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Serial changes of heart rate variability after coronary artery bypass surgery

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Aim of the present study was to assess autonomic modulation of heart rate by heart rate variability (HRV) analysis in frequency domain after coronary artery bypass graft surgery (CABG) in patients with coronary artery disease, its relations with clinical variables and dynamics during follow-up period.

Twenty patients (mean age 46.8 ± 8.8 years) with coronary artery disease, submitted to CABG, entered the study. All the patients were examined clinically and electrocardiogram, chest X-Ray and two-dimensional echocardiogram were performed. Heart rate variability was assessed by means of frequency-domain analysis (Fourier transform). Investigations were undertaken before, 7 days, 30 days and 3 months after surgery.

A significant overall reduction occurred in HRV component's powers after CABG ($p < 0.0001$), followed by a gradual increase with restoration of preintervention levels in the 3rd month after surgery. The attenuation of HRV indices was dependent on duration of aortic cross clamping time ($r = -0.62$, $p < 0.003$) and cardiopulmonary bypass time ($r = -0.60$, $p < 0.004$).

In conclusion, heart rate variability decreases after coronary artery bypass surgery, with further restoration in the 3rd month after surgery. The deterioration of HRV indices is dependent on the duration of cardiopulmonary bypass time and aortic cross-clamping time. *J Clin Basic Cardiol 1999; 2: 69–72.*

Key words: heart rate variability, CABG

Alterations in cardiac autonomic regulation have been described in patients with coronary artery disease after coronary artery bypass grafting (CABG) [1, 2].

Heart rate variability (HRV) analysis, either in time or frequency domain using autoregressive model or fast Fourier transform (FFT), has gained widespread approval in the assessment of cardiac autonomic modulation [3–6]. Spectral analysis of heart rate variability, extracted from short-term electrocardiographic recordings, identifies three frequency components: a high frequency component (0.15–0.40 Hz), related with respiration and parasympathetic modulation, a low-frequency component (0.04–0.15 Hz), which is thought to be under modulation of both sympathetic and parasympathetic influences and a very low frequency component (0.00–0.04 Hz), the physiological meaning of which is not yet established [3–7].

Attenuated values of HRV indices after myocardial infarction have been shown to be a strong and independent predictor of mortality [8–10]. Several clinical investigations have also revealed attenuation in time and frequency domain measures of HRV early after CABG [11, 12].

Although a lot of factors, such as systemic and topical hypothermia, cold crystalloid cardioplegia, myocardial ischaemia, general anaesthesia are held to be responsible for those modifications of cardiac autonomic regulation [1, 11], little is known of the factors affecting heart rate variability and how it changes in time in patients after CABG.

This study has been undertaken to assess autonomic regulation of heart rate by HRV analysis in frequency domain (FFT) after CABG surgery in patients with coronary artery disease, its change in time and its relations with clinical variables and dynamics during follow-up period.

Table 1. Clinical characteristics

Parameters	M ± SD
Age, years	46.8 ± 8.8
Men, %	80 (16)
Women, %	20 (4)
Risk factors	
Smoking, %	90 (18)
Hypertension, %	25 (5)
Diabetes, %	5 (1)
History of myocardial infarction	85 (17)
Anterior, %	64.7 (11)
Inferior, %	35.2 (6)
Mean number of stenosed CA	2.4 ± 0.7
LV EF, %	49.7 ± 7.2
SBP, mmHg	124.6 ± 15.8
DBP, mmHg	79.2 ± 9.4
HR, beats/min	72.9 ± 12.6
CPBT, minutes	100.9 ± 33.8
ACCT, minutes	57.1 ± 18.8

CA – coronary arteries, LVEF – left ventricular ejection fraction, SBP – systolic blood pressure, DBP – diastolic blood pressure, HR – heart rate, CPBT – cardiopulmonary bypass time, ACCT – aortic cross clamping time.

Material and methods

Clinical characteristics (Table 1)

Twenty patients (mean age 46.8 ± 8.8 years; 16 men and 4 women) with coronary artery disease who had submitted to CABG surgery entered the study. Patients with clinically overt heart failure, history of recent myocardial infarction (< 2 months), and those on digitalis, β-blockers and angiotensin converting enzyme inhibitors were excluded from the study. One of the patients had diabetes mellitus and 4 had history of hypertension, but remained normotensive preoperatively.

History of old myocardial infarction (more than 2 months) was present in 17 (85 %) patients; 11 (64.7 %) had old anterior and 6 (35.2 %) had old inferior myocardial infarction. Mean

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left ventricular ejection fraction (LV EF) preoperatively was 49.7 ± 7.2 %. All patients had taken medications such as acetylsalicylic acid, nitrates and calcium antagonists preoperatively.

