Biomed Tech 2011; 56:185–193 © 2011 by Walter de Gruyter • Berlin • Boston. DOI 10.1515/BMT.2011.017

Preserved autonomic regulation in patients undergoing transcatheter aortic valve implantation (TAVI) – a prospective, comparative study

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Abstract

Heart rate and blood pressure variability as well as baroreflex sensitivity (BRS) lead to additional insights on the patients' prognosis after cardiovascular events. The following study was performed to assess the differences in the postoperative recovery of the autonomic regulation after transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement (SAVR). Fifty-eight consecutive patients were enrolled in a prospective study; 24 underwent TAVI and 34 SAVR. BRS was calculated according to the Dual Sequence Method, heart rate variability (HRV) was evaluated using standard linear as well as nonlinear parameters. HRV and BRS parameters were reduced after surgery in patients with SAVR only (meanNN: $p<0.001$, sdNN: $p<0.05$, Shannon: $p<0.01$, BRS: $p<0.01$), while these indexes were preserved in patients after TAVI. Simultaneously, an increased complexity of blood pressure (BP) in SAVR patients (fwShannon: $p<0.001$, fwRenyi4: $p<0.001$), but not in TAVI patients was recorded. In this study we were able to demonstrate for the first time that, in contrast to patients undergoing conventional open surgery, there are fewer alterations of the cardiovascular autonomic system in patients with TAVI.

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Keywords: baroreflex sensitivity; blood pressure variability; heart rate variability; transcatheter valve procedures.

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 [2, 14]. In particular, the imbalance of the 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 [15]. 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 [3, 4, 7]. The role of direct surgical trauma to the autonomic nerves, also leading to a depression of the cardiovascular autonomic function, has been clarified by performing a comparative, prospective study which analysed patients undergoing isolated mitral valve and isolated aortic valve replacement [22]. The lack of recovery one week after surgery was significantly higher in patients undergoing isolated mitral valve surgery than for isolated aortic valve replacement so that a direct surgical damage of autonomic fibres is most certain [22]. Despite the improved recovery of patients undergoing isolated aortic valve replacement, compared to those who underwent isolated mitral valve surgery, cardiovascular autonomic function remains depressed after surgery with the heart-lung machine at least during one week. Therefore we still face an imbalance of the cardiovascular autonomic function which is normally associated with predominant sympathetic activity, as mentioned above. Thus the risk of postoperative arrhythmias, especially in the vulnerable phase which persists until two weeks after surgery, continues to be high.

The new technology of transcatheter aortic valve implantation has been developed to minimize the operative trauma in high-risk patients with severe symptomatic aortic stenosis who are refused conventional surgical aortic valve replacement. After the pioneering works of Grube et al., Walther et al. and Webb et al. [10, 27, 28], who demonstrated the technical feasibility, a growing number of centres are introducing the transcatheter aortic valve implantation procedure. Hereby, the teams usually specialise in either the percutaneous transfemoral or the transapical access, depending on their specialisation (cardiology or surgery). In contrast, our basic approach to the treatment of severe aortic stenosis is to offer the most adequate treatment for the individual patient.

Table 1 Patient characteristics of this study.

	Surgical aortic valve replacement		Transcatheter aortic valve replacement		Significance
n	34		24		
Gender (m/f)	21/13		7/17		$p<0.05$
Mean age (years)		64.6±13.8		80.5±7.3	$p<0.001$
Mortality (30 days)	2	5.8%	1	4.1%	n.s.
Major comorbidities	12	35%	19	79%	$p<0.01$
Mean time of surgery (min)		237±76		102±35	$p<0.001$
Prev. myocardial infarction	0	0%	6	25%	ND
Prev. stroke	0	0%	0	0%	ND
Diabetes	5	15%	8	33%	n.s.
Hypertonic	25	74%	16	66%	n.s.

The comparison of surgical aortic valve replacement vs. transcatheter aortic valve replacement was done by means of χ^2-test (comparison of proportions) and t-test (comparison of means). For both tests, the significance level was $\alpha=0.05$ (n.s.: p-value is greater or equal α, ND, not defined, χ^2-test cannot be applied for tables with cells equal to 0).

Furthermore, since procedural complications mainly require interventions by surgeons, the entire implantation lies in the hands of one team. Therefore, we established both the transarterial and the transapical implantation technique by a surgical team in a hybrid suite [6]. Neither procedure requires the use of the heart-lung machine and a cardioplegic arrest of the heart. Furthermore, time of anaesthesia is significantly shortened. The exclusion of these risk factors by performing those procedures leads to the hypothesis that the cardiovascular autonomic function is less affected compared to conventional surgery.

Materials and methods

Subjects

A total of 58 consecutive patients undergoing either transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR) with the heart-lung machine and being in stable sinus rhythm were enrolled in a prospective study. Thirty-four of them underwent SAVR and 24 of them TAVI, 12 of them receiving a Medtronic CoreValve prosthesis (Medtronic, Minneapolis, USA) by transfemoral access and the remaining 12 an Edwards Sapien prosthesis (Edwards Lifesciences Corp., Irvine, USA) through the left ventricular apex. Due to maintaining 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. Patients with concomitant coronary heart disease were excluded for the known effects of atherosclerosis. The patient characteristics are shown in Table 1. This study was approved by the local ethics committee and informed consent was obtained from all subjects.

