Impairment of cardiovascular autonomic control in patients early after cardiac surgery

R. Bauernschmitt\textsuperscript{a},*, H. Malberg\textsuperscript{b}, N. Wessel\textsuperscript{c}, B. Kopp\textsuperscript{a}, E.U. Schirmbeck\textsuperscript{a}, R. Lange\textsuperscript{a}

\textsuperscript{a}Clinic for Cardiovascular Surgery, German Heart Center Munich, Lazarettstr. 36, D-80636 Munich, Germany
\textsuperscript{b}Forschungszentrum Karlsruhe GmbH, Institute for Applied Informatics, Postfach 3640, D-76021 Karlsruhe, Germany
\textsuperscript{c}Institute for Nonlinear Dynamics, University of Potsdam, Am Neuen Palais 10, D-14415 Potsdam, Germany

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Abstract

Objective: Impairment of the baroreceptor reflex activity reflects an alteration of the autonomous regulation of the cardiovascular system and has proven to predict fatal outcome in patients after acute myocardial infarction. The following study was performed to analyse the baroreceptor sensitivity, heart rate variability and blood pressure variability in patients early after coronary surgery.

Methods: Twenty-five male patients undergoing coronary artery bypass were examined in a prospective study; normal values were obtained from healthy volunteers. Arterial pressure signals were recorded from a radial artery catheter for 30 min preoperatively and in short intervals after surgery. Mechanical manipulations and pharmacological interventions were avoided during the sampling periods. Baroreflex function was calculated according to the dual sequence method, heart rate variability and blood pressure variability were calculated including nonlinear methods.

Results: Initial values of the patients did not differ from healthy volunteers. The strength of baroreflex sensitivity (increase in blood pressure causing a synchronous decrease of heart rate) is low 2 h postoperatively. The number of delayed tachycardic changes of heart rate, which are caused by sympathetic activation, is only moderately reduced as compared to values obtained from healthy volunteers. Heart rate variability is widely unchanged as compared to preoperative values; blood pressure variability showed an increase of low-frequency components, again indicating sympathetic predominance. Nonlinear analyses revealed reduced system complexity at the beginning of the postoperative course.

Conclusion: Obviously, there is a vagal suppression 20 h after surgery, while the sympathetic tonus works in a normal range. This unbalanced interaction of the autonomous systems is similar to findings in patients after myocardial infarction. The predictive value of these markers has to be elucidated in further clinical studies.

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1. Introduction

The past decade has witnessed an increasing interest in markers of the autonomous regulation for characterisation or even risk stratification of patients with cardiovascular diseases [1]. The integrity of the autonomous nervous system can be quantified by the analysis of the baroreflex sensitivity (BRS) representing the capability of the cardiovascular system to modify heart frequency in response to fluctuations of blood pressure. In previous studies it was demonstrated that the BRS was significantly depressed in patients with dilated cardiomyopathy [2]. After acute myocardial infarction, low BRS, heart rate variability (HRV) and the recently developed heart rate turbulence were significantly correlated to cardiac death in prospective studies [3–6]. It was recently demonstrated that a multivariate approach combining classical HRV-analysis and the use of nonlinear methods improved the results of risk stratification in patients with coronary heart disease (CHD) [7,8].

While there is a large quest for risk stratification in patients in the intensive care unit (ICU) after cardiac surgery, real-time analysis of biosignals using methods of computational intelligence is rarely applied. The reasons are mainly problems in the integration of complex real-time...
systems, the occurrence of artefacts and noise during the signal acquisition, and the influence of mechanical interventions and drug application. Using recently developed methods for BRS quantification, data preprocessing and nonlinear methods, this study is an attempt at a comprehensive description of autonomic control in the postsurgical patient and to yield basic information to support further clinical studies on the predictive value of autonomic control.

2. Methods

2.1. Patients

Twenty-five male patients with a mean age of 66.5 ± 14.2 years were included, all of them suffering from three-vessel CHD. Left ventricular ejection fraction (LVEF) was normal or moderately reduced in all patients (45–68%, mean 56%). Diabetes was present in 14 patients, and 14 patients had experienced prior myocardial infarction. Each patient was treated with \( \beta \)-blockers before surgery. Exclusion criteria were emergent operations, severely depressed LV-function, antiarrhythmic therapy, history of alcohol or drug abuse and history of atrial or ventricular arrhythmias. Patients requiring inotropic support exceeding 5 \( \mu \)g/kg BW per minute of dopamine or antiarrhythmic therapy at any time during the observation period were also excluded. Normal values were obtained from healthy volunteers.

