# DECREASED BAROREFLEX SENSITIVITY: PREDICTOR FOR POSTOPERATIVE ATRIAL FIBRILLATION?

R. Bauernschmitt*, N. Wessel**, H. Malberg***,
G. Brockmann*, C. Zinser*, R. Lange*

* German Heart Center Munich, Dept. of Cardiovascular Surgery, Munich, Germany
** Dept. of Physics, University of Potsdam, Germany
***Institute for Applied Informatics, Karlsruhe Research Center, Germany

Bauernschmitt@dhm.mhn.de

**Abstract: Atrial fibrillation (AF) occurs in 20-40% of patients after open heart surgery, leading to incrased morbidity and prolonged hospital stay. Cardiac surgery per se leads to decreased baroreflex sensitivity (BRS) and heart rate variability (HRV), so the aim of the present study was to analyse the impact of the cardiovascular autonomic system on the development of postsurgical AF. 51 patients undergoing open heart surgery were included. Blood pressure, ECG, peripheral oxygen saturation and respiratory rate were recorded the day before and 24h after surgery. BRS was calculated by the Dual Sequence Method, HRV and nonlinear dynamics by standard methods. 18 patients developed AF during the first postoperative week, while 33 remained in sinus rhythm throughout the observation period. Patients with AF showed a significantly reduced BRS concerning the bradycadic regulation reduced tachycardic response. In both groups, surgery caused a decrease of BRS and HRV. Nonlinear dynamics revealed a tendency towards decreased system complexity; this trend was more pronounced in patients remaining in sinus rhythm. Patients experiencing postoperative AF suffer from impaired baroreflex sensitivity present already before surgery.**

## Introduction

Supraventricular arrhythmias occur with an incidence range of 20 - 40% after open heart surgery despite improvements in anesthesia, surgical technique and medical therapy [1].

It is well known from earlier studies, that the state of the autonomic system has a major impact on survival and occurrence of arrhythmias in patients after myocardial infarction and is severely altered in patients with dilated cardiomyopathy. Inspired by these findings, we demonstrated in a pilot study, that severe imbalance of the vagal and sympathetic response is present immediately following open heart surgery potentially indicating increased susceptibility for arrhythmic events. The aim of the present study was to analyse the influence of autonomic control on the occurence of postoperative AF.

## Materials and Methods

58 consecutive patients undergoing isolated aortocoronary bypass surgery, isolated aortic valve surgery or combined aortic valve replacement and bypass surgery were included into the study after approval of the local committee of ethics and informed consent. Exclusion criteria were emergency operations, history of atrial fibrillation or ventricular arrhythmias, and use of the radial artery as bypass graft.

Occurrence of atrial fibrillation or severe psychosyndrome within the first postoperative day, mechanical ventilation for longer than 20 hours after surgery and the need for inotropic support exceeding low-dose dopamine 24 hours after surgery lead to post-hoc exclusion, so 51 patients remained for analysis. 1 week after surgery, the patients were divided into two groups according to the occurence of AF (18) or maintaining sinus rhythm (SR, 33). 30-min recordings of continuous noninvasive blood pressure and ECG were performed the day before surgery and at 24 hours after surgery at a sampling frequency of 1000 Hz. BRS was calculated by the Dual Sequence Method, HRV parameters and nonlinear dynamics of beat-to-beat intervals were estimated using standard methods.