Surgical procedures

Open heart surgery Perioperative medication was standardised. 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. All operations were carried out with median sternotomy, cardiopulmonary bypass in mild hypothermia (32–34°C); cold crystalloid cardioplegia was used for cardiac arrest. Surgical access to the aortic valve was achieved by horizontal transsection of the anterior aspect of the ascending aorta. The calcified leaflets were resected, and the prosthesis was implanted by interrupted sutures.

Table 2 Description of time- and frequency domain parameters, standards from Task Force Heart Rate Variability (1996 [13]) and additional measures.

Variables	Units	Definition
Time domain parameters		
MeanNN	ms resp. mm Hg	Mean BBI resp. mean BP
sdNN	ms resp. mm Hg	Standard deviation of all BBI resp. BP values
Shannon	None	Shannon entropy of the histogram (density distribution of the BBIs resp. BP values)
fwShannon	None	Shannon entropy of the word distribution
fwRenyi4	None	Renyi entropy of order 4 of the word distribution
Frequency domain parameters		
LF/P	n.u.	Normalised low frequency power 0.04–0.15 Hz
HF/P	n.u.	Normalised high frequency power 0.15–0.4 Hz
LF/HF	n.u.	Quotient of LF and HF

n.u., Normalized units; P, total spectral power.

Catheter procedures We opted to perform the procedures with the patients under general anaesthesia to ensure stable hemodynamics and to avoid patient movements during valve implantation. Pharmacologic treatment was the same except for muscle relaxation, which was not done in transcatheter patients. After the procedure, the patients were transferred to the intensive care unit and usually extubated within 2–4 h. Postoperative medical and pharmacologic care was standardized and not different between groups.

Recording protocol

For all patients, breathing excursions, standard electrocardiogram, and non-invasive blood pressure (BP) were simultaneously measured (Task Force Monitor of CNSystems, Austria) the day before surgery, 24 h and seven days after surgery in the intensive care unit. The patients were in the supine position. After 10-min equilibrations, data were sampled for a 30-min period. Care was taken to perform the measurements during the same time of the day for each patient. From the electrocardiogram the times between successive R-peaks, the so-called beat-to-beat intervals (BBI), were extracted. The beat-to-beat systolic BP and diastolic BP were the maximum and minimum values of the continuous BP curve in each BBI, respectively. Premature beats, artifacts and noise were excluded using an adaptive filter considering the instantaneous variability [30].

Computation of heart rate and blood pressure variability

Standard methods of heart rate variability (HRV) analysis include time and frequency domain parameters [23]. Time domain parameters are based on 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. Other parameters quantify the distributions of special geometrical forms of BBI.

Frequency domain HRV parameters enable us to analyse periodic dynamics in the heart rate time series [1, 5]. The Task Force on HRV (1996 [23]) recommended that power spectral analysis of at least 5-min electrocardiogram recordings should be used to assess autonomic physiology and pharmacology. The power spectrum can be estimated from the extracted BBI. The normalised high frequency power (HF/P, see Table 2) reflects modulation of vagal activity by respiration whereas the normalised low frequency power (LF/P, see Table 2) represents vagal and sympathetic activity via the baroreflex loop. The low-to-high frequency ratio (LF/HF, see Table 2) is used as an index of sympathovagal balance [19].

Heart rate variability 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. Thus the detailed description and classification of dynamic changes using time and frequency measures is often

