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RESEARCH ARTICLE | *Integrative Cardiovascular Physiology and Pathophysiology*

Acute effects of transcatheter aortic valve replacement on the ventricular-aortic interaction

Stamatia Pagoulatou,[1] Nikolaos Stergiopulos,[1] Vasiliki Bikia,[1] Georgios Rovas,[1] Marc-Joseph Licker,[3] Hajo Müller,[2] Stéphane Noble,[2] and Dionysios Adamopoulos[2]

[1]*Laboratory of Hemodynamics and Cardiovascular Technology, Institute of Bioengineering, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland;* [2]*Cardiology Division, Department of Medicine, Geneva University Hospitals, Geneva, Switzerland; and* [3]*Division of Anesthesiology, Geneva University Hospitals, Geneva, Switzerland*

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Pagoulatou S, Stergiopulos N, Bikia V, Rovas G, Licker MJ, Müller H, Noble S, Adamopoulos D. Acute effects of transcatheter aortic valve replacement on the ventricular-aortic interaction. *Am J Physiol Heart Circ Physiol* 319: H1451–H1458, 2020. First published October 16, 2020; doi:10.1152/ajpheart.00451.2020.—Transcatheter aortic valve replacement (TAVR) is increasingly used to treat severe aortic stenosis (AS) patients. However, little is known regarding the direct effect of TAVR on the ventricular-aortic interaction. In the present study, we aimed to investigate changes in central hemodynamics after successful TAVR. We retrospectively examined 33 cases of severe AS patients (84 ± 6 yr) who underwent TAVR. Invasive measurements of left ventricular and aortic pressures as well as echocardiographic aortic flow were acquired before and after TAVR (maximum within 5 days). We examined alterations in key features of central pressure and flow waveforms, including the aortic augmentation index (AIx), and performed wave separation analysis. Arterial parameters were determined via parameter-fitting on a two-element Windkessel model. Resolution of AS resulted in direct increase in the aortic systolic pressure and maximal aortic flow (131 ± 22 vs. 157 ± 25 mmHg and 237 ± 49 vs. 302 ± 69 mL/s, $P < 0.001$ for all), whereas the ejection duration decreased ($P < 0.001$). We noted a significant decrease in the AIx (from 42 ± 12 to 19 ± 11%, $P < 0.001$). Of note, the arterial properties remained unchanged. There was a comparable increase in both forward (61 ± 20 vs. 77 ± 20 mmHg, $P < 0.001$) and backward (35 ± 14 vs. 42 ± 10 mmHg, $P = 0.013$) pressure wave amplitudes, while their ratio, i.e., the reflection coefficient, was preserved. Our results highlight the impact of TAVR on the ventricular-aortic interaction by affecting the amplitude, shape, and related attributes of the aortic pressure and flow pulse and challenge the interpretation of AIx as a solely vascular measure in AS patients.

NEW & NOTEWORTHY Transcatheter aortic valve replacement (TAVR) is linked with an immediate increase in aortic systolic blood pressure and maximal flow, as well as steeper aortic pressure and flow wave upstrokes. After TAVR, the forward wave pumped by the heart is enhanced. Although the arterial properties remain unchanged, the central augmentation index (AIx) is markedly decreased after TAVR. This challenges the interpretation of AIx as a solely vascular measure in patients with aortic valve stenosis.

aortic valve stenosis; aortic valve replacement; augmentation index; TAVR

INTRODUCTION

Severe aortic valve stenosis (AS) currently affects 2 to 9% of adults older than 65 yr of age, and its prevalence is likely to increase in the future as the population steadily ages (24). In the presence of AS, cardiovascular hemodynamics are significantly affected (5). Importantly, the valvular stenosis poses an obstruction to the left ventricular (LV) outflow, hence causing a rise in the LV afterload. Chronic pressure overload triggers LV remodeling, usually in the form of hypertrophy (25), and gradually leads to inadequate cardiac output (CO) and ultimately heart failure (11).

Accordingly, symptomatic severe AS is correlated with high mortality rates (4) and requires aortic valve replacement. Transcatheter aortic valve replacement (TAVR) has emerged in the past years as a desirable alternative to open-heart surgery and has transformed the outlook for high and intermediate surgical risk patients. Several studies have confirmed the improvement of clinical outcomes after TAVR, even showing significantly higher rates of survival at 1 yr compared with classical surgical valve replacement even in low surgical risk patients (1, 16, 26).

However, we have only limited understanding of the effect of TAVR on cardiovascular hemodynamics. The work of Muller et al. (19) recently analyzed the periprocedural changes in pulse wave features by examining noninvasive measures of carotid and radial pressure as well as echocardiographic indexes. They demonstrated that TAVR leads to an improvement of myocardial perfusion and LV contractility. They also reported changes in the reconstructed aortic pressure features, commonly regarded as vascular parameters (29), i.e., the augmentation pressure (AP) and augmentation index (AIx).

In the present study, we aimed to extend previous literature on the direct effect of TAVR on cardiovascular hemodynamics by acquiring invasive measurements of LV and aortic pressure as well as echocardiographic flow data. Our analysis examined alterations in key features of both central pressure and flow waveforms. We further investigated changes in the ventricular-aortic interaction by means of wave separation analysis. Particular attention was given to the interpretation of AIx as a vascular measure in the setting of AS.

METHODS

Study population. In this retrospective study, we examined the medical files of all patients who underwent TAVR at the Geneva University

*Correspondence: S. Pagoulatou (stamatia.pagoulatou@epfl.ch).

