Comparison of Sequential Changes in Heart Rate Variability After On-Pump and Off-Pump Coronary Artery Bypass Grafting

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Jurij-Matija Kalisnik[1] , Viktor Avbelj[2], Roman Trobec[2], Borut Gersak[1]

[1]Department of Cardiovascular Surgery, University Medical Center, Zaloska 7, SI-1000 Ljubljana, Slovenia
[2]Department of Communications and Computer Networks, Jozef Stefan Institute, Jamova 39, SI-1000 Ljubljana, Slovenia

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Address correspondence and reprint requests to: Jurij-Matija Kalisnik, MD, MSc, Department of Cardiovascular surgery, Medical Center, 1000 Ljubljana, Slovenia, Phone & fax: +386 1 433 4162, Email: jurij-matija.kalisnik@mf.uni-lj.si

ABSTRACT

Background: Cardiac vagal modulation is reduced in patients with coronary artery disease or previous myocardial infarction. The propensity to lethal arrhythmias and oxygen consumption is thus increased. The objective of the present study was to assess the effect of different techniques used in coronary artery bypass grafting (CABG), namely on-pump versus off-pump, on the level of vagal modulation in the immediate postoperative period.

Methods: Thirty-three patients, aged 34–76 years were enrolled in the study. Six patients undergone off-pump CABG; the rest were operated on-pump. The electrocardiograms (ECG) and respiratory waveform signals were recorded in the afternoons in supine position. Power spectra of the heart rate variability (HRV) were computed using Fast Fourier Transform analysis (FFT). The following HRV indexes were calculated: total power (TP) of spectra was defined in the range of 0.01-0.40 Hz, high frequency (HF) power within 0.15-0.40 Hz, low frequency (LF) power within 0.04-0.15 Hz. Normalized power (n) was defined as the ratio of power in each band / total power. The nHF power indicated cardiac vagal modulation; nLF power indexed sympathetic baroreflex modulated activity. The LF/HF ratio represented sympathovagal balance. Kolmogorov-Smirnov test, paired t-test or Wilcoxon signed rank and Mann-Whitney U test have been applied in statistical analysis, a value of $p<0.05$ was considered significant.

Results: The HRV indexes were diminished markedly after CABG regardless of the technique applied. TP, HF, LF, LF/HF ratio changed by 40 – 70%, the differences were significant on fourth and seventh postoperative day. Comparing off-pump versus on-pump group, the HF power was significantly higher by factor 2 in off-pump patients on the fourth and seventh day after CABG.

Conclusions: The results indicate marked attenuation of HRV indexes with no signs of restoration after one week regardless of the technique applied. However, a tendency to higher vagal modulation has been observed in beating heart patients may indicate tendency toward better preserved cardiac vagal autonomous regulation in off-pump patients.

INTRODUCTION

Profound derangement of autonomic regulation of cardiac function has been reported in severe cardiac diseases like myocardial infarction, coronary artery disease (CAD) [Bigger 1995] and after CABG [Kuo 1999]. Associated attenuation of HRV indexes, providing information about cardiac sympathetic and parasympathetic modulation, has been shown to be an independent predictor of mortality after myocardial infarction [Kleiger 1987]. CABG improves the prognosis of patients with CAD, in particular those with three-vessel disease and left ventricular impairment [Holmes 1986], however marked depression of HRV indexes occurs simultaneously what might worsen the prognosis. Higher vagal modulation proved protective in termination of potentially lethal cardiac arrhythmias [Juhani 1999]. In CABG procedures it has been established that cardiopulmonary bypass (CPB) including topical cooling with ice slush results in transient impairment of cardiac sympathetic efferent regulation [Murphy 1992]. Absence of respiratory sinus arrhythmia and severely depressed baroreflex sensitivity was reported even one year after operation in patients undergoing on-pump CABG procedure [Marin-Neto 1983]. Therefore, the aim of present study was to determine the dynamic changes of HRV measures immediately after CABG, especially in relation to different operative techniques applied.

MATERIALS AND METHODS

Ethical considerations: Slovenian State Research Ethics Committee approved the study; informed consent was obtained from each patient before participating.

Study subjects. Thirty-eight patients admitted to the department for cardiovascular surgery for elective CABG were invited to form the study group. Two patients refused further cooperation after operation. Research exclusion criteria included diabetes mellitus with documented late neurological impairment, atrial fibrillation, coexisting valvular heart disease, cardiac conduction abnormalities and the presence of kidney and/or liver disease. Clinical and preoperative data are presented in Table 1.

