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Non-invasive examination of the vascular adaption in patients with aortic valve stenosis after transcatheter aortic valve implantation

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To my parents, my siblings and my partner.

Thank you for everything.

"Dad, what causes wind?"

"Trees sneezing."

"Really?"

"No, but the truth is much more complicated."

Calvin and Hobbes - Bill Watterson

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List of abbreviations

2DST	Two-dimensional speckle tracking
AS	Aortic stenosis
AVA	Aortic valve area
AVR	Aortic valve replacement
CS	Circumferential strain
CSR	Peak strain rate
CV	Cardiovascular
CVD	Cardiovascular disease
FMD	Flow-mediated dilation
MPG	Mean pressure gradient
NO	Nitride oxide
RHI	Reactive hyperemia index
RH-PAT	Reactive hyperemia peripheral arterial tonometry
SAVR	Surgical aortic valve replacement
TAVI	Trancatheter aortic valve implantation
VEC	Endothelial cell
VICs	Valve interstitial cells

List of publications

Publication I

Arnold L, Haas NA, Jakob A, Fischer J, Massberg S, Deseive S, Oberhoffer FS. Transcatheter aortic valve implantation and its impact on endothelial function in patients with aortic stenosis. Microvasc Res. 2024;157:104735.

Publication II

Arnold L, Haas NA, Jakob A, Fischer J, Massberg S, Deseive S, Oberhoffer FS. Short-Term Changes in Arterial Stiffness Measured by 2D Speckle Tracking in Patients Undergoing Transcatheter Aortic Valve Implantation. J Clin Med. 2023;13(1):222.

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1 Description of author's contribution

1.1 Contribution to publication I

Arnold L, Haas NA, Jakob A, Fischer J, Massberg S, Deseive S, Oberhoffer FS. Transcatheter aortic valve implantation and its impact on endothelial function in patients with aortic stenosis. Microvasc Res. 2024;157:104735.

Publication I was published in 2024. As the first author, I contributed to the conceptualization and the study design. With the support of all my supervisors, I wrote and submitted the application for ethical approval. After receiving ethical approval, I recruited the patients and collected all data with the help of FSO and JF. I carried out sonography examinations, pulse wave analysis and collected baseline patient data. I performed the offline analysis of the sonography evaluation for the 2DST. After data collection, I developed the analysis plan, performed all statistical analysis and prepared the results for publication. The original draft was written by me with support by FSO. All corresponding authors were involved in the reviewing and editing of the final manuscript.

1.2 Contribution to publication II

Arnold L, Haas NA, Jakob A, Fischer J, Massberg S, Deseive S, Oberhoffer FS. Short-Term Changes in Arterial Stiffness Measured by 2D Speckle Tracking in Patients Undergoing Transcatheter Aortic Valve Implantation. J Clin Med. 2023;13(1):222.

I am the first author of publication II. The study design was developed together with the design for publication I and supported by my supervisors. After receiving ethical approval, I performed the EndoPAT® examinations on the recruited patients and collected baseline patient records. I conducted the offline analysis of the EndoPAT® recordings. I was also responsible for the full analysis plan and performed all statistical analysis and prepared the results, including tables and figures. The original draft for the manuscript was prepared by me with the assistance of FSO. All corresponding authors reviewed and edited the manuscript for publication.

2 Introduction

2.1 Epidemiology and pathophysiology of aortic valve stenosis

Calcific aortic valve stenosis (AS) is the most prevalent valvular heart disease in high-income countries, especially afflicting the geriatric population. The burden of disease increases with age, making it a more and more relevant public health challenge in aging populations.[1] It is generally estimated that AS affects around 4% of adults aged 70 years and older, but this number can vary depending on the age group limits, definition, and methods of assessment of AS chosen in the study.[2–4] The true prevalence of AS is most likely unknown, especially for mild and moderate AS, but newer studies started to address this issue.[5] While the reasons for the observed and projected increase of AS are still under discussion, the need for a correct risk stratification and identification of AS patients for treatment is clear.[6]

The development of AS is a complex process, marked by inflammation, lipid deposition, and finally calcification of the valve (Figure 1). Oscillatory sheer stress leads to valvular endothelial cell (VEC) dysfunction, which makes the adhesion and infiltration of platelets and inflammatory cells possible, as well as the diffusion of lipids and haemoglobin. Local inflammation of the valve leads to an oxidative modification of the lipids, which in turn leads to increased inflammation and an expression of adhesion molecules. An angiogenic response leads to vascularisation of the valve, perceptible through intraleaflet haemorrhage. Extracellular microparticles are released in the pro-oxidant environment of the valve, which in turn reinforces the endothelial dysfunction and platelet aggregation. Herewith, the perfect conditions for the final phase, also called the propagation phase, are prepared. First, valve interstitial cells (VICs) differentiate into myofibroblastic cells activated by cytokine. Extracellular matrix remodelling and the production of collagen is triggered. During the last step, myofibroplastic VICs differentiate into osteoblastic-like cells. A process similar to bone formation, together with the dysregulation of the phosphocalcic metabolism, leads to the calcification of the valve.[7,8]

Development and progression of AS is highly dependent on the individual patient and contradictory grading results are no exception.[9] Grading of severity is based on three parameters: the mean pressure gradient (MPG), echocardiographic peak velocity and the aortic valve area (AVA).[10,11] Additional parameters like the stroke volume index can be taken into account, especially to assess the flow status.[12] Patients are classified into mild, moderate or severe AS with a further division into symptomatic or asymptomatic severe AS.[11] The presence or absence of symptoms, the left ventricular ejection fraction and surgical risk are assessed to decide how and when patients are treated. This is especially important since mortality is high in patients with untreated severe AS.[13] No pharmacological prevention or treatment for AS exists so far, but new treatment strategies are being investigated.[14] Despite the fact that AS shares aspects and risk factors with atherosclerosis, treatment and prevention differs.[12] Historically, surgical aortic valve replacement (SAVR) was the treatment of choice for AS patients and has undergone significant development since the invention of the first mechanic valve around 1960.[15–17] Approximately 20 years ago, transcatheter aortic valve implantation (TAVI) was established. The first TAVI was described in 2002 and since then, the procedure has been intensely researched and developed.[18,19] The indications for TAVI have slowly been widened to now include not just older, high-risk patients with severe AS, but also patients with intermediate surgical risk.[12] Additionally, the safety

and efficacy of TAVI in patients with severe AS and low surgical risk has been of great interest in recent years.[20,21] Today, more TAVIs than SAVRs are performed in Germany, making it the treatment of choice.[22] The same development can be observed in other countries, but treatment decisions still vastly differ.[23,24]

It is important to note that AS is not just a local alteration in the valve, but also affects the whole cardiovascular system. Progressively, the blood flow is obstructed by the calcified valve. The subsequent pressure gradient between the heart and the aorta leads to left ventricular hypertrophy, a compensatory mechanism to maintain cardiac output.[25] This can be exacerbated by reduced arterial compliance, adding to the increased afterload.[26,27] The cause and effect of AS and arterial or aortic stiffness are receiving continuing interest.[28,29] It is still not entirely clear how arterial stiffness is impacted in patients with AS, but studies have started to explore the value of arterial function markers in patients with AS.[30,31] Additional arterial biomarkers have the potential to assist in the evaluation, management and treatment of patients with AS.[28]