*Baroreflex: Dual Sequence Method (DSM).* Using the DSM, the most relevant parameters for estimating the spontaneous baroreflex are the slopes as a measure of sensitivity [2] . The DSM is based on standard sequence methods with several modifications: Two kinds of BBI responses were analysed: bradycardic (an increase in systolic blood pressure (SBP) that causes an increase in the following beat-to-beat-intervals (BBI) and tachycardic fluctuations (a decrease in SBP causes a decrease in BBI) fluctuations. Both types of fluctuations were analysed both in a synchronous and in a 3-interbeat-shifted mode. The bradycardic fluctuations primarily represent the vagal spontaneous baroreflex, analysis of the tachycardic fluctuations represent the delayed responses of heart rate (shift 3) assigned to the slower sympathetic regulation. The following parameter groups are calculated by DSM: (1) the total numbers of slopes in different sectors within 30 min; (2) the percentage of the slopes in relation to the total number of slopes in the different sectors ; (3) the numbers of bradycardic and tachycardic slopes; (4) the shift operation from the first (sync mode) to the third (shift 3 mode) heartbeat triple; and (5) the average slopes of all fluctuations. DSM parameters are defined as described by Malberg et al [3].

*HRV*. Regarding HRV, the following standard parameters are calculated from the time series: MeanNN (mean value of normal beat-to-beat intervals): Is inversely related to mean heart rate. sdNN (standard deviation of intervals between two normaLR-peaks): Gives an impression of the overall circulatory variability. SdaNNI (the standard deviation of successive one minutes' NN-interval mean values): Quantifies long-range variabilities. Rmssd (root mean square of successive RR-intervals): Higher values indicate higher vagal activity. pNN50 (percentage of RR-interval-differences greater than 50 ms): Again, higher values indicate higher vagal activity. Shannon (the Shannon entropy of the histogram): Quantification of RR-interval distribution.

New parameters can be derived from methods of nonlinear dynamics, which describe complex processes and their interrelations. These methods provide additional information about the state and temporal changes in the autonomic tonus. Several new measures of non-linear dynamics in order to distinguish different types of heart rate dynamics as proposed by Wessel [4] were used. 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.

The Shannon and Renyi entropies calculated from the distributions of words ('fwshannon', 'fwrenyiO25' - a = 0.25, ˡfwrenyi4' - a = 4) are suitable measures for the complexity in the time series (,a' represents a threshold parameter). Higher values of these entropies refer to higher complexity in the corresponding time series and lower values to lower ones. A high percentage of words consisting only of the symbols '0' and '2' ('wpsumO2') reflects decreased HRV, increased HRV ('wpsum13') is characterised by a high percentage of all words containing the symbols T and '3'.

The parameter 'Forbidden words' reflects the number of words which never or very rarely occur. A high number of forbidden words is typical for regular behaviour, while in highly complex time series, only very few forbidden words are found.

**Results**

*Baroreflex sensitivity*. In patients with postoperative sinus rhythm, strength of regulation was significantly decreased after surgery for the bradycardic and tachycardic regulations, patients experiencing postoperative AF showed a trend, but not a significant decrease caused by the operation. There was a trend to a decrease in the total number of tachycardic regulations in both groups, which failed to be significant. In more than one third of the 200 parameters included into the DSM analyses, patients in the AF group had a decreased bradycardic and tachycardic regulation preoperatively as compared to patients remaining in sinus rhythm. Postoperatively, there were no differences between the two groups (Figures 1 to 3, selected parameters).

