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Transcatheter aortic valve implantation and its impact on endothelial function in patients with aortic stenosis

Leonie Arnold [a,*], Nikolaus Alexander Haas [a], André Jakob [a], Julius Fischer [b], Steffen Massberg [b], Simon Deseive [b,1], Felix Sebastian Oberhoffer [a,1]

[a] Division of Pediatric Cardiology and Intensive Care, University Hospital, LMU Munich, Munich, Germany
[b] Department of Medicine I, University Hospital, LMU Munich, Munich, Germany

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ABSTRACT

Vascular function is impaired in patients with aortic valve stenosis (AS). The impact of transcatheter aortic valve implantation (TAVI) on endothelial function is inconclusive so far. Therefore, we sought to assess the short-term influence of TAVI on endothelial dysfunction in patients with AS.

We recruited 47 patients (76.6 % male, 80.04 years old) with AS scheduled for TAVI. Endothelial function was assessed by fingertip reactive hyperemia peripheral arterial tonometry (RH-PAT). Measurements were conducted one day before and three days after TAVI. Patients were grouped according to RH-PAT change after TAVI.

Overall, RH-PAT measurements did not significantly improve after TAVI (Reactive Hyperemia Index: 1.5 vs 1.6, $p = 0.883$; logarithm of the Reactive Hyperemia Index: 0.44 vs. 0.49, $p = 0.523$). Interestingly, patients with no RH-PAT improvement after TAVI displayed a more severe AS and had lower blood pressure after TAVI. This might be due to a more disturbed blood flow in patients with a smaller aortic valve area and higher peak aortic valve velocity.

The relationship between AS severity, endothelial dysfunction and TAVI has to be investigated in future research that apply longitudinal study designs.

1. Introduction

Aortic valve stenosis (AS) is the most common valvular diseases in the western world and is associated with systemic endothelial dysfunction (Fujisue et al., 2013; Lindman et al., 2016; Trimaille et al., 2023). Multiple factors behind this mechanism are assumed such as mechanical stress causing dysfunction of the valvular endothelial cells leading to local inflammation, lipid deposition and finally calcification (Trimaille et al., 2023). Moreover, AS is linked to the release of extracellular microparticles and activation of platelets promoting endothelial dysfunction (Horn et al., 2015; Trimaille et al., 2023). Several cross-sectional and longitudinal studies have quantified the relationship between endothelial dysfunction and AS (Fujisue et al., 2013; Horn et al., 2015; Moscarelli et al., 2019; Tanaka et al., 2021).

Flow-mediated dilatation (FMD) is the non-invasive method of choice to measure endothelial function and is able to record changes in endothelial dysfunction in AS patients receiving aortic valve replacement (AVR) (Sena et al., 2022). However, FMD is observer dependent, requires a high level of skill and high-resolution ultrasound equipment. Fingertip reactive hyperemia peripheral arterial tonometry (RH-PAT) was developed as an alternative to FMD with less dependence on the skill level and training of the observer (Sena et al., 2022). Both techniques utilize the same mechanism: NO dependent vasodilatation after an induced hyperemic reaction. The target regions differ greatly though. While FMD measures the endothelial function in the conduit artery, the RH-PAT measures the endothelial function in the peripheral resistance arteries(Kato, 2021). Studies have shown, that they are not closely related, but prospective studies have also shown that they are both independent predictors of cardiovascular events (Hamburg et al., 2011; Matsuzawa et al., 2015). Horn et al. explained the restoration of endothelial function through the improved wall sheer stress (WSS), increased stroke volume and pulsatile flow pattern after transcatheter aortic valve implantation (TAVI) (Horn et al., 2015). The same effects could be expected if RH-PAT values are similarly influenced by

* Corresponding author at: LMU Klinikum, Marchioninistraße 15, 81377 München, Germany.
E-mail address: leonie.arnold@med.uni-muenchen.de (L. Arnold).
[1] These authors contributed equally

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hemodynamic parameters. Several studies have shown that FMD improves significantly after transcatheter or surgical valve replacement (TAVI/SAVR) in AS patients (Horn et al., 2015; Moscarelli et al., 2019; Tanaka et al., 2021). Research addressing the change in endothelial function measured by RH-PAT in AS patients is more scarce and inconclusive so far. Several small studies with few patients could not find a significant change after AVR (Comella et al., 2019; Melo et al., 2017).

In this study we aimed to assess endothelial functioned measured by RH-PAT before and after TAVI. We further investigated differences in patients undergoing TAVI depending on the observed change in endothelial function.

2. Methods

2.1. Ethical approval

This study was conducted in accordance with the revised version of the Declaration of Helsinki (World Medical Association, 2013). The local ethics committee "Ethikkommission der Medizinischen Fakultät der LMU München"approved this study (project number: 21–0418, date of approval: 1st June 2021). All patients signed written informed consent.

