

Autonomic Control and Baroreflex Sensitivity Before and After Transcatheter Aortic Valve Implantation

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Abstract

Transcatheter aortic valve implantation (TAVI) is preferred in patients with aortic stenosis and high surgical risk. In this category of patients, the assessment of cardiovascular control and baroreflex, especially during a postural challenge evoking an autonomic response could improve risk stratification.

Cardiovascular control and baroreflex were here assessed in 22 patients (age: 80.73±6.63 yrs, 9 females) scheduled for TAVI studied one day before (PRE) and within 7 days after the intervention (POST) via the analysis of heart period (HP) and systolic arterial pressure (SAP) at rest in supine position (REST) and during active standing (STAND). Time and frequency domain markers were computed to quantify cardiovascular control and cross-spectral indexes from SAP to HP to estimate baroreflex sensitivity.

At REST a tendency towards an increased sympathetic modulation and vagal withdrawal was observed in POST compared to PRE, thus resulting in a significant decrease of baroreflex sensitivity after TAVI. STAND induced a post-procedural increase of the sympathetic modulation during POST. Results suggest a more reactive sympathetic control after TAVI in presence of a depressed baroreflex function and this situation could lead to a greater exposition of TAVI patients to develop post-implantation adverse events.

1. Introduction

Patients with severe aortic valve stenosis at high cardiovascular risk are used to receive indication to transcatheter aortic valve implantation (TAVI) with respect to the more traditional surgical aortic valve replacement (SAVR). Anyway, TAVI is known to be

related to the occurrence of adverse post-procedural events as stroke (3%) and cognitive decline (up to 40%) [1, 2] that have been associated with a higher risk of mortality [3].

Indications about the state of autonomic nervous system and baroreflex control can be derived noninvasively from the analysis of heart period (HP) and systolic arterial pressure (SAP) spontaneous fluctuations [4,5]. Scanty data are present in literature about cardiovascular control and baroreflex function in TAVI patients [6-8]. These studies suggest that autonomic control was not affected by TAVI, while a major depression of the cardiovascular control was observed after SAVR [6,7,9]. In addition, it was observed that, compared to healthy controls, TAVI patients had a higher sympathetic drive before the procedure that was reduced after TAVI [8]. However, the lack of a stressor inducing a modification of the sympatho-vagal balance might have weakened final conclusions. A study assessing the modification of autonomic function and baroreflex sensitivity in response to a postural challenge known to evoke sympathetic activation and vagal withdrawal [10] before and after TAVI has not performed so far. Being the procedure weakly invasive, we hypothesize that autonomic control of TAVI patients could be preserved after the procedure.

The aim of this study, thus, was to evaluate autonomic markers and baroreflex sensitivity indexes as derived from HP and SAP variability in patients scheduled from TAVI before (PRE) and after (POST) the intervention. Active standing (STAND) was utilized to evoke a sympathetic activation in response to a baroreflex unloading [11].

2. Experimental protocol and data analysis

2.1. Experimental protocol

Twenty-two patients (age: 81 ± 7 yrs, 9 females, 13

males) with aortic stenosis scheduled for TAVI were enrolled at the Department of Clinical and Interventional Cardiology of IRCCS Policlinico San Donato, San Donato Milanese, Italy. The study was performed according to the Declaration of Helsinki and was previously approved by the ethical review board of the San Raffaele Hospital, Milan, Italy (approval number: 68/int/2018; approval date: 05/04/2018) and authorized by IRCCS Policlinico San Donato (authorization date: 13/04/2018). All patients gave their written informed consent prior to participate.

From each patient, electrocardiogram (ECG) and non-invasive arterial pressure (AP) acquired via volume-clamp photoplethysmography (CNAP Monitor 500, CNSystems, Graz, Austria) were synchronously sampled with a commercial acquisition system (Powerlab, ADInstruments, Australia). Sampling rate was 400 Hz. Patients were studied one day before the intervention (PRE) and within one week after the procedure (POST) just before being discharged from the hospital. Acquisition took place in a quiet room with patients lying in supine position (REST) for 10 minutes followed by 10 minutes of STAND. Ten minutes of adaptation at REST was left to the instrumented subject before starting the acquisition session.

2.2. Series extraction

HP was extracted from the ECG as the time distance between two consecutive R-wave peaks. SAP was detected as the maximum of AP within the current HP. Series were visually inspected and manually corrected if necessary. Stationary time series with length of 256 beats were selected from each patient and each experimental condition. Selection was made in a random position within each recording session paying attention to avoid the first three minutes of acquisition.