Coronary anatomy
The mean number of stenosed coronary arteries (CA) was 2.4 ± 0.7. Eight patients (40 %) had two-vessel and twelve (60 %) had three-vessel disease. Left main disease was present in 5 (25 %) of patients.

Surgical approach
The standard operative technique was utilized on all the patients using cardiopulmonary bypass. Cardiopulmonary bypass was established with a single two-stage right atrial cannula after systemic heparinization. During bypass the haematocrit value was maintained between 20 % and 25 %, pump flows between 2.0 and 2.5 l/min per square meter, and mean arterial pressure between 50 and 60 mmHg with administration of vasodilators and inotropes as required. Body temperature was lowered to 28° C and topical hypothermia was established. After aortic cross-clamping cardioplegia was induced by administration of 1000 ml intermittent antegrade cold crystalloid solution. In the early postoperative period inotropic and vasodilator agents were used as necessary. Mean duration of cardiopulmonary bypass time (CPBT) was 100.9 ± 33.8 minutes and the duration of aortic cross clamping time (ACCT) was 57.1 ± 18.8 minutes. None of the patients had signs of perioperative myocardial infarction.

All the patients had clinical examination, electrocardiography, chest X-Ray, and blood chemistry analysis.

2-Dimensional echocardiography studies were accomplished using a Toshiba SSH 160A system with 3.75 MHz pulse wave transducer, with simultaneous recording of electrocardiogram and phonocardiogram. Tracings of end diastolic and end systolic left ventricular contours using two-chamber apical view approach were obtained for further calculation of left ventricular ejection fraction [13].

HRV acquisition and processing
Electrocardiograms were recorded with a Kardiosis Ars-LP Recorder, a PC-based high-resolution system. Bipolar X deviation (0.5–340 Hz) was recorded and sampled at a rate of 1000 samples/second and digitised using a 12-bit A/D converter. Each recording lasted 7 minutes and raw data were stored to a hard disk for post processing.

HRV was processed using Medsoft™ Heart Rate Dynamics System [14]. A Fast Fourier transform of the analytic signal was used as frequency representation of HRV. Power estimation based on Fourier transform was done according to previously described method [15]. The following frequency-domain measures were submitted to statistical analysis: powers of very low (0.00–0.04 Hz, VLFP), low (0.04–0.15 Hz, LFP), high (0.15–0.40 Hz, HFP) frequency components, total power (0.00–0.56 Hz, TP) and low frequency component power to high frequency component powers ratio (LFP/HFP). The relative powers of each HRV spectral component (VLFRP, LFRP and HFRP) were obtained using the formula: absolute power of each component/total power x 100.

Investigations were undertaken before, 7 days, 30 days after and 3 months after CABG surgery at the same time of day.

Statistical analysis
Data are expressed as mean ± standard deviation. Differences between pre- and post-operative (7^{th} day after) values of HRV were tested with the paired Student's t-test.

For testing the associations of postoperative HRV indices with clinical (age, history of myocardial infarction, left ventricular ejection fraction) and intraoperative (cardiopulmonary bypass time, CPBT, aortic cross-clamping time, ACCT) variables a multiple regression analysis was accomplished.

Further analysis of variances for repeated measurements was used for the assessment of temporal HRV changes during follow-up period. Post hoc comparisons (Scheffe's test) were used to test differences between postoperative 7^{th} day, 30^{th} day and 3^{rd} month of observation.

Results

Effects of CABG on HRV indices
A significant decrease of all HRV components was observed one week after surgery (Tab. 2). VLFP, LFP, HFP, and TP reduced markedly in comparison with baseline preoperative value ($p < 0.0001$ for all). There was also a reduction of LFRP ($p < 0.05$) after CABG, while changes of VLFRP, HFRP and LF/HF ratio were not significant.

HRV component's powers (VLFP, LFP, HFP, TP) remained reduced on the 30^{th} day, but further gradually increased in the 3^{rd} month of observation (Tab. 3). The HRV components

Table 2. Effects of CABG on HRV and LV EF in patients with CAD

Parameters	pre CABG	Post CABG (7^{th} day)	p
VLFP, msec^2	321.9 ± 265.9	63.3 ± 87.4	< 0.0001
VLFRP, %	47.2 ± 14.0	44.3 ± 13.5	NS
LFP, msec^2	242.8 ± 201.4	37.7 ± 56.6	< 0.0001
LFRP, %	34.3 ± 9.2	27.5 ± 12.0	< 0.05
HFP, msec^2	122.3 ± 137.8	16.3 ± 15.7	< 0.0001
HFRP	15.1 ± 9.4	18.8 ± 14.3	NS
TP, msec^2	719.7 ± 530.4	129.1 ± 157.4	< 0.0001
LFP/HFP	3.02 ± 1.7	2.7 ± 2.9	NS
LV EF, %	49.7 ± 7.2	42.8 ± 4.0	< 0.002

VLFP – very low frequency component power, VLFRP – very low frequency components related power, LFP – low frequency component power, LFRP – low frequency components related power, HFP – high frequency component power, HFRP – high frequency components related power, TP – total power, LF/HF – ratio of low frequency component power to high frequency component power, LVEF – left ventricular ejection fraction.