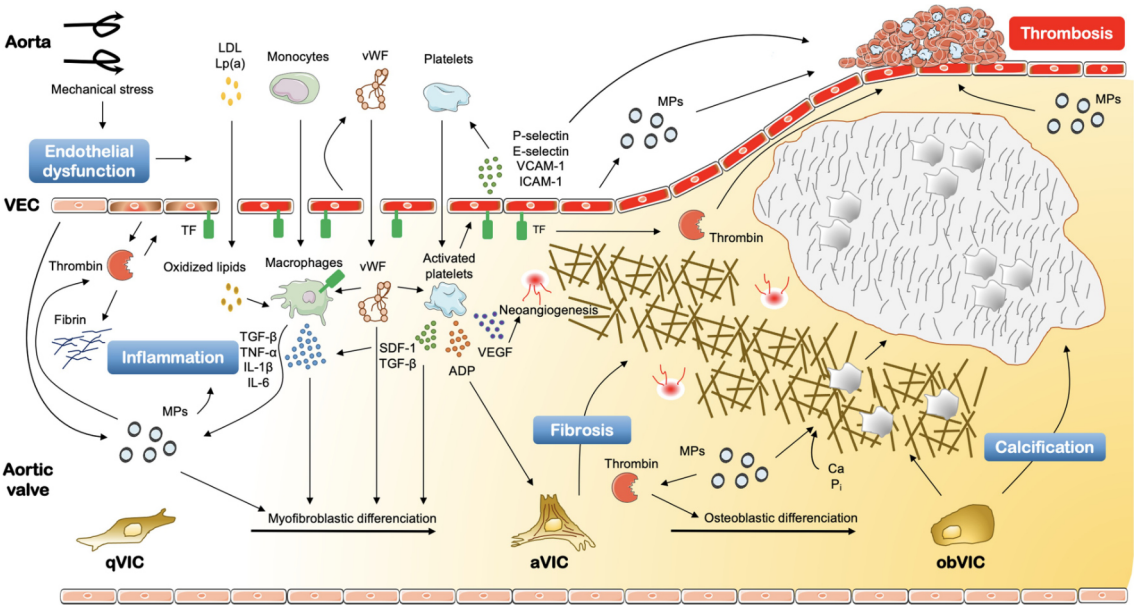

***Figure 1**. Overview of the development of AS on a cellular level. Initial endothelial dysfunction, followed by inflammation and finally calcification of the valve. ADP: adenosine diphosphate; aVIC: activated valvular interstitial cell; Ca: calcium; ECM: extracellular matrix; ICAM-1: intercellular adhesion molecule-1; IL: interleukin; qVIC: quiescent valvular interstitial cell; MPs: microparticles; obVIC: osteoblastic-like valvular interstitial cell; Pi: inorganic phosphate; SDF-1: stromal cell-derived factor-1; TF: tissue factor; TGF-β: transforming growth factor-β; TNF-α: tumour necrosis factor-α; VCAM-1: vascular cell adhesion molecule-1; VEGF: vascular endothelial cell growth factor; vWF: von Willebrand factor. European Society of Cardiology, Aortic stenosis and the hemostatic system, Cardiovascular research, 2023, 119, 6, 1310-1323, 10.1093/cvr/cvac192. Reprinted by permission of Oxford University Press on behalf of the European Society of Cardiology.*

2.2 Aortic valve stenosis and vascular function

The vascular system of the human body encompasses two circulatory systems: the blood vessels and the lymphatic vessels. Arteries, veins and capillaries transport blood from and to the heart. This transport systems brings oxygen, nutrients and immune cells to tissues throughout the body

and takes waste products away. It is an integral part of the respiratory, digestive and urinary system and the temperature control of the body. Arterial function encompasses all aspects of the physiological properties of the arterial tree, including the regulation of vessel tones, the permeability and the upkeep of the structural integrity of all vessels.[32] The term "vascular function" covers all these aspects of the normal functioning of the vascular system.

Potentially the most studied aspect of arterial function in patients with AS is arterial stiffness.[28,29,33] Arterial stiffness is a change in the mechanical behaviour of an artery leading to a loss of distensibility of the vessel. This can be a direct effect of changes in the wall structure, but also an indirect effect of wall geometry and tension.[34,35] Arterial stiffness can relate to both the systemic assessments of function, but also local or regional stiffness of central or peripheral arteries.[36] Whilst these are all passive mechanisms, the active processes that precede arterial stiffness are complex and multilayered. Signalling pathways that alter the structure of the vessel are included here, as well as genetic factors and direct alterations of muscle cells.[34] All layers of the vessel wall and the surrounding connective tissue with the autonomic nervous system and the vasa vasorum contribute to these effects. Arterial stiffness is a well-established predictor for overall cardiovascular (CV) risk.[37–39] In patients with AS, it has been investigated as a possible tool in several areas: better understanding of the pathophysiology and development of AS, evaluation of AS, risk stratification, treatment management and the prognostic value of arterial stiffness, with promising results.[28,29] Studies have shown that arterial stiffness is directly impacted by aortic valve replacement (AVR) and severity is an important contributor to this, which can aid in the evaluation of AS patients.[33,40–44] Baseline arterial stiffness is also a valuable marker for future cardiovascular events and prognosis.[30,31,45]

In terms of vascular function, endothelial (dys)function can be seen as a subtopic of arterial stiffness in a pathophysiological sense. Changes in, for example, nitride oxide (NO) release of the endothelial cells have a direct impact on arterial stiffness. But there are also indicators that this relationship is reciprocal and that arterial stiffness alters endothelial function.[46,47] A clear definition of endothelial dysfunction does not exist, but a literal interpretation is that the function of the endothelial cells of vessels is impaired in all functional areas. This means that the regulation of the vessel tone, the permeability, adhesive properties and the thromboresistance are impacted. To draw more attention to the fact that endothelial dysfunction is an active process, Deanfield et al. suggested the term "endothelial activation". Whilst less descriptive, it incorporates the underlying mechanism of a change in phenotype that results in the activation of several mechanisms, like the expression of adhesion molecules and cytokines.[47] It also underlines the active process involved in endothelial dysfunction. Endothelial dysfunction has received some interest in patients with AS, but is less well studied than arterial stiffness. It is a marker for overall cardiovascular disease (CVD) risk and has been shown to be impaired in patients with AS.[48–52] After AVR, studies have found an improvement in endothelial function in AS patients, most likely due to the normalization of the cardiovascular physiology.[53–57] Whilst pathophysiologically a close relationship exists, in a clinical setting endothelial dysfunction and arterial stiffness are often treated as separate entities.[58] Methodology differs greatly, even for similar target outcomes. Agreement between methods is often low, revealing the complexity of the topic.[59–61] The assessment of vascular function can therefore be seen as more than a redundant repetition of studies, but a necessary exploration of the physiological mechanisms. A comparison of the assessment methods of vascular function can be found in the next chapter.

2.3 Vascular function assessment methods

The range of vascular function assessment methods is as diverse as the aspects of vascular function itself. The interest in measuring vascular function, such as arterial stiffness, has increased in recent decades due to its role in the development of cardiovascular disease.[62] Methods can be classified into various categories, but a unified taxonomy does not exist so far and category membership is not necessarily mutually exclusive. The most important and most applied categorization is invasive versus non-invasive methods. Additional overarching themes are[58,63]:

- Arterial stiffness
- Endothelial dysfunction
- Microvascular endothelial function
- Biomarkers

Arterial stiffness is often additionally divided into local versus systemic stiffness and peripheral versus central.[36] The same has been proposed for endothelial function, where central and peripheral methods also exist.[64,65] The question of how we define arterial function adds more complexity to the topic of categorizing vascular function assessment methods. Physiologically, the distinction between stiffness and endothelial function might be arbitrary and not all authors distinguish between the two.[47,64] But especially in a clinical setting, it still seems to be a common distinguisher.[36,58,65,66] Additionally, assessments could be categorized by the level of validation, clinical application or cost-effectiveness. Agreement between methods and reliability could also be an important factor, especially concerning research and when methods are used to categorize patients, e.g. in risk groups or treatment groups.

