Cerebral Autoregulation in Transcatheter Aortic Valve Implantation Patients

Francesca Gelpi¹, Vlasta Bari², Beatrice Cairo¹, Sara Pugliese², Martina Anguissola², Beatrice De Maria³, Elena Acerbi⁴, Mattia Squillace¹, Marco Ranucci², Francesco Bedogni⁴, Alberto Porta¹,²

¹Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
²Department of Cardiothoracic, Vascular Anaesthesia and Intensive Care, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy
³IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy
⁴Department of Clinical and Interventional Cardiology, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy

Abstract

In patients suffering from severe aortic stenosis, transcatheter aortic valve implantation (TAVI) could modify cerebrovascular control. Little is known about cerebral autoregulation (CA) before and after TAVI. In 11 patients (age: 78 ± 6 yrs, 3 females, 8 males) scheduled for TAVI, we assessed CA indexes from spontaneous variations of mean arterial pressure (MAP) and mean cerebral blood velocity (MCBv) such as the transfer function gain and phase, squared coherence and autoregulation index (ARI). Markers were computed before (PRE) and within 7 days after (POST) TAVI at supine resting (REST) and during active standing (STAND). None of the time and frequency domain indexes varied across time points and experimental conditions, even though a tendency towards an amelioration of cerebrovascular control was visible after TAVI. Our preliminary data indicate that TAVI has no impact on CA, but they suggest enlarging the population to check whether some tendencies could be confirmed.

1. Introduction

Transcatheter aortic valve implantation (TAVI) is a minimally invasive treatment for patients with severe aortic stenosis. TAVI led to an increase of cerebral blood flow (CBF) and this raise was taken as a positive outcome of TAVI linked to the post-procedural enhancement of the cardiac output [2]. However, TAVI is accompanied by the development of micro emboli inducing acute lesions [1] but their impact on the cognitive function is not clinically relevant [3].

Cerebral autoregulation (CA) is the control mechanism that limits CBF variability despite variations in perfusion pressure by modulating cerebrovascular resistances [4]. Standard assessment of dynamic CA comprises the estimation of the transfer function (TF) phase and gain [5,6] and autoregulation index (ARI) [4,7,8] derived from spontaneous oscillations of mean arterial pressure (MAP) and CBF, usually approximated via mean cerebral blood velocity (MCBv) acquired via a transcranial Doppler probe. This assessment is usually carried out under challenging situations increasing the variability of arterial pressure (AP) such as during orthostatic challenge [9].

Given the strong impact of TAVI on cerebral circulation, this study aims at investigating CA before and after TAVI. Active standing (STAND) was exploited to induce spontaneous variations of AP and challenge CA.

2. Experimental protocol and data analysis

2.1. Experimental protocol

We enrolled 11 patients (age: 78 ± 6 yrs, 3 females, 8 males) undergoing TAVI at IRCCS Policlinico San Donato, San Donato Milanese, Italy. The study was performed according to the Declaration of Helsinki. The study was 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 the Policlinico San Donato, San Donato Milanese, Milan, Italy (authorization date: 13/04/2018). All patients gave their written informed consent.

Subject were instrumented to continuously monitoring electrocardiogram (ECG), noninvasive continuous finger AP by volume-clamp photoplethysmography (CNAP Monitor 500, CNSystems, Austria), and cerebral blood velocity (CBv) via a transcranial Doppler device (Multi-Dop X, DWL, San Juan Capiatrustro, CA, USA) from the
Table 1. Time and frequency domain markers in PRE and POST at REST and during STAND.

