Depression of cardiovascular autonomic function is more pronounced after mitral valve surgery: evidence for direct trauma

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The analysis of baroreflex sensitivity (BRS) and heart rate variability (HRV) leads to additional insights into patients' prognosis after cardiovascular events. The following study was performed to assess the differences in the post-operative recovery of autonomic regulation after mitral valve (MV) and aortic valve (AV) surgery with a heart–lung machine. Among the 43 consecutive male patients enrolled in a prospective study, 26 underwent isolated AV surgery and 17 isolated MV surgery. Blood pressure as well as ECG signals were recorded the day before, 24 hours after and one week after surgery. BRS was calculated according to the dual sequence method, and HRV was calculated using standard linear as well as nonlinear parameters. There were no major differences between the two groups in the pre-operative values. At 24 hours a comparable depression of HRV and BRS in both groups was observed, while at 7 days there was partial recovery in AV patients, which was absent in MV patients: p(AV versus MV) < 0.001. While the response of the autonomic system to surgery is similar in AV and MV patients, there is obviously a decreased ability to recover in MV patients, probably attributed to traumatic lesions of the autonomic nervous system by opening the atria. Ongoing research is required for further clarification of the pathophysiology of this phenomenon and to establish strategies to restore autonomic function.

Keywords: cardiac surgery; baroreflex sensitivity; heart rate variability

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1. Introduction

In the past decade, alteration of cardiovascular autonomic function has been identified as a powerful predictor of fatal outcome in patients after myocardial infarction. Especially, the imbalance of sympathetic and parasympathetic nervous system resulting in a relative predominance of the sympathetic tone puts the patient at a higher risk of adverse cardiac events (La Rovere *et al.* 2001). The well-known depression of cardiovascular autonomic function following cardiac surgery is related to a variety of reasons such as anaesthesia and the use of the heart–lung machine (Brown *et al.* 2003; Bauernschmitt *et al.* 2004, 2007). The role of direct surgical trauma to the autonomic nerves (ANs) is still unclear owing to the fact that earlier studies analysed either patients with isolated coronary surgery with trauma to nerve fibres being unlikely, or cohorts with mixed surgical procedures with surgical trauma supposed to be different among the individuals. As no comparative, prospective studies analysing operative strategies leading to different amounts of traumatization have been performed so far, the hypothesis of direct surgical damage of autonomic fibres remained highly speculative (Brown *et al.* 2003). The following study was performed comparing patients with isolated aortic valve (AV) replacement (the surgical trauma to AN is considered to be low) or isolated mitral valve (MV) surgery (high surgical trauma to AN is expected). With regard to the hypothesis that there is a traumatic lesion of the cardiovascular autonomic nervous system by opening the atria, we observe the post-operative recovery of AV and MV patients.

2. Methods

(*a*) *Subjects*

A total of 60 consecutive male patients undergoing either isolated MV or isolated AV surgery and being in stable sinus rhythm were enrolled in a prospective study. Prolonged intubation time and/or prolonged need for inotropic support after surgery led to ex-post exclusion of the respective patient, so 43 patients remained for analysis (table 1). Of them, 26 underwent AV surgery and 17 MV surgery. In order to maintain the best possible uniformity of the cohorts, patients with concomitant cardiac diseases and/or additional procedures on the heart or great vessels were excluded from the study. The mean age of the AV patients and MV patients was 62 ± 13 years and 59 ± 12 years, respectively. Patients with concomitant coronary heart disease were excluded for the known effects of atherosclerosis.