2.3. Computation of cardiovascular control and baroreflex indexes

From the series, time and frequency domain markers describing cardiovascular control were extracted. Mean and variance of HP and SAP time series were assessed and labeled as: μ_{HP} , σ^2_{HP} , μ_{SAP} , σ^2_{SAP} . Indexes were respectively expressed in ms, ms^2 , mmHg, $mmHg^2$. After linear detrending, univariate power spectral density was assessed via an autoregressive model, exploiting Levinson-Durbin recursion to assess the coefficients of the model. The model order was optimized via the Akaike information criterion in the range between 10 and 14. Then, power spectral density was decomposed in frequency components [12], labeling each one as low frequency (LF) or high frequency (HF) powers whether the central frequency of the components was, respectively, in the range between 0.04 and 0.15 Hz and between 0.15 and 0.4 Hz [4,5]. The power of HP series in the HF band was then taken as an index of parasympathetic modulation directed to the sinus node [4], while the power of SAP series in LF band was taken as an index of sympathetic modulation directed to the vessels [5]. The ratio of the LF power to the HF one computed over the HP series, describing the sympatho-vagal balance, was extracted as well [5]. Indexes were labeled as HF_{HP} , LF_{SAP} , LF_{HP}/HF_{HP} and expressed, respectively, in ms^2 , $mmHg^2$, and dimensionless units.

BRS was assessed according to the spectral technique as the square root of the ratio of the HP power to the SAP one in the LF band [13]. The marker was labeled as α_{LF} and expressed in $ms \cdot mmHg^{-1}$. Cross-spectral analysis from SAP to HP series was also used to quantify baroreflex function. The squared coherence K^2 was calculated as the modulus of the cross-spectral density from SAP to HP, estimated via a bivariate autoregressive model with the model order fixed to 10, divided by the product of the power spectral densities [14]. K^2 always ranged between 0

Table 1. Time and frequency domain indexes derived in PRE and POST at REST and during STAND in TAVI patients.

Index	PRE		POST	
	REST	STAND	REST	STAND
μ_{HP} [ms]	912±130	862±145	870±176	762±195
σ^2_{HP} [ms^2]	626±710	459±719	347±473	393±601
HF_{HP} [ms^2]	220±410	181±509	62±63	117±252
LF_{HP}/HF_{HP}	7.8±29.9	2.1±3.3	0.4±0.3	0.9±2.2
μ_{SAP} [mmHg]	145±19	138±30	127±15	140±22
σ^2_{SAP} [$mmHg^2$]	23.2±18.0	25.3±13.6	27.2±19.3	48.6±37.1*,#
LF_{SAP} [$mmHg^2$]	2.2±2.6	4.4±4.6	6.0±7.5	4.6±5.5

REST = at rest in supine position; STAND = during active standing; TAVI = transcatheter aortic valve implantation; PRE = one day before TAVI; POST = within 7 days after TAVI; HP = heart period; SAP = systolic arterial pressure; μ = mean; σ^2 = variance; LF = low frequency; HF = high frequency. The symbol * indicates $p < 0.05$ with respect to REST, while the symbol # indicates $p < 0.05$ with respect to PRE.

and 1, with 0 meaning null coupling between HP and SAP and 1 perfect coupling. The transfer function (TF) gain was assessed as the modulus of the cross-spectral density from SAP to HP divided by the power spectral density of SAP. This function was taken as an index of baroreflex sensitivity (BRS_{TF}). The phase Ph of the power cross-spectral density was also calculated and taken as a marker of the delay between HP and SAP, with negative phases indicating that SAP changes lagged HP ones. K^2 , BRS_{TF} and Ph were sampled at the maximum of K^2 in the LF band. Markers were then labelled as K^2_{LF} , $BRS_{TF,LF}$, and Ph_{LF} and expressed, respectively, as dimensionless units, $ms \cdot mmHg^{-1}$, and radians (rad).

2.4. Statistical analysis

Two-way analysis of variance (Holm–Sidak test for multiple comparisons) was applied to verify the significance of the differences between experimental conditions (i.e., REST and STAND) within the same time point and between the different acquisition sessions (i.e., PRE and POST) within the same experimental condition. Results are reported as mean \pm standard deviation. Analyses were performed using a commercial statistical program (Sigmaplot, v.14.5, Systat Software, Inc., Chicago, IL, USA) and a type I error probability p below 0.05 was always deemed as significant.

