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Ventricular arrhythmic disturbances and autonomic modulation after beating-heart revascularization in patients with pulmonary normotension

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Summary. *Background:* De-novo ventricular arrhythmias are potentially life-threatening complications after beating-heart revascularization (off-pump CABG). Whether pulmonary hypertension can influence initiation of ventricular arrhythmias through increased sympathetic activity is controversial. In order to determine the influence of pulmonary hypertension on its relative contribution to ventricular arrhythmia, we first had to define the role of cardiac autonomic modulation in patients with pulmonary normotension. We aimed to observe how parameters of linear and nonlinear heart rate variability are changed pre- and postoperatively in patients with pulmonary normotension undergoing off-pump CABG.

Methods: Fifteen-minute ECG recordings were collected before and after off-pump CABG in 54 patients with multivessel coronary artery disease and pulmonary normotension to determine linear (TP, HF, LF, LF:HF ratio) and nonlinear detrended fluctuation analysis ($\alpha 1$, $\alpha 2$) and fractal dimension (average, high and low) parameters of heart rate variability. Arrhythmia was monitored preoperatively in 24-hour Holter recordings and postoperatively by continuous monitoring and clinical assessment.

Results: Deterioration from simple (Lown I–II) to complex (Lown III–V) ventricular arrhythmia was observed in 19 patients, and improvement from complex to simple arrhythmia in five patients (P = 0.022). Patients with postoperative deterioration of ventricular arrhythmia had preoperatively significantly lower values of TP, HF and LF (P = 0.024–0.043) and postoperatively significantly higher values on the low fractal dimension index (P = 0.031) than patients with postoperative improvement of arrhythmia.

Conclusion: Patients experiencing postoperative deterioration of ventricular arrhythmia already have impaired autonomic regulation before surgery. Higher postoperative values on the low fractal dimension index indicate that sympathetic predominance with or without concomitant vagal withdrawal is the underlying neurogenic mechanism contributing to ventricular arrhythmia.

Key words: Ventricular arrhythmias, off-pump CABG, nonlinear heart rate dynamics, heart rate variability, detrended fluctuation analysis, fractal dimension.

Introduction

New onset ventricular arrhythmias (VAs), varying from ventricular ectopy to malignant tachyarrhythmias such as sustained ventricular tachycardia and ventricular fibrillation represent the most serious arrhythmic complication following open heart surgery, including arrested and beating heart revascularization (on- and off-pump coronary artery bypass graft [CABG]) [1, 2]. Although the exact electrophysiological mechanisms of initiation and maintenance of VAs have not been completely elucidated [3], recent studies indicate that a deranged state of cardiac autonomic modulation may be one of the most important triggers or arrhythmic substrate promoters for their occurrence [2–4]. Profound derangement of sympathovagal regulation is present in various states of cardiac disease and in arrested or beating heart surgery [5]. However, the contribution of the alteration in pulmonary pressure to changes of autonomic regulation has not been completely clarified [6, 7]. Some animal models and clinical studies suggest that pulmonary hypertension might be associated with sympathovagal imbalance resulting from increased sympathetic activity [6–9].

Analysis of heart rate variability (HRV) is a well recognized noninvasive tool in investigation of the autonomic regulation of the heart [10]. Conventionally, linear methods of HRV analysis have been used to derive information about sympathetic and parasympathetic cardiac modulation [10]. Since the basic physiologic dynamics of normal sinus rhythm have been shown to have fractal-like features, a number of new, nonlinear HRV measurements based on fractal geometry and complex dynamics have been developed as a new ap-

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proach in evaluation of subtle heart rate fluctuation not evident with conventional linear analysis [11, 12].

Our aim in this study was to associate de-novo postoperative VA with nonlinear HRV parameters after off-pump CABG in patients with pulmonary normotension as a basis for our further studies where patients with pulmonary hypertension and underlying structural pulmonary disease will be observed.

Patients, materials and methods

The design of the prospective study was accepted by the National Medical Ethics Committee of Slovenia. Informed consent was obtained from all patients.

Patients

Sixty-seven consecutive patients admitted to the Department of Cardiac Surgery for elective off-pump CABG were invited to form the study group. Inclusion criteria were as follows: isolated stable multivessel coronary artery disease, sinus rhythm, documented pulmonary normotension, long-term β-blocker treatment and >95% pure sinus beats in the recordings. Exclusion criteria were concomitant valve disease, any rhythm other than sinus rhythm as confirmed by 24-hour Holter electrocardiographic recordings, permanent pacemaker, diabetes mellitus with late neurological impairment, recent myocardial infarction (<1 month), <95% pure sinus beats in the recordings, emergency operation and conversion to on-pump CABG. After CABG, 13 participants were excluded: three died after the procedure (one due to a massive perioperative myocardial infarction and two for non-cardiac reasons), one patient required an emergency conversion from off-pump to on-pump and nine were excluded because their preoperative or postoperative recordings comprised more than 5% ectopic beats and measurement artifacts. Finally, ECG recordings from 54 patients were considered for analysis.