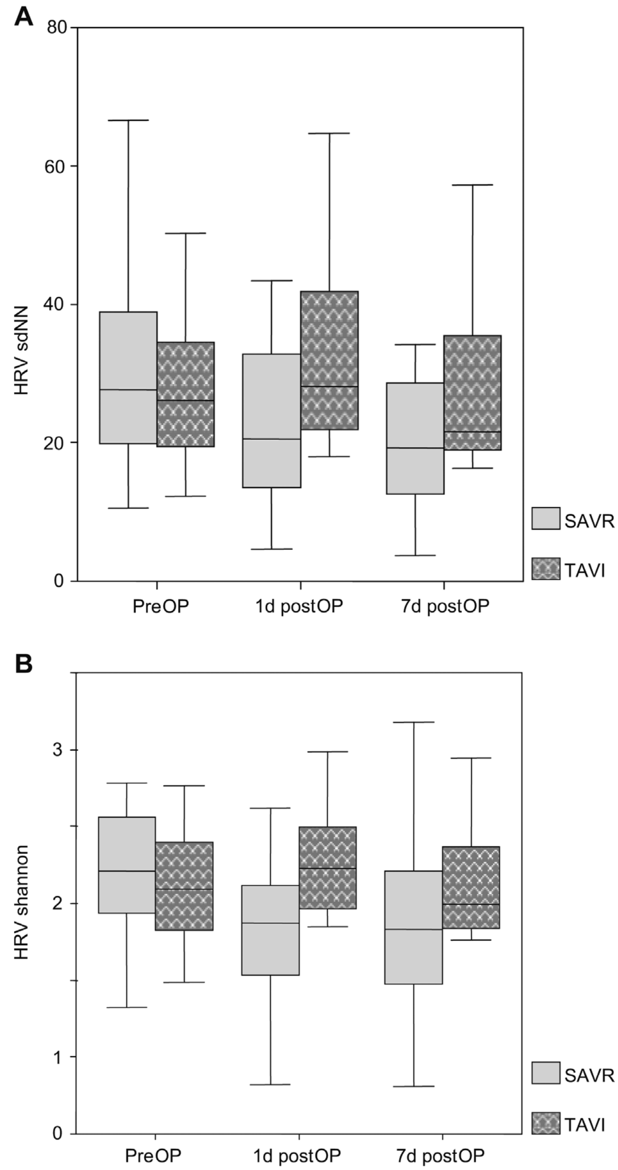

Figure 1 (A) Standard deviation of the beat-to-beat intervals in SAVR (surgical aortic valve replacement) and TAVI (transcatheter aortic valve implantation) in units of ms. For each group pre- and postoperative states (PreOP, 1d postOP – 1 day, 7d postOP – 7 days) are compared by a Kruskal-Wallis test ($p<0.05$ in SAVR, n.s. in TAVI). (B) Shannon entropy of the beat-to-beat intervals in SAVR (surgical aortic valve replacement) and TAVI (transcatheter aortic valve implantation). For each group pre- and postoperative states (PreOP, 1d postOP – 1 day, 7d postOP – 7 days) are compared by a Kruskal-Wallis test ($p<0.01$ in SAVR, n.s. in TAVI).

not sufficient [25]. A classical value of complexity is the Shannon entropy

$$shannon = -\sum_i p_i \log p_i$$

where p_i is the histogram of the BBIs.

We have shown already in 1995 that symbolic dynamics is an efficient approach to analyse dynamic aspects of HRV [13, 24] because it allows a selective consideration of defined properties. The first step in this analysis is the transformation of the time series into symbol sequences with symbols S_i from a given alphabet.

$$S_i(BBI_i)=\begin{cases} 0: & \mu < BBI_i \leq (1+a)\mu \\ 1: & (1+a)\mu < BBI_i < \infty \\ 2: & (1\text{-}a)\mu < BBI_i \leq \mu \\ 3: & 0 < BBI_i \leq (1\text{-}a)\mu \end{cases}$$

Some detailed information is lost in this process, but the coarse dynamic behaviour can be analysed. μ denotes the mean value of BBIs and a is a special parameter that is set to 0.05.

(i) The Shannon entropy calculated from the distribution of words with length 3 in S_i is the classic measure for complexity in time series and is defined by

$$fwShannon=-\sum_{\omega\in W,\, p(\omega)>0} p(\omega)\log p(\omega)$$

W is the set of possible words of length 3 composed by the given alphabet. p is the probability of each word ω and is estimated by the relative frequency. 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 which never or only seldom occur. A high number of forbidden words stands for 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) In order to increase the influence of more frequent words on the complexity measurement the Renyi entropy of order 4 is used which is defined by

$$fwRenyi4=\frac{1}{1\text{-}4}\log_2 \sum_{\omega\in W,\, p(\omega)>0} p(\omega)^4$$

For BP series all described HRV parameters can be accordingly calculated; only some statistical parameters as well as ones of symbolic dynamic need to be adapted (e.g., pNN50 makes no sense for BP variability – the standard deviation for BP series differs from 5 to 10 mm Hg). The physiological interpretation of the linear parameter of the frequency domain differs from that of HRV. The HF component characterises the mechanical influence of the respiratory movement on the intra-thoracic pressure [20] and the LF power mainly reflects the sympathetic activity. A list of considered parameters is given in Table 2.

Computation of baroreflex sensitivity

Using the Dual Sequence Method [16–18], the most relevant parameters for estimating the spontaneous baroreflex are the slopes as a measure of sensitivity. The Dual Sequence Method is based on standard sequence methods but distinguishes two kinds of beat-to-beat interval (BBI) responses: bradycardic (an increase in systolic BP causes an increase in the following BBI) and tachycardic fluctuations (a decrease in systolic BP causes a decrease in following BBI). A baroreflex event is assumed if there are monotonic ramps of three successive values in systolic BP and BBI. The local baroreflex sensitivity (BRS) is estimated by the slope of a linear regression of these BBI values over the corresponding BP. After that, the BRS is calculated by the average of these local values.

Bradycardic fluctuations as well as tachycardic fluctuations represent variations in vagal and sympathetic regulations, whereas bradycardic fluctuations indicate a dominance of the vagal activity and tachycardic fluctuations indicate a dominance of the sympathetic regulation. The mean value of tachycardic and bradycardic BRS is the common BRS of a standard sequence method.

Statistical analysis

In order to quantify the recovery of the autonomous control of the cardiovascular system after cardiac surgery, the para-

Table 3 Mean values ± SD of heart rate variability parameters.