(*b*) *Surgical procedures*

Peri-operative medication was standardized. Anaesthesia was standardized; 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 and arterial pressure by cannulation of the radial artery. All operations were carried out with

Table 1. Patient characteristics.

	mitral valve	aortic valve
n	17 (39.53%)	26 (60.47%)
mean age (years)	58.82 ± 12.13	62.19 ± 12.98
NYHA	2.29 ± 0.77	2.7 ± 0.54
hypertonic	4 (23.53%)	12 (46.15%)
LVEF	0.64 ± 0.15	0.57 ± 0.17
time at heart–lung machine	108.71 ± 36.11	91.24 ± 29.83
diabetes	0 (0%)	4 (15.38%)
beta blocker	7 (41.18%)	11 (42.31%)
ACE inhibitors	9 (52.90%)	12 (46.15%)

cardiopulmonary bypass in mild hypothermia (32–34°C) and pulsatile perfusion mode, cold crystalloid cardioplegia was used for cardiac arrest after cross-clamping the aorta. Surgical access to the AV was achieved by horizontal transection of the anterior aspect of the ascending aorta, while access to the MV was performed by opening the left atrium close to the interatrial groove. After declamping, most of the patients needed one countershock to terminate ventricular fibrillation.

(*c*) *Recording protocol*

After 10 min equilibrations to the environment, non-invasive blood pressure signals were collected from the radial artery by a tonometer (Colin Medical Instruments) at 1000 Hz. Data were channelled into a bedside laptop after A/D conversion and stored for analysis. Simultaneously, breathing excursions and a standard ECG were monitored. Data were sampled for a 30 min period the day before, 24 hours after and 7 days after surgery in the intensive care unit. Care was taken to perform the measurements at the same time of day in each patient. From the recorded data, the beat-to-beat intervals (BBIs) as well as the beat-to-beat systolic and diastolic values were extracted; premature beats, artefacts and noise were excluded using an adaptive filter considering the instantaneous variability (Wessel *et al.* 2007).

(*d*) *Heart rate variability*

Standard methods of analysis of heart rate variability (HRV) include time- and frequency-domain parameters (Task Force 1996). Time-domain parameters are based on simple statistical methods derived from the RR intervals as well as the differences between them. Mean heart rate is the simplest parameter, but the standard deviation over the whole time series (sdNN) is the most prominent HRV measure for estimating overall HRV. A list of calculated parameters is given in table 2. Time-domain geometrical methods (Task Force 1996) are methods where the BBIs are converted into special geometrical forms quantifying their distribution. A disadvantage of these methods is that they require a considerable number of RR intervals, and thus they are not applicable to very short-term time series. We introduced a more robust method to quantify

Table 2. Description of time- and frequency-domain parameters, standards (Task Force 1996) and additional measures we developed (•). (BBI here stands for the filtered BBIs (NN intervals).)

variable	units	definition
time-domain methods		
meanNN	ms	mean BBI
sdNN	ms	standard deviation of all BBI values
cvNN	none	coefficient of variation: sdNN/meanNN
rmssd	ms	root mean square of successive BBI differences
pNN50	%	percentage of NN-interval differences greater than 50 ms
•pNNX	%	percentage of beat-to-beat differences greater than X ms (e.g. $X = 100/200$ ms)
•pNNlX	%	percentage of beat-to-beat differences lower than X ms (e.g. $X = 10/20/30$ ms)
•Shannon	none	Shannon entropy of the histogram (density distribution of the BBI values)
•RenyiX	none	Renyi entropy of order X of the histogram (e.g. $X = 2/4/0.25$)
frequency-domain methods		
P	ms^2	total power from 0 to 0.4 Hz
VLF	ms^2	very low-frequency band 0.0033–0.04 Hz
LF	ms^2	low-frequency band 0.04–0.15 Hz
HF	ms^2	high-frequency band 0.15–0.4 Hz
LF/HF	none	quotient of LF and HF
LFn	none	normalized low-frequency band (LF/(LF+HF))

the distribution (Voss *et al.* 1995) based on information theory; in particular the method uses the Shannon and the Renyi entropy of the histogram. We demonstrated the usefulness for risk stratification after 2 years in a blinded study (Voss *et al.* 1998).

