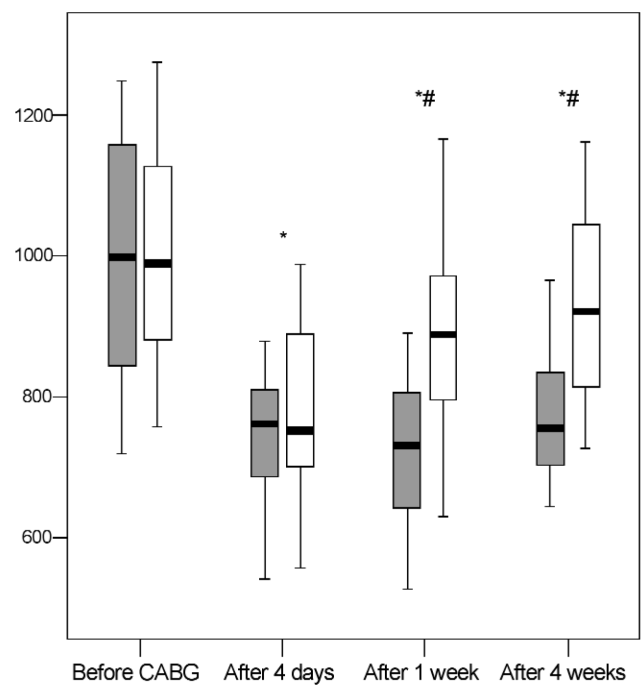

Figure 2. Time course of the mean RR interval in off- vs on-pump coronary artery bypass grafting (CABG) (*P < .05 for contrast with baseline; #P < .05 for difference between groups). Boxplots: horizontal line denotes median, box denotes 1st and 3rd quartile, whiskers denote 1st and 9th decile; filled boxes indicate the on-pump group, empty boxes the off-pump group.

Table 3. Descriptive Statistics and Summary of ANOVA and Regression Models for QT Interval*

Time-Point	P†	On-Pump CABG	Off-Pump CABG	P‡
QT, milliseconds				
Before CABG	NA	325 ± 45	318 ± 40	NS
After 4 days	.004	285 ± 26	291 ± 51	NS
After 1 week	.013	279 ± 39	310 ± 43	NS
After 4 weeks	.028	284 ± 28	315 ± 55	NS
QTc, milliseconds				
Before CABG	NA	319 ± 28	323 ± 30	NS
After 4 days	NA	332 ± 20	331 ± 37	NS
After 1 week	NA	324 ± 39	334 ± 35	NS
After 4 weeks	NA	323 ± 25	331 ± 39	NS
QT variability index				
Before CABG	NA	−1.3 ± 0.5	−1.2 ± 0.6	NS
After 4 days	<.05	−0.5 ± 0.6	−0.8 ± 0.4	<.05
After 1 week	<.05	−0.2 ± 0.6	−0.8 ± 0.7	<.05
After 4 weeks	NA	−0.7 ± 0.6	−1.0 ± 0.5	NS
QTSD, milliseconds				
Before CABG	NA	2.82 ± 2.52	2.27 ± 1.53	NS
After 4 days	NA	2.91 ± 1.64	2.67 ± 1.67	NS
After 1 week	NA	2.86 ± 1.24	2.59 ± 1.49	NS
After 4 weeks	NA	2.40 ± 1.58	2.66 ± 1.29	NS

*Numeric variables are reported as mean ± SD; CABG indicates coronary artery bypass grafting; NA, not applicable; NS, not significant.

†*P* for contrast with preoperative mean, from ANOVA.

‡*P* for group differences, from multiple regression, controlling for number of bypasses performed and β-blocker use.

both groups. Peak values were attained 1 week after CABG in both groups, but the peak value was significantly higher in on-pump group ($P < .05$). Four weeks after the procedure, the QTVI returned to preoperative values in both groups (Figure 3).

QT-RR correlation after CABG. The correlation between the length of the QT interval and the length of the RR interval dropped significantly after CABG and remained shortened thereafter (Figure 4) ($P < .05$ for comparison with day 4, week 1, and week 4 after CABG).

DISCUSSION

This study examined the effects of on- and off-pump CABG on heart rate, ventricular repolarization, and QT-RR correlation in the early postoperative period. We observed that regardless of the CABG technique, the RR interval shortened after CABG but exhibited faster normalization toward the preoperative baseline in the off-pump group. Advanced QT-RR analyses showed significant disparity between beat-to-beat heart-rate changes and rate-dependent ventricular repolarization adaptation. This disparity increased after the procedure irrespective of the CABG technique applied. The observed repolarization lability after the CABG procedure seemed to be transient and more pronounced after on-pump CABG, and this increased repolarization lability