Parameters	Group	PreOP	1d postOP	7d postOP	p-Values
MeanNN	SAVR	905 ± 136	749 ± 119	838 ± 305	< 0.001
	TAVI	883 ± 138	827 ± 160	816 ± 121	n.s.
sdNN	SAVR	30 ± 12.4	22.9 ± 11.7	27 ± 26.3	< 0.05
	TAVI	28.3 ± 11	32.5 ± 13.7	28.4 ± 13.5	n.s.
Shannon	SAVR	1.7 ± 0.4	1.35 ± 0.5	1.3 ± 0.6	< 0.01
	TAVI	1.6 ± 0.36	1.7 ± 0.34	1.7 ± 0.4	n.s.
LF/HF	SAVR	2.9 ± 2.4	1.9 ± 3	2.6 ± 3	n.s.
	TAVI	1.9 ± 1.7	1 ± 0.6	1.6 ± 1.3	n.s.
LF/P	SAVR	0.23 ± 0.1	0.19 ± 0.1	0.17 ± 0.1	n.s.
	TAVI	0.25 ± 0.1	0.16 ± 0.1	0.21 ± 0.14	n.s.
HF/P	SAVR	0.14 ± 0.1	0.19 ± 0.14	0.18 ± 0.16	n.s.
	TAVI	0.2 ± 0.12	0.22 ± 0.16	0.22 ± 0.17	n.s.

For each group pre- and postoperative state (PreOP, 1d postOP – 1 day, 7d postOP – 7 days) parameters were compared by a Kruskal-Wallis test. In the SAVR (surgical aortic valve replacement) group three significant different parameters were found; all frequency domain parameters differed insignificantly. In the TAVI (transcatheter aortic valve implantation) group all parameters differed insignificantly.

meters of heart rate and BP variability as well as baroreflex sensitivity were considered. For each group, Kruskal-Wallis tests compared the outcome of each parameter the day before surgery, 24 h and seven days after surgery in the intensive care unit.

Results

The mean age of patients was 64 ± 14 years (SAVR group) and 81 ± 7 years (TAVI group). This difference is due to the current consensus on using TAVI in high-risk patients (see Table 1).

In cardiovascular variability and baroreflex sensitivity, there were no major differences between the two groups preoperatively. At 24 h after surgery, in contrast to the TAVI group, the SAVR group showed a depression of HRV and BRS parameters which normally is followed by a tendency to recover one week after surgery. At every time of the examination the HRV- and BRS-data of the patients undergoing TAVI represented a stable level without any significant up- and downturns.

HRV

Regarding the parameters of HRV, the above-quoted depression after 24 h is shown in SAVR-treated patients but not those in the TAVI group. The best significant parameters are meanNN, sdNN and Shannon of the beat-to-beat intervals (see Figure 1A and B and Table 3). In fact, no parameter shows significant differences in heart rate variability in the TAVI group before and after surgery. In contrast, the heart rate increases and HRV decreases significantly after intervention by means of SAVR. The p-values of the applied Kruskal-Wallis test were $p<0.001$ (meanNN), $p<0.05$ (sdNN) and $p<0.01$ (Shannon). After one week, a recovery to preoperative values could not be observed.

Blood pressure variability

The contrary phenomenon as in HRV was detectable in the variability of the systolic BP. The changes are best described by fwShannon and fwRenyi4 (see Figure 2A and B and Table 4). Both parameters of symbolic dynamic showed a significant elevation after SAVR which continued during the following week (fwShannon: $p<0.001$; fwRenyi4: $p<0.001$). For TAVI, no such significant changes could be observed. The results for the diastolic blood pressure are given in Table 5.

BRS

Total baroreflex sensitivity as well as his bradycardic and tachycardic components show significant depression in SAVR patients caused by surgery (see Figure 3A, B and C). This decrease was even more pronounced in tachycardic fluctuations than in bradycardic ones (compare Figure 3B with C). The p-values of the applied Kruskal-Wallis tests were $p<0.05$ (bradycardic BRS), $p<0.01$ (tachycardic BRS), and $p<0.01$ (BRS). For all three parameters, there were no alterations in patients undergoing TAVI (Figure 3A, B and C).

Discussion and conclusions

The last decade has witnessed a strong increase in basic knowledge of the cardiovascular autonomic system. It has been demonstrated that the analysis of linear and nonlinear