Table 3. Dynamic changes of HRV indices after CABG surgery during follow-up period

Parameters	post CABG (7^{th} day)	30 days after	3 months after	F	P
VLFP, msec^2	63.3±87.4	178.5±178.1	375.0±274.4*°	9.0	<0.0001
LFP, msec^2	37.7±56.0	84.0±58.1	221.5±171.4*°	11.4	<0.0001
HFP, msec^2	16.3±15.7	29.8±19.2	116.5±167.0*	5.7	<0.001
TP, msec^2	129.1±157.4	301.8±233.1	703.9±599.9*°	10.1	<0.0001
LFP/HFP	2.7±2.9	3.72±3.1	2.8±1.4	2.2	NS
LFRP, %	27.5±12.0	30.1±8.1	31.1±8.6	2.0	NS
EF, %	42.8±4.0	46.3±6.4*	58.9±3.1*°	8.1	<0.0001

* – Scheffe's test significant < 0.05 in comparison with postoperative (7^{th} day) state
° – Scheffe's test significant < 0.05 in comparison with 30^{th} day after CABG
VLFP – very low frequency component power, LFP – low frequency component power, HFP – high frequency component power, TP – total power, LFRP – low frequency component's related power, LF/HF – ratio of low frequency to high frequency components power, LVEF – left ventricular ejection fraction.

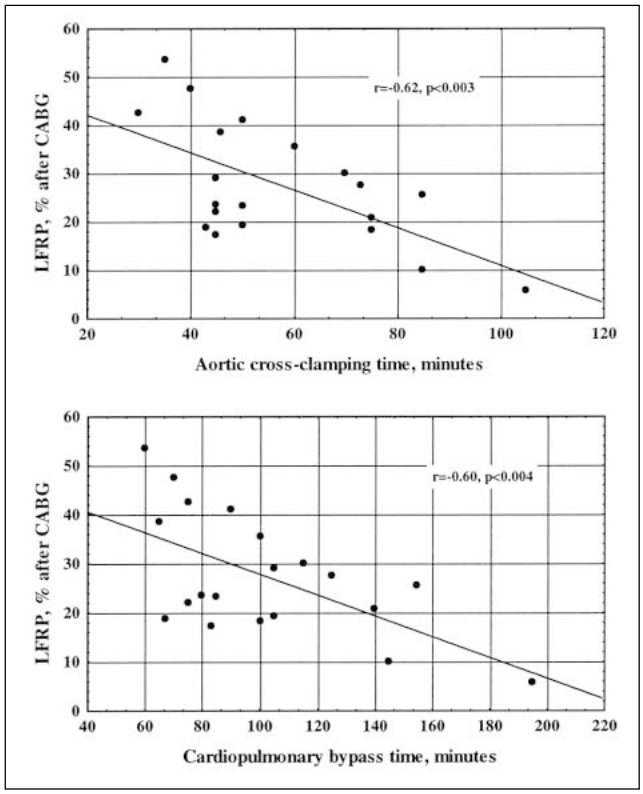

Figure 1. Relationship of LFRP with aortic cross-clamping time (a) and total cardiopulmonary bypass time (b)

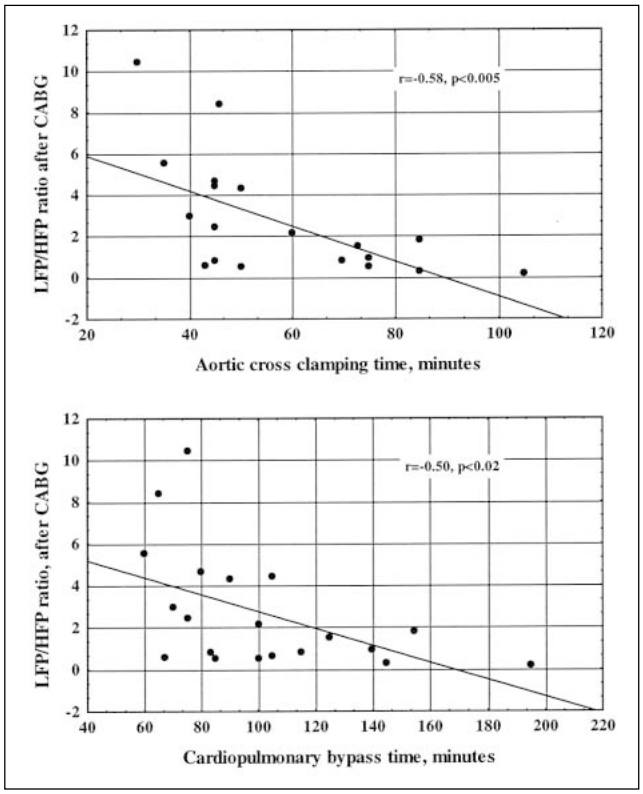

Figure 2. Relationship of LFP/HFP ratio with aortic cross-clamping time (a) and total cardiopulmonary bypass time (b)