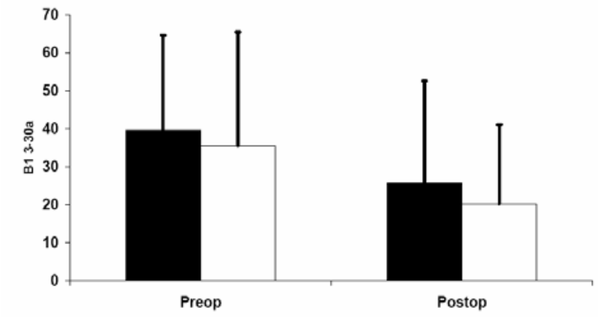


Figure 1: Number of regulations (bradycardic). Black bars: SR; white bars: AF

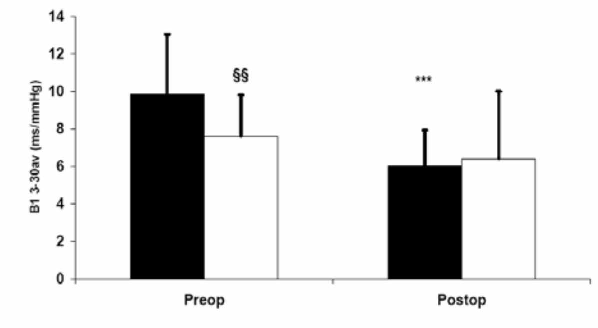


Figure 2: Strength of regulation (bradycardic). §§: $p<0.01$ vs. SR, **: $p<0.001$ vs. Preop.

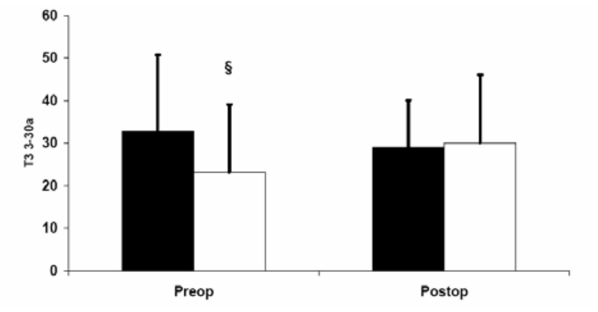


Figure 3: Number of regulations (tachycardic). §: $p<0.05$ vs. SR


ISSN: 1727-1983 © 2005 IFMBE

*Heart rate variability*. The intragroup comparison showed a significant drop of variability parameters caused by the surgical intervention in both groups. No differences were noticed between groups, either pre- or postoperatively (sdNN and SdaNN1 exemplarily depicted in figures 4 and 5). The parameters rmssd and pNN50 (data not shown) showed a similar behaviour.

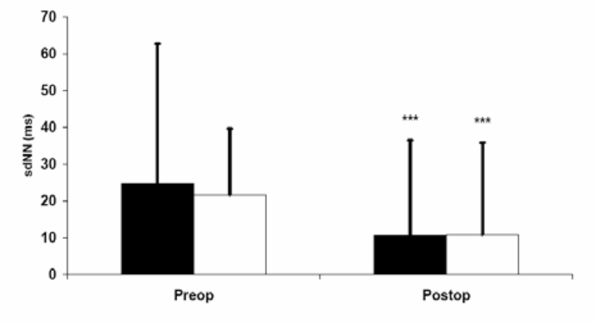


Figure 4: Standard deviation of normal-to normal intervals (sdNN) ***: $p<0.0001$ vs. Preop.

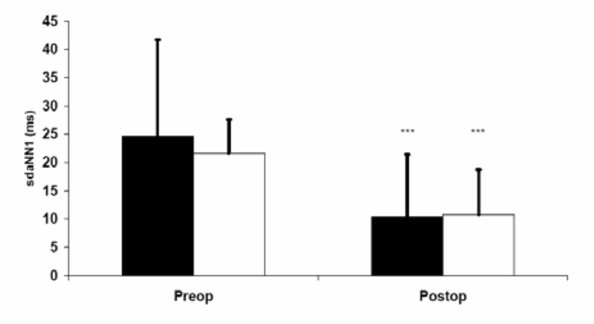


Figure 5: Standard deviation of normal-to normal intervals (sdNN) ***: $p<0.0001$ vs. Preop.

*Nonlinear dynamics.* The number of ‚Forbidden Words' is depicted in figure 6. Patients remaining in sinus rhythm had a significant increase after surgery, in patients with postoperative AF the trend was not significant. Preoperatively, the AF group had a higher number of forbidden words as compared to the SR-group, postoperative analyses did not reveal intergroup differences. The Shannon Entropy showed a uniform decrease in both groups (Figure 7).