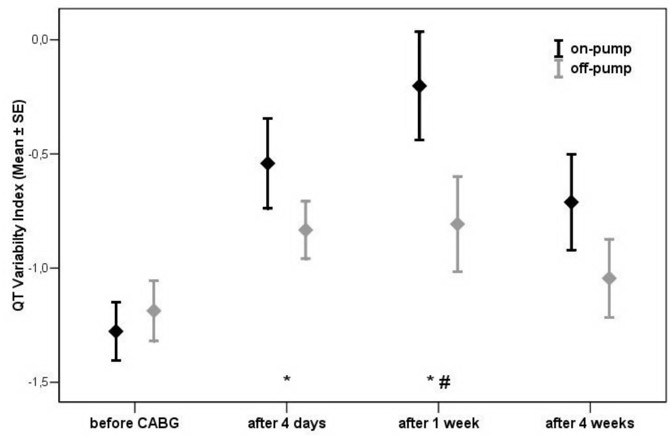

Figure 3. QT variability index in off-pump and on-pump coronary artery bypass grafting (CABG) (*$P < .05$ for contrast with preoperative level; #$P < .05$ for difference between groups).

coincided with increased frequency of arrhythmic events after on-pump CABG.

Electrophysiological remodeling of the heart associated with heart rate has been recognized as an important mechanism leading to a number of atrial and ventricular arrhythmias [Zipes 2003]. The patients who developed atrial fibrillation after CABG had higher heart rates and more frequent atrial ectopy [Hogue 1998]. Similarly, the group of patients presenting with atrial fibrillation after major noncardiac surgery in the absence of documented cardiac disease had elevated heart rates [Amar 2003]. Faster heart rates indicate pronounced adrenergic activation, increased sympathetic tone, and/or decreased parasympathetic tone and have been associated with higher risk for sudden as well as nonsudden cardiac death [Abildstrom 2003]. In the present study increased heart rates were associated with excessive adrenergic activation in both the off- and on-pump groups, similar to the extent found in previous studies [Niemela 1992; Kalisnik 2007]. Studying the effects of off- and on-pump CABG on cardiac autonomic regulation, we found profound but equal impairment of cardiac autonomic

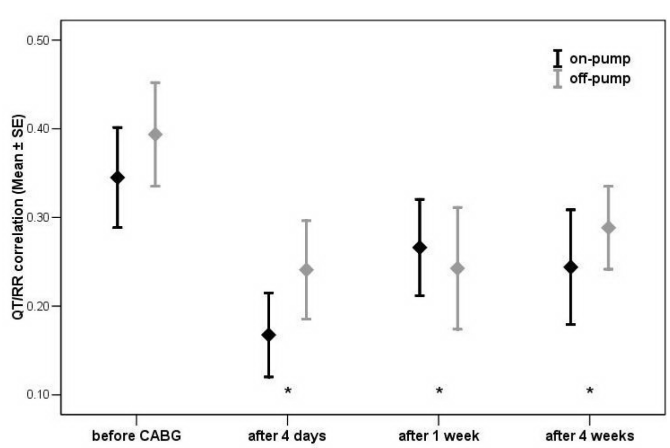

Figure 4. QT-RR correlation in off-pump and on-pump coronary artery bypass grafting (CABG) (*$P < .05$ for contrast with preoperative level; #$P < .05$ for difference between groups).

modulation after CABG, regardless of the technique applied [Kalisnik 2007]. Consistently shorter RR intervals after CABG found in the present study in the setting of increased repolarization lability and loss of rate-dependent ventricular repolarization adaptation indicate that cardiac autonomic (de)regulation contributes equally to autonomic nervous system–mediated sympathetic excitation after on- or off-pump CABG. However, the finding of significantly shorter RR after on-pump CABG suggests that sympathetic activation attains the highest levels after CABG with CPB, indicating the presence of additional nonautonomic factors. Moreover, the latter coincides with a higher incidence of arrhythmic disturbances in the on-pump group. Increased heart rates and multiple atrial or ventricular extrasystoles as well as short runs of atrial fibrillation were shown to precede the onset of postoperative atrial fibrillation after on-pump CABG [Taylor 2002]; however, structural changes of the heart reflected in changed ventricular repolarization properties after surgery have not been studied in detail. The patients with coronary artery disease or dilated cardiomyopathy who were at increased risk of sudden death were found to have increased QT-interval variability [Berger 1997; Zareba 2005]. Patients with diseased hearts do not necessarily present with abnormal values of conventional measures such as QT and QT-corrected intervals, a situation that can delay timely diagnostic and therapeutic actions [Lombardi 1998; Savelieva 1999]. Similarly, we did not observe any differences between conventional parameters for assessing ventricular repolarization. By applying repolarization dynamicity measures, however, we found that QT variability increased after surgery and remained elevated until postoperative day 7. The identified ventricular repolarization lability coincided with a higher incidence of arrhythmic events on postoperative days 4 and 7 compared to the values before and 4 weeks after surgery. Of note, off-pump patients presented with lesser repolarization lability on day 7 after CABG, a finding that again corresponded to lower frequency of arrhythmic events in that group. The notion that preoperative arrhythmias influenced the occurrence of postoperative arrhythmic events confirms the importance of previously present arrhythmic substrates in the generation of arrhythmic disturbances in the early period after myocardial revascularization [Zipes 2003]. To our surprise, however, the operative technique influenced the occurrence of arrhythmic disturbances 1 week after surgery in the on-pump group to a greater extent than did the preoperative arrhythmic substrate. Given that at 1 and 4 weeks after CABG cardiac sympathetic and parasympathetic modulation is profoundly but equally impaired after both on- and off-pump CABG [Kalisnik 2007], a possible explanation of this notion lies in the profile of QT dynamicity after both on- and off-pump CABG. Faster heart rates per se are insufficient to promote arrhythmic disturbances. When concomitant impairment of ventricular repolarization is present, the latter results in higher incidence of arrhythmic disturbances. This finding further indicates that structural alterations take place that affect ventricular repolarization after on-pump surgery to greater extent than after off-pump surgery.