2.2. Study design

We conducted this prospective single-center observational study between August 2021 and March 2022 at the Department of Medicine I University Hospital, LMU Munich. Patients referred to the clinic for TAVI procedure were contacted for study participation if they met the inclusion criteria. Inclusion criteria were AS diagnosis with an indication for TAVI. Exclusion criteria were peripheral artery disease, peripheral neurological disease and any reasons that prohibit adequate signal acquisition with RH-PAT. AS was defined according to the guidelines of the joint taskforce of the European Society of Cardiology and European Association for Cardio-Thoracic surgery as well as the German commentary of the guideline (Baldus et al., 2022; Vahanian et al., 2022). Indication for TAVI was determined by the University hospital LMU heart team based on the current guidelines.

Patients were examined 24 to 48 h before TAVI procedure and 72 h after TAVI. If patients suffered from complications post-TAVI this period was extended until the examination was possible and before discharge. Patients with major complications were not included in the study (e.g. stroke, systemic infection). Patients that did not complete pre- and post-TAVI examinations were excluded from the study. All examinations were performed by the same investigator.

2.3. Data collection

Baseline patients' characteristics including medical history, concomitant medication intake, laboratory parameters and transthoracic echocardiographic findings were collected from medical records. Mean pressure gradient (MPG), maximum pressure gradient (MaxPG), aortic valve area (AVA) and peak aortic valve velocity (PVel) were evaluated during transthoracic echocardiography. Post-interventional data was collected at the time of follow-up.

2.4. Assessment of endothelial function

Patients were positioned in supine position, resting for at least 15 min before the test. Blood pressure was measured non-invasively by an oscillometric blood pressure device (Mobil-O-Graph®, IEM GmbH, Stolberg, Germany) at least 5 min before the RH-PAT examination on the control arm. EndoPAT® (Itamar Medical Ltd., Caesarea, Israel) is a non-inasive device using digital plethysmography to assess endothelial function. Measurements were taken on the right arm if possible and on the same arm before and after TAVI. Temperature was monitored to assure correct conditions between 21 and 24 degrees Celsius. After checking the standby mode for at least one minute to ensure sufficient data quality and system setup, baseline measurements were taken for 5 min. Arterial occlusion was initiated with at least 60 mmHg above systolic blood pressure or 200 mmHg. If occlusion was not sufficient, cuff pressure was increased in steps up to 300 mmHg. After the occlusion period of 5 min the cuff was rapidly deflated, and the post occlusion period was started for 5 min. The collected data was analyzed with the built-in automated algorithm, which calculates the EndoScores reactive hyperemia index (RHI) and the natural logarithm of the RHI (lnRHI). The lnRHI is calculated to achieve a more normal distribution. Occlusion borders were adjusted where necessary. RHI, lnRHI and the augmentation index adjusted for heart rate (AIx@75) were calculated for each patient pre- and post-TAVI. An RHI $>$ 1.67 and lnRHI $>$0.51 are considered normal EndoScores.

2.5. Statistics

Prior to the beginning of this study, a sample size calculation was performed. Based on the available literature, a median RHI of 2.0 with a standard deviation of 0.5 was estimated (Comella et al., 2019; Melo et al., 2017). To detect a change in RHI of at least 10 % and after adding a dropout rate of 20 %, a necessary sample size of 60 participants was arrived at.

Data was assessed for normal distribution by visual inspection (qq-plot, histogram) and the Shapiro-Wilk test. Normally distributed data was presented as mean $\pm$ SD, non-normally distributed data as median $\pm$ IQR. Pre- and post-TAVI measurements of endothelial function and hemodynamic parameters were compared by paired *t*-test or paired Wilcoxon rank sum test. Additionally, a *p*-value corrected for age, sex, heart rate and mean arterial pressure was calculated by a linear mixed model with patient as a random intercept. To assess the relationship between the EndoScores and baseline patients' characteristics, hemodynamic measurements and laboratory parameters, univariate analysis was performed using the Pearson or Spearman correlation coefficient, or the point-biserial correlation for binary variables.

Patients were divided into two groups depending on the change in lnRHI, calculated by subtracting the post-TAVI lnRHI from the pre-TAVI lnRH. The first group included patients with either no or a negative change in lnRHI (ΔlnRHI $\leq$0, no/negative change group), the second group included patients with a positive change in lnRHI (ΔlnRHI $>$0, positive change group). Depending on the outcome type and distribution, the baseline characteristics of the two groups were compared by *t*-test, Wilcoxon rank sum test, chi squared test or Fishers exact test. The pre-TAVI and post-TAVI RHI and lnRHI values of the two groups were compared by *t*-test and Wilcoxon rank sum test. Differences in baseline characteristics, hemodynamic and laboratory parameters were compared for each timepoint (pre- and post-TAVI) between the groups by paired *t*-test, Wilcoxon rank sum test, chi-squared test or Fishers exact test.