<table>
<thead>
<tr>
<th>Index</th>
<th>PRE (n=11)</th>
<th>POST (n=4)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>REST (n=10)</td>
<td>STAND (n=9)</td>
</tr>
<tr>
<td>$\mu_{\text{MAP}}$ [mmHg]</td>
<td>103.3±19.2</td>
<td>92.6±22.4</td>
</tr>
<tr>
<td>$\sigma^2_{\text{MAP}}$ [mmHg$^2$]</td>
<td>19.6±13.5</td>
<td>21.2±12.9</td>
</tr>
<tr>
<td>VLF$_{\text{MAP}}$ [mmHg$^2$]</td>
<td>3.7±7.5</td>
<td>5.5±12.4</td>
</tr>
<tr>
<td>LF$_{\text{MAP}}$ [mmHg$^2$]</td>
<td>1.6±3</td>
<td>3±3.8</td>
</tr>
<tr>
<td>HF$_{\text{MAP}}$ [mmHg$^2$]</td>
<td>4.2±3.6</td>
<td>3.3±2.6</td>
</tr>
<tr>
<td>$\mu_{\text{MCBv}}$ [cm·s$^{-1}$]</td>
<td>44.9±19.8</td>
<td>52±19.1</td>
</tr>
<tr>
<td>$\sigma^2_{\text{MCBv}}$ [cm$^2$·s$^{-2}$]</td>
<td>18.7±23.7</td>
<td>53.8±52.3</td>
</tr>
<tr>
<td>VLF$_{\text{MCBv}}$ [cm$^2$·s$^{-2}$]</td>
<td>1.7±2.9</td>
<td>10.2±13</td>
</tr>
<tr>
<td>LF$_{\text{MCBv}}$ [cm$^2$·s$^{-2}$]</td>
<td>0.9±1.2</td>
<td>8.5±14.1</td>
</tr>
<tr>
<td>HF$_{\text{MCBv}}$ [cm$^2$·s$^{-2}$]</td>
<td>7±13.1</td>
<td>9.5±8.1</td>
</tr>
</tbody>
</table>

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; MAP = mean arterial pressure; MCBv = mean cerebral blood velocity; $\mu$ = mean; $\sigma^2$ = variance; VLF = very low frequency; LF = low frequency; HF = high frequency.

left or right middle cerebral artery. Signals were sampled at 400 Hz. Recordings lasting 10 min were made at rest in supine position (REST) and during STAND. The experiment was performed 1 day before TAVI (PRE) and it was repeated within 7 days after the procedure (POST). PRE sessions were carried out in all subjects, while solely in 4 patients in POST due to the refusal of the patients in relation to his/her post-procedural physical debilitation. In PRE data were of good quality in 10 and 9 patients at REST and during STAND respectively, and in POST in 4 and 3 patients.

2.2. Beat-to-beat series extraction

From the ECG, we computed the heart period (HP) as the time distance between two consecutive R-peaks. On the AP, we detected the $n$th systole as the AP minimum within the $n$th HP. Then, the $n$th diastole was taken after the $n$th systole as the AP maximum. The $n$th MAP and MCBv were computed as the ratio of the definite integral of AP and CBv, respectively, between the $(n-1)$th and nth diastolic occurrences to the interdiastolic interval. The series were manually inspected and a maximum of 5% of values was corrected in case of misdetections or isolated arrhythmic events via linear interpolation. Sequences of 250 consecutive values were selected at REST and during STAND.

2.3. Time and frequency domain MAP and MCBv markers

Time domain markers such as mean and variance of MAP and MCBv were computed and labelled respectively $\mu_{\text{MAP}}, \sigma^2_{\text{MAP}}, \mu_{\text{MCBv}}$ and $\sigma^2_{\text{MCBv}}$. They were expressed in mmHg, mmHg$^2$, cm·s$^{-1}$ and cm$^2$·s$^{-2}$, respectively. Frequency domain markers were computed via autoregressive parametric power spectral analysis [5]. The model order was optimized via the Akaike information criterion in the range from 8 to 16 [5]. The power spectral density was factorized into components whose central frequencies fell into the very low frequency (VLF, from 0.02 to 0.07 Hz), low frequency (LF, from 0.07 to 0.15 Hz) and high frequency (HF, from 0.15 to 0.4 Hz) bands [6].

2.4. CA indexes

TF was estimated via a traditional parametric cross-spectral method [6]. The cross-spectral density was calculated after the identification of a bivariate autoregressive model [5]. The model order was fixed at 10 [5]. The TF was estimated as the ratio of the cross-spectral density from MAP to MCBv to the power spectral density of MAP. The TF gain ($\text{TFG}_{\text{MAP-MCBv}}$), expressed in cm$^2$·s$^{-4}$·mmHg$^{-1}$, represents the magnitude of MCBv changes per unit variation of MAP. The TF phase ($\text{Ph}_{\text{MAP-MCBv}}$) was expressed in radians (rad) and ranged between -π and +π. Negative values indicate that the MCBv changes lagged MAP variations. Squared coherence $K^2_{\text{MAP-MCBv}}$ was computed as the ratio of the square cross-spectral density modulus to the product of the power spectral density of MAP and MCBv. $K^2_{\text{MAP-MCBv}}$ was dimensionless and ranged between 0 and 1, indicating respectively full uncoupling and perfect association between MAP and MCBv. $\text{TFG}_{\text{MAP-MCBv}}, \text{Ph}_{\text{MAP-MCBv}}$ and $K^2_{\text{MAP-MCBv}}$ were sampled at the frequency where $K^2_{\text{MAP-MCBv}}$ peaked the
maximum in VLF, LF, and HF bands, and denoted respectively as TFG
MAP-MCBv (VLF), TFG
MAP-MCBv (LF), TFG
MAP-MCBv (HF), Ph
MAP-MCBv (VLF), Ph
MAP-MCBv (LF), Ph
MAP-MCBv (HF), K
2MAP-MCBv (VLF), K
2MAP-MCBv (LF) and
K
2MAP-MCBv (HF).
ARI was computed via a time domain approach [8]. Briefly, the normalized and resampled beat-to-beat MAP series fed the Tiecks’ differential equations, allowing the computation of predicted MCBv [4]. The equations were set with ten different sets of parameters, corresponding to ARI graded from 0 to 9 according to the efficiency in performing CA, with 4 being the limit between impaired and intact CA. ARI was selected at the best matching between the original and predicted MCBv series calculated using the normalized mean square prediction error.