Frequency-domain HRV parameters enable one to analyse periodic dynamics in the heart rate time series (Akselrod *et al.* 1981). The Task Force (1996) recommended that power spectral analysis of at least 5 min ECG recordings should be used to assess autonomic physiology and pharmacology. Very low, low and high frequencies (table 2) can be estimated from such ECG recording. The high-frequency power reflects the modulation of vagal activity by respiration whereas the low-frequency power represents vagal and sympathetic activities via the baroreflex (BR) loop. The low- to high-frequency ratio is used as an index of sympathovagal balance (Malliani *et al.* 1991). The capability of frequency-domain parameters for risk stratification of post-infarction patients was proven by Bigger *et al.* (1992)—a reduction in the ultra low- and very low-frequency power is associated with pathologies.

HRV reflects the complex interactions of many different control loops of the cardiovascular system. In relation to the complexity of the sinus node activity modulation system, a predominantly nonlinear behaviour has to be assumed (Porta *et al.* 2009; Voss *et al.* 2009). Thus, the detailed description and classification of dynamic changes using time and frequency measures are often not sufficient. We have shown already in 1995 that symbolic dynamics is an efficient

approach to analyse dynamic aspects of HRV (Kurths *et al.* 1995; Voss *et al.* 1995). The first step in this analysis is the transformation of the time series into symbol sequences with symbols from a given alphabet. Some detailed information is lost in this process, but the coarse dynamic behaviour can be analysed. We consider the following measures of complexity.

(i) The Shannon entropy H_k ('FWshannon') calculated from the distribution p of words is the classic measure for complexity in time series,

$$H_k = - \sum_{\omega \in W^k, p(\omega)>0} p(\omega) \log p(\omega), \qquad (2.1)$$

where W^k is the set of all words of length k. Larger values of Shannon entropy refer to higher complexity in the corresponding tachograms and lower values to lower ones.

(ii) Next, we count the 'forbidden words' in the distribution of words with length 3—that is, the number of words that never or only seldom occur. A high number of forbidden words indicates a rather regular behaviour in the time series. If the time series is highly complex in the sense of Shannon, only a few forbidden words will be found.

(iii) To quantify low-variability epochs, we introduce the parameter POLVAR10 (Wessel *et al.* 2000, 2003). In this way, successive symbols of another simplified alphabet, consisting of only symbols '0' and '1', were analysed. Here the symbol 0 stands for a small difference between two successive beats, whereas 1 represents those cases where the difference between two successive beats exceeds this special limit:

$$s_n = \begin{cases} 1: & |x_n - x_{n-1}| \geq 10 \text{ ms} \\ 0: & |x_n - x_{n-1}| < 10 \text{ ms}. \end{cases} \qquad (2.2)$$

Only those words consisting of a unique type of symbol (either all 0 or all 1) were counted. To get a statistically appropriate estimate of the word distribution, we choose words of length 6 where again a maximum of 64 different types of word can occur. POLVAR10 represents the probability of occurrence of the word type '000000' and is able to detect even intermittent decreased variability. Note that the special limit of 10 ms can be adapted to other values if necessary, for instance in animal studies.

(e) Baroreflex sensitivity

Using the dual sequence method (DSM; Malberg *et al.* 2002), similar to the method proposed by Bertinieri (Bertinieri *et al.* 1985), the most relevant parameters for estimating the spontaneous BR are the slopes as a measure of sensitivity. The DSM is based on the standard sequence methods with several modifications—two kinds of BBI responses were analysed: bradycardic (an increase in systolic blood pressure (SBP) causes an increase in the following BBI) and tachycardic fluctuations (a decrease in SBP causes a decrease in BBI). The two types of fluctuations were analysed both in a synchronous and in