All data were analyzed in R version 4.2.1 (R Core Team, 2022) *P*-values $<$0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

An overview of the patients' characteristics is presented in Table 1. During recruitment, 61 patients were included in the study. Of those, 14 patients were lost to follow-up or excluded due to the following reasons: procedure was rescheduled ($n = 8$), second examination was refused or not possible ($n = 6$), including three patients with major complications after TAVI (stroke $n = 1$, systemic infection $n = 2$). The final study population consisted of 47 patients.

The mean age of the study population at baseline was 80 $\pm$ 6 years and 77 % were male ($n = 36$). Mean baseline AVA was 0.74 $\pm$ 0.15 mm^2.

Table 1
Baseline patients' characteristics of all patients receiving transcatheter aortic valve replacement (TAVI) and patients grouped by improvement (ΔLnRHI >0) or no/negative change (ΔLnRHI ≤0) of the natural logarithm of the reactive hyperemia index (lnRHI) measured before and after TAVI by fingertip reactive hyperemia peripheral arterial tonometry (RH-PAT).

	N all	All patients ($n = 47$)	ΔLnRHI ≤ 0 ($n = 19$)*	ΔLnRHI > 0 ($n = 22$)*	*p*-value
		mean ± SD/Median ± IQR or No. (%)			
Patients' characteristics					
Sex (male)	47	36 (76.6 %)	13 (68.4 %)	18 (81.8 %)	0.528[a]
Age (years)	47	80.04 ± 6.065	79.58 ± 6.012	79.96 ± 5.859	0.841[a]
BMI (kg/m^2)	47	28.73 ± 4.372	27.82 ± 4.365	29.01 ± 4.198	0.382[a]
Arterial hypertension	47	44 (93.6 %)	17 (89.5 %)	21 (95.5 %)	0.588[b]
Diabetes	47	15 (31.9 %)	6 (31.6 %)	9 (40.9 %)	0.769[a]
Atrial fibrillation	47	18 (38.3 %)	5 (26.3 %)	10 (45.5 %)	0.345[b]
CAD	47	27 (57.4 %)	13 (68.4 %)	12 (54.5 %)	0.557[a]
Lipid metabolism disorders	47	29 (61.7 %)	14 (73.7 %)	13 (59.1 %)	0.514[a]
Smoker (active or past)	47	15 (31.9 %)	6 (31.6 %)	9 (40.9 %)	0.769[a]
NYHA class	46				0.605[b]
I, n (%)		6 (13.0 %)	4 (22.2 %)	2 (9.1 %)	
II, n (%)		13 (28.3 %)	4 (22.2 %)	6 (27.3 %)	
III, n (%)		27 (58.7 %)	10 (55.6 %)	14 (63.6 %)	
V, n (%)		0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	
Time between pre-TAVI examination and TAVI procedure (hours)	47	52 ± 47.3	63 ± 60.510	47 ± 38.824	0.323[a]
Time between post-TAVI examination and TAVI procedure (hours)	47	82 ± 20.5	87 ± 21.482	77 ± 16.448	0.118[a]
AVA (mm^2)	47	0.74 ± 0.15	0.67 ± 0.156	0.77 ± 0.132	**0.032**[a]
PVel (m/s)	46	3.9 ± 0.56	4.16 ± 0.456	3.81 ± 0.567	**0.038**[a]
MPG (mmHg)	47	39.16 ± 11.43	44.01 ± 9.072	37.56 ± 11.584	0.053[a]
MaxPG (mmHg)	47	64.01 ± 17.85	73.16 ± 16.222	59.35 ± 16.321	**0.010**[a]
Low-flow low-gradient AS	47	8 (17.0 %)	1 (5.3 %)	5 (22.7 %)	0.191
Medication					
Coumarin	47	5 (10.6 %)	2 (10.5 %)	2 (9.1 %)	1.000[b]
Acetylsalicylic acid	47	20 (42.6 %)	10 (52.6 %)	9 (40.9 %)	0.662[a]
Clopidogrel	47	7 (14.9 %)	2 (10.5 %)	5 (22.7 %)	0.419[b]
Beta-blocker	47	25 (53.2 %)	11 (57.9 %)	13 (59.1 %)	1.000[a]
Angiotensin-converting enzyme inhibitor	47	19 (40.4 %)	8 (42.1 %)	8 (36.4 %)	0.956[a]
Angiotensin receptor blocker	47	12 (25.5 %)	2 (10.5 %)	8 (36.4 %)	0.075[b]
Diuretic	47	28 (59.6 %)	8 (42.1 %)	15 (68.2 %)	0.173[a]
Statin	47	31 (66.0 %)	13 (68.4 %)	14 (63.6 %)	1.000[a]
Laboratory parameters					
NT-proBNP (pg/mL)	45	1381.00 ± 4726.000	1220.00 ± 3267.250	1452.00 ± 4384.000	0.945[b]
Total cholesterol (mg/dL)	43	175.00 ± 62.000	162.00 ± 46.000	183.00 ± 67.000	0.769[b]
Triglycerides (mg/dL)	43	105.00 ± 83.500	105.00 ± 95.000	111.00 ± 83.000	0.736[b]
LDL-Cholesterol (mg/dL)	43	92.00 ± 49.000	88.00 ± 34.000	96.00 ± 42.000	0.490[b]
HDL-Cholesterol (mg/dL)	43	57.00 ± 21.500	61.00 ± 27.000	56.00 ± 19.000	0.872[b]
Non-HDL-Cholesterol (mg/dL)	43	108.00 ± 55.500	108.00 ± 17.000	106.00 ± 49.000	0.837[b]