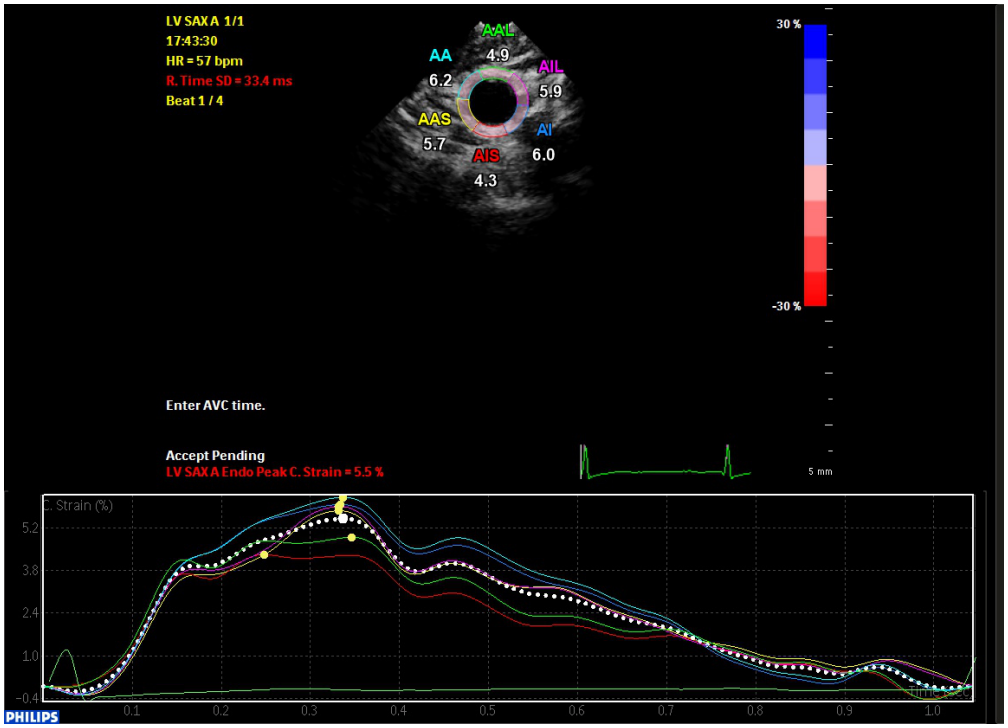

Figure 2. Two-dimensional speckle tracking (2DST) of the common carotid artery (CCA) with region of interested selected and the results of the peak circumferential strain (CS) visible.

2.3.1 Two-dimensional speckle tracking

Two-dimensional speckle tracking (2DST) can be seen as an extension of local arterial stiffness facilitated by ultrasound, like the stiffness index ß or the distensibility, that are calculated from the diameter change of the vessel in relation to the change in pressure.[36,67]

Whilst 2DST is mostly utilized to assess myocardial deformation, its application has been extended to other areas.[68,69] An algorithm calculates the movement of so-called speckles to estimate deformation. This can be expressed as the peak circumferential strain (CS, %), the peak strain rate (CSR, 1/s) or the change in area (cm^2). Speckles are produced by the interaction between the ultrasound waves and the tissue or blood. In vascular assessment, this is a fairly new method, but it has certain advantages. Sonography is readily available in most clinical settings. The utilization of the vessel circumference and not just the diameter, means more information is retained compared to more classical methods, like the stiffness index. Greater automatization of the analysis means it is less dependent on the observer. Several studies have evaluated the value of 2DST of the carotid artery.[70–72] Studies in patients with AS are still scarce, but first results have shown that carotid stiffness is a promising new marker.[73]

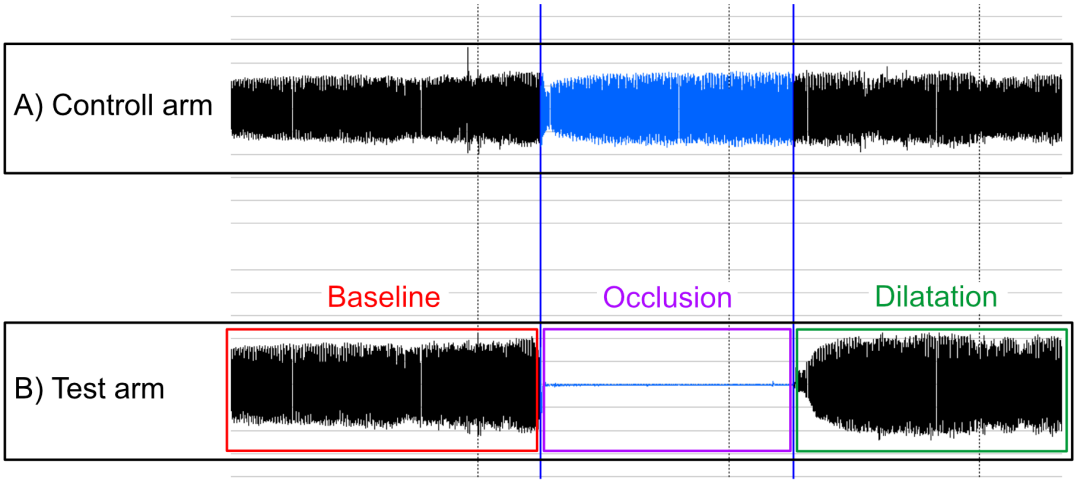

Figure 3. EndoPAT® signal of A) the control arm and B) the test arm with eh occlusion. The PAT ratio is calculated by first calculating the ratio between the dilatation and baseline period for both arms and dividing the results.

2.3.2 Fingertip reactive hyperemia peripheral arterial tonometry

The fingertip reactive hyperemia peripheral arterial tonometry (RH-PAT) is often grouped as a method together with flow-mediated dilation (FMD) as a measure for endothelial dysfunction. Whilst both methods are based on the same phenomenon: the induced hyperemic response after occlusion of the vessels in the arm, the two methods also differ in several key points. FMD measures the change of the diameter of brachial artery using ultrasound.[74] FMD is well established and evaluated, but has several issues. It is observer-dependent and requires a high level of skill and specific equipment. RH-PAT measures the change of the pulsatile arterial volume change using fingertip plethysmography.[65] Patients are positioned in a supine position and need to rest for at least 15 minutes before the test. A five minute baseline amplitude is recorded, followed by 5 minutes of occlusion using a blood pressure cuff that is rapidly inflated to 60 mmHg above systolic

blood pressure. The post-occlusion period, where the dilatation can be observed, lasts another 5 minutes. The recorded data is analysed with a built-in algorithm, that calculates the PAT ratio from the ratio between the dilatation period and baseline period for the test and the control arm. The RH-PAT is much easier to perform and less observer-dependent with fewer skills needed, but also requires specific equipment.[64] In a clinical setting, the RH-PAT could have certain advantages, because the application can be standardized quite easily and be applied by various personnel. This could be a great advantage in a search for a simple and standardized endothelial dysfunction marker.

2.4 Aims of the thesis

The two studies presented in this work focus on different aspects of arterial function in patients with AS and the impact of TAVI on the outcomes. The methods applied in the studies have both not been researched extensively in TAVI patients in the past, so we offer new insights into the application of RH-PAT and 2DST on vessel function. 2DST offers a readily available and easy approach to measure arterial stiffness without the need of specialized equipment. RH-PAT is a less observer-dependent and lower in training than FMD to measure endothelial dysfunction. The overarching hypothesis is, that arterial function in AS patients changes after TAVI. We aimed to quantify this change using two novel methods and explore possible predictors of this change.