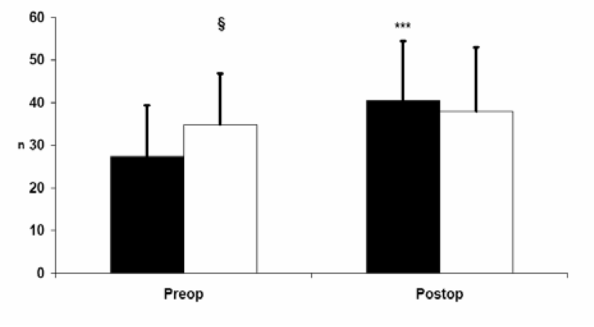


Figure 6: Forbidden words. §: $p<0.05$ vs. SR ***: $p<0.0001$ vs. Preop.

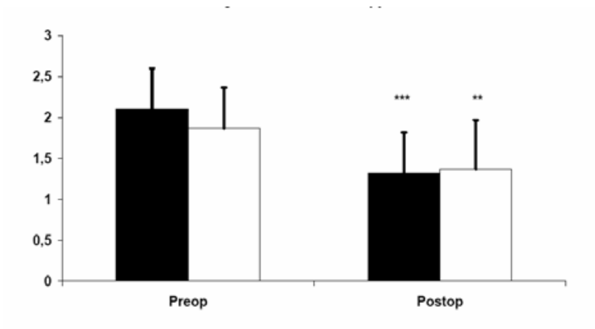


Figure 7: Shannon entropy. **: $p<0.001$ vs. Preop. ***: $p<0.0001$ vs. Preop.

## Discussion

In contrast to several previous studies, we used a more complex and multiparametric approach, including bradycardic and tachycardic fluctuations of BRS, time domain analysis of HRV, and nonlinear dynamics of HRV; the combination of these parameters proved to more effectively characterise the functional state of the cardiovascular autonomic system in earlier works [5]. Atrial fibrillation is the most frequent complication after cardiac surgery, potentially leading to subsequent adverse events like stroke and to prolonged hospital stay. Attempts have been numerous to predict this complication from demographic data, ECG-abnormalities or the atrial size, less attention has been focused on the autonomous control of the cardiovascular system. In a previous study we were able to show that heart surgery with ECC leads to a marked alteration of baroreflex sensitivity and heart rate variability, as expressed by time and frequency domain parameters and nonlinear dynamics, respectively [6]. This study included only patients with isolated CABG-surgery, normal LV-function and a mean age of 60 years. As expected, the rate of AF and other postoperative complications was low, and therefore no correlation analysis of the autonomous function and clinical parameters was performed. The present study was designed to analyse the impact of the cardiovascular autonomous regulation on the occurence of postoperative AF. One third of the patients experienced postoperative AF, which was within the expected range.

*Baroreflex sensitivity*. In the preoperative DSM-analyses, a significantly lower BRS for the bradycardic and tachycardic regulation was found in patients developing postoperative AF. At first sight, these findings seem to sharply contrast with an earlier work published by Chen et al [7], where BRS was found to be increased in patients with atrial fibrillation. However, Chen's study was done in patients without surgery and paroxysmal AF; therefore, the discrepancies may just reflect the different pathophysiological mechanisms leading to spontaneous or postsurgical AF. Herweg and coworkers [8] even demonstrated, that AF can be preceded either by an increase or decrease of the HF-component of the power spectrum, indicating that vagal stimulation or depression can cause paroxysmal AF. These data confirm the assumption, that the problem of induction of different types of AF in different patients is far from being solved. Our results are partially in accordance with data from patients suffering from recurrent AF after cardioversion [9] or recurrence of ventricular arrhythmias [10] demonstrating a decreased BRS as a predictor for the onset of recurring arrhythmias. Patients remaining in SR showed a significant decrease of the strength of regulation in the bradycardic responses, thus closely matching the results of our pilot study. In patients developing postoperative AF, this reduction was not significant. The intergroup differences were not evident any more at 24h after surgery, indicating that the occurrence of postsurgical AF is not solely an effect of surgery, but also due to a certain predisposition present already prior to surgery. From these data, it can be hypothesized, that a higher ability of the autonomous nervous system to react to pressure fluctuations may be protective to overcome the strong arrhythmic stimuli obviously generated by the surgical intervention.