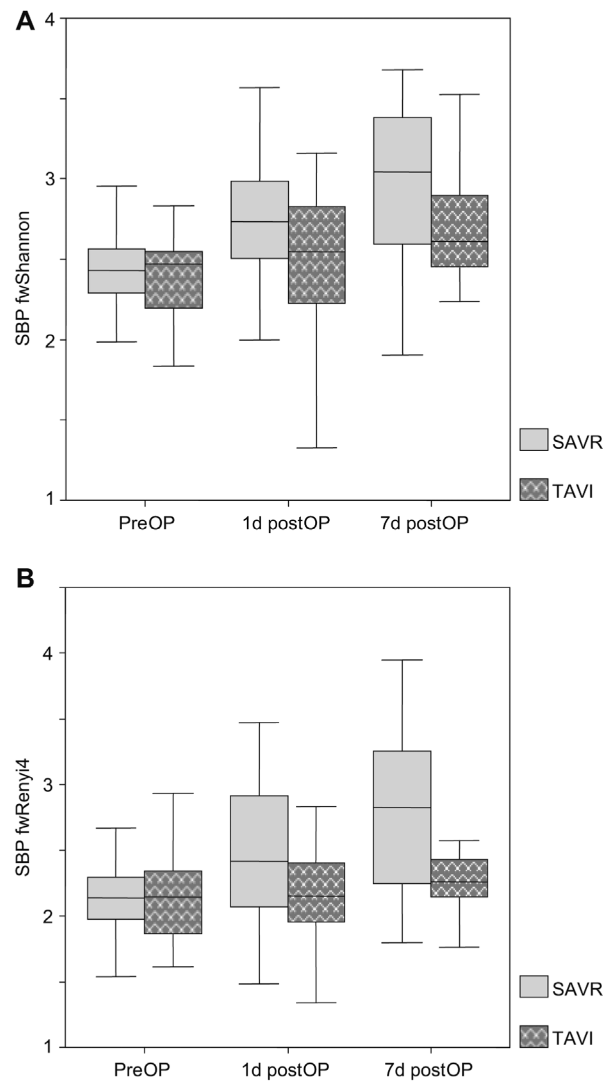

Figure 2 (A) Shannon entropy of the symbolic words (length 3) distribution referring to the systolic blood pressure. For SAVR (surgical aortic valve replacement) and TAVI (transcatheter aortic valve implantation) pre- and postoperative states (PreOP, 1d postOP – 1 day, 7d postOP – 7 days) are compared by a Kruskal-Wallis test ($p<0.001$ in SAVR, n.s. in TAVI). (B) Renyi entropy of order 4 of the symbolic words (length 3) distribution referring to the systolic blood pressure. For SAVR (surgical aortic valve replacement) and TAVI (transcatheter aortic valve implantation) pre- and postoperative states (PreOP, 1d postOP – 1 day, 7d postOP – 7 days) are compared by a Kruskal-Wallis test ($p<0.001$ in SAVR, n.s. in TAVI).

Table 4 Mean values ± SD of systolic blood pressure parameters.

Parameters	Group	PreOP	1d postOP	7d postOP	p-Values
Mean SBP	SAVR	112 ± 16	118 ± 14	118 ± 25	n.s.
	TAVI	111 ± 20	118 ± 20	112 ± 24	n.s.
sdNN	SAVR	7 ± 2.1	8.3 ± 4.6	7.7 ± 4.6	n.s.
	TAVI	6.9 ± 3.7	8.9 ± 4.9	8.7 ± 4.6	n.s.
fwShannon	SAVR	2.5 ± 0.4	2.7 ± 0.5	3 ± 0.5	< 0.001
	TAVI	2.4 ± 0.4	2.5 ± 0.5	2.7 ± 0.3	n.s.
fwReniy4	SAVR	1.7 ± 0.3	2.0 ± 0.5	2.3 ± 0.6	< 0.001
	TAVI	1.7 ± 0.3	1.7 ± 0.4	1.8 ± 0.4	n.s.
LF/P	SAVR	0.17 ± 0.09	0.12 ± 0.08	0.17 ± 0.07	< 0.05
	TAVI	0.12 ± 0.05	0.11 ± 0.07	0.1 ± 0.05	n.s.
HF/P	SAVR	0.04 ± 0.05	0.13 ± 0.1	0.12 ± 0.1	< 0.001
	TAVI	0.05 ± 0.05	0.08 ± 0.1	0.06 ± 0.04	n.s.

For each group pre- and postoperative state (PreOP, 1d postOP – 1 day, 7d postOP – 7 days) parameters were compared by a Kruskal-Wallis test. In the SAVR (surgical aortic valve replacement) group four significant different parameters were found. In the TAVI (transcatheter aortic valve implantation) group all parameters differed insignificantly.

components of heart rate and BP variability and baroreflex sensitivity can be a powerful tool to estimate a patient's risk of death or life-threatening events [29]. We demonstrated the usefulness of this approach for risk stratification two years later in a blind study [26]. Now, this study indicates their ability in distinguishing the recovery of autonomous control of the cardiovascular system after different cardiac surgical procedures. However, as far as alterations in the cardiac patient and in patients undergoing heart surgery are concerned, we are still at the beginning.

Meanwhile, it is well known that open cardiac surgery leads to an early depression of autonomic function, and that there is potential for recovery after a certain timeframe [8, 11]. It is also established that surgical trauma of the left or right atrium causes damage of the autonomic fibres avoiding postoperative recovery of the cardiovascular autonomic function [22]. While it has been reported that surgical stress alone (without operating on the heart or using cardiopulmonary bypass) leads to significant depression of baroreflex function [12], the influence of different traumatic components on patients undergoing open heart surgery is still not clarified.

TAVI has been introduced in the recent years as a new, less invasive treatment option for patients at high risk for conventional aortic valve replacement [21]. Avoiding sternotomy, cardiopulmonary bypass and cardioplegic arrest was considered to reduce surgical trauma and thus improve mortality and morbidity following aortic valve replacement.

To date, nothing is known about the effects of TAVI on cardiovascular autonomic function. To emphasise the consequences of the invasiveness and to pronounce the therefore depressed cardiovascular autonomic function, it was reasonable to compare patients undergoing TAVI and SAVR.