powers were significantly higher in the 3rd month after surgery as compared with postoperative 7th day and 30th day after surgery ($p < 0.05$, $p < 0.05$, respectively). Left ventricular ejection fraction was significantly higher in the 3rd month of observation in comparison with preoperative and postoperative states ($p < 0.05$).

Relationship of postoperative HRV indices with clinical and intraoperative variables

A significant inverse correlation existed between postoperative LFRP with ACCT and CPBT ($r = –0.62$, $p < 0.003$ and $r = –0.60$, $p < 0.004$, respectively) (Fig. 1) and postoperative LFP/HFP ratio with ACCT and CPBT ($r = –0.59$, $p < 0.005$ and $r = –0.50$, $p < 0.02$, respectively) (Fig. 2). No significant association revealed between postoperative HRV indices and age, history of MI, and postoperative left ventricular ejection fraction.

Discussion

Heart rate variability, when explored in frequency domain has been proposed as reflecting the autonomic modulation of heart rate [4–7]. The high frequency component of HRV signal is reduced after standing and parasympathetic blockade and is modulated solely by parasympathetic influences [6]. Low frequency component is modulated by both sympathetic and parasympathetic influences [3, 7]. Its absolute power declines after parasympathetic blockade and decreases or does not change during standing, while, when expressed in normalised units, it increases after standing [3, 5, 6]. Several authors have accepted the low frequency component, expressed in normalized units, as a marker of sympathetic modulation of heart rate and the ratio of absolute powers (LFP/HFP) as a marker of sympathovagal balance [6, 7, 16]. Though these statements have been criticized by others [17].

Our study demonstrates an overall reduction of HRV absolute powers and LFRP in patients after coronary artery bypass surgery. This attenuation of HRV persisted after 1 month of observation and gradually increased with restoration of preintervention levels in the 3rd month of observation. There was a significant association of the postoperative low frequency component's relative power (LFRP) and LFP/HFP ratio with the duration of cardiopulmonary bypass time and aortic cross-clamping time.

These findings allow one to assume that there is a reduction of sinus node response to parasympathetic and sympathetic modulations after CABG, it being pronouncedly lower in those patients with longer duration of CPBT and ACCT.

Our findings are in agreement with the results of previous works [11, 12, 18] that HRV values both in time and frequency domain decline after coronary artery bypass surgery.

The reasons for attenuation of autonomic modulation of heart rate after CABG are not clearly defined. One can assume that general anaesthesia, perioperative stress response or other factors in the early postoperative period may contribute to the deterioration of HRV, but Hogue et al. failed to demonstrate such association [11]. Heart rate variability in coronary artery disease has been related to age, history of myocardial infarction, LV dysfunction, use of β-blockers and digitalis [9, 19–22], but these variables did not deal with HRV alteration after bypass surgery.

Cardiopulmonary bypass per se through its haemodynamic effects may modify reflexes originating from the myocardium [23]. Diminished cardiac norepinephrine release [2] and decline of cardiac sympathetic activity after CABG were attributed to the direct inhibitory effects of cold cardioplegia on epicardial sympathetic endings [1, 2]. Experimental studies have clarified that constituents of cardioplegic liquid (eg, high potassium level), transitory ischaemia and increased reflow after revascularisation can induce functional damage of both

sympathetic and parasympathetic neural endings [24, 25]. Clinical studies have referred to HRV alterations during acute coronary occlusion produced by percutaneous transluminal coronary angioplasty and transitory episodes of ischaemia during 24-hour ECG recordings [26, 27]. There may be also a link between HRV and deterioration of myocardial performance, though we did not find the correlation with left ventricular ejection fraction [20, 28].

Abolishment of functional derangement of autonomic modulation, induced by cardiopulmonary bypass and improvement of LV function may explain restoration of HRV indices in the 3rd month of observation. Whether HRV indices would reach higher levels, should the follow-up period be longer is not clear.

Since prolonged cardiopulmonary bypass time is a determinant of perioperative myocardial infarction after CABG [29] and reduced HRV is an independent predictor of mortality in patients with myocardial infarction [9, 10], the prognostic significance of decreased HRV in CABG patients needs clarification.

In conclusion, heart rate variability decreases after coronary artery bypass surgery, with further restoration in the 3rd month after surgery. The deterioration of HRV indices is dependent on the duration of cardiopulmonary bypass time and aortic cross-clamping time.

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