Pulmonary arterial pressure was non-invasively estimated by Doppler assessment in the tricuspid valve pressure-gradient method [13]. Preoperative medication with β-blockers was routinely omitted on the day of surgery and resumed postoperatively, guided by hemodynamic criteria, but in no patient later than the third postoperative day.

Operation and surveillance of arrhythmia

The anesthetic procedure included fentanyl, midazolam, propofol and pancuronium. All off-pump CABG procedures were performed by the same surgical team in a standardized manner as described elsewhere [5]. At the end of the surgery patients were transferred to the intensive care unit.

To detect preoperative rhythm disturbances, 24-hour Holter recordings were performed the day before the surgical procedure. For detection of postoperative VAs, heart rate and rhythm were continuously monitored with an automated arrhythmia detector for the first four days after the operation. Later, clinical observation and repeat 12-lead ECG recordings were performed daily; in any suspicion of arrhythmia occurrence, an ECG was recorded and continuous monitoring restarted. 24-hour Holter recordings were repeated on the seventh postoperative day. Ventricular rhythm disturbances were classified as simple (Lown I–II) or complex (Lown III–V) VA, (non)sustained ventricular tachycardia and ventricular fibrillation.

Electrocardiographic recordings and HRV analysis

One day before operation and on the third and seventh postoperative days 15-minute ECGs were recorded using a DEKG 1-channel digital recorder (Intekom, Slovenia) with a sampling frequency of 1000 Hz.

Electrocardiographic recordings were automatically scanned with a HolCard 24W analyzer (Aspel, Poland) using an R wave peak detection algorithm and later manually reviewed and corrected, if necessary. After eliminating all abnormal beats and beats succeeding premature beats, a moving average filter was applied. Only recordings with >95% pure sinus beats were included in the analysis.

For linear measurements of HRV the sum of spectral components within the frequency range 0.01–0.40 Hz was defined as total power. The areas of spectral peak in subranges between 0.04 Hz and 0.15 Hz were defined as low frequency power, indicating modulated sympathetic activity, and between 0.15 Hz and 0.40 Hz as high frequency power, indicating vagal activity. The sympathovagal balance was calculated as the ratio of low and high frequency powers [10].

The dynamic aspect of HRV analysis was computed using two nonlinear methods: detrended fluctuation analysis (DFA) and fractal dimension (FD).

DFA is a modified root mean square analysis of a random walk that quantifies fractal-like correlation properties of the time series [14, 15]. In this study, the correlation properties were measured for both short-term (≤11 beats, α1) and long-term (>11 beats, α2) fluctuations of RR intervals. The parameter DFA α1, indicating vagal activity, is one of the most powerful risk markers for sudden cardiac death, mortality after myocardial infarction and arrhythmias [11, 12, 15–18], whereas DFA α2 changes, indicating sympathetic derangement, have not yet been related to a distinct clinical condition [11].

FD is the exponent of the number of self-similar windows into which a waveform can be broken [19, 20]. Average, low and high FD was calculated for all, short (≤9 beats) and long (≥9 beats) windows sizes using Higuchi's algorithm [21]. Average FD, indicating parasympathetic activity, is reduced in the presence of ectopic activity and arrhythmias, myocardial ischemia and impulse conduction disorders [19]. Although low and high FD parameters have been associated with the normal development of the fetal autonomic system during pregnancy, their precise clinical significance has not been completely clarified [20].

Table 1. Clinical details of patients (n = 54)

Age (years)	63.5 ± 9.8
Men : women	36:18
Coronary artery disease	
2 vessel	16 (29.6%)
3 vessel	38 (70.4%)
Previous myocardial infarction	30 (55.5%)
Hypertension	49 (90.7%)
Diabetes mellitus	15 (27.7%)
Dyslipidemia	54 (100%)
LVEF (%)	55.3 ± 9.8
LA (cm)	4.0 ± 0.5
TVPG + CVP (mmHg)	24 ± 7
Euro SCORE	2.9 ± 2.6
Grafts performed	2.5 ± 0.9
Beta-blocker therapy	54 (100%)
Admission/discharge	54 (100%)

Numerical variables are reported as mean ± SD. *LVEF* left ventricular ejection fraction; *LA* left atrium diameter; *TVPG* tricuspid valve pressure gradient; *CVP* central venous pressure.