Hospitals between September 2018 and January 2020 (n = 110). These patients were referred for TAVR according to standard indications after evaluation by the local heart team. Four TAVR interventions were performed on a previously implanted prosthetic valve ("valve in valve" procedure) for either severe stenosis (n = 2) or aortic regurgitation (n = 2) and thus were excluded from the final cohort. Twenty-three patients were excluded because of missing or low-quality hemodynamic curve recordings during the intervention and eight because of significant arrhythmia compromising pulse wave analysis. One patient was excluded because of a periprocedural myocardial infarction and three patients because the TAVR was performed in an emergency setting due to a baseline cardiogenic shock state. To avoid the potential confounding effect of low myocardial contractility, patients with moderate or severe left ventricular dysfunction (LVEF < 40%, n = 8) were also excluded. Only patients with available data on baseline CO measured by thermodilution were included in the final cohort. Finally, we considered only successful TAVR interventions as defined by *1*) the absence of periprocedural mortality, *2*) the correct positioning of a single prosthetic heart valve in the correct anatomic location and *3*) intended performance of the prosthetic heart valve (mean transprosthetic gradient <20 mmHg and no moderate or severe prosthetic valve regurgitation) according to the Valve Academic Research Consortium (VARC)-2 criteria (14). A detailed description of the study population inclusion/exclusion criteria is presented in Fig. 1.

The final cohort consisted of 33 patients. Baseline demographics and clinical and echocardiographic data were available for all subjects. TAVR was performed without general anesthesia for all patients except one. Seventeen patients received an Evolut Pro (Medtronic), six an Evolut R (Medtronic), five a SAPIEN S3 (Edwards Lifesciences), and five an Accurate Neo (Boston Scientific) prosthetic valve. Transfemoral access was used for all interventions. The 30-days composite safety end point was reached for all patients (14). Patient data were anonymized before analysis. Informed, written consent had been previously obtained from each patient for inclusion in the local TAVR database as part of the Swiss prospective registry (NCT1368250) that was approved by the local ethics committee.

Pressure measurements during the TAVR procedure. The routine TAVR procedure included a baseline left heart catheterization with simultaneous recording of the pressure in both the left ventricle and the aortic root. A first 6-Fr "pigtail" catheter (Cordis) was advanced through the stenotic valve into the left ventricle from the vascular access for the transcatheter heart valve, and a second 6-Fr pigtail catheter was advanced to the aortic root using the second vascular access; both were then connected to a pressure line and transducer. The pressure curves in the left ventricle and in the ascending aorta were simultaneously recorded over several heartbeats after careful calibration of the pressure transducer. The TAVR procedure was then performed, and a second set of pressure measurements was taken immediately after the TAVR procedure.

On a separate day before the TAVR, all patients underwent a baseline diagnostic left and right heart catheterization. For all patients, invasive measurements of CO by the standard thermodilution method were collected.

Analysis of invasive data. Multiple LV and ascending aortic pressure curves captured before and after the TAVR procedure were digitized for each patient. A custom, in-house Matlab code was developed to automatically identify the beginning and end of each heartbeat, and the average pressure curves were computed. Subsequently, key features of the pressure waveforms were determined, including *1*) the peak LV pressure, *2*) the invasive mean ventricular-aortic pressure gradient, which is the gradient between the LV and aortic pressures integrated throughout the ejection period and is considered the optimal indicator of AS severity in the presence of normal LV systolic function and stroke volume (6, 21), *3*) the aortic systolic (SBP), diastolic (DBP), mean (MAP), and pulse (PP) pressures, *4*) the timing of the aortic SBP, *5*) the maximal slope of the aortic pressure upstroke (dP/dt_{max}), *6*) the characteristic inflection point of the aortic pressure curve [pressure (P_{inf}) and timing (t_{inf})], provided that such a point could be explicitly identified, *7*) the aortic AP, calculated as the difference between the aortic SBP and P_{inf}, and *8*) the aortic AIx, defined as the ratio AP/PP according to previous literature (15, 20) (Fig. 2).