Operative procedures. After general anesthesia induction, intubation and insertion of Swan-Ganz catheter, CABG was performed either on beating or arrested heart. In on-pump patients cardiopulmonary bypass (CPB) was accomplished with double stage venous cannula and cannulation of the ascending aorta. Moderate haemodilution and normothermia was used, mean perfusion pressure was maintained at 55 mmHg. Cold blood retrograde and antegrade cardioplegic solutions were used for myocardial protection. In off-pump patients Octopus II stabilizer was used during manipulation of the heart to keep the operative field quiet. To better expose the marginal system, Lima stitch has been applied. Distal anastomoses have been performed either by snaring pledged sutures proximally to the site of incision or inserting 1.5 – 2.5 mm intraluminal shunts.

Study protocol

All the measurements were performed one and two days before operation and second, fourth and seventh day after operation in a warm, quiet surrounding using DEKG measuring device [Jozef Stefan Institute, Ljubljana, Slovenia]. Modified V [1] and V [5] lead ECG and respiratory waveform pattern using tip nose thermistor probe were recorded for 10 minutes after 10- minute supine rest to allow haemodynamic stabilization. All the measurements were taken in the afternoons in postprandive state to avoid any diurnal variations. The subjects were requested not to drink any caffeinated beverages 24 hours prior to measurements.

Data acquisition

Sampled electrocardiographic and respiratory signals were transmitted to personal computer. The sampling frequency for both signals was 450 Hz. Off-line analysis has been subsequently performed on the later retrieved data using DEKG R-R detection software package [Jozef Stefan Institute, Ljubljana, Slovenia]. Data were manually supervised and five-minute segments stored for further power spectral analysis. Sinus pause, atrial or ventricular arrhythmic episodes were deleted and the measurements discarded from further analysis if percentage of deletion exceeded 5%. The peaks of respiratory wavefront were identified and the respiratory frequency determined from the corresponding five-minute segments.

Power spectral analysis

Power spectra were computed from five-minute stable ECG recordings using Fast Fourier Transform analysis [DEKG program package, Jozef Stefan Institute, Ljubljana]. The power of the direct current component was excluded before the calculation of the power spectrum. Total power of spectra was defined in the range of 0.01-0.40 Hz, HF power within 0.15-0.40 Hz, LF power within 0.04-0.15 Hz. Normalized power [n] was defined as the ratio of [power in each band / total power]. The nHF power indicated cardiac vagal modulation; nLF power indexed sympathetic baroreflex modulated activity. The LF/HF ratio represented sympathovagal balance.

Statistical analysis

Values of HRV measures were presented as mean ± SD. After Kolmogorov-Smirnov testing for normality, preoperative and postoperative HRV measures were compared using paired t-test and Wilcoxon signed rank sum test in on-pump and off-pump group, respectively. Left ventricular ejection fraction, HRV measures and breathing frequencies on each successive day were compared in on- and off-pump group using Mann-Whitney test. Chi-square test has been applied to compare categorical data among the two groups of patients. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 3.02 for Windows and GraphPad InStat version 3.00 for Windows 95 [GraphPad Software, San Diego, California, USA].

RESULTS

Patient characteristics. Two patients were excluded from the analysis due to occurrence of frequent arrhythmic episodes and precipitation of delirious state postoperatively. Additional two patients were excluded due to changed course of cardiac operation: in one, iatrogenic type A aortic dissection required circulatory arrest and in the second patient, CABG plus mitral valvuloplasthy have been performed due to intraoperativelly reported massive mitral insufficiency. The percentage of deletion of ectopic beats due to atrial or ventricular arrhythmia was >5% in 12% of all recordings which were subsequently rejected from further analysis. The clinical characteristics of on-pump and off-pump group of patients are shown in Table 1.

As expected, HRV indexes in on- and off-pump patients did not differ significantly two and one day before operation. However, substantial reduction of TP and LF power was observed in on-pump patients on second, fourth and seventh postoperative day with respect to the preoperative values (Table 2). HF power was markedly depressed on fourth day postoperatively, whilst nHF power showed transient increase on second postoperative day and then did not differ appreciably from preoperative levels. In off-pump patients, TP and LF changed profoundly on fourth and seventh day after operation. Transient increase of nHF and nLF was observed on fourth day, as shown in Table 3. Mean RR period decreased by 25% on second and remained so on fourth and seventh day after operation in both study groups. Cross-comparison between on- and off-pump patients on respective days showed significantly higher values of HF power on fourth and seventh day (Table 2). Normalized HF power was significantly higher on fourth postoperative day and failed to reach statistical significance on seventh postoperative day.

Analysis of breathing

Respiration may significantly affect the RR-interval variability [Brown 1993]. Therefore, breathing pattern has been monitored during recordings. On the second day after operation there has been significantly higher breathing rate found in off-pump patients. The breathing rates on successive days are presented in Table 3.