Statistical analysis

Descriptive statistics were calculated for all the studied parameters (results are reported as mean ± SD). Paired-samples *t*-tests or Mann–Whitney tests were used for calculating numerical data and Fischer's exact test for calculating categorical data. Differences in ventricular ectopic activity before and after the procedure were tested with Wilcoxon's signed-rank test. A P value <0.05 was considered statistically significant. The statistical package SPSS for Windows 14.0.2 (SPSS Inc., Chicago, IL, USA, 2006) was used for the analyses.

Results

The clinical characteristics of the patients are listed in Table 1.

Ventricular arrhythmias

Analysis of preoperative 24-hour Holter ECG recordings showed that all patients presented with sinus rhythm prior to the surgical procedure. Ventricular ectopic activity was present in all patients, and varied from Lown I to Lown V (Table 2). Simple (Lown I–II) VA was observed in 24 patients and complex (Lown III–V) VA in 30 patients (Table 2). No episodes of nonsustained ventricular tachycardia or malignant ventricular rhythm disturbances were documented preoperatively.

During the first week after the procedure, VA disturbances were more complex and occurred significantly more frequently than preoperatively ($P = 0.022$, Wilcoxon's signed-rank test) (Table 2). Postoperatively,

Table 2. Pre- and postoperative ventricular ectopic activity as represented by a score based on Lown classification

		Postoperative ventricular ectopic activity						All patients
		I	II	III	IVa	IVb	V	
Preoperative ventricular ectopic activity	I	5	0	7	2	3	3	20
	II	0	0	3	0	1	0	4
	III	2	0	14	1	2	0	19
	IVa	0	0	3	0	1	0	4
	IVb	1	1	1	2	1	0	6
	V	1	0	0	0	0	0	1
All patients		9	1	28	5	8	3	54*

* $P = 0.022$ (Wilcoxon's signed-rank test for comparison of pre- and postoperative ventricular ectopy in all patients).

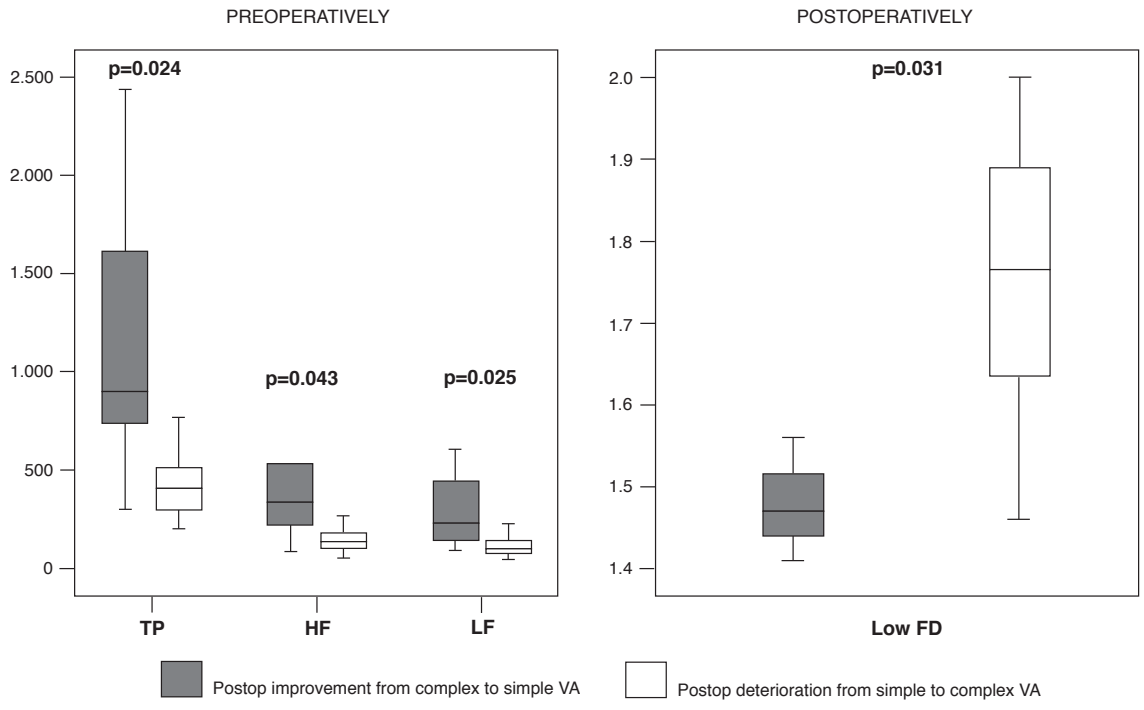

Fig. 1. Pre- and postoperative TP, HF, LF and low FD in patients with deterioration (Lown I–II to III–V, empty boxes) and improvement (Lown III–V to Lown I–II, filled boxes) of ventricular arrhythmias (VA) after off-pump CABG. Horizontal line denotes median, box denotes 1st and 3rd quartile, T-bars denote 1st and 9th decile