3. Results

Table 1 shows the cardiovascular markers derived from HP and SAP variability series in time and frequency domain. μ_{HP} , σ^2_{HP} , HF_{HP} , LF_{HP}/HF_{HP} , μ_{SAP} and LF_{SAP} remained unvaried between experimental conditions (i.e. REST vs STAND) and time points (i.e. PRE vs POST). During POST an exaggerated response to STAND led σ^2_{SAP} to increase compared to REST and to PRE.

Table 2 shows baroreflex markers derived from the analysis of HP and SAP variability series. At REST α_{LF} and $BRS_{TF,LF}$ decreased in POST compared to PRE. All the other markers resulted unchanged between experimental conditions and time points. Ph_{LF} was negative.

4. Discussion

The main findings of this work can be summarized as follows: i) TAVI patients exhibited a depressed autonomic control before the procedure; ii) SAP variability increased in response to STAND after TAVI; iii) baroreflex control was reduced after TAVI and this decline was already evident at REST.

STAND is expected to evoke tachycardia, higher sympathetic drive, and vagal withdrawal as well as the decrease of BRS [10,11,15,16]. Conversely, in PRE the μ_{HP} , LF_{SAP} , HF_{HP} , α_{LF} , and $BRS_{TF,LF}$ did not change with the orthostatic challenge, thus suggesting an impairment of autonomic function and baroreflex function already present before the procedure. The less reactive autonomic control and baroreflex function could be the result of either the age of the patients [17] or the pathological state of patients [7,9].

On the contrary, in POST, STAND evoked the expected increase of the sympathetic modulation, thus suggesting an increased reactivity of sympathetic nervous system [10,15]. Furthermore, after TAVI at REST we observed a tendency towards the increase of sympathetic modulation, as inferred from the LF_{SAP} power, and a vagal withdrawal, as measured via the HF_{HP} power. This pattern results in a significant decrease of α_{LF} and $BRS_{TF,LF}$ in POST compared to PRE. Such findings could suggest a sympathetic overactivity and a limited ability of TAVI patients in POST to reduce the variability of SAP with suitable baroreflex-mediated responses. This situation might expose TAVI patients to adverse events such as postural intolerance and even stroke. Results suggested that, although TAVI might lead to a preservation of the control mechanisms [6] as suggested by the post-procedure increase of the LF_{SAP} power during STAND, caution has to be taken in indicating that the new situation is favorable for the patient. Future studies, in addition to compare directly TAVI and SAVR patients [18], should monitor adverse events and correlate them with the post-operative state of the control mechanisms. The limited size of the cohort and the short follow-up might be factors that deserve

Table 2. Baroreflex markers derived in PRE and POST at REST and during STAND in TAVI patients.

Index	PRE		POST	
	REST	STAND	REST	STAND
α_{LF} [$ms \cdot mmHg^{-1}$]	5.92 \pm 6.52	3.70 \pm 2.59	1.63 \pm 2.03 [#]	2.71 \pm 5.29
K^2_{LF}	0.35 \pm 0.15	0.33 \pm 0.23	0.39 \pm 0.22	0.28 \pm 0.18
$BRS_{TF,LF}$ [$ms \cdot mmHg^{-1}$]	3.32 \pm 3.14	2.11 \pm 1.12	1.60 \pm 1.07 [#]	1.18 \pm 1.12
Ph_{LF} [rad]	-1.05 \pm 1.62	-0.75 \pm 1.44	-1.27 \pm 1.42	-1.78 \pm 1.52

REST = at rest in supine position; STAND = during active standing; TAVI = transcatheter aortic valve implantation; PRE = one day before TAVI; POST = within 7 days after TAVI; α = baroreflex sensitivity assessed via spectral method; K^2 = squared coherence; BRS_{TF} = baroreflex sensitivity assessed via transfer function; Ph = phase; LF = low frequency; HF = high frequency. Markers were computed in the LF band. The symbol # indicates $p < 0.05$ with respect to PRE.

improvement in future evaluations. From a methodological standpoint, methods accounting for directionality of the interactions might be applied to assess baroreflex and cardiorespiratory pathway [19,20] and compared to the more traditional indexes exploited in the present study.

5. Conclusions

This study investigated autonomic control and baroreflex function in patients before and after TAVI under orthostatic challenge. Findings show that TAVI patients had a depressed autonomic control before the procedure and TAVI reduced even more their ability to control AP variations especially. This situation could expose TAVI patients to a high risk of post-intervention adverse events. Future studies will be aimed to compare TAVI to SAVR patients and to investigate the possible link between cardiovascular control markers and the occurrence of adverse events such as postural intolerance and stroke.