DISCUSSION

Short-term analysis of HRV measures was used in this study to further extend the findings of previous studies reporting on HRV changes after CABG [Hogue 1994, Niemela 1996, Kuo 1999]. Additionally, breathing rate analysis has been performed to evaluate the influence of breathing on acquisition of HRV spectra. Significant attenuation of HRV measures was found in the present study after CABG, in beating as well as in non-beating operative procedure.

Impact of breathing on HRV spectra

Respiratory rate markedly influences HRV power spectra. Major reduction occurs between 7.5 and 15 breaths/min for HF power and between 6 and 10 breaths/min for LF power indicating significantly low gain-breathing frequency response both for LF and HF power between 15 and 24 breaths/min [Brown 1993]. Respiratory breathing frequency range spanned from 17 to 24 breaths/min, thus we conclude that breathing rate did not influence the HRV spectra in our study appreciably. Significantly lower breathing rate in on-pump patients (Table 3) might have contributed to higher values of HF on second day after operation. In contrast, the observed measures of HF and nHF power were higher on fourth day and 1 week after operation in off-pump patients at faster breathing rates suggesting involvement of mechanisms other than respiratory in reduction of HRV after on-pump as well as off-pump CABG.

Several factors have been proposed to be responsible for the attenuation of HRV immediately after CABG. Among them are nonspecific effects of recovery from general anesthesia, myocardial infarction or ischemia, reduced left myocardial function, perioperative stress responses, concomitant medication, or procedure-related causes, such as inadequate myocardial protection during operation, direct mechanical injury to vagus nerve, phrenic nerve or sinus node, or subclinical central nervous system involvement due to intraoperative microembolisms [Kuo 1999]. The observation that considerable reduction of HRV measures occurs regardless of the type of operation in both groups suggests that procedure-related causes are less likely to be the primary cause for HRV reduction, because: (1) off-pump procedure does not imply the concomitant use of CPB thus avoiding deleterious effects of nonspecific inflammation and central venous microembolisms [Smith 1986], (2) off-pump procedure does not require any hypothermia or topical cooling with ice slush, which could potentially result in altered cardiac regulation due to direct injury to the epicardial nerve fibers, vagal and phrenic nerve [Murphy 1992] (3) the observed changes of HRV measures are gradual and partially reversible after CABG [Kuo 1999] in both groups rendering direct cause due to surgical transection less likely. Repeated 12-lead standard ECG recordings, absence of clinical signs and/or symptoms and supervising the CK and CK- MB fraction levels regularly after operation have ruled out perioperative infarction or ischemia. Pain has been effectively treated by careful titration of analgesic agents; however, perioperative stress responses and residual anesthesia effects might have influenced the sympathovagal balance to some extent after operation.

Speculating further on possible mechanisms involved, various levels of ischemia, necrosis and reperfusion can trigger cardiac reflexes to various extent. Cardiac sympathetic and parasympathetic reflex responses may be interrupted or attenuated soon after the onset of ischemia or altered later in the course due to mechanosensitive, chemosensitive overstimulation and dennervation hypersensitivity [Zipes 1990]. In procedures, off-pump as well as on-pump CABG, the varying haemodynamic conditions during operation might predispose to profound autonomic derangement. We assume that different intraoperative conditions in on-pump and off-pump surgery, respectively might result in different levels of mechanosensitive, chemosensitive stimulation and consequently altered sympatho-parasympathetic cardiac regulation due to type operation.

Beating heart versus non-beating heart operation

The results of the present study indicate tendency towards better preserved cardiac autonomous regulation in off-pump patients in the immediate postoperative period. Several plausible mechanisms may account for this observation:

(1) Topical myocardial cooling with ice slush results in severely impaired efferent sympathetic responses of the heart [Murphy 1992].

(2) Localized ischemia without profound cardiac deterioration in contrast to global ischemia elicits predominant sympathoexcitatory reflex rather than vagal inhibition [Joho 1999]. In accordance with this observation we found lower HRV measures suggesting increased sympathetic excitation in off-pump patients and higher HRV measures due to possible sympathetic withdrawal in on-pump patients second day after operation.

(3) Respiratory sinus arrhythmia and baroreceptor sensitivity was better preserved in patients operated on without CPB [Marin-Neto 1983]. Similarly, higher values of HF found in our study suggest possible higher vagal modulation in off-pump patients.