2.5. Statistical analysis

Two-way analysis of variance (Holm–Sidak test for multiple comparisons) was used to check the significance of the differences between the time points (i.e., PRE and POST) within the same experimental condition (i.e., REST or STAND) and between experimental conditions within the same session. Results are reported as mean ± standard deviation. Statistical analysis was carried out using a commercial statistical program (Sigmaplot, v.14.0, Systat Software, Inc., Chicago, IL, USA). A p<0.05 was always considered as significant.

3. Results

Table 1 summarizes the time and frequency domain markers computed from MAP and MCBv series at REST and during STAND. No significant variation was detected across time points and experimental conditions. Remarkably, a tendency toward a reduction of σ
2MCBv during STAND in POST compared to PRE was detectable.

Table 2 lists the CA markers in PRE and POST at REST and during STAND. TAVI did not induce significant changes of CA markers within the same experimental condition and orthostatic challenge did not affect CA indexes within the same time point. Remarkably, a tendency toward a more positive Ph
MCBv-MAP and a higher ARI at REST in POST compared to PRE was visible.

4. Discussion

The main finding of the study is that TAVI did not modify CA markers and this result held even during an orthostatic challenge. It is worth notice that some parameters indicated a tendency toward a CA improvement after TAVI that deserves additional check over a larger population.

4.1. CA in patients before TAVI

In healthy young subjects, the orthostatic stressor induces a decrease of 14% of μMCBv [10] and a doubling of σ
2MCBv with STAND [7]. This result was explained because of sympathetic vasoconstriction and increased AP variations imperfectly buffered by changes of cerebral
vessel diameter during the orthostatic challenge [8,11]. In an elderly population the reduction of MCBv with STAND is less relevant [12]. In our study, we did not detect a decrease of $\mu_{\text{MCBv}}$, while an increase of $\sigma^2_{\text{MCBv}}$ was detectable even though it was not significant. The invariance of CA markers with STAND before TAVI suggest a preserved CA that it is a typical feature of elderly individuals [12].

4.2. Impact of TAVI on CA

Our indexes could not detect any variation of cerebrovascular circulation induced by TAVI either at REST or during STAND. At difference with [2] we did not detect at REST even the post-procedural increase of $\mu_{\text{MCBv}}$ resulting from a raise of the cardiac output due to the new valve implantation. Given that the old age of our patients could not explain the missing increase of $\mu_{\text{MCBv}}$ [13], we take this result as an indication of a working CA. Remarkably, we observed a tendency toward a post-procedural decrease of $\sigma^2_{\text{MCBv}}$ and a more positive phase shift during STAND, being all indications of an amelioration of CA after TAVI. These trends deserve further check over a larger population.

5. Conclusions

Our exploratory study investigated CA in patients undergoing TAVI. Our patients before TAVI exhibited the expected cerebrovascular response to STAND in relation to their age. Markers of cerebral circulation and CA was not affected by TAVI, even though some tendencies towards an improvement of CA were present and should be investigated further on a larger population. Future studies will compare CA markers derived from TAVI patients with those obtained in a population who underwent a more invasive procedure such as surgical aortic valve replacement [5] and will apply methodological approaches to characterize closed loop dynamic interactions between MAP and MCBv [14,15].

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References


Address for correspondence:
Dr. Francesca Gelpi
Department of Biomedical Sciences for Health,
University of Milan
Piazza E. Malan 2
20097 San Donato Milanese, Milan, Italy
email: francesca.gelpi@unimi.it