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References

- [1] O. Abdul-Jawad Altisent et al. "Neurological damage after transcatheter aortic valve implantation compared with surgical aortic valve replacement in intermediate risk patients," *Clin. Res. Cardiol.*, vol. 105, pp. 508–517, 2016.
- [2] W. Vlastra et al. "Cerebral blood flow in patients with severe aortic valve stenosis undergoing transcatheter aortic valve implantation," *J. Am. Geriatr. Soc.*, vol. 69, pp. 494–499, 2021.
- [3] M. Pagnesi et al. "Silent cerebral injury after transcatheter aortic valve implantation and the preventive role of embolic protection devices: A systematic review and meta-analysis," *Int. J. Cardiol.*, vol. 221, pp. 97–106, 2016.
- [4] 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*, vol. 93, pp. 1043–1065, 1996.
- [5] M. Pagani et al. "Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans," *Circulation*, vol. 95, pp. 1441–1448, 1997.
- [6] B. Retzlaff et al. "Preserved autonomic regulation in patients undergoing transcatheter aortic valve implantation (TAVI): a prospective, comparative study," *Biomed. Tech.*, vol. 56, pp. 185–193, 2011.
- [7] L. Compostella et al. "Impact of type of intervention for aortic valve replacement on heart rate variability," *Int. J. Cardiol.*, vol. 197, pp. 11–15, 2015.
- [8] N. Dumonteil et al. "Transcatheter aortic valve implantation reduces sympathetic activity and normalizes arterial spontaneous baroreflex in patients with aortic stenosis," *JACC Cardiovasc. Interv.*, vol. 6, pp. 1195–1202, 2013.
- [9] A. Porta et al. "Evaluation of the impact of surgical aortic valve replacement on short-term cardiovascular and cerebrovascular controls through spontaneous variability analysis," *PLoS ONE*, vol. 15, art. no. e0243869, 2020.
- [10] A. Marchi et al. "Calibrated variability of muscle sympathetic nerve activity during graded head-up tilt in humans and its link with noradrenaline data and cardiovascular rhythms," *Am. J. Physiol.*, vol. 310, pp. R1134–R1143, 2016.
- [11] J.C. Milan-Mattos et al. "Influence of age and gender on the phase and strength of the relation between heart period and systolic blood pressure spontaneous fluctuations," *J. Appl. Physiol.*, vol. 124, pp. 791–804, 2018.
- [12] G. Baselli et al. "Spectral decomposition in multichannel recordings based on multi-variate parametric identification," *IEEE Trans. Biomed. Eng.*, vol. 44, pp. 1092–1101, 1997.
- [13] M. Pagani et al. "Changes in autonomic regulation induced by physical training in mild hypertension," *Hypertension*, vol. 12, pp. 600–610, 1988.
- [14] V. Bari et al. "Comparison of causal and non-causal strategies for the assessment of baroreflex sensitivity in predicting acute kidney dysfunction after coronary artery bypass grafting," *Front. Physiol.*, vol. 10, art. no. 1319, 2019.
- [15] W. H. Cooke et al. "Human responses to upright tilt: a window on central autonomic integration," *J. Physiol.*, vol. 517, pp. 617–628, 1999.
- [16] B. De Maria et al. "Characterization of the asymmetry of the cardiac and sympathetic arms of the baroreflex from spontaneous variability during incremental head-up tilt," *Front. Physiol.*, vol. 10, art. no. 342, 2019.
- [17] A. Porta et al. "Effect of age on complexity and causality of the cardiovascular control: comparison between model-based and model-free approaches," *PLoS ONE*, vol. 9, art. no. e89463, 2014.
- [18] V. Bari et al. "Characterization of cardiovascular and cerebrovascular controls via spectral causality analysis in patients undergoing surgical aortic valve replacement during a three-month follow-up," *Physiol. Meas.*, vol. 44, art.no. 094001, 2023.
- [19] A. Porta et al. "Conditional self-entropy and conditional joint transfer entropy in heart period variability during graded postural challenge," *PLoS ONE*, vol. 10, art. no. e0132851, 2015.
- [20] A. Porta et al. "Paced breathing increases the redundancy of cardiorespiratory control in healthy individuals and chronic heart failure patients," *Entropy*, vol. 20, art. no. 949, 2018.

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