*Heart rate variability.* Most of the time and frequency domain parameters of HRV showed a strong tendency towards less variability and a predominance of sympathetic regulation after the operation; there were no major differences between the two groups, which corresponds to the previous findings by other authors. A reduction of HRV during surgery has already been observed by Souza and coworkers [11] and was attributed to the influences of anesthesia. The postoperative analyses in our patients, however, were done several hours after termination of sedative agents, so the persisting contribution of anesthesia is unlikely. These long-term effects, obviously lasting for months [12], are probably caused by direct damage of neural fibres during surgery [13]. In nonlinear dynamics, there are only minor differences in the intergroup comparison regarding the pre- and postoperative state, respectively. However, the intergroup comparison between the pre- and postoperative measurements showed a highly significant trend towards a reduced system complexity in patients remaining in SR, while patients with AF only showed a weak tendency. So the major difference between both groups concerning these parameters is not manifested at the pre- or postoperative state, but rather by the dynamics of the process. The physiological explanation of this phenomenon is difficult. AF-patients show a tendency towards lower overall dynamic behaviour in the preoperative measurements, which may be caused by a smaller regulation power and therefore may be less affected by surgery. From these results, it can be hypothesized, that mechanisms controlling classical HRV and nonlinear dynamics are at least in part independent from each other. There are only few reports in the literature on the nonlinear dynamic behaviour of the cardiovascular system following surgery. After an initial reduction of complexity, fast recovery is described as well as persisting low complexity, depending on the parameters chosen [14]. After a look at the results of our study, these conflicting findings may be caused by the variability of initial conditions in different patients.

In the present study, a marked alteration of baroreflex sensitivity and heart rate variability caused by heart surgery with cardiopulmonary bypass could be demonstrated, thus closely matching the results of a pilot study done in a smaller, more homogenous patient collective.

Furthermore it was shown, that patients experiencing atriai fibrillation after the operation presented an overall lower baroreflex sensitivity concerning the tachycardic and bradycardic regulation; HRV-analyses using time- and frequency-domain parameters and symbolic dynamics did not show major preoperative differences between the groups. Postoperatively (which means, after surgery, but still before the first onset of AF) no differences between the groups could be detected, demonstrating the major influence of the surgical procedure.

For the future development of a risk stratification tool, the focus has to be on the preoperative state of the autonomous regulation. The effects of surgery per se seem to equalize any differences between groups. However, there may be a role of the dynamics from pre- to postoperative, which has to be further elucidated. This analysis was not done to add another risk factor for postoperative AF, but rather to get closer insight into the contributing mechanisms. Age, for example, is a very well known risk factor, but the term ,,age" is a fuzzy summary for the entity ,,pathophysiological changes usually related to age" [15] - which, in several patients, may well be present in their earlier years and in others be absent even later in life. Therefore, knowing the variety of clinical risk factors already determined, we intended to go one step beyond and to analyse not preexisting clinical conditions, but related alterations in the cardiovascular autonomous system. Further studies in larger patient populations now have to evaluate the predictive value of BRS for postoperative AF and to define a subset of the most suitable parameters and their cutoff-points. These informations may be used to guide prophylactic antiarrhythmic therapy.