Recent studies introduced dynamic assessment of the QT/RR relationship, presenting the possibility of identifying patients prone to developing an arrhythmic episode [Savelieva 1999]. Less tight coupling between QT and RR intervals has been found in patients with severe chronic heart failure, coronary artery disease, dilated myocardiopathy, or unstable angina pectoris, and consequently QT- and RR-interval coupling has been proposed as an additional factor for enhanced arrhythmic risk [Faber 2003]. Similarly, to further explore the dynamic aspect of QT variation in relation to heart rate, we performed QT/RR interdependence analysis and found an early destabilizing effect of any type of CABG procedure on ventricular repolarization. This effect has been manifested by increased uncoupling between RR and QT intervals and consequently impaired rate-dependent QT interval adaptation for as long as 4 weeks after CABG.

We observed increased electrical instability after both off- and on-pump CABG. Consequently, the direct effect of the cardiac autonomic system or CPB in the on-pump group might not be the only cause for the observed derangement, as has been speculated [Niemela 1992]. In particular, this evidence suggests that apart from increased adrenergic responses and autonomic nervous system impairment following revascularization procedures, reperfusion of postischemic myocardium per se may contribute significantly to increased electrical instability in the early period after surgery similarly as that described for percutaneous revascularization procedures [Bonnemeier 2003]. These surprising results have also been reported in other studies, suggesting that revascularization and reperfusion of the postischemic myocardium requires a definite time for adaptation to the new conditions, thus creating an even more vulnerable proarrhythmic state than before surgery [Yavuz 2007]. However, Yavuz at al studied only on-pump CABG patients, and because of the different design of the study were unable to establish the relationship between altered postoperative QT dynamicity and occurrence of arrhythmic events [Yavuz 2007]. In contrast, data from our study provide information about profiles of QT dynamicity after both beating- and arrested-heart revascularization and demonstrate that the first signs of adaptation occur as early as 1 week after surgery, with further improvement by week 4 after surgery, when arrhythmic disturbances again correspond only to the preoperative proarrhythmic substrate.

The multifactorial involvement of the heightened proarrhythmic state is nicely demonstrated in the present study by the postoperative relations of RR, QTVI, and QT/RR profiles after CABG in the on- and off-pump groups. The state of excessive adrenergic activation, loss of rate-dependent ventricular adaptation, and structural ventricular alteration culminate in higher incidence of arrhythmic disturbances. Unless all 3 factors act in combination, the arrhythmic disturbances largely rely on the presence of previously present proarrhythmic substrate as seen on day 4 and week 4 after surgery in both groups.

This study had several potential limitations. Although contemporary computerized techniques improved the reliability of QT-interval assessment, difficulties determining the characteristics of the T-wave might substantially affect advanced analyses in ECG recordings with low T-wave amplitudes [Savelieva 1999]. Therefore, only recordings having T-wave amplitude ≥0.15 mV were considered for further analyses, in accordance with the current technical standards and requirements for the analyses applied [Iacoviello 2007]. β-Blockers may affect postoperative arrhythmias, heart rate, ventricular repolarization, and cardiac sympathetic autonomic modulation [Crystal 2002; Huikuri 2003]. Accordingly, we eliminated the potential confounding effect of β-blockers by entering the use of β-blockers into multivariate regression models in all the statistical analyses performed. Thereby, the observed differences between the on- and off-pump groups could not be explained by different numbers of patients on β-blocker therapy.

In conclusion, increased electrical instability of the heart was found after both on- and off-pump CABG in the early postoperative period. The observed increased repolarization lability in the first days after reperfusion of postischemic myocardium is an additional previously unreported mechanism contributing to higher incidence of postoperative arrhythmic disturbances after both on- and off-pump heart revascularization, especially at higher and/or rapidly changing heart rates. However, it remains to be determined to what extent the observed effects are direct or indirect consequences of myocardial revascularization and/or reperfusion of the postischemic myocardium. Also requiring further investigation is the reversibility or irreversibility of impaired QT/RR coupling in the long term after CABG, especially in conjunction with contemporary treatment strategies for preventing perioperative arrhythmia.

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