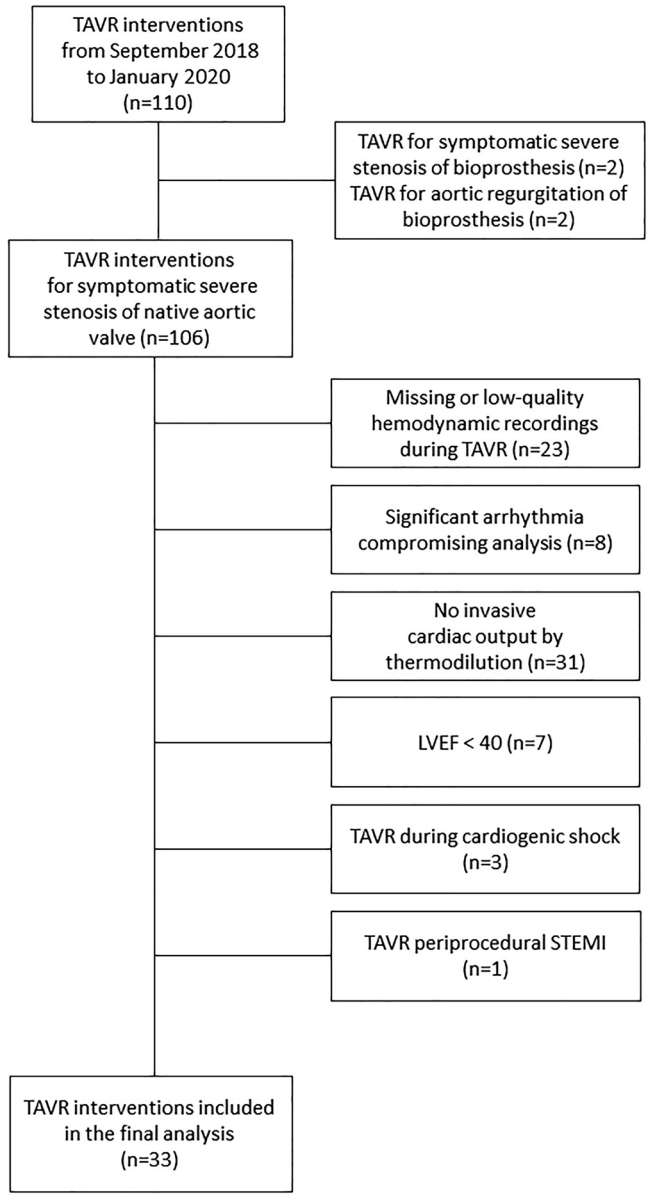

Fig. 1. Flow diagram of study patients according to the inclusion/exclusion criteria. TAVR, transcatheter aortic valve replacement; LVEF, left ventricular ejection fraction.

Echocardiography. A complete transthoracic echocardiographic examination was performed before the TAVR and after the procedure (for 32 patients within 48 h and for 1 patient 5 days after TAVR). The diameter of the left ventricular outflow track (LVOT) was measured in the parasternal long axis view during midsystole. The proximal peak velocity profile was acquired at the level of the LVOT via transthoracic pulsed-wave Doppler echocardiography in the apical five-chamber view. The aortic flow waveform was subsequently calculated using the measured instantaneous peak velocity. This was done by assuming an appropriate velocity profile based on the Witzig–Womersley theory (32) and integrating the velocity over the corresponding circular cross-sectional area. End-diastolic (EDV) and end-systolic (ESV) left ventricular volumes were also measured retrospectively according to

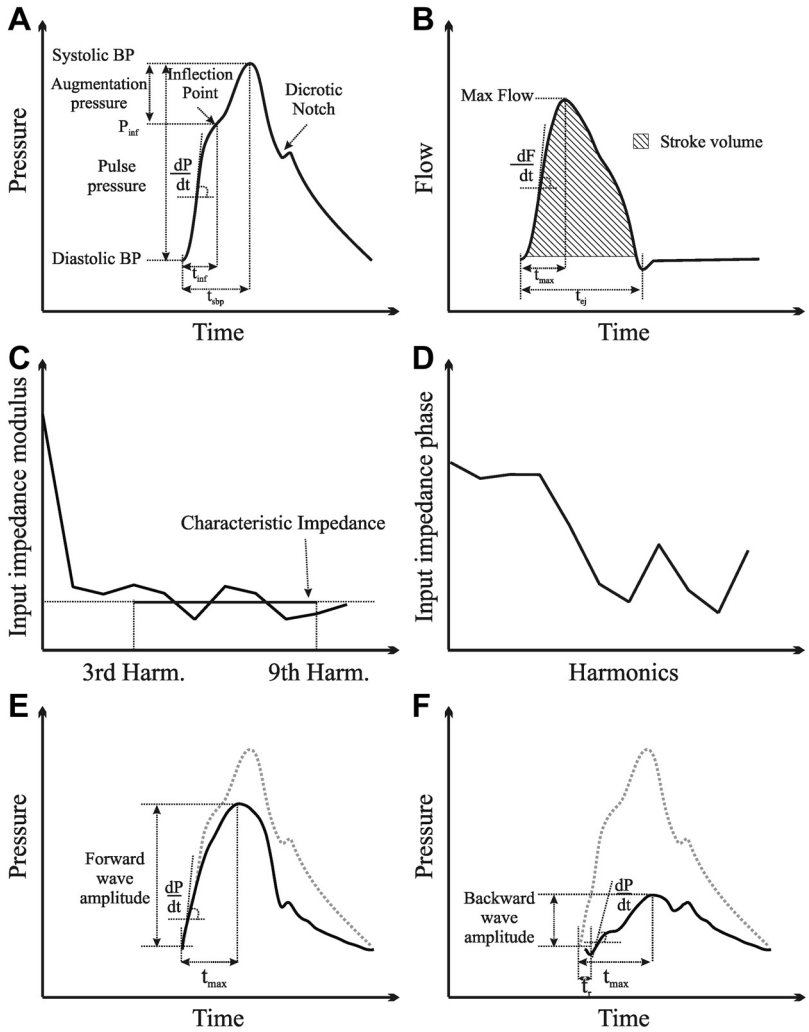

Fig. 2. Aortic pressure and flow pulse wave analysis in the time domain and frequency-based wave separation of the pressure wave into its forward and backward components. A: aortic pressure wave features. *B*: aortic flow wave features. *C* and *D*: input impedance modulus (*C*) and phase (*D*) calculated in the frequency domain. *E* and *F*: computed forward (*E*) and backward (*F*) pressure wave components (continuous lines). BP, blood pressure; P_{inf}, pressure at the inflection point; t_{inf}, time to the inflection point; dP/d*t*, maximal slope of the pressure waveform during the ejection period; dF/d*t*, maximal slope of the flow waveform during the ejection period; t_{ej}, ejection duration; t_{max}, time to the maximal point of the waveform; t_r, transit time.