2.5. Summary of study results

2.6 Results publication I

Arterial stiffness was examined in 47 patients with AS one day before and three days after TAVI. 2DST of the common carotid artery was used to calculate CS and CSR from sonography examinations of all patients. Significant improvement in CS was found after TAVI (4.5% vs. 5.1%, $p = 0.012$), as well as in CSR (0.9 1/s vs. 1.4 1/s, $p = 0.002$). These changes correlated with cardiovascular risk factors like BMI, MPG and AVA, but not with other arterial stiffness markers, such as pulse wave analysis and augmentation index. This indicated that 2DST is distinctly different from other vascular function markers. Overall, our results offer new insights in the application of 2DST as a tool for the assessment of arterial stiffness in AS patients. Future research is needed to establish the additional value of CS and CSR for patients.

2.7 Results publication II

Between August 2021 and March 2022 47 patients with severe AS were treated with TAVI. Endothelial dysfunction measured by RH-PAT was tested shortly before and after TAVI. Patients showed a slight, but non-significant improvement in RH-PAT after valve replacement (Reactive hyperemia index (RHI) 1.5 vs. 1.6, $p = 0.883$). This change was mainly driven by patients with less severe AS, who had a lower RHI and lnRHI pre-TAVI, but higher values post-TAVI. Patients with more severe AS had decreased RHI and lnRHI values post-TAVI. Whilst the two groups did not differ in characteristics like age, sex, etc., patients with no or negative improvement had lower blood pressure and a smaller AVA and a higher MPG. A possible explanation is the impact of the stenotic valve on the blood flow and a therefore higher NO release in patients with more severe AS. More research is needed on the impact of TAVI on microvascular flow in patients with AS, but in the future this knowledge could help to develop new risk markers for patients with AS.

3 Zusammenfassung

Die Aortenklappenstenose (AS) ist die häufigste erworbene Herzklappenerkrankung in Industrieländern, mit einer geschätzten Prävalenz von 4 % in über 70-Jährigen. Viele Studien gehen davon aus, dass die Häufigkeit in den nächsten Jahrzehnten weiter steigen wird. Als Gründe sind dafür der demografische Wandel, aber auch eine bessere Diagnostik zu nennen. Umso wichtiger ist es daher, effektive Möglichkeiten zu finden, Patienten in Risikogruppen einzuteilen, Behandlungsentscheidungen treffen zu können und das Management zu verbessern.

Die Pathophysiologie der AS ist ein komplexer, dreistufiger Prozess: zuerst eine lokale Entzündung der Klappe, gefolgt von der Einlagerung von Lipiden, und als finaler Schritt die Kalzifizierung. Während diese lokalen Prozesse ablaufen, betrifft eine AS aber auch das ganze kardiovaskuläre System. Der Klappendurchmesser reduziert sich fortschreitend und behindert den Blutfluss. Dies führt zu einer Linksherzbelastung und kann zusätzlich noch durch eine reduzierte arterielle Compliance und endotheliale Dysfunktion verstärkt werden. Um ein besseres Verständnis für die AS zu entwickeln, wird dieses Zusammenspiel zunehmend erforscht um Ansatzpunkte für neue Marker zu finden. Der Ablauf und die Progression von AS sind je nach Patient sehr individuell. Daher ist auch die Einteilung von AS in Schweregrade kompliziert und nicht immer eindeutig. Die wichtigsten Faktoren für die Einteilung sind der Druckgradient, die Klappenöffnungsfläche und die Flussgeschwindigkeit. Daneben können für die Therapieentscheidung noch das Operationsrisiko und die Symptomatik relevant sein. Trotz fortschreitender Forschung gibt es bis jetzt keine medikamentöse Therapie für Patienten mit AS. In Deutschland hat die Transkatheter-Aortenklappenimplantation (TAVI) den chirurgischen Klappenersatz als häufigste Intervention überholt.

Um besser zu verstehen, wie die Gefäßfunktion bei Patienten mit AS durch die Behandlung mit TAVI beeinflusst wird, haben wir zwei neuartige Methoden zur Messung der Gefäßfunktion vor und nach TAVI verglichen. Das zwei-dimensionale Speckle Tracking (2DST) ist eine nicht-invasive Methode, die eingesetzt werden kann um die Gefäßsteifigkeit der Carotis zu messen. Dabei wird die Bewegung sogenannter Speckle, Reflektionen der Ultraschallwellen im Gewebe, mit einem Algorithmus automatisch verfolgt. Der große Vorteil von 2DST ist, dass es einfach anzuwenden ist und keine speziellen Gerätschaften benötigt, anders als viele andere Methoden zur Messung der Gefäßsteifigkeit. Computerprogramme zur Auswertung von Ultraschalldaten für 2DST sind heutzutage außerdem weitverbreitet. Als Zweites wurde die endotheliale Funktion mittels reaktiver Hyperämie peripherer arterieller Tonometrie (RH-PAT) über die Fingerkuppen gemessen. Auch hier sind Vorteile die einfachere Anwendung und die geringere Untersucherabhängigkeit als bei anderen etablierten Methoden.

Wir haben gefunden, dass die Gefäßfunktion gemessen mit 2DST sich signifikant verbessert hat nach TAVI, während der RH-PAT keine signifikante Verbesserung zeigte. Um genauer zu verstehen, ob sich der RH-PAT generell nicht verändert, wurden die Patienten weiter unterteilt in zwei Gruppen: keine oder negative Veränderung des RH-PAT versus eine positive Veränderung. Interessanterweise waren die Patienten mit schwererer AS häufiger in der Gruppe mit keiner oder negativer Veränderung. Dies ist wahrscheinlich auf die ausgeprägtere Einschränkung des Blutflusses bei Patienten mit kleinerer Aortenklappenöffnung und höherer Flussgeschwindigkeit zurückzuführen. Auch bei der Veränderung der Gefäßsteifigkeit waren die hämodynamischen

Parameter wichtige Einflussfaktoren, jedoch primär mit der entgegengesetzten Auswirkung. Patienten mit schwererer AS zeigten eine ausgeprägtere Verbesserung der Gefäßsteifigkeit. Der mikrovaskuläre Fluss scheint also anders auf TAVI zu reagieren als der Blutfluss und die Gefäßsteifigkeit der großen Gefäße.

Diese Ergebnisse unterstreichen die Relevanz und Indikation unterschiedlicher Messmethoden zur Erfassung der Gefäßfunktion und die Komplexität der Interaktion zwischen TAVI, dem Herz und den Gefäßen. Unsere Ergebnisse können daher potenziell helfen, Patienten mit AS vor und nach Intervention besser zu beobachten. Langfristig sind weitere Studien nötig, um zu etablieren ob sich 2DST und RH-PAT auch als Risikomarker für die Morbidität und Mortalität eignen. Beide Parameter könnten in Zukunft helfen das Verständnis der Gefäßfunktion in Patienten mit AS zu verbessern und dringend benötigte Marker zu liefern.

4 Abstract

Aortic stenosis (AS) is the most common acquired valvular heart disease in high-income countries. It has an estimated prevalence of 4% in the age group of 70 years and older. Many studies predict that this will increase in the next decades due to an ageing population and improved diagnostic methods. This adds even more importance to finding effective tools for risk prediction, treatment decisions and patient management.