a three-interbeat-shifted mode. The bradycardic fluctuations primarily represent the superiority of vagal regulation (increased vagal tone or decreased sympathetic tone), while tachycardic fluctuations represent the predominance of the sympathetic system. The effects of vagal regulation usually can be observed very early, i.e. in the following heartbeat; sympathetic fluctuations are best monitored after a three-heartbeat delay (shift 3). The following parameter groups are calculated by DSM: (i) the total numbers of slopes in different sectors within 30 min, (ii) the percentage of the slopes in relation to the total number of slopes in the different sectors, (iii) the numbers of bradycardic and tachycardic slopes, (iv) the shift operation from the first (sync mode) to the third (shift 3 mode) heartbeat triple, and (v) the average slopes of all fluctuations. Then

$$\text{BRS} = \frac{\Delta\text{BBI}}{\Delta\text{SBP}}. \tag{2.3}$$

In contrast to the classical BR sensitivity (BRS) methods, the DSM defines slope sectors that allow one to quantify the BRS slope distribution. Sectors with a range of 5 ms mm Hg^{-1} have been proven to act as a suitable partition. The slope sectors are defined as

$$\text{slope sector}\,[\text{ms mm Hg}^{-1}]: \quad \text{`0}-5\text{' (very low BRS slopes)}$$

$$\text{slope sector}\,[\text{ms mm Hg}^{-1}]: \quad \text{`5}-10\text{', ..., `25}-30\text{', `} <30\text{'} \tag{2.4}$$

$$\text{(expected physiological BRS).}$$

Then, the percentages of BRS events in different slope sectors to the total BRS number can be estimated. Moreover, these values are normalized to the mean heart rate. These parameters are calculated for bradycardic as well as tachycardic fluctuations, which are synchronous or delayed, to analyse a possibly delayed response of the heart rate to the same blood pressure oscillation. Using this DSM method, sequences of length 3 are quantified; longer sequences turned out not to be useful for spontaneous BRS estimation because of their low occurrence. From the DSM, additional parameters have been derived. The parameter 'BBI slope' represents the average increases of three consecutive BBIs in ms per beat. This phenomenon can be assigned to the BRS, the respiratory sinus arrhythmia and other influences. 'BBI slope range' is assigned to the average difference between the maximum and the minimum BBI during such a BBI slope.

Statistical analysis was performed by the non-parametric Mann–Whitney *U*-test.

3. Results

The post-operative clinical course was comparable in both patient groups. The number of major post-operative complications was low without differences between groups (table 3).

There were no major differences between the two groups pre-operatively. At 24 hours after surgery, both groups showed a depression of HRV and BRS parameters, which was more pronounced in the MV group. One week after

Table 3. Major post-operative complications. (VPB, ventricular premature beats; ICU, intensive care unit.)

	AV	MV
post-operative infection	1	0
circ. instability	0	0
VPB	1	2
AV block III	2	0
ICU stay (days)	5.3 ± 5	4.7 ± 3.2
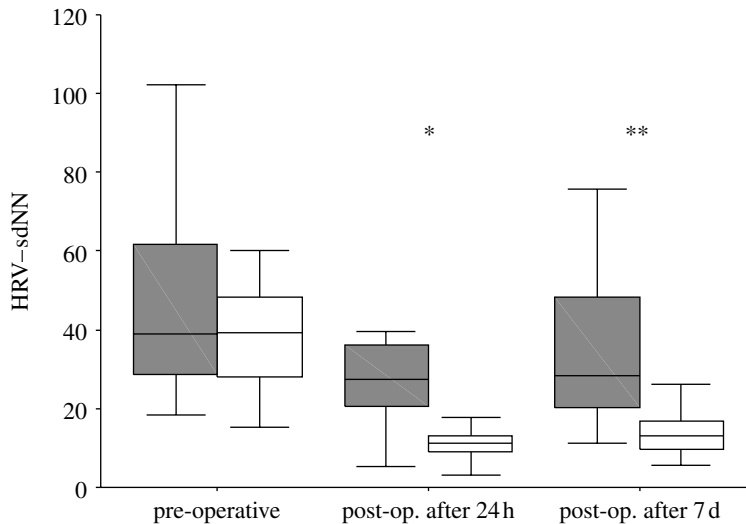
Figure 1. HRV–sdNN: HRV–standard deviation of the BBIs ($^{*}p < 0.01$, $^{**}p < 0.001$; MV (open bars) versus AV (filled bars) surgery).