Simpson's method in monoplane (4-chamber view). The measurements were conducted by an experienced cardiologist with the patient in the supine position and according to standard recommendations for echocardiography (3). Transvalvular and transprosthetic pressure gradients as well as qualitative evaluation of valve abnormalities were collected retrospectively from the echocardiography reports.

Data analysis and wave separation. The proximal aortic pressure curve acquired invasively, and the flow curves obtained from echocardiography, were interpolated and combined for subsequent analysis using Matlab. Note that any difference in heart rate between the pressure and flow measurements was accounted for by truncating or extending the diastolic portion of the aortic flow wave. Since pressure and flow were not measured simultaneously, synchronization of the signals was required. To this aim, we adopted the second-derivative approach, whereby the time lag between the two signals was corrected by calculating the maxima of the second time derivatives (22). After synchronization, the signals were used for the calculation of the equivalent total vascular resistance (TVR) and total arterial compliance (C). This was achieved via parameter-fitting on a two-element Windkessel model, as described in the pulse pressure method (PPM) paper by Stergiopulos et al. (27).

Wave separation analysis was performed by applying the standard methodology in the frequency domain (Fig. 2). The characteristic impedance was calculated by averaging the input impedance modulus of the third to ninth harmonics. The waves were then separated into their corresponding forward and backward components as described by Westerhof et al. (31). Key features of the forward and backward pressure waves were identified, including the magnitude and timing of the peak pressure as well as the wave amplitude. Finally, the reflection coefficient was evaluated as the ratio of the backward wave to the forward wave amplitudes (Fig. 2).

Statistical analysis. Data are reported as means ± SD for continuous variables, and as percentages for categorical variables. For comparing continuous variables before and after TAVR, a paired *t* test was used. The inflection point could not be explicitly identified on the aortic pressure upstroke of seven patients; hence, those seven cases were excluded from the AIx analysis (30). Pearson's correlation coefficient (*r*), root mean squared error normalized for the range (nRMSE), and Bland–Altman analysis were used to assess the correlation, accuracy, and agreement between the echocardiographic and thermodilution-derived CO values obtained before the TAVR procedure. Statistical significance was considered for *P* values lower than 0.05. Statistical analysis was performed in SPSS (version 13.0, Chicago, IL).

RESULTS

The demographic characteristics, comorbidities, and presenting symptoms of the study participants are summarized in Table 1. Average age was 84 ± 6 yr, 17 (52%) were females and 24

Table 1. *Demographic characteristics, comorbidities, and presenting symptoms of the study participants*

n	33
Age, yr	84 ± 6
Males, *n* (%)	16 (48.5)
Height, cm	166 ± 8
Weight, kg	76 ± 15
BMI, kg/m^2	27.5 ± 5.5
BSA, m^2	1.8 ± 0.2
Smokers, *n* (%)	1 (3)
Ex-smokers, *n* (%)	16 (48.5)
Arterial hypertension, *n* (%)	24 (72.7)
Dyslipidemia, *n* (%)	22 (66.7)
Diabetes, *n* (%)	11 (33.4)
Previous stroke or TIA, *n* (%)	6 (18.2)
Coronary artery disease, *n* (%)	17 (51.5)
Peripheral artery disease, *n* (%)	4 (12.1)
COPD, *n* (%)	4 (12.1)
Renal failure, *n* (%)	17 (51.5)
Atrial fibrillation/flutter, *n* (%)	11 (33.3)
Oncological disease, *n* (%)	8 (24.2)
EuroSCORE 1	13.4 ± 7.2
EuroSCORE 2	4.5 ± 3.0
STS score	3.4 ± 1.8
NYHA III or IV, *n* (%)	22 (66.6)
Angina, *n* (%)	4 (12.1)
Syncope, *n* (%)	7 (21.2)
ACE inhibitors or ARBs, *n* (%)	19 (57.6)
β-blockers, *n* (%)	14 (42.4)
Ca^{2+} blockers, *n* (%)	6 (18.2)
Diuretics, *n* (%)	15 (45.5)

Values are means ± SD for continuous variables or percentages for categorical variables. TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; STS, Society of Thoracic Surgeons; ACE, angiotensin-converting-enzyme; ARBs, angiotensin receptor blockers; BSA, body surface area.

(72.7%) presented with baseline arterial hypertension, which was the most common cardiovascular risk factor. Most patients (n = 22, 66.6%) presented with moderate to severe dyspnea (NYHA III or IV) before the TAVR.

As expected, TAVR acutely decreased LV peak pressure, ventricular-aortic pressure gradients, echocardiographic maximal aortic velocity, and valvular-arterial impedance in all patients, as shown in Table 2. Aortic surface increased from 0.8 ± 0.2 cm^2 for the native valve to 1.9 ± 0.4 cm^2 for the prosthetic valve ($P < 0.001$). Table 2 also contains information on the LV ejection fraction and end-systolic and end-diastolic volumes as assessed by Simpson's monoplane in four-chamber view in standard echocardiography. We noted that the LV ejection fraction increased after TAVR (63 ± 15 vs. 68 ± 14%, P = 0.001). This was mainly driven by a significant decrease in the end-systolic volume (from 27 ± 15 to 23 ± 14 mL, P = 0.007).