10 patients presented with simple and 44 with complex VA. Postoperative improvement from complex to simple VA was seen in five patients, whereas postoperative deterioration from simple to complex VA was observed in 19 patients. No significant differences in pre- (age, LVEF, LA diameter, two- or three-vessel disease, EuroSCORE assessment, etc.), intra- (number of bypasses performed, differing surgical techniques) or postoperative (adherence to β-blocker therapy) clinical variables were observed between the two groups. No episodes of (non) sustained ventricular tachycardia or ventricular fibrillation were documented in the first postoperative week.

Correlation between linear and nonlinear HRV parameters and postoperative ventricular arrhythmia

In patients with postoperative deterioration from simple (Lown I–II) to complex (Lown III–V) VA, the parameters total power, high frequency and low frequency were already significantly lower preoperatively (P from 0.024 to 0.043), whereas no intergroup differences were observed for nonlinear HRV parameters preoperatively (Fig. 1). However, on the third postoperative day the parameter low FD was significantly higher (P = 0.031) in patients deteriorating from simple to complex VA than in patients improving from complex to simple VA (Table 3, Fig. 1). Postoperatively no significant intergroup differences were observed for linear HRV and DFA indices (P from 0.113 to 0.951).

Discussion

The main findings of this study are that patients experiencing postoperative deterioration of VA already have impaired autonomic regulation before surgery and that sympathetic predominance regardless of concomitant vagal withdrawal represents an important underlying neurogenic mechanism contributing to the VA.

Although the influence of deranged autonomic heart regulation on initiation and maintenance of VA has not been completely explained, recent studies indicate that perturbations in sympathovagal regulation could generate a trigger or a substrate for the arrhythmia [2–4]. However, unlike the atria, where both sympathetic and parasympathetic activity are thought to exert convergent effects on tissue refractoriness and conduction, thus promoting rhythm disturbances, in the ventricles sympathetic activation is believed to promote vagal stimulation to protect against development of arrhythmias [2, 4, 10]. Our patients with postoperative deterioration of VA from simple to complex ectopy already had significantly lower levels of total power, high frequency and low frequency parameters of linear HRV analysis preoperatively than patients with postoperative improvement of VA. Preoperative alteration of linear HRV indices suggests that a certain degree of autonomic imbalance already exists before the surgical procedure; however, the concurrent decline of parameters indicating both sympathetic and vagal impairment in arrhythmic patients does not enable unequivocal understanding of the state of the autonomic system using linear HRV methods.

In the present study changes of nonlinear parameters are more informative. Our patients with postoperative deterioration from simple to complex VA had postoperatively significantly higher values on the low FD index than individuals with postoperative improvement from complex to simple VA. Previous reports have pointed out that the nonlinear low FD index and the linear low frequency index show similar changes during the

Table 3. Pre- and postoperative values of linear and nonlinear parameters of HRV in patients with postoperative ventricular arrhythmias

	Before surgery		3rd postoperative day		7th postoperative day	
	Deterioration from simple to complex VA	Improvement from complex to simple VA	Deterioration from simple to complex VA	Improvement from complex to simple VA	Deterioration from simple to complex VA	Improvement from complex to simple VA
TP	431.2 ± 166.5	1195.0±839.5*	235.4 ± 154.8	204.3 ± 6.4	230.2 ± 96.9	312.0 ± 211.1
HF	144.9 ± 62.3	467.4 ± 421.4*	65.2 ± 66.3	39.7 ± 3.5	57.6 ± 46.5	97.3 ± 60.7
LF	119.5 ± 62.6	303.4 ± 216.6*	51.1 ± 35.5	64.7 ± 20.5	59.5 ± 21.5	77.5 ± 63.4
LF:HF	0.9 ± 0.3	0.8 ± 0.3	1.0 ± 0.6	1.7 ± 0.6	1.3 ± 0.8	0.83 ± 0.45
α1	1.14 ± 0.22	1.16 ± 0.17	1.03 ± 0.40	1.50 ± 0.10	1.23 ± 0.31	1.05 ± 0.38
α2	0.93 ± 0.12	0.94 ± 0.11	1.01 ± 0.17	1.04 ± 0.20	1.01 ± 0.12	0.97 ± 0.13
Low FD	1.72 ± 0.10	1.70 ± 0.13	1.74 ± 0.17	1.48 ± 0.08*	1.63 ± 0.17	1.77 ± 0.17
High FD	1.92 ± 0.06	1.97 ± 0.05	1.86 ± 0.09	1.84 ± 0.14	1.87 ± 0.09	1.87 ± 0.07
Average FD	1.81 ± 0.06	1.81 ± 0.08	1.78 ± 0.11	1.65 ± 0.07	1.72 ± 0.10	1.79 ± 0.12