2.2. Anaesthesia, operations and postoperative care

Anaesthesia was standardised; induction was performed with sufentanil and midazolam. For maintaining narcosis, a continuous infusion of propofol was given; muscle relaxation was achieved by pancuronium. Central venous pressure and pulmonary artery pressure were monitored by a Swan-Ganz catheter, arterial pressure by cannulation of the radial artery.

All operations were carried out with cardiopulmonary bypass (CPB) in mild hypothermia (32–34 °C) and pulsatile perfusion mode, cold crystalloid cardioplegia was used for cardiac arrest. After declamping, most of the patients needed one countershock to terminate ventricular fibrillation. Mean time of extracorporeal circulation was 73 ± 25 min, mean crossclamping time was 45 ± 22 min.

Weaning from CPB was uneventful in each patient. After surgery, the patient was transferred to the ICU during ongoing mechanical ventilation; propofol infusion was continued for the first postoperative hour. Extubation was possible between 6 and 8 h after ICU-admission in all patients. If reduction of afterload was necessary, nitrates were given, but not immediately before or during the data sampling period.

2.3. Measurements

Radial artery pressure was A/D-converted and stored for 30 min in a bed-side laptop during the following times:

- Preoperative (before induction of anaesthesia)
- Time 1: 2 h
- Time 2: 4 h
- Time 3: 6 h
- Time 4: 8 h
- Time 5: 20 h after surgery.

Data were recorded with a frequency of 800 Hz. During the measurement periods, care was taken to avoid any mechanical manipulations or pharmacological interventions on the patient.

2.4. Parameters

After filtering to minimize artefact influences and to exclude ventricular premature complexes (data preprocessing as suggested by Malberg [2]), beat-to-beat-intervals (BBI) and systolic blood pressure were extracted from the registered curves (Fig. 1). BRS was calculated using the dual sequence method (DSM). In contrast to pharmaco-logically induced BRS-analysis (phenylepinephrin injection), the DSM determines changes in heart rate in response to spontaneous changes of blood pressure. BRS is calculated from the ratio of heart rate changes and initial pressure alterations. For detailed analysis of BRS, fluctuations were termed brady (bradycardiac changes: rise of pressure leads to decrease of frequency), or tachy (tachycardic changes, drop of pressure leads to increase of frequency, Fig. 2). A shift operation differentiates between synchronous (\( \text{sync} \)) and delayed (\( \text{shift 3} \), see Fig. 3) regulations; vagal answers usually cause synchronous activity of the baroreflex, while sympathetic activation leads to delayed reflex answers [9, 10]. In addition to reflex sensitivity, percentage of regulations in discrete intervals and total number of regulations within the observation period is calculated.

HRV and blood pressure variability (BPV) are calculated in time and frequency domain and by methods of nonlinear dynamics to facilitate the discrimination of changes within the autonomous regulation.

![Blood Pressure [mmHg]](image)

Fig. 1. Beat-to-beat-interval (BBI) as derived from the invasively registered curve (A. radialis).
Analysing HRV, the following standard parameters were calculated from the time series:

- SDNN (standard deviation of intervals between two normal R-waves): gives an impression of the overall circulatory dynamics.
- RMSSD (square root of square of mean value of the sum of all differences between two consecutive normal RR-intervals): higher values indicate higher vagal activity.
- pNN50 (percentage of intervals more than 50 ms longer or shorter than the preceding interval): again higher values indicate higher vagal activity.

Beside the parameters mentioned above, the analysis of BRV was focussed on high-frequency components (HF, high values indicating vagal activity) and low-frequency components (LF, high values indicating sympathetic activity).

In addition, HRV and BRV were analysed by methods of nonlinear dynamics. For this purpose, established methods derived by symbolic dynamics \[11,12\] were used to distinguish between different states of autonomic interactions. The concept of symbolic dynamics is based on a coarse-graining of dynamics. The difference between the current value (BBI or systolic blood pressure) and the mean value of the whole series is transformed into an alphabet of four symbols \(0, 1, 2, 3\). Symbols ‘0’ and ‘2’ reflect low deviation (decrease or increase) from mean value, whereas ‘1’ and ‘3’ reflect a stronger deviation (decrease or increase over a predefined limit). Subsequently, the symbol string is transformed to ‘words’ of three successive symbols explaining the nonlinear properties and thus the complexity of the system. From this symbolic dynamics the following parameters were calculated:

- Shannon entropy: the classical parameter for system complexity calculated from the distribution of words. Larger values refer to a higher complexity of the series.
- ‘Forbidden words’: the number of words which never or very rarely occur. A high number of forbidden words reflect regular behaviour, while in highly complex time series, only very few forbidden words are found.