surgery, however, marked differences were present: sdNN 15 ± 5 (MV) versus 27 ± 13 (AV), $p < 0.001$ (figure 1); Shannon 1.11 ± 0.28 (MV) versus 1.55 ± 0.34 (AV), $p < 0.001$ (figure 2). Similar kinetics was found for the other linear HRV parameters calculated in this study (table 4).

Regarding the nonlinear parameters quantifying decreased complexity, there was a significant elevation present already 24 hours after surgery for both groups, which, again, was more pronounced for MV patients. These alterations were even more distinct after one week (figures 3 and 4; forbidden words 48.5 ± 5.7 (MV) versus 38.6 ± 11.5 (AV), $p < 0.01$; POLVAR10 0.33 ± 0.20 (MV) versus 0.18 ± 0.22 (AV), $p < 0.01$).

The BR was impacted in a similar way for both the number and the strength of regulations (number of bradycardic synchronous BR events 3.2 ± 3.9 (MV) versus 11.2 ± 12.1 (AV), $p < 0.01$; average slope of bradycardic synchronous BR 5.2 ± 2.6 (MV) versus 6.2 ± 4.4 (AV), $p < 0.01$; figures 5 and 6). The tachycardic part of the BR, however, for both the aortic and the mitral patients failed to recover after one week (cf. 'av. slope tachy shift BR' in table 4).
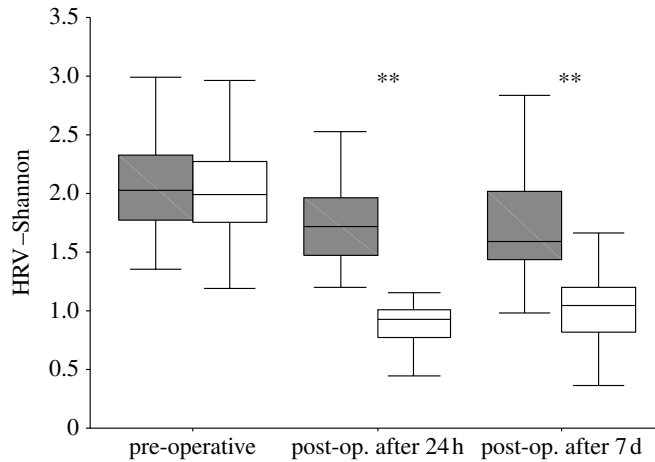
Figure 2. HRV, the Shannon entropy of the histogram ([**]$p < 0.001$; MV (open bars) versus AV (filled bars) surgery).

Table 4. Results of selected HRV as well as BRS parameters one week after cardiac surgery (Mann–Whitney U-test; n.s., not significant).