Numerical variables are reported as mean ± SD. Deterioration from simple to complex ventricular arrhythmia (VA): group of patients deteriorating from simple (Lown I–II) to complex (Lown III–V) VA; improvement from complex to simple VA: patients improving from complex (Lown III–V) to simple (Lown I–II) VA. *TP* total power; HF high frequency power; *LF* low frequency power; *LF:HF* low frequency/high frequency ratio; *DFA* detrended fluctuation analysis; *α1* short-term scaling exponent; *α2* long-term scaling exponent; *FD* fractal dimension; * $P < 0.05$ for comparison between groups.

fetal autonomic system development [20, 22], suggesting that low FD reflects the sympathetic activity or that it better describes sympathetic modulation in hyperadrenergic settings. Thus, our results indicate that after the surgical procedure patients with complex VA have higher sympathetic activity, supporting earlier anticipations that increased sympathetic activity with or without decreased vagal activity is clearly the main neurogenic promoter of postoperative development of VA [2, 3].

Differing states of pulmonary disease, such as COPD, have traditionally been associated with disturbances of heart rhythm, in particular with atrial fibrillation resulting from hypoxia, electrolyte disturbances and changes in pulmonary hemodynamics [23]. However, the precise role of pulmonary hypertension as a possible factor inducing perturbation of autonomic regulation is poorly understood [6]. It has been shown that pulmonary hypertension may induce right ventricular hypertension, sinus node malfunction resulting from pressure overload in the right ventricle and atrium, and modification of the number and characteristics of beta receptors [8]. Some animal models and clinical trials have pointed out that sympathetic predominance resulting from increased sympathetic modulation can be observed in animals and individuals suffering from pulmonary hypertension [6, 8, 24], suggesting that pulmonary hypertension may favor the development of arrhythmias through the alteration of autonomic modulation. However, the exact pre- and postoperative changes of sympathovagal balance in this subgroup of patients remains to be investigated. Since our results in patients with pulmonary normotension clearly show that individuals with higher sympathetic activity are prone to development of VA, it would be interesting to observe whether all patients suffering from pulmonary hypertension manifest with the same degree of sympathovagal disturbance or whether there is among these individuals a distinct group of patients with an even higher degree of sympathetic predominance who are yet more prone to VA.

This study has several limitations. First, the relatively small sample size provided a small number of arrhythmic events, risking spurious associations and possibly missing subtle associations that a richer dataset would reveal. Furthermore, because of the rarity of (non)sustained ventricular tachycardia and ventricular fibrillation after the CABG procedure, our sample group was too small to observe derangement of the autonomic nervous system in patients with malignant VA. Second, although non-invasive ECG provides an established and reliable assessment of autonomic system activity, supplementary measurements of humoral status, such as urine catecholamine levels as a measure of sympathetic humoral activation, would add further value in (co)relating the levels of nervous and humoral autonomic regulation that remain to be determined in subsequent studies.

In conclusion, our data show that patients with pulmonary normotension experiencing postoperative deterioration of VA already have impaired autonomic regulation before surgery. Furthermore, higher postoperative values of the parameter low FD indicate that sympathetic predominance is the underlying neurogenic mechanism contributing to progression of VA not necessarily associated with concomitant vagal withdrawal. The effect of pulmonary hypertension on pre- and postsurgical autonomic settings and arrhythmias after CABG remains to be addressed. Although our preliminary data indicate that nonlinear measurements of HRV have considerable potential to assess sympathovagal fluctuation and that they may offer prognostic information, larger prospective studies with longitudinal follow-up are needed to determine the sensitivity, specificity and predicting accuracy of these measurements that can eventually be used in arrhythmia screening and diagnostics using high resolution ECG technologies.

Conflict of Interest
The authors declare that there is no conflict of interest.

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