RHI = Reactive hyperemia index, LnRHI = natural log of RHI, CAD = Coronary artery disease, SD = standard deviation, AVA = Aortic valve area.
[a] T-test/Chi-squared test.
[b] Wilcoxon rank sum test/Fishers exact test.
* LnRHI group information missing $n = 6$.

TAVI was successfully performed in all included patients and MPG decreased from 39.16 ± 11.43 to 11.11 ± 3.92 mmHg, whilst PVel decreased from 3.90 ± 0.56 to 2.20 ± 0.37 m/s post-TAVI (Table 2).

3.2. Impact of TAVI on endothelial function

Endothelial function measured by RHI and lnRHI was slightly increased after TAVI (RHI: 1.50 ± 0.51 to 1.60 ± 0.72, lnRHI: 0.44 ± 0.39 to 0.49 ± 0.29), but did not reach significance (RHI: $p = 0.883$, lnRHI: $p = 0.465$) (Table 2). At baseline, 14 (31.1 %) patients had a normal EndoScore larger than 1.67. After TAVI, this was slightly increased to 16 (38.1 %) patients.

Pre-TAVI lnRHI significantly negatively correlated with age for both RHI and lnRHI and with trigylcerides for lnRHI. Post-TAVI, the correlation with age was attenuated and only remained significant for RHI. PVel and MPG were also significantly negatively correlated with post-TAVI EndoScores (full results presented in the supplementary material).

3.3. Differences between EndoScore groups

Whilst the group of patients with no/negative change was slightly smaller (19 vs. 22 patients), the two groups did not significantly differ in age, sex, BMI, medication and comorbidities (Table 1). The no/negative change group had a significantly higher RHI and lnRHI pre-TAVI, therefor 11 patients in this group had a normal EndoScore, whilst only three patients had a normal EndoScore in the positive change group. This difference was attenuated post-TAVI and the positive change group had a non-significantly slightly higher endothelial function than the no/negative change group (see also Fig. 1). An example recording of an EndoPAT® examination before and after TAVI of a patient in each lnRHI change group is presented in Fig. 2. After TAVI, 10 patients in the positive change group had a normal EndoScore and only 6 patients in the no/negative change group had a normal EndoScore. After the exclusion of patients with low-flow low-gradient AS the results remained the same (additional analysis is presented in the supplementary material).

Pre-TAVI, patients in the positive change group had a significantly lower PVel ($p = 0.038$) and maximum pressure gradient (MaxPG) ($p = 0.010$). AVA was also significantly higher ($p = 0.032$). Blood pressure, HR and laboratory parameters did not significantly differ between the groups pre-TAVI (Table 3). Post-TAVI, systolic blood pressure (SBP) and diastolic blood pressure (DPB) were significantly higher in the positive change group (SBP $p = 0.007$, DBP $p = 0.023$). MPG, MaxPG und PVel were very similar in both groups without significant differences (Table 3). Overall, AIx@75 significantly decreased the in the study population post TAVI (Table 2). Pre-TAVI the positive change group had

Table 2
Endothelial function, hemodynamic and laboratory parameters of patients receiving transcatheter aortic valve replacement (TAVI) for two timepoints.

		Pre-TAVI		Post-TAVI		
Parameter	N	Mean ± SD or Median ± IQR	N	Mean ± SD or Median ± IQR	p-value[a]	p-value[b]
Endothelial function						
RHI[d]	45	1.50 ± 0.510	42	1.60 ± 0.718	0.872	0.883
LnRHI[c]	45	0.44 ± 0.391	42	0.49 ± 0.289	0.523	0.465
Hemodynamic parameters						
AIx@75 (%)[d]	46	14.28 ± 31.315	46	7.618 ± 36.761	**0.002**	
PVel (m/s)[c]	46	3.9 ± 0.56	45	2.2 ± 0.37	**<0.001**	
MPG (mmHg) [c]	47	39.16 ± 11.43	41	11.11 ± 3.916	**<0.001**	
MaxPG (mmHg) [c]	47	64.01 ± 17.85	47	19.89 ± 6.818	**<0.001**	
SBP (mmHg) [c]	45	130.33 ± 18.073	45	125.60 ± 16.694	0.232	
DBP (mmHg) [c]	45	77.92 ± 8.831	45	75.35 ± 12.274	0.239	
MAP (mmHg) [c]	45	100.79 ± 11.137	45	96.50 ± 11.473	0.070	
HR (bpm) [c]	46	67.09 ± 10.604	46	72.43 ± 10.515	**<0.001**	

RHI = Reactive hyperemia index, LnRHI = natural log of RHI, AIx@75 = Augmentation index normalized to heart rate, PVel = Peak aortic valve velocity (m/s), MPG = Mean pressure gradient (mmHg), MaxPG = Maximum pressure gradient (mmHg), SBP = Systolic blood pressure (mmHg), DBP = Diastolic blood pressure (mmHg), MAP = Mean arterial pressure (mmHg), HR = Heart rate.