	mitral valve	aortic valve	p-value
meanNN (ms)	748.43 ± 72.90	828.71 ± 113.48	n.s.
cvNN (a.u.)	0.02 ± 0.01	0.03 ± 0.01	< 0.01
rmssd (ms)	9.50 ± 2.49	19.31 ± 14.31	< 0.01
LF (ms^2)	0.01 ± 0.02	0.09 ± 0.12	< 0.01
HF (ms^2)	0.01 ± 0.01	0.05 ± 0.08	< 0.01
LF/HF (a.u.)	2.97 ± 4.02	3.31 ± 1.90	n.s.
LFn (a.u.)	0.60 ± 0.19	0.71 ± 0.15	n.s.
FWshannon (a.u.)	1.80 ± 0.33	2.53 ± 0.75	< 0.001
Pbrady (%)	13.15 ± 3.19	13.51 ± 3.64	n.s.
Ptachy (%)	18.25 ± 3.36	16.63 ± 4.60	n.s.
activation (%)	24.55 ± 11.18	25.03 ± 13.53	n.s.
number brady sync 10–15 ms mm Hg^{-1}	0.09 ± 0.30	2.12 ± 3.31	< 0.05
perc. brady sync 10–15 ms mm Hg^{-1} (%)	0.91 ± 3.02	6.58 ± 7.96	< 0.05
number tachy shift BR	47.18 ± 13.71	40.88 ± 19.33	n.s.
av. slope tachy shift BR (ms mm Hg^{-1})	2.16 ± 0.78	4.00 ± 2.77	< 0.05
BBI slope (ms per beat)	5.39 ± 1.19	12.05 ± 8.93	< 0.001
BBI slope range (ms)	10.77 ± 2.39	24.10 ± 17.85	< 0.001

4. Discussion and conclusions

The last decade witnessed a strong increase in basic knowledge about the cardiovascular autonomic system. It has been demonstrated that the analysis of linear and nonlinear components of HRV and BRS can be a powerful tool to estimate a patient's risk of death or life-threatening events (La Rovere *et al.* 2001). However, as far as alterations in the cardiac patient and in patients undergoing open-heart surgery are concerned, we are still at the very start. Meanwhile, it is
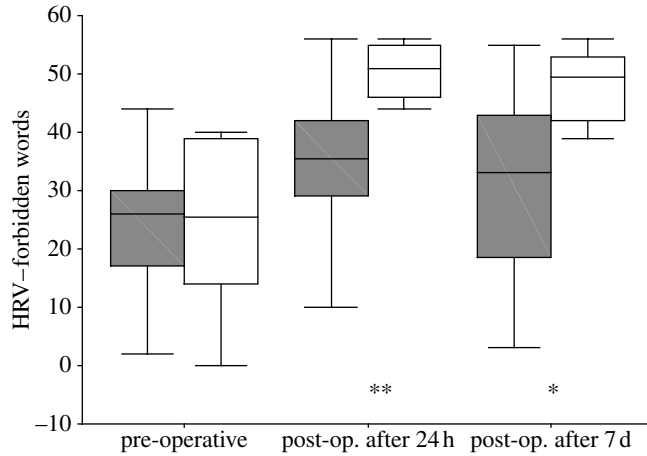
Figure 3. Nonlinear HRV, the 'forbidden words' in the distribution of words—that is, the number of words that never or only seldom occur ($^*p < 0.01$, $^{**}p < 0.001$; MV (open bars) versus AV (filled bars) surgery). A higher number of forbidden words indicates a lower complexity in the time series.
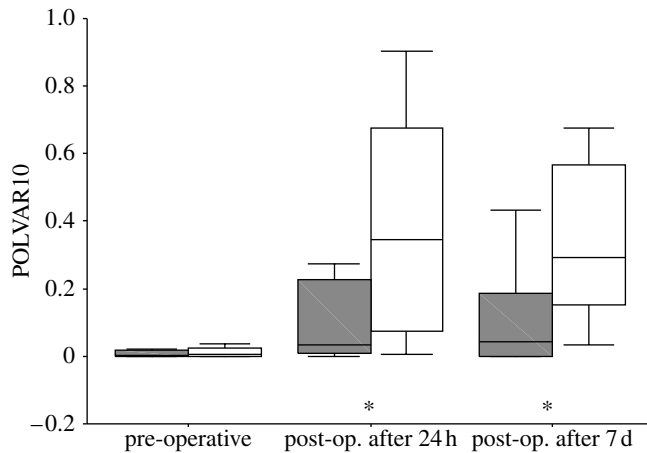

Figure 4. Nonlinear HRV, POLVAR10 represents the probability of low variability (cf. §2) and is able to detect even intermittent decreased variability ($^*p < 0.01$; MV (open bars) versus AV (filled bars) surgery).