Table 3 summarizes the major hemodynamic changes related to TAVR. After valve replacement, aortic flow had a higher maximal value (237 ± 49 vs. 302 ± 69 mL/s, $P < 0.001$) and reached its maximal value earlier in the systole (0.14 ± 0.03 vs. 0.10 ± 0.02 s, $P < 0.001$). Concurrently, the duration of ejection decreased (0.35 ± 0.04 vs. 0.31 ± 0.04 s, $P < 0.001$). The heart rate as well as the stroke volume showed an increase after TAVR (64 ± 11 to 70 ± 12 beats/min, P = 0.002, and 58 ± 13 vs. 63 ± 17 mL, P = 0.05, respectively). This led to a rise in cardiac output (4.1 ± 0.7 vs. 4.7 ± 1.2 L/min, P = 0.003).

TAVR acutely affected the aortic pressure waveform (Table 3 and Fig. 3). Within minutes after the resolution of AS, we observed an increase in the aortic SBP (from 131 ± 22 to 157 ± 25 mmHg, $P < 0.001$) and DBP (from 53 ± 11 to 57 ± 12 mmHg, P = 0.04). This entailed a rise in PP (78 ± 17 vs. 100 ± 21 mmHg, $P < 0.001$) and MAP (79 ± 13 vs. 91 ± 14 mmHg, $P < 0.001$). The invasive aortic pressure curve became steeper at early ejection (512 ± 149 vs. 1,001 ± 408 mmHg/s, $P < 0.001$), and the peak pressure occurred earlier in the systole (0.26 ± 0.04 vs. 0.23 ± 0.03 s, P = 0.001). Subsequently, we applied pulse wave analysis to study the periprocedural changes in the aortic AP and AIx. We found that the inflection point occurred at significantly higher pressures (101 ± 16 vs. 135 ± 25 mmHg, $P < 0.001$). Consequently, AP decreased after the procedure (34 ± 14 vs. 19 ± 12 mmHg, $P < 0.001$) and aortic AIx presented a decrease from 42 ± 12 to 19 ± 11% ($P < 0.001$; Table 3).

Immediately after TAVR, the properties of the arterial system remained unchanged as assessed via the PPM (Table 3). Concretely, because of the moderate increase in MAP combined with the improved CO, the total arterial resistance did not change (1.40 ± 0.32 vs. 1.39 ± 0.38 mmHg·s/mL). The total arterial compliance had a minor decreasing trend (0.45 ± 0.12 vs. 0.42 ± 0.15 mL/mmHg) as a result of increases in aortic MAP (by approximately +15%) and PP (by approximately +27%), which, however, did not reach statistical significance.

After analyzing the input impedance in the frequency domain, we estimated that the characteristic impedance was unaffected by the valve replacement (Table 3). By further applying wave separation analysis, we found that both forward (61 ± 20 vs. 77 ± 20 mmHg, $P < 0.001$) and backward pressure wave (35 ± 14 vs. 42 ± 10 mmHg, P = 0.013) components were

Table 2. *Invasive hemodynamic and echocardiographic characteristics of the study population before and after TAVR*

	Pre-TAVR	Post-TAVR	*P* Value
Heart rate, beats/min	64 ± 11	70 ± 12	0.002
Invasive LV peak pressure, mmHg	179 ± 25	161 ± 24	<0.001
Invasive mean ventricular-aortic pressure gradient, mmHg·s	16.1 ± 6.2	1.8 ± 1.2	<0.001
Ejection fraction, Simpson 4C, %	63 ± 15	68 ± 14	0.001
End-diastolic volume, Simpson 4C, mL	69 ± 26	68 ± 28	0.60
End-systolic volume, Simpson 4C, mL	27 ± 15	23 ± 14	0.007
Echocardiographic mean ventricular-aortic pressure gradient, mmHg	44 ± 14	8 ± 3	<0.001
Echocardiographic max ventricular-aortic pressure gradient, mmHg	75 ± 21	15 ± 6	<0.001
Maximal aortic velocity, cm/s	427 ± 62	193 ± 40	<0.001
Aortic/prosthetic valve surface, cm^2	0.8 ± 0.2	1.9 ± 0.4	<0.001
Valvular-arterial impedance, mmHg/mL/m^2	6.1 ± 1.7	4.3 ± 1.0	<0.001
Aortic regurgitation, %			
NS or minimal	15 (43.4)	14 (42.5)	
Discrete or discrete to moderate	18 (56.6)	19 (57.5)	
Mitral regurgitation, %			
NS or discrete	30 (91)	30 (91)	
Discrete to moderate	1 (3)	2 (6)	
Moderate	1 (3)	1 (3)	
Moderate to severe	1 (3)	0 (0)	

Values are means ± SD for continuous variables or percentages for categorical variables. LV, left ventricle; NS, not significant; TAVR, transcatheter aortic valve replacement.

Table 3. *Effect of TAVR on vascular parameters assessed via the PPM and on the aortic pressure wave components assessed via frequency-based wave separation analysis*