[a] p-value calculated by t-test for normal data and Wilcoxon rank sum test for non-normal data.

[b] p-value derived from mixed model corrected for age (years), sex, heart rate (bpm) and mean arterial pressure (mmHg).

[c] Central tendency and dispersion displayed as mean ± SD.

[d] Central tendency and dispersion displayed as median ± IQR.

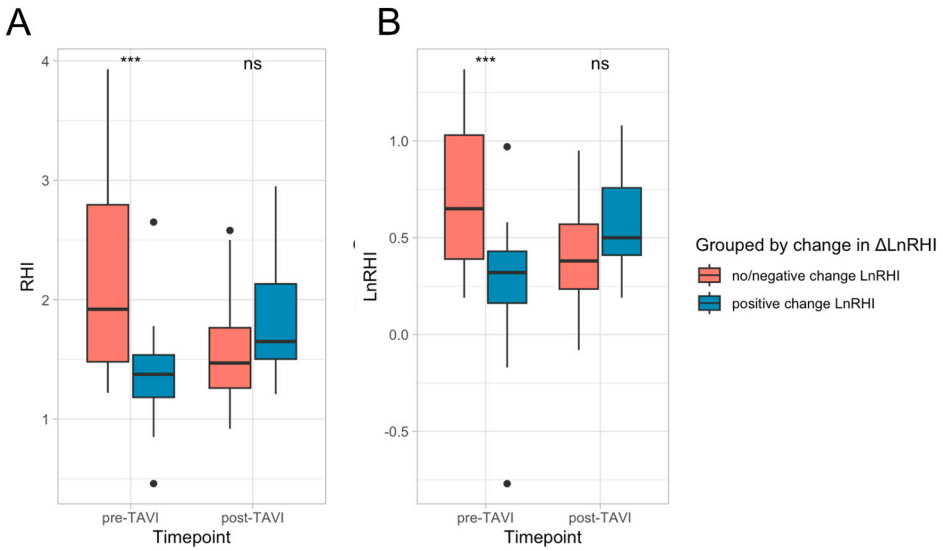

Fig. 1. A) Reactive hyperemia index (RHI) and B) the natural logarithm of the RHI (lnRHI) of patients before and after transcatheter aortic valve implantation (TAVI) grouped by improvement (ΔlnRHI >0) or no/negative change (ΔlnRHI ≤0) of the lnRHI. *t*-test RHI by group: pre-TAVI $p < 0.001$, post-TAVI $p = 0.065$. t-test lnRHI by group: pre-TAVI $p < 0.001$, post-TAVI $p = 0.073$.

a higher AIx@75 than the no/negative change group, without reaching significance ($p = 0.371$). This difference disappeared post-TAVI and both groups had very similar AIx@75 values (Table 3).

4. Discussion

In this study we show, that the endothelial function measured by RH-PAT in patients with AS does improve slightly without reaching significance in the overall study sample. However, once the patients are grouped based on the increase or decrease/no change of EndoScores after TAVI, clear differences between the two groups could be distinguished. Overall, the patients with a negative change in EndoScores after TAVI had lower EndoScores to begin with, had more severe AS and lower blood pressure post-TAVI. The significantly higher EndoScores of the no/negative change group disappeared after the intervention and the positive change group had a slightly higher, but non-significant RHI and lnRHI. These changes might indicate that TAVI has not only a positive effect on the heart and the vasculature, but also on the microvascular and the endothelial function in some patients.

4.1. Endothelial dysfunction and aortic valve replacement

Previous studies on the impact of AVR in patients with aortic stenosis have yielded conflicting results. Most studies apply FMD, the most commonly applied non-invasive method to measure endothelial function. Studies in patients with AS receiving either TAVI or SAVR have shown an improvement in FMD or no change (Chenevard et al., 2006; Comella et al., 2021; Horn et al., 2015; Moscarelli et al., 2019; Quast et al., 2024; Takata et al., 2015; Tanaka et al., 2021). Data on endothelial function in AS patients measured by RH-PAT is scarce. Two small studies showed no improvement in TAVI patients (Comella et al., 2019; Melo et al., 2017). Both studies cited small sample size as an explanation, but Melo et al. also already alluded to a relationship between AS severity and endothelial dysfunction. Our study, which includes a much

