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The effect of surgical versus transcatheter aortic valve replacement on endothelial function

Running head: endothelial function in aortic stenosis

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ABSTRACT

Background: The effects of surgical aortic valve replacement versus transcatheter aortic valve replacement on endothelial function are unknown. We investigated the effects of surgical and transcatheter aortic valve replacement on early and 90-day endothelial function measured by brachial flow mediated dilation and apoptotic rate in the human umbilical vein endothelial cells in patients with significant aortic stenosis, intermediate risk of surgery, and no coronary artery disease.

Methods: We conducted a prospective observational case control single-blind study at a single tertiary center. Endothelial function was measured at baseline, early post-procedure (4 days), and follow-up (90 days). A blood pressure cuff was used to elicit reactive hyperemia for measuring brachial wall shear stress and flow mediated dilation. The apoptosis rate was observed in the human umbilical vein endothelial cells after 48-hour incubation with 20% serum from patients. The rate of apoptosis was assessed by determining the number of annexin V and propidium iodide positive cells by flow cytometry.

Results: Early post-procedure flow dilation was significant lower in the surgical group ($p < 0.003$). At follow-up, both groups showed incremental increases in flow mediated dilation. Surgical group apoptotic rate did not significantly change, while transcatheter apoptotic rate steadily decreased, suggesting a trend toward improved endothelial function.

Conclusions: The data suggest that conventional surgical aortic valve replacement may be associated with an early and transient decrease in endothelial function, likely due to the use of cardio-pulmonary bypass.

Keywords: aortic valve, endothelial function, flow-mediated dilation, aortic valve replacement, transcatheter aortic valve replacement.

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1. INTRODUCTION

Aortic stenosis (AS) affects not only the left ventricle but also vascular and endothelial function [1]. Patients with endothelial dysfunction have an increased risk of cardiovascular events [2]. Yet, the influence of conventional surgical aortic valve surgery (SAVR) with the aid of cardiopulmonary bypass (CPB) and cardioplegic myocardial protection versus transcatheter aortic valve replacement (TAVR) on endothelial function is unknown [3]. TAVR is indicated in high-risk patients, but growing evidence suggests that a percutaneous approach may be equally beneficial for intermediate-risk patients [4]. Technique superiority is judged based on standard outcomes such as mortality, morbidity, and long-term freedom from reintervention; however, novel markers of hemodynamic performance such as flow-mediated dilation (FMD) and apoptotic rate in the human umbilical vein endothelial cells (HUVECs) as a measure of endothelial dysfunction are increasing in popularity [5,6]. Therefore, the aim of this study was to evaluate the effects of SAVR and TAVR on early and late (90-day) endothelial function in patients with significant AS and intermediate risk for surgery.

2. MATERIAL AND METHODS

The study was a prospective observational case control single-blind design conducted at a single tertiary center in Italy. We screened all patients with prevalent AS and intermediate risk for surgery. Risk was estimated based on the risk model developed by the Society of Thoracic Surgeons (STS; a score of 4–8%) [4,7][4]. Patients with a STS risk score < 4.0% were also eligible if they had additional comorbidities that were not represented in the risk model. We excluded patients with significant coronary disease, previous coronary artery bypass grafting and percutaneous angioplasty, and a need for concomitant procedures. The Heart Team selected SAVR or TAVR for each patient after the evaluation of preoperative investigations including coronary angiography, transthoracic echocardiography, chest radiography, laboratory test results, and CT scanning to evaluate peripheral access. FMD and transthoracic echocardiography were performed at baseline and at 4 and 90 days post-procedure. Apoptotic rate of HUVECs was obtained in 10 patients for each group at the same time point.

The study was conducted in accordance with the Declaration of Helsinki and the study protocol was reviewed and approved by the University of Bari Institutional Review Board and registered as EndoTAVI (SN 350/15). The requirement for patient consent was waived.

2.1. SAVR

Median sternotomy was performed under general anesthesia. Heparin was administered and followed by the institution of normo-thermic CPB. Antegrade normo-thermic potassium-enriched cardioplegia was administrated after cross clamping. Next, accurate decalcification of the native annulus was performed and, after sizing, a tissue valve (Mosaic™, Medtronic, USA) was implanted with single sutures. Trans-esophageal echocardiography was used to check for para-valvular leaks. All patients received aspirin (100 mg) from day 1 after surgery. All procedures were performed by a single surgeon (M.M.).