The present study confirms earlier results as far as the clinical outcome is concerned. Although patients undergoing TAVI were significantly older and had more major comorbidities as compared to patients with conventional surgery, the early mortality was not different between the groups, and in both groups major adverse cardiovascular events did not occur.

The time domain parameters meanNN (inverse to the heart rate) and sdNN (the standard deviation of RR intervals during the examination period) are two of the best known values and have been extensively analysed in cardiovascular medicine, sports and rehabilitation. A low value of sdNN indicates a rather uniform heart rhythm, which is considered to reflect low vagal activity, thus being a predictor of death and adverse events in a variety of studies performed earlier. As described earlier, meanNN and sdNN significantly decline one day after conventional heart surgery with no tendency to recovery throughout the observation period, while in

Table 5 Mean values ± SD of diastolic blood pressure parameters.

Parameters	Group	PreOP	1d postOP	7d postOP	p-Values
MeanDBP	SAVR	68 ± 11	66 ± 10	70 ± 11	n.s.
	TAVI	61 ± 9.5	60 ± 12	57 ± 8.8	n.s.
sdNN	SAVR	4.6 ± 1.7	5.5 ± 2.9	4.9 ± 2.9	n.s.
	TAVI	4.2 ± 2.1	5.1 ± 2.1	4.1 ± 1	n.s.
LF/P	SAVR	0.17 ± 0.09	0.13 ± 0.11	0.18 ± 0.07	< 0.05
	TAVI	0.14 ± 0.07	0.11 ± 0.06	0.15 ± 0.08	n.s.
HF/P	SAVR	0.06 ± 0.06	0.12 ± 0.1	0.08 ± 0.09	< 0.05
	TAVI	0.08 ± 0.05	0.09 ± 0.1	0.1 ± 0.1	n.s.

For each group pre- and postoperative state (PreOP, 1d postOP – 1 day, 7d postOP – 7 days) parameters were compared by a Kruskal-Wallis test. In the SAVR (surgical aortic valve replacement) group two significant different parameters were found. In the TAVI (transcatheter aortic valve implantation) group all parameters differed insignificantly.