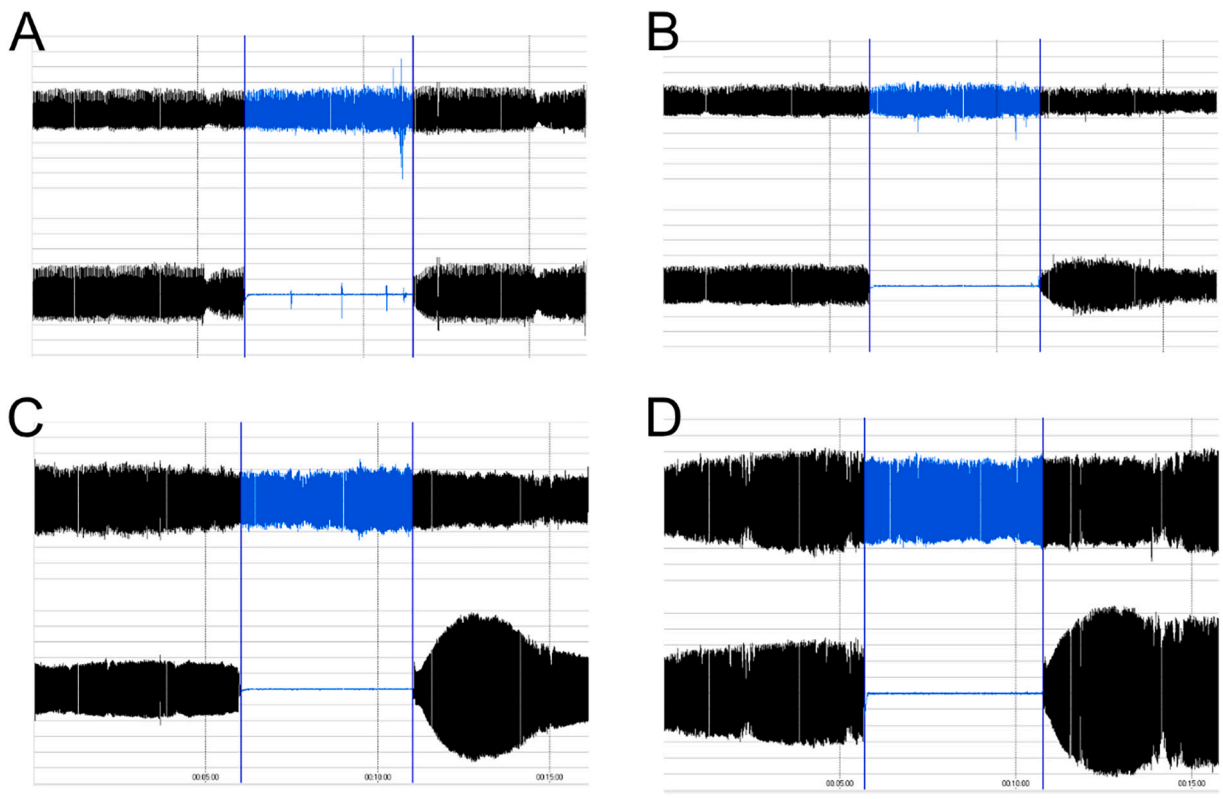

Fig. 2. Recordings of EndoPAT® examination of two patients. Pre-TAVI (A) and post-TAVI (B) examination of a patient with a higher natural logarithm of the reactive hyperemia index (lnRHI) after TAVI, and pre-TAVI (C) and post-TAVI (D) examinations of a patient with a lower lnRHI after TAVI.

Table 3
Hemodynamic and laboratory parameters of patients before and after transcatheter aortic valve replacement (TAVI) grouped by improvement (ΔlnRHI >0) or no/negative change (ΔlnRHI ≤0) of the natural logarithm of the reactive hyperemia index (lnRHI).