2.2. TAVR

All patients underwent transfemoral valve placement. Patients received aspirin (100 mg) and clopidogrel (≥ 300 mg) before the procedure, heparin during the procedure, and post-procedural aspirin (indefinitely) and clopidogrel (minimum 1 month post-procedure). Procedures were performed under local anesthesia with a mild analgesic and sedative regimen. The percutaneous puncture site was closed with suture-based closure device (1 Prostar XL or 2 ProGlide systems, Abbott Vascular Inc.). The Medtronic CoreValve Evolut R with inLine Sheath EnVeo R delivery catheter (Medtronic Inc., Minneapolis, Minnesota) was used in all cases. Events were defined in accordance with the Valve Academic Research Consortium-2 (VARC-2) [8]. Implantation depth was measured on angiographic images and correct implantation was defined as a depth ≤ 6 mm below the annulus plane; depths > 6 mm were considered to be low implantations [9]. Post-procedural aortic regurgitation severity was assessed on angiography in accordance with the Sellers classification [10]. All procedures were performed by a single operator (A.M.).

2.3. FMD for the assessment of endothelial function

FMD was measured as previously described[11]. Patients continued medication during FMD. Briefly, the probe was positioned 4–5 cm above the elbow of the patient in a supine position to obtain a long-axis view projection of the brachial artery. After a 60-s resting period, the sphygmomanometer cuff was placed distally to the imaging transducer at the forearm level and inflated to 250 mmHg for 300 s. Rapid deflation of the blood pressure cuff was then performed to induce a brief increase in blood flow (reactive hyperemia) and resulting increase in shear stress for dilatation of the brachial artery. Acquisitions of diameter and flow velocity were continued for 300 s. Normal maximum speeds were 50–70 cm/s and reactive hyperemia was calculated as the ratio of the maximal velocity during reactive hyperemia to the maximal velocity at baseline [12]. The maximum FMD recovery value was calculated as the ratio of the change in diameter (maximum − baseline) to the baseline value.
FMD studies were performed using high-resolution ultrasonography (Philips Sonos 5500) integrated with an image analysis system certified by the National Research Council of Pisa (QUIPU, Cardiovascular suit, IT), (positivity test value was set < 5%). All ultrasound examinations were performed by the same physician (F.D.) or under her direct supervision in order to reduce variability. Data analyses were conducted off-line after study completion by 2 operators (M.C. and P.L.) who were blinded to patient treatment allocations. Intra-observer reliability was calculated for determining FMD.

2.4. Brachial wall shear stress (BWSS) calculation

The increase in wall shear stress represented the stimulus for FMD. Flow was calculated as $\pi \times (\text{diameter} \div 2) \times 2 \times$ flow velocity (V). BWSS was calculated as $8 \times \mu \times (V \div \text{diameter})$, where blood viscosity (μ) was assumed to be constant at 0.035 dyne/s/cm [13,14].

2.5. Cell culture

Endothelial function was also determined by assessing the rate of apoptosis HUVECs after 48-hour incubation with 20% serum from patients as previously reported [15,16]. Briefly, the rate of apoptosis was assessed by determining the number of annexin V and propidium iodide positive cells with flow cytometry. Apoptosis rate was expressed as percentage (%) of positive cells as compared to the total

number of cells. Analyses were performed at the Department of Morphology, Surgery and Experimental Medicine University of Ferrara, (It).

2.6. Primary and secondary outcome

The primary outcome was endothelial function assessed as FMD and apoptotic rate in the HUVECs values at: a) baseline (pre-op), b) early after surgery (post-operative day 4), and c) at follow-up (post-operative day 90). Secondary outcomes included relevant in-hospital and follow-up events.

2.7. Statistical analysis

The normality of each variable distribution was tested with the Shapiro–Wilk test. Normally distributed variables were reported as the mean ± standard deviation or median (interquartile range). Categorical variables were reported as the number (percentage). Intergroup comparisons of unpaired data were performed with 2-tailed Student t tests for continuous variables or $\chi 2$ tests for categorical variables. Correlations were explored with Pearson's product moment correlation. Mann Whitney U tests were used to compare results at single time points (baseline, early, and follow-up) and mixed models were used to detect repeated measures differences between groups. FMD values are presented as geometric mean ratios (GMRs). Type I error was significant if < 0.05. An interclass correlation coefficient was used to calculate the level of agreement between operators for calculating FMD. All analyses and data modeling were performed using R-project (R Core Team 2013, Vienna, Austria; http://www.R-project.org/) and the following package: pwr, aov, stats, and ggplot2 for data visualization.