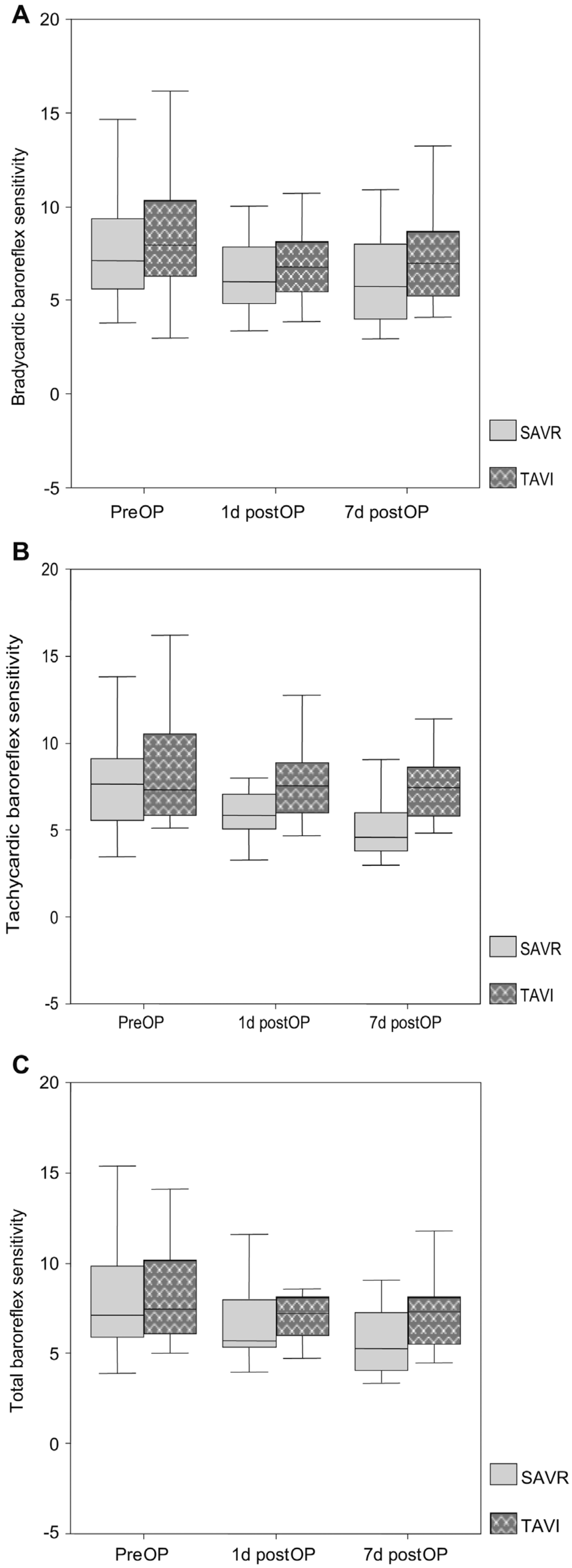

Figure 3 (A) Bradycardic baroreflex sensitivity (slope of simultaneous increase in systolic blood pressure and following beat-to-beat interval) in units of ms/mm Hg. For SAVR (surgical aortic valve replacement) and TAVI (transcatheter aortic valve implantation) pre- and postoperative states (PreOP, 1d postOP – 1 day, 7d postOP – 7 days) are compared by a Kruskal-Wallis test ($p<0.05$ in SAVR, n.s. in TAVI). (B) Tachycardic baroreflex sensitivity (slope of simultaneous decrease in systolic blood pressure and following beat-to-beat interval) in units of ms/mm Hg. For SAVR (surgical aortic valve replacement) and TAVI (transcatheter aortic valve implantation) pre- and postoperative states (PreOP, 1d postOP – 1 day, 7d postOP – 7 days) are compared by a Kruskal-Wallis test ($p<0.01$ in SAVR, n.s. in TAVI). (C) Baroreflex sensitivity (slope of simultaneous increase or decrease in systolic blood pressure and following beat-to-beat interval) in units of ms/mm Hg. For SAVR (surgical aortic valve replacement) and TAVI (transcatheter aortic valve implantation) pre- and postoperative states (PreOP, 1d postOP – 1 day, 7d postOP – 7 days) are compared by a Kruskal-Wallis test ($p<0.01$ in SAVR, n.s. in TAVI).

patients following TAVI stable values were recorded until the seventh day after the procedure. The same effect was observed for the Shannon entropy, describing the level of complexity in time series. It was described previously that open heart surgery results in decreased complexity, which could be reproduced in our study. On the other hand, however, there was no postprocedural change in Shannon entropy, either on day 1 or 7 after the procedure. So whatever mechanisms are responsible for this decline of autonomic function in the early postoperative period, they may be related to the trauma of open surgery and to the overall higher invasiveness of a procedure with the heart-lung machine.

Standard frequency domain parameters reflecting autonomic balance [23] do not differ significantly before operation and during follow up (Table 3). The LF and HF components are both reduced due to a decreased overall HRV, therefore the applicability of these measures is questionable after cardiac surgery. Additionally, one has to bear in mind that pharmacological treatments in both groups may have masked a possible sympathetic balance change.

Regarding baroreflex function, again major differences could be noted with respect to the procedure performed. The bradycardic component (reduction in heart rate in response to spontaneous rises of BP) and the tachycardic part (increase of heart rate in response to decrease in pressure) are both significantly suppressed in the SAVR group, but not in the TAVI group. The reason for this finding remains speculative. Surgical trauma *per se* (direct cutting of autonomic nerves) may not be a major issue; we demonstrated earlier that it is most unlikely that direct trauma leads to autonomic depression, at least in patients undergoing open surgery for aortic valve replacement. So again the differences between the groups may be explained by a variety of influences caused by cardiopulmonary bypass, cardioplegic arrest and the overall perioperative management. Again, it is surprising that not only the initial values but also the response to the intervention was less pronounced in TAVI patients, because usually the depression of baroreflex function is more pronounced in aged patients [9]. As mentioned above, this may demonstrate that results obtained from patients without cardiovascular disease cannot be transferred to patients with heart disease requiring surgical or interventional procedures.

The above demonstrated results affirm the hypothesis of conserved cardiovascular autonomic function in patients treated by TAVI. All parameters reflecting HRV and BRS of TAVI-treated patients present a stable level pre- and post-operatively without any significant up- and downturns. The cardiovascular autonomic system seems not to be influenced at all by this procedure. Moreover, even a tendency to an increase in all HRV parameters is shown. In contrast, the SAVR-treated patients represent the typical phenomenon already described in patients undergoing open heart surgery.

Further studies will focus on the effects of different strategies of transcatheter procedures (transarterial vs. transapical) to shed light on the impact of procedural details in this difficult cohort of patients.

TAVI has emerged as a promising new treatment option for aortic valve replacement in patients at high risk for open surgery. Even if controlled, randomised studies are lacking to date, avoiding sternotomy, cardiopulmonary bypass and cardioplegic arrest is considered to lead to superior outcomes and faster recovery of this critically ill cohort of patients. For the first time we were able to demonstrate in this study that in contrast to patients undergoing conventional open surgery, there are fewer alterations of the cardiovascular autonomic system in patients with TAVI.

Acknowledgements

This study was supported by grants from the Deutsche Forschungsgemeinschaft (BA 1581/4-1, BR 1303/8-1, KU 837/20-1, BA 1581/6-2, BR 1303/8-3, KU-837/29-2) as well as the European projects EU NEST-pathfinder and BRACCIA.

References

[1] Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981; 213: 220–222.

[2] Barthel P, Schneider R, Bauer A, et al. Risk stratification after acute myocardial infarction by heart rate turbulence. Circulation 2003; 108: 1221–1226.

[3] Bauernschmitt R, Malberg H, Wessel N, Kopp B, Schirmbeck EU, Lange R. Impairment of cardiovascular autonomic control in patients early after cardiac surgery. Eur J Cardiothorac Surg 2004; 25: 320–326.