Any present uncertainty about the underlying mechanisms, however, does not detract from the importance of the observation that higher HRV measures found in off-pump patients may imply less impairment of cardiac autonomous regulation and may be consequently regarded more cardioprotective and arrhythmia preventive. However, in a related study [Kuo 1998], only three out of six measured spectral indexes were importantly different between the age matched normal and coronary artery disease group. Similarly, there were three spectral indexes statistically different between on- and off-pump group on fourth postoperative day and one on seventh postoperative day in our study. The latter prevents us from making any final conclusions, however it reveals the need to obtain additional data in larger study population, preferably with random selection of the type of the operation. Non-randomization according to the beating or non-beating heart procedure selection prior to cardiac operation is yet a limitation of the present study to be overcome in the future research, as the number of grafted coronary arteries in on-pump group significantly outnumbers the off-pump group (Table 1). The latter does not exclude perhaps more severe coronary artery disease in on-pump group and consequently lower HRV indexes obtained. Finally, our observations are in accordance with two recent observations, namely that, CPB inclusive of cardiac arrest is the main independent predictor of postoperative atrial fibrillation in CABG patients [Ascione 2000] and that the prevalence of occurrence of cardiac arrhythmias is lower in CABG patients operated on off-pump [Stamou 2000]. HRV analysis separately in on- and off-pump patients over longer intervals after operation might give us further insight into the HRV recovery profile evaluating long-term effect of different surgical techniques on cardiac autonomous regulation, as well as dismantling underlying mechanisms involved.

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TABLES

Table 1. *Characteristics of patients operated by off- and on-pump CABG.*

	Off-pump (n=6)	On-pump (n=27)		p Value
Age[a] (yrs)	63 ± 9	62 ± 8	NS	p=0.79
Gender (M/F)	5/1	20/6	NS	p=0.73
MI	3 (50%)	12 (50%)	NS	p=0.65
AH	5 (83%)	15 (60%)	NS	p=0.30
DM	0	5 (21%)	NS	p=0.55
LVEF[a] (%)	53 ± 10	55 ± 11	NS	p=0.64
Graft[a]	2,7 ± 0,8	3,5 ± 0,8	*	p=0.05
Medication				
ß-blocker	5 (83%)	15 (63%)	NS	p=0.90
Calcium antagonist	0	5 (21%)	NS	p=0.54
Nitrates	4 (67%)	13 (54%)	NS	p=0.93
ACE inhibitor	3 (50%)	15 (63%)	NS	p=0.90

MI, myocardial infarction; AH, arterial hypertension; DM, diabetes

mellitus.
LVEF, left ventricular ejection fraction; ACE, angiotensin-converting enzyme.
* Statistically significant. [a] Mean ± SD.

Table 2: *Indexes of Heart rate variability in patients after on/off pump CABG.*

Day	2 preop		1 preop		2 postop		4 postop		7 postop	
On pump (n=27)										
TP	853	± 792	720	± 775	405	± 739	157	± 180	76	± 87
HF	237	± 255	193	± 246	260	± 576	48	± 71	17	± 25
LF	262	± 282	207	± 257	76	± 115	44	± 55	18	± 15
nHF	0.28	± .15	0.27	± .15	0.43	± 115	0.25	± .17	0.26	± .19
nLF	0.31	± .12	0.2	± .13	0.24	± .13	0.28	± .11	0.26	± .15
LF/HF	1.4	± 1.2	1.7	± 1.3	1	± 1.1	1.7	± 1.4	1.8	± 1.8
RR	1021	± 100	995	± 158	744	± 106	750	± 94	713	± 89
Off pump (n=6)										
TP	568	± 423	605	± 460	132	± 97	337	± 339	156	± 162
HF	157	± 96	236	± 256	54	± 73	239	± 304	73	± 131
LF	207	± 225	81	± 40	25	± 26	51	± 37	19	± 12
nHF	0.3	± .06	0.37	± .24	0.28	± .28	0.61	± .23	0.41	± .28
nLF	0.33	± .14	0.2	± .13	0.21	± .11	0.2	± .13	0.2	± .14
LF/HF	1.2	± 0.8	0.75	± .57	2.03	± 1.9	0.41	± .40	0.8	± 0.9
RR	1028	± 100	1040	± 120	747	± 180	723	± 97	725	± 67

TP = total power, HF = high frequency power, LF = low frequency power, nHF = normalized high frequency power, nLF = normalized low frequency power, LF/HF = low frequency power / high frequency power ratio.
Preop = preoperatively, postop = postoperatively, n = number of patients. The results are expressed mean ± SD.
_ = Statistically significant between respective days in respective group.
_ = Statistically significant between on/off- pump group.
_ p value = 0.06, comparison between successive days in each group.

Table 3. *Pattern of breathing in on/off pump CABG patients on respective day.*

Day	off-pump	on-pump	p value
2 preop	17.5 ± 3.1	16.8 ± 3.5	NS
1 preop	18.6 ± 3.9	17.7 ± 3.3	NS
2 postop	22.7 ± 2.5	17.4 ± 3.5	*
4 postop	17.8 ± 5.7	21 ± 3.6	NS
7 postop	23.4 ± 1.8	21.8 ± 4.2	NS

Expressed as
Mean [breath /min] ± SD.
* statistically
significant;
NS, not significant.