3. RESULTS

From November 2015 to September 2017, 60 patients with AS satisfied the study eligibility criteria and underwent conventional SAVR (n = 30) or TAVR (n = 30) at Anthea Hospital, GVM Care & Research in Bari, Italy. Patients in the TAVR group were at higher risk for surgery as calculated by STS score than those in the SAVR group (SAVR vs. TAVR, 4.2±0.6 vs. 6.1±1.8, p = 0.04; Table 1). Procedural details for each group are shown in Table 2.

3.1. In-hospital outcome and follow-up

One patient died during the transcatheter procedure after ventricle perforation followed by unsuccessful sternotomy and surgical correction. There was no in-hospital mortality in the SAVR group. Patient outcomes are summarized in Supplemental Table 1. At 90-day follow-up (100% compliance), there were 2 deaths related to cardiac causes in the TAVR group and no deaths in the SAVR group.

3.2. Flow mediated dilation

Patients in the TAVR group had significantly lower FMD at baseline than those in the SAVR group (SAVR vs. TAVR, 6.4 ± 0.7 vs. 5.5 ± 0.4, $p < 0.0001$). At early evaluation (day 4), FMD was significantly lower in the SAVR group than in the TAVR group (4 ± 0.9 vs. 5.4 ± 0.4, $p < 0.003$). Both groups showed incremental increases in FMD at follow-up (day 90), but FMD remained higher in the SAVR than in the TAVR group (6.6 ± 0.7 vs. 5.9 ± 0.5, $p < 0.003$(Figure 1A, Supplemental Table 2).

FMD was not significantly increased at follow-up compared to baseline in either group (SAVR: 6.4 ± 0.7 vs. 6.6 ± 0.7, $p = 0.32$; TAVR: 5.5 ± 0.4 vs. 5.9 ± 0.5, $p = 0.54$). Overall, FMD was 4% higher in the TAVR population (Figure 1B, density plot; GMR [SAVR/TAVR] = 0.96, 95% confidence interval = 0.33–1.74, $p < 0.001$). The interclass correlation coefficient for operator agreement was 0.92 (variation 2.8%).

3.3. Brachial wall shear stress

In the SAVR group, there were significant correlations between FMD and peak shear stress at baseline ($r = 0.92$, $p < 0.001$), early evaluation ($r = 0.81$, $p < 0.001$), and follow-up ($r = 0.95$, $p < 0.001$). Similar results were obtained in the TAVR group (baseline $r = 0.68$, $p < 0.001$; early evaluation $r = 0.72$, $p < 0.001$; and follow-up $r = 0.49$, $p < 0.006$) (Supplemental Table 2, Figure 2A-C).

3.4. Apoptotic rate HUVECs

Baseline apoptosis rate was higher in the TAVR group: 9.3±2.5 vs 9.9±1.6 %, (SAVR vs TAVR respectively) but not statistically significant (p=0.3). There was also no significant difference at early (day 4) and late (day 90) evaluation between groups 8.4±1.8 vs 8.9±1.9 %, p=0.3; and 10.2±2.6 vs 8.9±1.7 %, p=0.5, SAVR vs TAVR respectively (Figure 3 A). Overall there was a tendency toward reduced apoptotic rate in the TAVR group (geometric mean ratio (GMR) 1.01, 95% CI (0.94, 1.27), p=0.5) (Figure 3B).

4. DISCUSSION

The present study found that patients who underwent SAVR showed a significant decrease in endothelial function (FMD) early after the procedure; however, reduced FMD was not associated with a poorer outcome. Marginal but non-significant increases FMD were observed in both groups at 90 days follow-up. We also identified positive correlations between BWSS and FMD in both groups. SAVR apoptotic rate did not significantly change, while TAVR apoptotic rate steadily decreased, suggesting a trend toward improved endothelial function; however that was not significant.

To the best of our knowledge, this is the first study to investigate endothelial function in patients undergoing SAVR and TAVR.