The pathophysiology of AS is a complex, three-stage process: it starts with local inflammation of the valve, followed by lipid deposition and finally calcification. Importantly, AS is not just a local alteration of the valve but impacts the whole cardiovascular system. The valve area decreases and obstructs the blood flow leading to left ventricular hypertrophy as a compensatory mechanism. This process can be exacerbated by reduced arterial compliance and endothelial dysfunction. The interaction between arterial function and AS is receiving increasing interest to gain a better understanding of the development of AS, but also to find new cardiovascular markers. The development and progression of AS are highly individual in each patient. Grading can be difficult and even contradictory. Aortic valve area, pressure gradient and maximum velocity are the main grading factors. Additionally, surgical risk, symptoms and left ventricular ejection fraction are important for treatment decisions. No pharmacological treatment for AS exists so far. Surgical aortic valve replacement has long been the standard therapy, but transcatheter aortic valve implantation (TAVI) is now the most frequent intervention in Germany.

To gain a better understanding of how vascular function is affected by TAVI in patients with AS, we compared two novel methods for measuring vascular function before and after TAVI. Two-dimensional speckle tracking (2DST) is a non-invasive method, that can be used to quantify vascular stiffness of the carotid artery. The movement of so-called speckles, reflections of ultrasound waves in the tissue, is automatically tracked using an algorithm. The great advantage of 2DST is that it is easy to use and does not require any special equipment, unlike many other methods for vascular stiffness. Additionally, computer-programs for the evaluation of ultrasound data for 2DST are widely available today. Secondly, endothelial function was measured using fingertip reactive hyperemia peripheral arterial tonometry (RH-PAT). It has similar advantages, such as a simpler application and less observer dependency than other established methods for endothelial dysfunction.

We could demonstrate that vascular function measured by 2DST improved significantly after TAVI, while RH-PAT showed no significant improvement. To gain a better understanding why RH-PAT does not change in general, patients were further divided into two groups, one with no or negative change in RH-PAT and one with positive change. Interestingly, patients with more severe AS were more likely to be in the group with no or negative change. This is probably due to the more pronounced blood flow restrictions in patients with a smaller aortic valve area and higher flow velocities. Hemodynamic parameters were also an important influencing factor for the change in vascular stiffness, but with the opposite effect. Patients with more severe AS showed a more pronounced improvement in vascular stiffness. Microvascular flow therefore appears to respond differently to TAVI than the blood flow and vascular stiffness of larger vessels.

These results underline the relevance and indication of different measurement methods for vascular function and the complexity of the interaction between TAVI, the heart and the vessels.

Our results can potentially help to better monitor patients with AS before and after intervention. In the long term, further studies are needed to establish whether 2DST and RH-PAT are also suitable as risk markers for morbidity and mortality. Both parameters could help to improve the understanding of vascular function in patients with AS in the future and provide much-needed markers.

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Short-Term Changes in Arterial Stiffness Measured by 2D Speckle Tracking in Patients Undergoing Transcatheter Aortic Valve Implantation

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Abstract: Arterial stiffness has received increasing interest as a cardiovascular marker in patients with aortic valve stenosis (AS). So far, studies on the impact of aortic valve replacement (AVR) on arterial stiffness have been equivocal. Two-dimensional speckle tracking (2DST) is a novel, non-invasive method to measure the motion of the vessel wall. In this prospective observational study, we aimed to assess the change in arterial stiffness of the common carotid artery (CCA) measured by 2DST in patients undergoing transcatheter aortic valve implantation (TAVI). A total of 47 patients were included in the study (age 80.04 ± 6.065 years). Peak circumferential strain (CS) was significantly improved after TAVI (4.50 ± 2.292 vs. 5.12 ± 2.958, $p = 0.012$), as was the peak strain rate (CSR) (0.85 ± 0.567 vs. 1.35 ± 0.710, $p = 0.002$). Body mass index (BMI), mean arterial pressure (MAP) and hemodynamic parameters were associated with this change. 2DST results did not correlate with aortic pulse wave velocity (aPWV) or augmentation index normalized to heart rate (AIx@75), suggesting a distinct difference between arterial stiffness of the CCA and other stiffness parameters. 2DST seems to be a promising new tool to assess arterial stiffness in TAVI patients.

Keywords: transcatheter aortic valve replacement; vascular stiffness; 2D speckle tracking

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1. Introduction

Aortic valve stenosis (AS) is the most common acquired valvular heart disease. As the prevalence increases with age, the burden of disease is only expected to rise in the future [1]. Mortality is low in patients with asymptomatic AS. However, once symptoms occur, the mortality rate increases dramatically unless aortic valve replacement (AVR) is performed [2]. Transcatheter aortic valve implantation (TAVI) is now more common in Germany than surgical valve replacement, and there is ongoing investigation into its indication in different low-risk groups [3,4].

In the general population, arterial stiffness has been established as an independent marker and predictor of cardiovascular events and all-cause mortality [5,6]. Interestingly, arterial stiffness is also gaining more and more interest as a prognostic cardiovascular marker in AS patients [7].

In recent years, a better understanding of the changes in central aortic stiffness after AVR has emerged. Central pulse wave velocity (PWV) increases as an immediate adaption to the load change after the reparation of the damaged valve. Studies suggest that this adaptation is not only limited to the aorta but also applies to other parts of the vascular system [8,9]. However, relevant data on this matter are scarce.

Two-dimensional speckle tracking (2DST) is a novel, non-invasive imaging technique to measure arterial stiffness of the common carotid artery (CCA). 2DST has wide application

in the assessment of left ventricular function. It has also been proposed as a direct measure to evaluate arterial stiffness of vessels, such as the CCA [10]. It can be used as a screening tool during routine sonographic examination and is easy to apply.

The objectives of this study were to assess the change in arterial stiffness of the CCA in patients undergoing TAVI using 2DST and to compare these results to other arterial stiffness parameters. Moreover, to investigate associations between arterial stiffness, its change after TAVI, and patient characteristics.

2. Materials and Methods

We conducted this study in accordance with the revised version of the Declaration of Helsinki [11]. The local ethics committee "Ethikkommission der Medizinischen Fakultät der LMU München" approved this study (project number: 21-0418, date of approval: 1 June 2021). All patients gave written informed consent. This prospective observational study took place between August 2021 and March 2022. Patients were recruited at the Department of Medicine I, University Hospital, LMU Munich. All patients scheduled for TAVI procedure that met the inclusion criteria were contacted for participation. Inclusion criteria were severe AS and a referral for TAVI. Severe AS was defined according to the guidelines of the joint taskforce of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery, and the German extension of the guidelines [12,13]. General exclusion criteria were peripheral artery and/or neurological disease and a history of carotid endarterectomy. Only patients who completed pre- and post-TAVI measurements were included in the study sample.

Patients were examined 24 to 48 h prior to TAVI and 72 h after TAVI. If patients suffered from TAVI-associated complications, this period was extended until the second examination was possible. Patients who could not be examined 14 days after TAVI were excluded. All patients were examined by the same study investigator. Information on patients' medical history, including pre-existing health conditions (arterial hypertension, diabetes, atrial fibrillation, coronary artery disease, lipid metabolism disorders, chronic renal disease), NYHA class, smoking status, regular medication (coumarin, acetylsalicylic acid, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, statins), and laboratory work (NT-proBNP, total cholesterol, triglycerides, LDL-cholesterol, HDL-cholesterol, non-HDL-cholesterol) were taken from clinical records and by questioning patients. Information on peak aortic valve velocity (PVel, m/s), mean pressure gradient (MPG, mmHg), maximum pressure gradient (MaxPG, mmHg), and aortic valve area (AVA, mm^2) were evaluated retrospectively through routine transthoracic echocardiography as part of the conventional TAVI examination.