3. Results

While it is a well-known phenomenon that autonomous regulation is depressed early after cardiac surgery as compared to preoperative values, the focus of our study was the immediate postoperative period. Markers of autonomic regulation were analysed in short intervals before and after extubation.

3.1. Bradycardic regulation

Spontaneous pressure rises lead to a decrease of frequency mediated by vagal activation within the next heart cycle, therefore no shift operation was necessary (brady-sync).

BRS plotted as the linear correlation of increase of systolic pressure and increase of the subsequent RR-interval.
was slightly depressed immediately after surgery (time 2 h: 7.6 ± 3 ms/mmHg, normal values 11–15 ms/mmHg, preoperative values in study patients: 11.8 ± 4.2 ms/mmHg). The number of spontaneous bradycardic fluctuations in low and medium regions of regulation and the total number of bradycardic regulations showed a decrease during the postoperative period (see Fig. 4).

3.2. Tachycardic regulation

Pressure drops leading to an increase in heart rate (decreased RR-interval) are sympathetically mediated and therefore were calculated using the three IBI-shift-operation. Fig. 5 shows changes during the postoperative course. While regulation is severely depressed immediately after surgery, partial recovery is observed until 6 h after the operation. At 8 h postsurgery, after extubation, tachycardic regulation shows another drop, but is almost recovered to normal values after 20 h.

3.3. Heart rate variability

Mean heart rate (duration of normal RR-interval) is displayed in Fig. 6. While mean NN (mean interval of normal-to-normal beat) is within the normal range at time 2 h (normal control value, 905 ± 134 ms; preoperative value of study patients, 840 ± 107 ms), it significantly decreases during the study (time 2 h vs. time 20 h: P < 0.05). SDNN, giving an overview of the dynamic state of circulatory action, did not significantly decrease during the postoperative period. Likewise, RMSSD had no tendency to increase (preoperative 51 ± 48; 47.55 ± 84.97 at time 2 h to 24.33 ± 25.91 at time 20 h, P = NS). The percentage of intervals with at least 50 ms difference from the preceding interval (pNN50) is not depressed and

![Fig. 4. Synchronous bradycardic fluctuations. Percentage of the number of bradycardic synchronous slopes > 3 ms/mmHg related to heart frequency. preop., preoperative value; *P < 0.01 vs. preop. value.](image1)

![Fig. 5. Delayed tachycardic fluctuations. Percentage of tachycardic slopes > 3 ms/mmHg related to the heart frequency. preop., preoperative value; *P < 0.01 vs. preop. value; 20 h not significantly different from preop. value.](image2)

![Fig. 6. (a) Heart rate variability: mean normal-to-normal intervals in milliseconds. *P < 0.01 vs. preop. value. (b) Heart rate variability. SD of normal-to-normal intervals in milliseconds. *P < 0.01 vs. preop. value.](image3)
remains constant throughout the observation period (2 h, 14.7%; 20 h, 11.3%; preoperative value, 14%).

3.4. Blood pressure variability

Mean and systolic blood pressures were constant throughout the postoperative course, also the variability of blood pressure was more or less unchanged and corresponded to preoperative values (Fig. 7). The LF band indicating sympathetic activity, corresponding to tachy-shift measurements, showed a stepwise increase until 6 h postoperatively, a drop after extubation (8 h) and again a rise until time 20 h (time 2 h vs time 20 h, \( P < 0.05 \)) The HF band indicating vagal activity was widely unchanged with a tendency to decrease at the later course (Table 1).

Likewise, the LF/HF-ratio giving an impression of sympathetic activity during the observation period increased until the end of the study period.

3.5. Nonlinear dynamics

Shannon entropy indicating the system complexity decreased in the first postoperative hours and then showed a tendency to rise again. The behaviour of forbidden words was similar; while there was a significant increase at the beginning indicating a more regular behaviour, the later values revealed renormalisation (Table 1).

3.6. Clinical course

There was no hospital mortality, no perioperative myocardial infarctions or other major complications within this selected group of patients. Four patients (16%) experienced atrial fibrillation in the later postoperative course.