[4] Bauernschmitt R, Malberg H, Wessel N, et al. Autonomic control in patients experiencing atrial fibrillation after cardiac surgery. PACE 2007; 30: 77–84.

[5] Bigger JT Jr, Fleiss JL, Steinman RC, Rolnitzky L, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 1992; 85: 164–171.

[6] Bleiziffer S, Ruge H, Mazzitelli D, et al. Results of percutaneous and transapical transcatheter aortic valve implantation performed by a surgical team. Eur J Cardiothorac Surg 2009; 35: 615–620.

[7] Brown CA, Wolfe LA, Hains S, Ropchan G, Parlow J. Spontaneous baroreflex sensitivity after coronary artery bypass graft surgery as a function of gender and age. J Physiol Pharmacol 2003; 9: 894–902.

[8] Brown CA, Wolfe LA, Hains S, Ropchan G, Parlow J. Heart rate variability following coronary artery bypass graft surgery as a function of recovery time, posture, and exercise. Can J Physiol Pharmacol 2004; 82: 457–464.

[9] Cividjian A, Meyrieux V, Gratadour P, et al. Post-operative pressure lability and cardiac baroreflex in normotensive patients as a function of age. Acta Anaesthesiol Scand 2008; 52: 1250–1258.

[10] Grube E, Schuler G, Buellesfeld L, et al. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis: device success and 30-day clinical outcome. J Am Coll Cardiol 2007; 50: 69–76.

[11] Johansson M, Karlsson AK, Myredal A, Lidell E. Arterial baroreflex dysfunction after coronary artery bypass grafting. Interact CardioVasc Thorac Surg 2009; 8: 426–430.

[12] Kohno N, Taneyama C. Surgical stress attenuates reflex heart rate response to hypotension. Can J Anaesth 1998; 45: 746–752.

[13] Kurths J, Voss A, Witt A, Saparin P, Kleiner HJ, Wessel N. Quantitative analysis of heart rate variability. Chaos 1995; 5: 88–94.

[14] La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998; 351: 478–484.

[15] La Rovere MT, Pinna GD, Hohnloser SH, et al. Baroreflex sensitivity and heart rate variability in the identification of patients at risk for life-threatening arrhythmias: implications for clinical trials. Circulation 2001; 103: 2072–2077.

[16] Malberg H, Wessel N, Schirdewan A, Osterziel KJ, Voss A. Duale Sequenzmethode zur Analyse der spontanen Baroreflexsensitivität bei Patienten mit dilatativer Kardiomyopathie. Z Kardiol 1999; 88: 331–337.

[17] Malberg H, Wessel N, Schirdewan A, Hasart A, Osterziel KJ, Voss A. Advanced analysis of the spontaneous baroreflex sensitivity using the Dual Sequence Method. Clinical Science 2002; 102: 465–473.

[18] Malberg H, Bauernschmitt R, Meyerfeldt U, Schirdewan A, Wessel N. Short-term heart rate turbulence analysis versus variability and baroreceptor sensitivity in patients with dilated cardiomyopathy. Z Kardiol 2003; 92: 547–557.

[19] Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991; 84: 482–492.

[20] Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation: a critical appraisal. Hypertension 1995; 25: 1276–1286.

[21] Piazza N, van Gameren M, Jüni P, et al. A comparison of patient characteristics and 30-day mortality outcomes after transcatheter aortic valve implantation and surgical aortic valve replacement for the treatment of aortic stenosis: a two-centre study. EuroIntervention 2009; 5: 580–588.

[22] Retzlaff B, Bauernschmitt R, Malberg H, et al. Depression of cardiovascular autonomic function is more pronounced after mitral valve surgery: evidence for direct trauma. Philos Transact A Math Phys Eng Sci 2009; 367: 1251–1263.

[23] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996; 93: 1043–1065.

[24] Voss A, Kurths J, Kleiner HJ, Witt A, Wessel N. Improved analysis of heart rate variability by methods of non-linear dynamics. J Electrocardiol 1995; 28: 81–88.
[25] Voss A, Kurths J, Kleiner HJ, et al. The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death. Cardiovasc Res 1996; 31: 419–433.
[26] Voss A, Hnatkova K, Wessel N, et al. Multiparametric analysis of heart rate variability used for risk stratification among survivors of acute myocardial infarction. Pacing Clin Electrophysiol 1998; 21: 186–192.
[27] Walther T, Falk V, Kempfert J, et al. Transapical minimally invasive aortic valve implantation: the initial 50 patients. Eur J Cardiothorac Surg 2008; 33: 983–988.
[28] Webb JG, Chandavimol M, Thompson CR, et al. Percutaneous aortic valve implantation retrograde from the femoral artery. Circulation 2006; 113: 842–850.
[29] Wessel N, Malberg H, Bauernschmitt R, Schirdewan A, Kurths J. Nonlinear additive autoregressive model-based analysis of short-term heart rate variability. Med Biol Eng Comput 2006; 44: 321–330.
[30] Wessel N, Malberg H, Bauernschmitt R, Kurths J. Nonlinear methods of cardiovascular physics and their clinical applicability. Int J Bifurkat Chaos 2007; 17: 3325–3371.

Received February 8, 2011; accepted July 18, 2011