well known that cardiac surgery leads to an early depression of autonomic function, and that there is potential for recovery after a certain time frame. The mechanisms for both phenomena are quite unclear, so the aim of the present study was to shed light on the precise role of direct surgical trauma. In contrast to the earlier studies, where different pre-operative conditions and different surgical procedures were mixed up, we focused on patients with isolated AV disease and isolated MV disease, thus excluding the well-known influences of atherosclerosis on cardiovascular autonomic function. Further on, we included male subjects only to make sure that the differences in certain regulation parameters among female and male subjects cannot influence our results. On purpose, the operative procedures carried out in these patients offer two entirely distinct entities of surgical trauma:
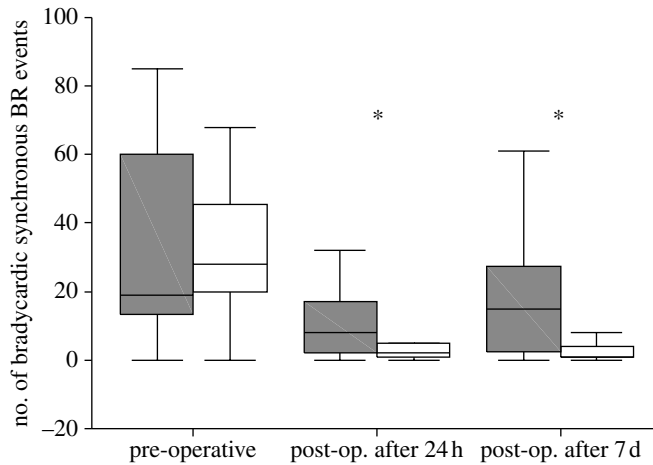
Figure 5. BRS, the number of bradycardic BR events ($^*p<0.01$; MV (open bars) versus AV (filled bars) surgery).
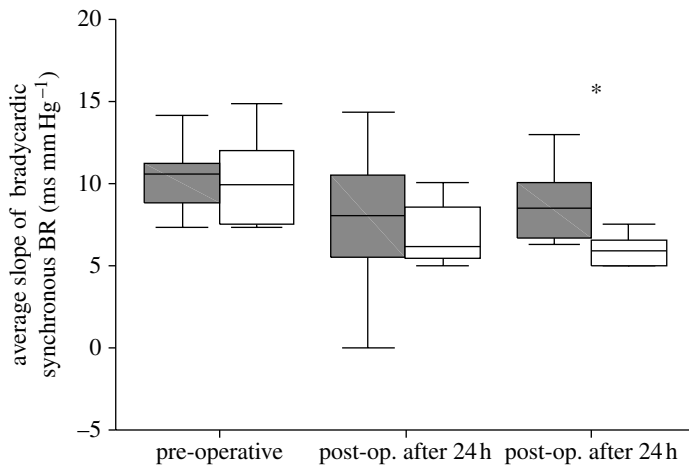

Figure 6. BRS, the average slope represents the strength of bradycardic regulations ($^*p<0.01$; MV (open bars) versus AV (filled) surgery).

while for AV replacement the heart is left more or less untouched and the valve is approached by an incision in the anterior aspect of the ascending aorta only, in MV operations both the caval veins are extensively dissected and the heart is opened by an incision right posterior to the interatrial groove, where an abundance of AN endings are supposed to be. In this study, both entities of surgical trauma are supported by distinct depressions of linear HRV parameters (e.g. sdNN) and BRS (e.g. average slope synchronous BR) as well as by clearly different elevations of the nonlinear HRV parameters (e.g. POLVAR10) for both groups. The similar depression in both groups observed at 24 hours may reflect the effects of standardized anaesthesia, general surgical trauma and peri-operative treatment being comparable in all patients. Compared with the AV patients, the MV patients showed a more pronounced depression of the autonomic system already