Impaired endothelial function has been associated with an increased risk of future cardiovascular events and a decreased probability of survival [17]. The majority of previous studies focused on a relationship between atherosclerosis and endothelial function, and few of these studies have been conducted in patients with AS [17]. A convincing body of evidence suggests that degenerative AS represents a form of atherosclerotic disease [18]; importantly, this study included individuals with intermediate risk for surgery and no significant or previously treated coronary ischemic disease in order to minimize the interference of ischemic disease and other comorbidities with endothelial function.

Only 4 previous studies have investigated the effects of SAVR on endothelial function. Our results are consistent with those of Morelos et al., who reported transient systemic endothelial dysfunction after SAVR; however, this study included patients with coronary disease and AS [19]. Our findings are also in line with Chenevard et al. [20], who did not report any beneficial effects of SAVR on

endothelial function at 5.3 months after surgery. Yet, this study only included 15 patients. In contrast, Takata et al. [21] reported significant improvements in FMD early after SAVR, but the study was limited by a small cohort of only 20 patients. No differences were found in indices of endothelial/vascular function after AVR at follow-up (2.4 months) in another study [22]. Taken together, there is weak evidence associating SAVR with improvements in FMD.

It is accepted that serum from patients with dysfunctional endothelium can determine apoptosis in HUVECs [6,23]. Although we did not find statistically significant difference in between groups, it seemed that serum from TAVR exerts less apoptosis rate, yet given the small sample size conclusions cannot be drawn.

We speculate that an early decrease in endothelial function after SAVR may have been related to the use of the CPB. Decreased nitric oxide bioavailability as indicated by decreases in the expression of endothelial nitric oxide synthase following CPB may reduce endothelial reactivity [24]; indeed, various studies have demonstrated an association between CPB or the duration thereof and nitric oxide consumption [24]; the latter association may correspond not only to hemolysis due to the surgical procedure and CPB, but also due to the use of cell saver devices, the transfusion of stored blood, and other factors [24]. Several studies have demonstrated the deregulation of vascular resistance after CPB. Magder et al. [25] described higher systemic vascular resistances with deregulation up to 18 h post-procedure. In our surgical case series, we observed a reduction in FMD at 4 days post-procedure; however, we did not measure vascular resistances. Of note, no patients were receiving intravenous inotrops or vasoconstrictors at the time of FMD analysis. Therefore, the transient side effects of CPB may explain early reductions in FMD after SAVR [26].

Few studies have investigated the relationship between TAVR and systemic endothelial function using non-invasive methods such as FMD and determination of circulating endothelial microparticles [18]. Jung et al. [27] demonstrated a positive decline in circulating endothelial and platelet microparticles as result of diminished endothelial stress after TAVR. Interestingly, the TAVR procedure itself is frequently associated with vascular or peri-procedural complications that ultimately lead to a systemic early inflammatory response and associated increases in endothelial microparticles [28]. Horn et al. demonstrated that the endothelial function was significantly improved after TAVR,

as witnessed by higher FMD values and lower levels of circulating endothelial microparticles compared to baseline [13]. Interestingly, the abrupt increase in cardiac output that follows the TAVR procedure may expose the vascular endothelium to rapid changes in mechanical forces, which affect vascular tone and endothelial activation but may also be associated with markers of tissue injury and inflammation [29].

An important strength of this study is its novelty in comparing the effects of SAVR and TAVR on FMD and laboratory markers in the early and late post-surgical periods. The study enrolled a series of patients who were at intermediate risk with no coronary disease in order to separate AS from atherosclerotic disease and reduce baseline heterogeneity. Additionally, FMD evaluations were conducted blindly (off-line) by 2 independent operators.

This study also had limitations. Patients were not randomized. The sample size was small. The apoptosis rate in the HUVECs was carried out as subgroup analysis hence was not possible to explore potential correlation between FMD and apoptotic rate. We also cannot separate the effects of medications from those of AVR on endothelial function in our study.

5. CONCLUSION

Conventional SAVR was associated with a transient decrease in endothelial function in the early post-operative period, probably due to the use of CPB.