	Pre-TAVR	Post-TAVR	*P* Value
Aortic flow			
Ejection duration, s	0.35 ± 0.04	0.31 ± 0.04	<0.001
Maximal aortic flow, mL/s	237 ± 49	302 ± 69	<0.001
Time to maximal aortic flow, s	0.14 ± 0.03	0.10 ± 0.02	<0.001
Stroke volume, mL	58 ± 13	63 ± 17	0.05
Stroke volume index, mL/m^2	31.8 ± 6.7	34.4 ± 8.7	0.07
Cardiac output, L/min	4.1 ± 0.7	4.7 ± 1.2	0.003
Aortic pressure waveform			
Aortic SBP, mmHg	131 ± 22	157 ± 25	<0.001
Aortic DBP, mmHg	53 ± 11	57 ± 12	0.04
Aortic PP, mmHg	78 ± 17	100 ± 21	<0.001
Aortic MAP, mmHg	79 ± 13	91 ± 14	<0.001
Time to aortic SBP, s	0.26 ± 0.04	0.23 ± 0.03	0.001
Maximal aortic pressure slope, mmHg/s	512 ± 149	1001 ± 408	<0.001
Aortic inflection point, mmHg	101 ± 16	135 ± 25	<0.001
Time to aortic inflection point, s	0.13 ± 0.04	0.13 ± 0.03	0.98
Aortic augmentation pressure, mmHg	34 ± 14	19 ± 12	<0.001
Aortic augmentation index, %	42 ± 12	19 ± 11	<0.001
Wave separation analysis			
Characteristic impedance, mmHg·s/mL	0.22 ± 0.12	0.22 ± 0.10	0.87
Forward wave amplitude, mmHg	61 ± 20	77 ± 20	<0.001
Time to forward wave peak, s	0.21 ± 0.03	0.16 ± 0.03	<0.001
Maximal forward wave slope, mmHg/s	730 ± 395	1290 ± 551	<0.001
Backward wave amplitude, mmHg	35 ± 14	42 ± 10	0.013
Time to backward wave peak, s	0.31 ± 0.06	0.27 ± 0.05	<0.001
Maximal backward wave slope, mmHg/s	278 ± 113	415 ± 151	<0.001
wave transit time, s	0.11 ± 0.06	0.09 ± 0.06	0.16
Reflection coefficient	0.57 ± 0.13	0.56 ± 0.14	0.57
2-Element Windkessel parameters			
Total vascular resistance, mmHg·s/mL	1.40 ± 0.32	1.39 ± 0.38	0.84
Total arterial compliance, mL/mmHg	0.45 ± 0.12	0.42 ± 0.15	0.11

Values are means ± SE. TAVR, transcatheter aortic valve replacement; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure.

amplified, had steeper upstrokes, and reached their respective peaks at earlier time points (Table 3 and Fig. 3). The increase in the wave amplitudes was not associated with any change in their ratio, which served as a measure of the reflection coefficient (0.57 ± 0.13 vs. 0.56 ± 0.14). Figure 3 demonstrates the periprocedural changes in the central hemodynamics for a severe AS patient, representative of the study population.

Reliability of echocardiographic flow measurements. Figure 4 depicts the correlation and agreement between the CO measured by echocardiography and thermodilution performed before the TAVR procedure. The correlation coefficient was $r = 0.57$, with nRMSE = 21%. The bias of the echocardiographic measurement was low ($\bar{d} = -0.2$ L/min) with acceptable limits of agreements [LA = (−1.8, 1.3) L/min]. Importantly, there was no statistically significant difference between the COs assessed by the two methods. The median difference in time between the two exams was 1 day (range: 25th quartile 1 day to 75th quartile 14 days).

DISCUSSION

In the present study, we investigated the acute effects of TAVR on central hemodynamics based on invasive measures of LV, aortic pressure, and echocardiographic flow data by means of standard pulse wave and wave separation analysis. Our main findings are that *1*) TAVR resulted in an immediate increase in aortic pressures with no significant changes in the total vascular resistance of the arterial tree; *2*) wave separation analysis showed a comparable amplification of both the forward and the backward pressure waves, while timing and reflection coefficient remained unchanged; and *3*) a notable decrease in the aortic AIx after the TAVR procedure was noted, despite an unaffected arterial compliance and reflection coefficient.

In all 33 AS cases, TAVR successfully resulted in the relief of the blood flow obstruction, as confirmed by the immediate and substantial decrease in the transvalvular resistance. The decreased mean ventricular-aortic pressure gradient was accompanied by a significant drop in the systolic LV pressure, demonstrating the expected beneficial influence of TAVR on cardiac afterload.

In the present cohort, valve replacement was also associated with an increase in aortic pressures, mainly systolic. This observation is in line with previous literature; some investigators suggest the development of hypertension within the first hours and days after the procedure (7, 8), while others also show long-term effects (23). The optimal management of post-TAVR hypertension remains unknown, since neither compliance nor vascular resistance is the responsible mechanism. Interestingly, previous studies suggest improved LV function and overall more favorable prognosis for patients who develop post-TAVR hypertension compared with those who maintain stable BP after the procedure (23). The underlying mechanisms that contribute to the improved outcomes in the presence of postprocedural hypertension require further investigation.

Considering CO, most previous works showed a significant improvement after TAVR (7, 8). Namely, Chrissoheris et al. (7), reported in their invasive examination of 52 cases a rise in CO from 3.8 ± 1.3 to 5.4 ± 1.7 L/min, as measured with thermodilution. In our study, we also report a significant improvement of the LV output after the valve replacement by ~0.6 L/min. Of note, this increase in CO was due to a significant increase in heart rate and a moderate increase in stroke volume.

TAVR and the ventricular-aortic interaction. With regard to the ventricular-aortic interaction, all hemodynamic cases examined in this study support the following paradigm. In the presence of chronic AS, the cardiovascular system gradually develops compensatory mechanisms to adapt to the high afterload (25). In other words, the system reaches a ventricular-arterial coupling that is optimal to overcome the great valvular resistance and achieve adequate perfusion of the arterial system. Since TAVR successfully resolves the aortic stenosis in a matter of minutes, the LV cannot adapt acutely to the new conditions. Downstream of the aortic valve, there is no radical alteration in the arterial properties immediately after TAVR (i.e., characteristic impedance, vascular resistance, and compliance).