	ΔlnRHI ≤ 0		ΔlnRHI > 0		
	N	Mean ± SD or Median ± IQR	N	Mean ± SD or Median ± IQR	p-value
Pre-TAVI					
AIx@75 (%)	19	9.51 ± 41.874	22	14.45 ± 23.259	0.371[b]
PVel (m/s)	18	4.16 ± 0.456	22	3.81 ± 0.567	**0.038**[a]
MPG (mmHg)	19	44.01 ± 9.072	22	37.56 ± 11.584	0.053[a]
MaxPG (mmHg)	19	73.16 ± 16.222	22	59.35 ± 16.321	**0.010**[a]
SBP (mmHg)	19	129.07 ± 17.932	20	131.23 ± 18.464	0.713[a]
DBP (mmHg)	19	77.18 ± 9.729	20	78.05 ± 8.107	0.763[a]
MAP (mmHg)	19	100.05 ± 11.567	20	101.19 ± 11.017	0.755[a]
HR (bpm)	19	67.26 ± 8.937	22	67.32 ± 11.227	0.986[a]
NT-proBNP (pg/mL)	18	1220.00 ± 3267.250	21	1452.00 ± 4384.000	0.945[b]
Total cholesterol (mg/dL)	17	162.00 ± 46.000	21	183.00 ± 67.000	0.769[b]
Triglycerides (mg/dL)	17	105.00 ± 95.000	21	111.00 ± 83.000	0.736[b]
LDL-Cholesterol (mg/dL)	17	88.00 ± 34.000	21	96.00 ± 42.000	0.490[b]
HDL-Cholesterol (mg/dL)	17	61.00 ± 27.000	21	56.00 ± 19.000	0.872[b]
Non-HDL-Cholesterol (mg/dL)	17	108.00 ± 17.000	21	106.00 ± 49.000	0.837[b]
Post-TAVI					
AIx@75 (%)	19	9.62 ± 36.728	22	9.75 ± 42.593	0.164[b]
PVel (m/s)	19	2.21 ± 0.271	20	2.12 ± 0.428	0.481[a]
MPG (mmHg)	17	11.32 ± 2.855	18	11.13 ± 4.674	0.882[a]
MaxPG (mmHg)	19	19.84 ± 4.561	22	20.23 ± 7.976	0.848[a]
SBP (mmHg)	19	119.08 ± 8.779	20	133.86 ± 20.466	**0.007**[a]
DBP (mmHg)	19	70.59 ± 7.028	20	79.78 ± 15.462	**0.023**[a]
MAP (mmHg)	19	92.61 ± 7.970	20	101.02 ± 14.214	0.079[a]
HR (bpm)	19	73.63 ± 11.171	22	72.32 ± 10.181	0.698[a]

RHI = Reactive hyperemia index, LnRHI = natural log of RHI, AIx@75 = Augmentation index normalized to heart rate, PVel = Peak aortic valve velocity (m/s), MPG = Mean pressure gradient (mmHg), MaxPG = Maximum pressure gradient (mmHg), SBP = Systolic blood pressure (mmHg), DBP = Diastolic blood pressure (mmHg), MAP = Mean arterial pressure (mmHg), HR = Heart rate.

[a] T-test.

[b] Wilcoxon rank sum test.

larger sample, comparable to most studies investigating FMD, is in line with these results. EndoScores did not change in general when the entire study sample was investigated, but upon closer inspection differences could be found between patients that did not improve after TAVI and patients that did. Interestingly, approximately halve of the patients had increased EndoScores after TAVI, and halve either decreased or showed no change at all. Both groups did not differ significantly in age, sex, BMI, etc., but baseline AVA, MPG and MaxPG were either close to or significantly different between the groups. On average, patients in the no/negative change group had more severe AS based on AVA, MPG and MaxPG, but also higher pre-TAVI RHI and LnRHI values, while the opposite was found in the positive change group. It is important to note, that patients with a low-flow low-grade AS were included in the study and those patients were predominantly in the positive change group. But even after excluding those patients (results presented in the appendix), patients still significantly differed in the two groups and the main results remained comparable.

4.2. Pathophysiological mechanisms

A relationship between AS severity and EndoScores has been found in the past. Fujisue et al. found significantly different RHI values in patients with AS depending on severity and also compared to matched controls without AS (Fujisue et al., 2013). This might seem counterintuitive at first, because patients in the no/negative change group had a higher pre-TAVI EndoScore and more severe AS, but it is important to note that Fujisue et al. compared patients with mild to moderate/severe AS and the AVA cutoff for this was an AVA of 1 cm^2. Our patient cohort is much more homogenous concerning severity and correlations of pre- and post-TAVI EndoScores revealed no relationship between severity and EndoScores. Why patients with more severe AS exhibit better EndoScores initially, but improve less after TAVI cannot ultimately be explained in this study, but several mechanisms come to mind. It is possible, that EndoScores do not have a linear relationship with markers of AS severity in patients with severe AS. Horn et al. could show that pre-TAVI FMD does not correlate with AS severity and Tanaka et al. and Schumm et al. found a higher PVel in patients with higher FMD values (Horn et al., 2015; Schumm et al., 2011; Tanaka et al., 2021). These results and our results suggest that AS severity is an important factor for endothelial dysfunction, but the relationship is more complex than just a linear relationship between severity of AS and endothelial dysfunction. Schumm et al. proposes that the stenotic valve leads to disturbances in the blood flow and therefor increased NO release and that the increased FMD is an reaction to increased pulse pressure and transvalvular gradients (Schumm et al., 2011). This translates well to the results observed in our studies, where patients with a higher PVel exhibited higher pre-TAVI EndoScores, which might point to more cardiovascular impairment and a possibly slower post-TAVI improvement. Blood pressure was similar in both groups pre-TAVI, but patients in the positive change group had a significantly higher blood pressure post-intervention. Studies have shown that lower blood pressure after TAVI is associated with increased mortality and that elevated blood pressure is associated with a better prognosis (Lindman et al., 2016; Perlman et al., 2013). This was mainly associated with an increase in cardiac output after TAVI independent of baseline cardiac function (Perlman et al., 2013). Further research is needed to unravel the relationship between endothelial dysfunction improvement and cardiovascular function in patients with AS. It is also important to establish whether the changes observed in this study have physiological and clinical significance. Long-term follow-up is essential to investigate whether EndoScore improvement occurs later in some patients and to understand whether, for example, vascular remodeling plays a role in why some patients improve more than others. This could improve overall understanding of AS pathophysiology and thus result into new clinical implications. Future risk stratification of patients based on changes in RH-PAT is required.