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Table 1. Baseline characteristics

	SAVR (n = 30)	**TAVR (n = 30)**	**Overall (N = 60)**	**p-value**
Age, years	80 ± 5.2	82.3 ± 6.1	81.1 ± 5.6	0.17
Male sex no. (%)	16 (53.3)	10 (33.3)	26 (43.3)	0.43
BMI	26.6 ± 5.1	27.5 ± 6.2	27 ± 5.6	0.48
STS risk score	4.2 ± 0.6	6.1 ± 1.8	5.1 ± 1.2	0.04
NYHA III or IV no. (%)	19 (63.3)	21(70)	29 (66.6)	0.96
Cerebral vascular disease no. (%)	4 (13.3)	7 (23.3)	11 (36.6)	0.61
Peripheral vascular disease no. (%)	11 (36.6)	14 (46.6)	25 (41.6)	0.79
Diabetes mellitus no. (%)	15 (50)	25 (83.3)	40 (66.6)	0.3
COPD no. (%)	6 (20)	10 (33.3)	16 (26.6)	0.54
Creatinine >2 mg/dl no. (%)	2 (6.6)	5 (16.6)	7 (11.6)	0.5
Atrial fibrillation no. (%)	2 (6.6)	4 (13.3)	6 (10)	0.72
Permanent pacemaker no. (%)	1 (3.3)	2 (6.6)	3 (5)	1
5-m walk test time > 7 s no. (%)	1 (3.3)	5 (16.6)	6 (10)	0.25
Left ventricle ejection fraction %	50.5 ± 7.1	52 ± 5.2	51.2 ± 6	0.72
Pulmonary pressure > 45 mmHg no. (%)	1 (3.3)	3 (10)	4 (6.6)	0.65
Medication no. (%)				
Coumadin	2 (6.6)	4 (13.3)	6 (10)	0.72
Aspirin	28 (93.3)	27 (90)	55 (91.6)	1
β-adrenergic antagonist	29 (96.6)	27 (90)	56 (93.3)	0.99
ACE inhibitor/ARB	15 (50)	18 (60)	33 (55)	0.83
Statin	29 (96.6)	28 (93.3)	57 (95)	1

Data are expressed as the mean ± standard deviation or number (percentage). ACE, angiotensin converting enzyme; ARB, angiotensive receptor blocker; BMI, body mass index; COPD, chronic

obstructive pulmonary disease; NYHA, New York Heart Association scale; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgery; TAVR, transcatheter aortic valve replacement.

Table 2. SAVR and TAVR procedural data

	Tissue, Mosaic (n = 30)
Cardio-pulmonary bypass, min	70.8 ± 15.4
Cross clamp time, min	52.5 ± 12.2
Operation time, min	180 ± 52.1
Prosthesis size, no. (%)	
19 mm	5 (16.6)
21 mm	10 (33.3)
23 mm	10 (33.3)
25 mm	5 (16.6)
≥ Moderate paraprosthetic leak	0
	Evolute R (n = 30)
Device success no. (%)	29 (99)
Procedural time, min	122 (70)
Fluoroscopy time, min	32 ± 10.2
Contrast media, ml	190 (70)
Prosthesis size no. (%)	
23 mm	4 (13.3)
26 mm	15 (50)
29 mm	11 (36.6)
Pre-dilatation no. (%)	5 (16.6)
Post-dilatation no. (%)	14 (46.6)
Valve malpositioning no. (%)	0
Coronary obstruction no. (%)	0
Cardiac tamponade no. (%)	1 (3.3)
Vascular access site complication no. (%)	4 (13.3)

≥ Moderate paraprosthetic leak no. (%)	4 (13.3)

Data are expressed as the mean ± standard deviation or number (percentage). SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Figure legends

Figure 1. A). Flow-mediated dilation (FMD, %), SAVR vs. TAVR: baseline, 6.4 ± 0.7 vs. 5.5 ± 0.4, p < 0.0001; day 4, 4.0 ± 0.9 vs. 5.4 ± 0.4, p < 0.003; follow-up, 6.6 ± 0.7 vs. 5.9 ± 0.5, p < 0.003, B). Geometric mean ratio (SAVR/TAVR) = 0.96, 95% confidence interval = 0.33–1.74, p < 0.001. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Figure 2. Correlation between brachial wall shear stress (BWSS) and flow-mediated dilation (FMD) in the SAVR and TAVR groups at (A) baseline, (B) day 4, and (C) follow-up (90 days). SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Figure 3. A). Apoptosis rate (%), SAVR vs. TAVR: baseline, 9.3±2.5 vs 9.9±1.6 %; day 4, 8.4±1.8 vs 8.9±1.9 %, p=0.3; follow-up, 10.2±2.6 vs 8.9±1.7, p=0.5. B). Geometric mean ratio (SAVR/TAVR) = 1.01, 95% CI (0.94, 1.27), p=0.5. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.