## References

[1] MOOSS A.N., WURDEMAN R.L., SUGIMOTO J.T. et al (2004): `Amiodarone versus sotalol for the treatment of atrial fibrillation after open heart surgery: the Reduction in Postoperative Cardiovascular Arrhythmic Events (REDUCE) trial`, *Am. Heart J.*,148, pp. 641-8


ISSN: 1727-1983 © 2005 IFMBE

[2] MALBERG H., WESSEL N., SCHIRDEWAN A., OSTERZIEL K.J., VOSS A. (1999): `Duale Sequenzmethode zur Analyse der spontanen Baroreflexsensitivitat bei Patienten mit dilatativer Kardiomyopathie`, *Z Kardiol*, 5(88), pp. 331-337

[3] MALBERG H., WESSEL N., HASART A., OSTERZIEL K.J., VOSS A. (2002):`Advanced analysis of the spontaneous baroreflex sensitivity, blood pressure and heart rate variability in patients with dilated cardiomyopathy`, *Clin. Sci.*, 102, pp. 465-473

[4] WESSEL N., VOSS A., MALBERG H. et al. (2000):`Nonlinear analysis of complex phenomena in cardiological data`, *Herzschr. Elektrophys.*, 11, pp. 159-173

[5] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996): `Heart rate variability: standards of measurement, physiological interpretation and clinical use`, *Circulation*; 93, pp. 1043-1065

[6] BAUERNSCHMITT R., MALBERG H., WESSEL N., KOPP B., SCHIRMBECK E.U., LANGE R. (2004): ´Impairment of cardiovascular autonomic control in patients early after cardiac surgery`, *Eur. J. Cardiothorac. Surg.*, 25, pp. 320-6

[7] CHEN Y.J., CHEN S.A., TAI C.T., WEN Z.C., FENG A.N., DING Y.A., CHANG M.S. (1998): `Role of atrial electrophysiology and autonomic nervous system in patients with supraventricular tachycardia and paroxysmal atrial fibrillation`, *J. Am. Coll. Cardiol.*, 32(3), pp. 732-8

[8] HERWEG B., DALAI P., NAGY B., SCHWEITZER P. (1998): `Power spectral analysis of heart period variability of preceding sinus rhythm before initiation of paroxysmal atrial fibrillation`, *Am. J. Cardiol.*, 1,82(7), pp. 869-74

[9] BUDEUS M., HENNERSDORF M., PERINGS C., STRAUER B.E. (2004): ´The prediction of atrial fibrillation recurrence after electrical cardioversion with the chemoreflex sensitivity`, *Z. Kardiol.* , 93(4), pp. 295-9

[10] RACZAK G., PINNA G.D., MAESTRI R., et al. (2004): `Different predictive values of electrophysiological testing and autonomic assessment in patients surviving a sustained arrhythmic episode`, *Circ. J.*, 68(7), pp. 634-8

[11] SOUZA NETO E.P., LOUFOUAT J., SAROUL C., PAULTRE C., CHIARI P., LEHOT J.J., CERUTTI C. (2004): `Blood pressure and heart rate variability changes during cardiac surgery with cardiopulmonary bypass`, *Fundam. Clin. Pharmacol.*, 18(3), pp. 387-96

[12] CYGANKIEWICZ I., WRANICZ J.K., BOLINSKA H., ZASLONKA J., JASZEWSKI R., ZAREBA W. (2004): `Influence of coronary artery bypass grafting on heart rate turbulence parameters`, *Am. J. Cardiol.*, 15, 94(2), pp. 186

[13] NIEMELA M.J., AIRAKSINEN K.E., TAHVANAINEN K.U., LINNALUOTO M.K., TAKKUNEN J.T. (1992): `Effect of coronary artery bypass grafting on cardiac parasympathetic nervous function`, *Eur. Heart J.*, 13(7), pp. 932-5

[14] STORELLA R.J., HORROW J.C., POLANSKY M. (1999): ´Differences among heart rate variability measures after anesthesia and cardiac surgery`, *J. Cardiothorac. Vase. Anesth.*, 13, pp. 451-3

[15] LIPSITZ L.A. (2004): ´Physiological complexity, aging, and the path to frailty´, *Sci. Aging Knowledge Environ.*, 21; p.16


ISSN: 1727-1983 © 2005 IFMBE