Therefore, for an unchanged arterial system, the left ventricle is expected to pump a more pronounced forward wave. Indeed, we found that after the procedure the forward pressure wave is enhanced in amplitude, has a steeper upstroke and reaches its peak earlier. The steeper upstroke, as can be observed in the early systolic part of the total aortic pressure curve, has also been reported by other groups. Muller et al. (19) showed an increase in the maximal rate of rise of aortic pressure and interpreted it as indicative of better LV contractility after valve replacement.

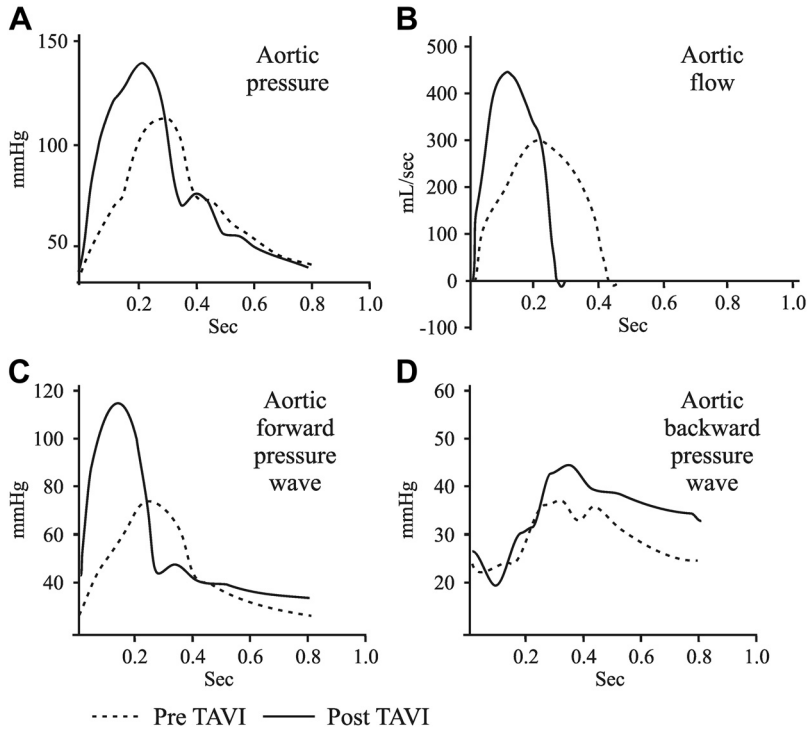

Fig. 3. Representative case of a patient with severe aortic stenosis before (dashed lines) and after (continuous lines) transcatheter aortic valve replacement (TAVR). Hemodynamic changes with respect to central pressure and flow waves are depicted. *A*: changes in aortic pressure wave features include an increase in the systolic blood pressure, pressure at the inflection point, and pulse pressure, whereas augmentation pressure and augmentation index decrease. *B*: changes in aortic flow waveform characteristics include increase in maximal flow and slope. Forward (*C*) and backward (*D*) pressure components present a rise in both wave amplitudes and slope. Their ratio is maintained after TAVR. Patient characteristics: female, 84 yr, BMI 22.6 kg/m^2, post-TAVR hypertension, ejection fraction increased from 40 to 57.5% after TAVR, Invasive mean ventricular-aortic pressure gradient decreased from 28.0 to 1.3 mmHg·s.

Subsequently, the enhanced forward wave propagates into the arterial system until it is reflected at peripheral sites of impedance mismatch. We found that the reflected pressure wave arriving back to the aorta is also enhanced in amplitude, while overall the reflection coefficient is maintained. This seems reasonable, given that there is no major change in the properties of the arterial tree.

AIx in patients with severe aortic stenosis. Following this paradigm, it is relevant to consider its implications for the interpretation of the AIx. The AIx is defined according to the inflection point observed on the upstroke of the pressure waveform. Traditionally, this inflection point is understood as the marker of the arrival of the backward traveling wave and of its superposition with the forward wave. Accordingly, AIx is often regarded as a vascular measure of aortic stiffness and wave reflection (29). However, there is concrete evidence suggesting that the AIx might not be a suitable marker for aortic stiffening. Previous investigations showed a nonlinear relationship between AIx and age (9, 17) as well as associations between lower AIx and higher cardiovascular risk factor burden (18).

In the present work, we demonstrate a significant drop in the aortic AIx due to TAVR. This finding was also previously