Sonographic examination of the CCA was performed by one investigator using a 3–8 MHz sector array transducer on a Philips iE33 xMatrix ultrasound machine (Philips Healthcare, Amsterdam, Netherlands). Loops were recorded under constant three-lead ECG. After 15 minutes of resting, patients were examined in a supine position with the neck extended at a 45° degree angle facing away from the investigator. Patients were instructed to hold their breath and not swallow during recordings, to minimize motion artifacts. Bilateral B-Mode sonographic recordings were taken approximately 1 cm below the carotid bifurcation over three consecutive heart cycles. The recordings were transferred to a workstation for further offline analysis (QLAB cardiovascular ultrasound quantification software version 11.1, Philips Healthcare, Amsterdam, Netherlands). Offline analysis was performed on sonographic recordings that met sufficient image quality requirements. Loops with motion artifacts were excluded. The evaluation was performed as previously described [14]. Peak circumferential strain (CS, %), the maximal deformation of the vessel wall in percent, and peak strain rate (CSR, 1/s), the maximal change of circumferential strain over time, were calculated semi-automatically. The software's SAX-A function and aCMQ tool were utilized. Loops of the left and right CCA were analyzed individually. The region of interest (ROI) was manually set to exactly match the endovascular border. The software then automatically tracked the movement of the speckles within the ROI

(Figure 1). The procedure was repeated three times, and the resulting values for CS, CSR, and the change in the vessel's change in area were averaged.

In addition, the stiffness index β (β_{area}) was calculated from sonographic data of the CCA. As proposed by Cho and Kim, the vessel's area, instead of diameter, was utilized [15]. The area offers more precise information regarding the vessel's deformation in comparison to the circumferential and longitudinal diameters. As the stiffness index β is dependent on blood pressure, which can be impacted by AVR, SS_{area} was normalized to blood pressure. For this reason, the reference blood pressure BP_{ref} was set to 100 mmHg, as proposed by Spronck et al. [16]:

$$\beta_{area} = \frac{\ln(SBP/DBP)}{(area_{max}/area_{min}) - 1} - \ln\left(\frac{DBP}{BP_{ref}}\right).$$

Blood pressure was taken from the brachial oscillometric measurement instead of local CCA pressure measurements, as suggested by some authors [17]. We deemed the necessary consistency to be provided, and the method to be sufficiently accurate due to the paired nature of the data.

Systolic (SBP, mmHg) and diastolic blood pressure (DBP, mmHg), mean arterial pressure (MAP, mmHg), aortic PWV (aPWV, m/s), augmentation index normalized to heart rate (AIx@75, %), cardiac index (CI, L/min × L/m^2), and total vascular resistance (dyn·s/cm^5) were measured using a non-invasive oscillometric blood pressure device with a brachial cuff and patented software with the ARCSOlver algorithm (Mobil-O-Graph, HMS CS Version 6.1, IEM GmbH, Stolberg, Germany) [18]. The Mobil-O-Graph is a validated method to measure aPWV [19]. The pulse wave is recorded at the A. brachialis over 10 s using a high-fidelity pressure sensor. A three-level algorithm analyzes the pressure waves. The algorithm tests plausibility, removes artifacts, and applies a transfer function [20]. Measurements were taken on the right arm, unless not possible. After a ten-minute acclimatization period in the supine position, measurements were repeated at least three times and averaged. The signal quality provided by the device had to be at least excellent or good, otherwise measurements were discarded.

We conducted a sample size calculation prior to this study. A mean of 4.0% and a standard deviation (SD) of 1.0% were estimated for CS from the literature. A 10% post-TAVI change was assumed, as no literature is available on the change in CS for patients post-TAVI. Adding a dropout rate of 20%, the necessary number of recruited patients was estimated to be 60.

Data were visually inspected and tested for normal distribution using qq-plots, histograms, and the Shapiro–Wilk test. Depending on the distribution, patients' characteristics were presented as mean ± SD, median ± IQR (interquartile range), or the number of patients (n) and percentage. Pre- and post-TAVI values of hemodynamic parameters and stiffness indices were compared by paired t-tests or Wilcoxon rank sum tests. Additionally, an adjusted *p*-value was produced by linear mixed regression with a random intercept for patient ID and the covariates age, sex, MAP, and heart rate (HR, bpm). HR and MAP were modeled as time-variant fixed effects, sex and age were time-invariant. β_{area} was not adjusted for MAP since the stiffness index itself is already corrected for blood pressure. Additionally, we compared the stiffness parameters of patients with atrial fibrillation (paroxysmal and permanent) to patients without atrial fibrillation by using the Wilcoxon rank sum test. To evaluate correlations between stiffness parameters, as well as factors influencing the stiffness indices, Pearson, Spearman or point-biserial correlation coefficients were calculated based on the distribution and the type of data. To assess the change, the delta was formed from the pre- and post-TAVI measurements for each patient. Covariates included sex, age, BMI, HR, MAP, hemodynamic measurements, and laboratory parameters. *p*-values < 0.05 were considered statistically significant. All analyses were performed in R version 4.2.1 (R Core Team, Vienna, Austria, 2022).

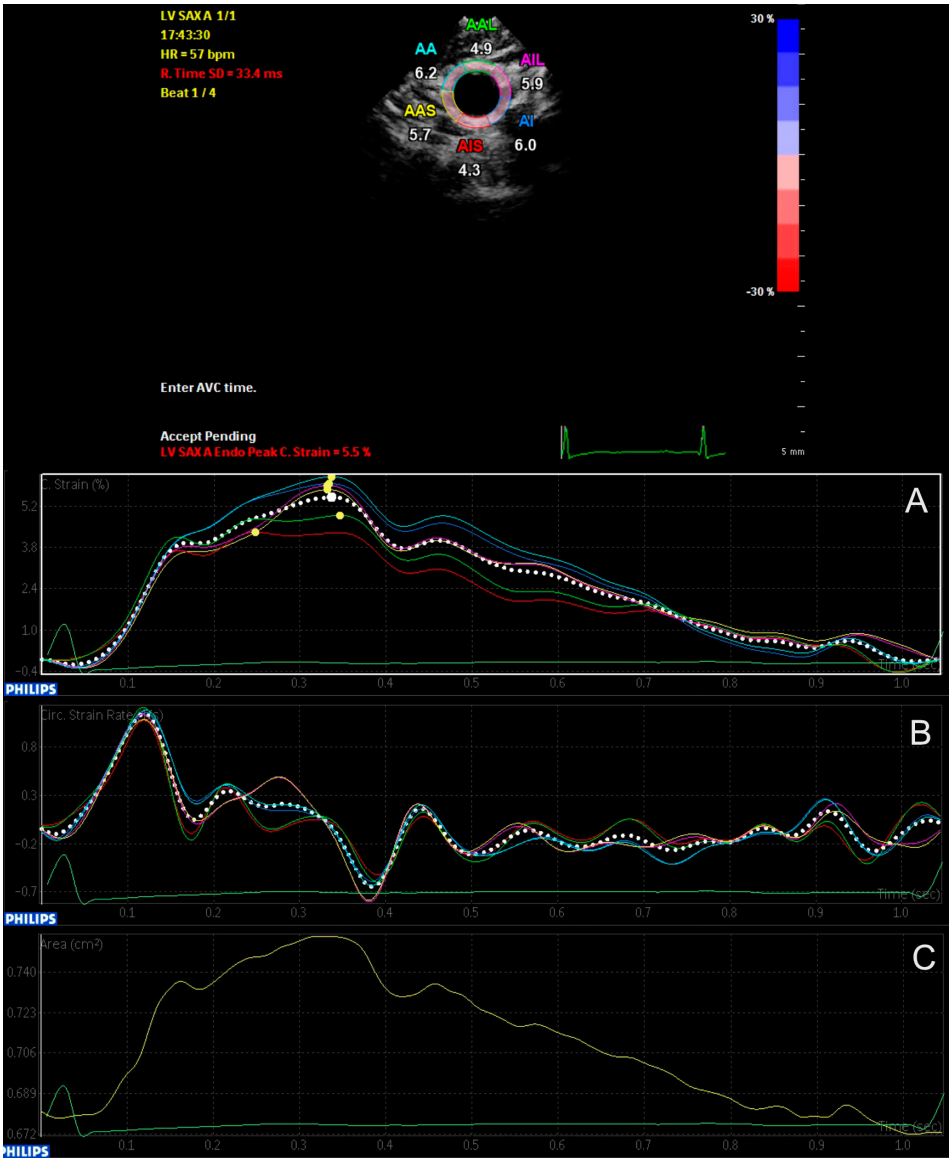

Figure 1. Two−dimensional speckle (2DST) tracking of the common carotid artery (CCA) for the measurement of (**A**) the region of interest and the peak circumferential strain (CS), (**B**) the peak circumferential strain rate (CSR) and (**C**) the change of area.