during the recordings 24 hours post-operatively, this effect being even more obvious after one week. In our opinion, this is a strong indicator of higher surgical trauma to AN, if the atria are dissected. Recovery of autonomic fibres is possible, even in heart transplant patients, as described earlier (Beckers *et al.* 2004); however, the situation in heart transplant recipients is entirely different from a clinical point of view owing to the complete transection of the entire heart when compared with only partial lesions in valve surgery, providing at least the possibility of faster nerve ingrowth. Apart from the effects of trauma, there is no other obvious explanation for the findings described. Demographic and operative variables and pre-operative medication were not different between the groups, with a tendency to a higher age, more advanced NYHA classification and lower left ventricular ejection fraction in patients with AV disease—thus, from a clinical standpoint, cardiac disease was more advanced in the aortic patients. This again emphasizes the role of surgical trauma in the changes of the autonomic tone. The relative predominance of the sympathetic system that has been described before (Brown *et al.* 2003; Bauernschmitt *et al.* 2004) obviously is persisting especially in patients undergoing MV surgery. Typical post-operative treatment strategies include the prescription of therapies aiming to reduce the sympathetic influence on the heart; according to our findings, special care should be taken in MV patients to additionally enhance parasympathetic function.

Analysing BR response, there was a surprising difference between bradycardic and tachycardic regulations. The parasympathetically mediated bradycardic response showed a steep decline 24 hours after surgery with a subsequent tendency to recover after one week (cf. figures 5 and 6). The sympathetically mediated tachycardic regulation was not altered or only slightly reduced 1 day after the operation, but had no tendency to recover or even revealed a further significant decrease one week after the operation. These results can be confirmed by the tachycardic-shifted BR regulation (sympathetic part, represented by 'number tachy shift BR' and 'av. slope tachy shift BR' in table 4) and the bradycardic synchronous regulation (cf. figures 5 and 6 and 'number+perc. brady sync 10–15 ms mm Hg^{-1}' in table 4) and the BBI slopes (vagal mediated regulation, cf. table 4). The BR-effective BP regulation showed no alteration after one week (cf. parameters 'Pbrady' and 'Ptachy' in table 4). So in contrast to the vagal portion, the sympathetically mediated part of the autonomic system seems to be more severely altered by changes taking place after the operation as compared with intra-operative adverse effects. A major influence of medication given in the post-operative period again can most probably be ruled out, because there was no striking difference in drugs applied at day 7. Scar formation accompanied by a sterile inflammatory reaction of the surface of the heart and the pericardium seems either to affect the sympathetic fibres or to amplify vagal modulations whereby finally the tachycardic regulation is impaired. However, owing to the vagal innervation being predominantly present in the endocardium, while sympathetic fibres end at both the epi- and endocardium (Marron *et al.* 1995), we suppose that processes affecting the surface of the heart may have a stronger influence on the sympathetic system.

Long-term changes were not assessed in this study. While it would be of interest in order to estimate the ongoing progression in recovery, on the other hand, during the hospital stay of the patient the influence of physiological perturbations and of various drug regimens can widely be controlled, thus allowing for the best possible

comparison among groups. After discharge, patients will start to exercise at different levels and will be pharmacologically treated by different home physicians, which may make meaningful comparisons very difficult. The left ventricular remodelling induced by AV or MV disease may differ from one another, and the extent of left ventricular hypertrophy in patients with AV disease is usually high. Patients with left ventricular hypertrophy for any reason are considered to have lower HRV parameters when compared with healthy controls (Alter *et al.* 2006). However, the baseline parameters in the two groups of our study did not reveal any differences, thus probably reflecting the effects of the pre-existing heart disease in both kinds of valvular lesions.

Summarizing, we found evidence indicating that direct surgical trauma is likely to be one of the mechanisms leading to the depression of cardiovascular autonomic function. The diversity of results in earlier studies may be caused by the case mix of patients, comprising different initial conditions as well as different extents of trauma.

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