4.3. Comparison of RH-PAT and FMD

Studies have shown the prognostic value of both FMD and RHI for cardiovascular events (Matsuzawa et al., 2015). Whilst both aim to quantify the same effect, the hyperemic reaction, they are not interchangeable as has been shown in the Framingham Heart Study (Hamburg et al., 2011). The FMD measures the reaction at the brachial artery, the target region of the RH-PAT is the digital vessel bed. Studies have shown that there is only a moderate correlation between the two methods (Hamburg et al., 2011). Toru Kato presents a compelling comparison in his commentary on a smoking cessation study and suggests that RHI and FMD capture different information on vascular function (Kato, 2021). FMD seems to be more sensitive to age and hypertension, whilst the RHI is more sensitive to BMI and Diabetes. The short study period and the paired design of our study account for most of this and age, BMI and Diabetes where similar in the two groups. Sensitivity to hypertension could explain the changes observed in FMD after TAVI that are reported by most authors, since blood pressure can be impacted, even though those changes are reported to be small in most studies (Yeoh and MacCarthy, 2019). After TAVI, blood pressure was significantly different between the two change groups, but the pre-TAVI differences in RHI were attenuated and did not reach significance. So, while blood pressure might have a slight influence on EndoScores, the extent has to be assessed in future studies.

4.4. Strengths and limitations

To the best of our knowledge, this is the largest study on endothelial function measured by RHI in patients before and after AS intervention. The paired design and a single observer for data collection are strengths of this study. Some limitations should however be acknowledged: this is a single-center study, the follow-up time was short and no long-term data were collected. Follow-up data on FMD after AVR has shown that the results are sustained long-term (Horn et al., 2015; Moscarelli et al., 2019). Further research should focus on longer-term changes in RHI after AVR, which might not present instantly. Even though a sample size calculation was performed, it is possible that the change in RHI in TAVI patients was too small to be detected. Larger, multi-center studies are needed to further investigate this. In this study, patients with severe complications were excluded. However, the patient cohort in this study was very heterogenous, including a diverse range of comorbidities and medications. Therefore, it is possible that unaccounted confounders influenced the results. On the other hand, TAVI patients tend to be fairly old and frail and our patient cohort mirrors this, adding external validity to our results. No controls were matched to our study sample, because not treating patients with AS and an indication for TAVI would be unethical and patients who receive SAVR do not match our patient set. However, data on healthy subjects compared to patients with AS is provided by Fujisue (Fujisue et al., 2013). A sampling bias could not be ruled out in this study. More men than women were included in the sample, which could be due to sampling or the known gender differences in AS diagnosis and treatment (Hervault and Clavel, 2018).

4.5. Clinical Implications and conclusion

Even though endothelial dysfunction assessed by RH-PAT did not significantly improve shortly after TAVI in patients with severe AS, small differences could be found between patients that improved and patients that did not improve. Patients with less severe AS had a greater improvement in RH-PAT than patients with more severe AS, indicating that microvascular flow is not restored in all patients equally. For the improvement of endothelial function, which is visualized by RH-PAT, patients with AS should be strongly encouraged to adhere to healthy lifestyle habits. Moreover, cardiovascular risk factors (e.g. excess weight, arterial hypertension, dyslipidemia) should be identified and treated at an early stage to improve RH-PAT (Hamburg et al., 2011;

Kurose et al., 2014). Post-TAVI patients with AS should be mobilized early.

In the short-term, this knowledge might help clinicians to better monitor patients before and after AVR. In the long-term, further research is required investigation whether RH-PAT can be used as a cardiovascular risk marker for morbidity and mortality. Further research is also needed to establish the additional value and differences between RH-PAT and FMD in patients receiving AVR.

CRediT authorship contribution statement

Leonie Arnold: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Nikolaus Alexander Haas:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization. **André Jakob:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization. **Julius Fischer:** Writing – review & editing, Investigation. **Steffen Massberg:** Writing – review & editing, Resources, Project administration, Conceptualization. **Simon Deseive:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Felix Sebastian Oberhoffer:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation.

Declaration of competing interest

The author(s) declare no competing interests.

Data availability

Data presented in this study is available upon reasonable request from the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mvr.2024.104735.

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