3. Results

3.1. Study Sample

Overall, 61 patients who met the inclusion criteria were recruited into the study. Of those, 14 patients were lost to follow-up or could not be examined post-TAVI and were therefore excluded. Reasons for this were: rescheduled procedure (n = 5), refusal of second examination/second examination not possible (n = 6), and patients diseased before the procedure (n = 3). In total, pre- and post-TAVI measurements were available for 47 patients.

The mean age of the patients was 80.04 years (±6.065) and patients were predominantly male (76.6%). A detailed illustration of patients' characteristics can be found in Table 1. Baseline AVA was 0.74 mm^2, PVel changed from 3.90 m/s pre-TAVI to 2.20 m/s post-TAVI ($p < 0.001$). MPG changed from 39.16 mmHg to 11.11 mmHg post-TAVI ($p < 0.001$) (Table 2).

Table 1. Baseline patients' characteristics of the study population.

	n	Mean ± SD or No. (%)
Patients' characteristics		
Sex (male)	47	36 (76.6%)
Age (years)	47	80.04 ± 6.065
BMI (kg/m^2)	47	28.73 ± 4.372
Arterial hypertension	47	44 (93.6%)
Diabetes	47	15 (31.9%)
Atrial fibrillation	47	18 (38.3%)
CAD	47	27 (57.4%)
Lipid metabolism disorders	47	29 (61.7%)
Chronic renal disease	47	9 (19.1%)
Smoker (active or past)	47	15 (31.9%)
NYHA class	46	
I		6 (13.0%)
II		13 (28.3%)
III		27 (58.7%)
IV		0 (0.0%)
Time between pre-TAVI examination and TAVI procedure (hours)	47	52 ± 47.3
Time between post-TAVI examination and TAVI procedure (hours)	47	82 ± 20.5
Medication		
Coumarin	47	5 (10.6%)
Acetylsalicylic acid	47	27 (57.4%)
Clopidogrel	47	7 (14.9%)
Beta-blocker	47	25 (53.2%)
Angiotensin-converting enzyme inhibitor	47	19 (40.4%)
Angiotensin receptor blocker	47	12 (25.5%)
Diuretic	47	28 (59.6%)
Statin	47	18 (38.3%)
Hemodynamic parameters		
AVA (mm^2)	46	0.74 ± 0.150
MaxPG (mmHg)	47	64.01 ± 17.850
MPG (mmHg)	47	39.16 ± 11.430
PVel (m/s)	46	3.90 ± 0.560
Low-flow low-gradient AS	47	8 (17.0%)
Laboratory parameters		
NT-proBNP (pg/mL)	45	3715.20 ± 5450.591
Total cholesterol (mg/dL)	43	177.12 ± 53.367
Triglycerides (mg/dL)	43	147.58 ± 133.655
LDL-Cholesterol (mg/dL)	43	99.05 ± 46.742
HDL-Cholesterol (mg/dL)	43	58.79 ± 17.614
Non-HDL-Cholesterol (mg/dL)	43	118.33 ± 52.251

BMI = body mass index (kg/m^2), CAD = coronary artery disease, SD = standard deviation, AVA = aortic valve area, MPG = mean pressure gradient, MaxPG = maximum pressure gradient, PVel = peak aortic valve velocity.

Table 2. Change in stiffness indices and hemodynamic parameters of the patient population with aortic valve stenosis (AS) before and after transcatheter aortic valve implantation (TAVI).

		Pre-TAVI		Post-TAVI		
Parameter	**N**	**Mean ± SD or Median ± IQR**	**N**	**Mean ± SD or Median ± IQR**	***p*-Value [1]**	***p*-Value [2]**
Stiffness indices						
CS (%)	44	4.50 ± 2.292	43	5.12 ± 2.958	0.035	0.012
CSR (1/s)	44	0.85 ± 0.567	43	1.35 ± 0.710	<0.001	0.002
β_{area}	43	4.99 ± 2.720	42	4.44 ± 2.440	0.241	0.143
aPWV (m/s)	38	11.92 ± 2.050	41	11.70 ± 1.400	0.101	0.894
AIx@75 (%)	41	29.00 ± 13.417	38	18.67 ± 14.333	0.005	0.002

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Table 2. *Cont.*

Parameter	Pre-TAVI N	Pre-TAVI Mean ± SD or Median ± IQR	Post-TAVI N	Post-TAVI Mean ± SD or Median ± IQR	*p*-Value [1]	*p*-Value [2]
Hemodynamic parameters						
PVel (m/s)	46	3.90 ± 0.560	45	2.20 ± 0.370	<0.001	
MPG (mmHg)	47	39.16 ± 11.430	41	11.11 ± 3.916	<0.001	
MaxPG (mmHg)	47	64.01 ± 17.850	47	19.89 ± 6.818	<0.001	
SBP (mmHg)	45	130.33 ± 18.073	45	125.60 ± 16.694	0.232	
DBP (mmHg)	45	77.92 ± 8.831	45	75.35 ± 12.274	0.239	
MAP (mmHg)	45	100.79 ± 11.137	45	96.50 ± 11.473	0.070	
CI (L/min × L/m^2)	38	2.40 ± 0.432	41	2.60 ± 0.400	0.004	
Total vascular resistance (dyn·s/cm^5)	38	1732.64 ± 340.212	41	1539.50 ± 222.133	0.010	
HR (bpm)	45	66.79 ± 12.275	44	72.23 ± 10.581	0.002	

[1] *p*-value calculated by *t*-test for normal data and Wilcoxon rank sum test for non-normal data; [2] *p*-value derived from mixed model corrected for age, sex, heart rate, and MAP; CS = circumferential strain, CSR = circumferential strain rate, β_{area} = normalized stiffness index based on area, aPWV = arterial pulse wave velocity, AIx@75 = augmentation index normalized to heart rate.

3.2. Changes in Arterial Stiffness after TAVI

Table 2 and Figure 2 present the changes in hemodynamic parameters and stiffness indices between pre- and post-TAVI time points. Models for the adjusted *p*-values can be found in Supplementary Table S2. CS and CSR measured by 2DST significantly increased after TAVI (CS $p = 0.012$, CSR $p = 0.002$), while the stiffness index β_{area} decreased ($p = 0.181$). aPWV decreased without reaching significance, whilst AIx@75 showed a significant decrease (aPWV $p = 0.894$, AIx@75 $p = 0.002$).