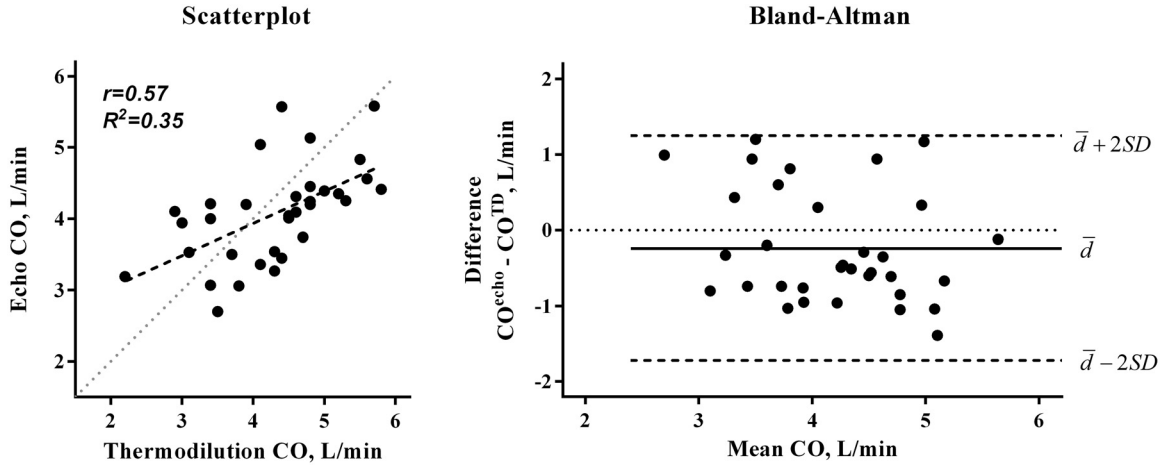

Fig. 4. Scatterplot (*left*) and Bland–Altman plot (*right*) comparing the cardiac output (CO) estimated before the transcatheter aortic valve replacement (TAVR) procedure via echocardiography and thermodilution (TD). In the scatterplot, the line of equality (dotted line) and the linear fit of the data (dashed line) are shown. In the Bland–Altman plot, the differences in the CO values between the two paired measurements are plotted against the average of these measures. Bias, $\bar{d}$, and limits of agreement, $\bar{d} \pm 2$SD, are also depicted.

reported by Muller et al. (19), who examined reconstructed aortic pressure waveforms in a similar setting. If the paradigm of AIx as a sole measure of stiffness and reflections were valid, then one would expect a concomitant decrease also in wave reflections after the valve replacement. However, as shown by means of wave separation analysis, TAVR had no effect on the reflection coefficient. This observation seriously challenges the view of AIx as a marker of stiffness in AS patients. Our data suggest that the decrease in AIx reflects changes in the ventricular-aortic interaction due to the resolution of AS. A plausible explanation for the decrease in AIx is that it is associated with the timing/slope of the enhanced forward wave. An earlier and steeper increase in early systolic (forward mainly) wave will result in much higher pressures before the arrival of the reflected wave, leading to a smaller relative contribution of wave reflections to the total pulse pressure and thus a lower AIx. This explanation is clearly supported by the typical features of the aortic waves before and after TAVR shown in Fig. 3. The concept of AIx reflecting both cardiac and vascular properties was also previously evoked in a recent study (12).

Study considerations and limitations. Arguably, echocardiography has limitations in the evaluation of aortic flow compared with the gold standard techniques, i.e., catheterization and thermodilution. In the present study, we examined the reliability of the echocardiographic flow measurements performed before the TAVR procedure by direct comparison with thermodilution measurements. We found that echocardiography tended to slightly underestimate cardiac output; this result is in line with previous literature (2). Nevertheless, the bias was low, and importantly there was no statistically significant difference between the two methods. These findings are corroborated by the observations of Antonini-Canterin et al. (2). The correlation we reported between the two CO methods was lower ($r = 0.57$) than the median value reported in the meta-analysis by Zhang et al. (33) ($r = 0.827$, range 0.140–0.998), which can be explained by the fact that the two measurements were not simultaneous in the present study.

We acknowledge that the aortic pressure and flow measurements were not performed simultaneously. Regarding the wave separation analysis, we accounted for the fact that the two measurements were not simultaneous by employing synchronization techniques to improve the quality of the results. Additionally, the use of two fluid-filled guide catheters for the measurement of intracardiac and aortic pressure has certain limitations in terms of precision compared with high-fidelity pressure tip catheters (10).

The cohort included mostly elderly with severe AS, given that this is the typical population selected for TAVR. Therefore, caution should be exerted in generalizing these results for other patient groups. Particularly, younger subjects undergoing TAVR might not develop these compensatory mechanisms to the same extent. Consequently, the study group was selected to exclude comorbidities that might influence the validity of our interpretations (e.g., hemodynamic shock, moderate or severe aortic valve regurgitation, left ventricular dysfunction).

An intriguing perspective is the application of this hemodynamic analysis to TAVR patients during stress. A recent study by Johnson et al. (13) performed graded dobutamine infusion before and after TAVR in a population of 16 patients with AS. Importantly, they demonstrated that measurements under resting conditions are not indicative of the hemodynamics of stable patients under stress, i.e., when valve effects are more prominent. Accordingly, they demonstrated how a stress index of AS might be more informative of the valve's flow reserve.

Conclusions. The present study offers novel insights into the alterations in the ventricular-aortic interaction due to successful TAVR. Our findings support the development of systolic hypertension shortly after TAVR, as previously demonstrated. Additionally, we found that TAVR was linked with the enhancement of the forward wave pumped by the heart. We demonstrated that AIx was markedly decreased after TAVR; a decrease that was not associated with any significant change in the stiffness of the vascular system or the wave reflection coefficient. Therefore, these results challenge the interpretation of AIx as a solely vascular measure in the setting of AS.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.Z.P., N.S. and D.A. conceived and designed research; S.Z.P. and S.N. performed experiments; S.Z.P. and D.A. analyzed data; S.Z.P., N.S. and D.A. interpreted results of experiments; S.Z.P. and D.A. prepared figures; S.Z.P. and D.A. drafted manuscript; N.S., V.B., G.R., M.L., H.M., S.N. and D.A. edited and revised manuscript; S.Z.P., N.S., V.B., G.R., M.L., H.M., S.N. and D.A. approved final version of manuscript.

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