4. Discussion

Monitoring of the patient status in postoperative intensive care usually means to display biosignals of the present status; therapy decisions and risk estimation are mainly based on the experience and intuition of the intensivist. Beside the present hemodynamic status, clinical indexes like LVEF or NYHA status are significant predictors for overall mortality, but they are useless in risk stratification for death due to fatal arrhythmias [13,14].

As patients after cardiac surgery are prone to experience a variety of complications in the early postoperative period, we believe that there is a need for predictive values of postoperative ICU course exceeding pure demonstration of the actual situation. Adequate processing of data available may be the way to increase information, because physiological data often have complex structures, which cannot be interpreted immediately [15].

Markers of autonomic control proved to have a major predictive value in patients suffering from heart disease. Experimental and clinical data suggest a major role of heart rate variability in risk stratification after myocardial infarction and probably in patients after cardiac surgery [3,4,16].

The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study demonstrated that analysis of the BRS has prognostic value independently of left ventricular function or ventricular arrhythmias and significantly adds to the information obtained by HRV alone [4]. Determining BRS, the classical methods induce pressure variation by interventions like application of phenylephrine. Repeated injections of vasoactive agents, however, are critical in postsurgical patients and may lead to clinical problems. By using the DSM, which analyses the response to spontaneous pressure variations, any intervention at the patient is avoided. Moreover, the method does not only provide information about the functional state of the vagal regulation, but also on sympathetic tone and is based
on a relatively stable biosignal (invasively registered arterial pressure) within acceptable time frames [17].

The purpose of the present pilot study was not to obtain a correlation of parameters of autonomous regulation with postoperative events. To achieve this goal, a deeper insight into typical patterns of postoperative autonomic dysfunction has to be gained. Analysing a homogenous, low-risk population of patients with normal preoperative baroreflex function, the aim of our study was to find a set of parameters, adequate times of measurement and an acceptable mode of biosignal recording enabling us to perform a prospective study on the predictive value of markers of autonomous control for risk stratification in the postoperative course.

By combining DSM with HRV and BPV we were able to demonstrate suppression of vagal regulation immediately after surgery, which does not recover within the first day; these findings confirm earlier works in the literature. There are a variety of hypotheses on the reasons for this suppression: mechanical trauma, use of heart lung machine, volume overloading or the influence of several accompanying diseases or conditions like diabetes, hypertension, age or preoperative smoking [18,19]. Despite extensive research, most attempts to improve perioperative strategies or to use these data for postoperative risk stratification—as successfully demonstrated in the ATRAMI-study—failed.

One reason may be that, in many of these studies, only a part of all parameters characterising the overall autonomic function was analysed. Therefore, we chose a more comprehensive approach including strength and number of bradycardic and tachycardic fluctuations in different regions of regulation, HRV, BPV and methods of nonlinear dynamics.

Sympathetic regulation is also depressed at the beginning of the observation period, but recovers until 20 h postoperatively. These data are supported by the analysing HF and LF of BPV. Thus a relative predominance of sympathetic regulation leading to a more regular behaviour of the cardiovascular system [2]. It is, however, unclear, why these parameters recover until 20 h, while sympathetic predominance still persists.

Heart rate turbulence, a parameter recently described to be useful in risk stratification after myocardial infarction, was not included, because the method is dependent on the existence of ventricular premature beats and an observation period of 30 min seems to be short for meaningful analysis [20].

In this study, we were able to demonstrate that analysis and description of postoperative autonomic control is possible using a comprehensive set of parameters and short-term registration of a comparably stable single biosignal. It is concluded that immediately after cardiac surgery suffer patients from an imbalance of vagal and sympathetic regulation, which is not recovered 20 h after surgery. Although this imbalance may lead to an increased susceptibility for tachyarrhythmia, this pilot study was only conceived as a first step to get a closer look at possible alterations of autonomic regulation during the postoperative ICU-course in patients with CHD. Due to the selection, these patients all had uneventful courses without major complications; therefore, a correlation with clinical parameters does not seem to yield meaningful information at the present state of knowledge. Further studies with larger patient cohorts, including patients at higher operative risk, are now warranted to elucidate a possible prognostic value of autonomic control for postoperative complications as for example fatal arrhythmias.

References


Appendix A. Conference discussion

Dr L. Bockeria (Moscow, Russia): Did you use the results you got in your practice?

Dr Bauernschmitt: Not yet, because I think we have to include more patients and patients who are prone to complications. Among these patients, only four, for example, had atrial fibrillation days after surgery, which is due to our patient selection, of course, because these were quite healthy patients. But I think in the future if we do more extended studies we could use it as a base of, for example, prophylactic antiarrhythmic therapy.