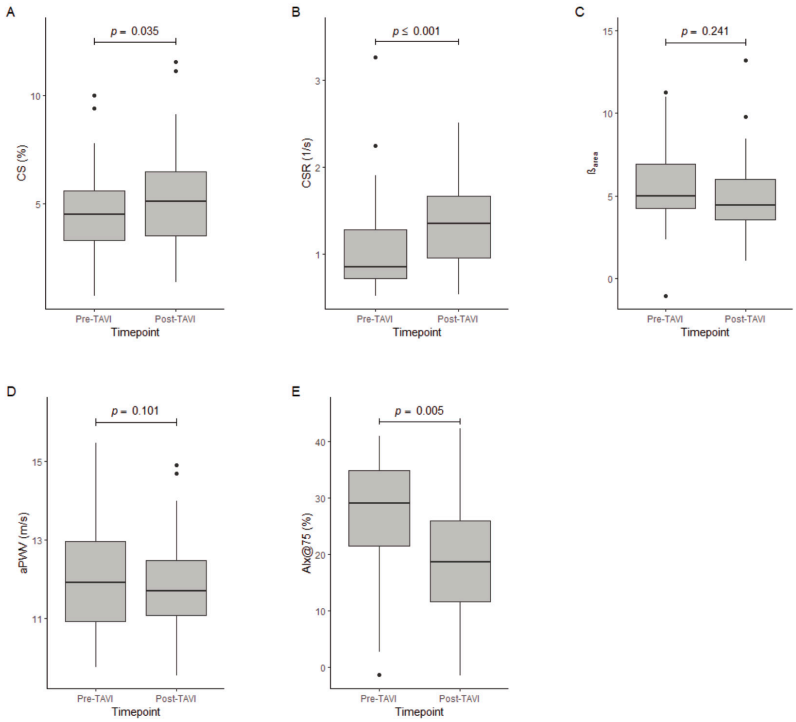

Figure 2. (**A**–**E**) Pre- and post-TAVI values of (**A**) CS, (**B**) CSR, (**C**) $ß_{area}$, (**D**) aPWV, and (**E**) AIx@75.

Univariate analysis revealed that a higher increase in CS was associated with a stronger decrease in MAP post-TAVI, as well as a stronger decrease in MaxPG. Patients with a lower

baseline BMI and a lower baseline AVA displayed a higher increase in CS, whilst a higher baseline NT-proBNP was associated with a higher change in CS post-TAVI (Supplementary Table S1). Similar associations were found for the change in CSR post-TAVI: whilst PVel and MPG were both negatively associated with CSR, no significant influence on AVA and MAP was found. The decrease in AIx@75 was positively associated with post-TAVI HR, total peripheral resistance, as well as the change in MPG and MaxPG (Supplementary Table S1).

Due to a high rate of atrial fibrillation in the patient cohort, additional analysis comparing patients with and without atrial fibrillation was performed. No significant differences in stiffness parameters between these groups were revealed (Supplementary Table S3).

3.3. Assessment of Arterial Stiffness

Pre-TAVI CS was negatively associated with age, as well as pre- and post-TAVI HR, whilst post-TAVI CS was no longer associated with age and pre-TAVI HR. Only post-TAVI HR remained as a significant, yet attenuated, correlation. In comparison, CSR was neither associated with age, nor HR, but negatively correlated with ΔMPG (Supplementary Table S1).

Pre- and post-TAVI β_{area} showed a similar picture. There were no correlations with baseline patient characteristics or hemodynamic measurements. Pre-TAVI aPWV was positively associated with age and NT-proBNP, whilst post-TAVI aPWV was also associated with post-TAVI HR. Pre- and post-TAVI AIx@75 were influenced by CI and total vascular resistance (Supplementary Table S1).

3.4. Agreement between Stiffness Parameters

CS and CSR did not correlate with aPWV before or after TAVI, or when looking at the change of these parameters. Only pre-TAVI CS and pre-TAVI aPWV showed a moderate significant correlation (Table 3). Correlations between CS, CSR, and AIx@75 were even lower, with no significant relationships at any time point. CS correlated slightly better with β_{area} than CSR, but all the time points and the change showed significant correlations for both stiffness parameters (Table 3). Pre-TAVI CS and β_{area} and post-TAVI CS and β_{area} had the highest agreement (pre-TAVI r = −0.71, $p < 0.001$; post-TAVI r = −0.80, $p < 0.001$) and pre-TAVI CSR and β_{area} and ΔCSR and β_{area} the lowest (pre-TAVI r = −0.67, $p < 0.001$; Δpre- and post-TAVI r = −0.34, $p < 0.001$).

Table 3. Correlation of arterial stiffness markers from 2D speckle tracking (2DST) of the common carotid artery (CCA) and aPWV, AIx@75, and β_{area} in patients with aortic valve stenosis (AS) before and after transcatheter aortic valve implantation (TAVI).

	Pre-TAVI Measurements					
	aPWV (m/s)		**AIx@75 (%)**		**β_{area}**	
	R	***p*-Value**	**R**	***p*-Value**	**R**	***p*-Value**
CS (%) [1]	−0.40	0.016	0.11	0.508	−0.71	<0.001
CSR (1/s) [1]	−0.23	0.184	0.13	0.458	−0.67	<0.001
	Post-TAVI Measurements					
	aPWV (m/s)		**AIx@75 (%)**		**β_{area}**	
	R	***p*-Value**	**R**	**R**	***p*-Value**	**R**
CS (%) [1]	−0.09	0.583	0.08	0.632	−0.80	<0.001
CSR (1/s) [1]	−0.11	0.528	0.09	0.573	−0.69	<0.001
	Change between Pre- and Post-TAVI Measurements					
	ΔaPWV (m/s)		**ΔAIx@75 (%)**		**$\Delta\beta_{area}$**	
	R	***p*-Value**	**R**	***p*-Value**	**R**	***p*-Value**
ΔCS (%) [2]	−0.34	0.055	0.08	0.675	−0.64	<0.001
ΔCSR (1/s) [2]	−0.21	0.242	−0.02	0.857	−0.34	<0.001

[1] Spearman correlation coefficient; [2] Pearson correlation coefficient.

4. Discussion

Our study showed a significant improvement in the arterial stiffness of the CCA as measured by 2DST, apparent by a rise in CS and CSR. Possible relationships between cardiovascular risk factors such as BMI, hemodynamic parameters such as MPG and AVA, and the change in arterial stiffness from pre- to post-TAVI were found. This extends recent discoveries about changes in central arterial stiffness and hemodynamic parameters in patients with AS undergoing AVR. It also adds to our understanding of arterial stiffness in AS patients and could be a valuable additional diagnostic and prognostic marker in the future.

Several factors most likely explain the post-TAVI decrease in arterial stiffness measured by 2DST. Whilst several recent studies have found a consistent increase in aortic stiffness measured by the gold standard carotid-femoral PWV, as well as brachial-ankle PWV and cardio-ankle vascular index, there is little understanding of arterial stiffness in other parts of the arterial tree [8,9,21,22]. Terentes-Pritzios et al. established the model of "acute load-mediated changes in elastic properties" for the aorta after AVR, and proposed an extension of this model to the peripheral vascular system [8]. In theory, peripheral vasodilation might occur to accommodate the increased stroke volume after AVR, but, so far, no study has measured this directly. The increase in CS and CRS observed in our study supports this model, offering a link between increased aortic stiffness and decreased peripheral arterial stiffness by examining the stiffness of the CCA. This takes into account that elastic properties are heterogeneous along the arterial tree and that the CCA might adapt differently after AVR than the aorta [17]. The instant change in arterial stiffness after TAVI is most likely driven by cellular elements of the vessel (e.g., mechanical properties, paracrine mediators), which facilitate short-term adjustments to the environment [23]. Whether long-term structural changes, such as an increase in collagen and elastin fibers, also occur remains unclear [8].

In our study, patients with a smaller baseline AVA, higher improvement in MPG and MaxPG post-TAVI, and a lower BMI, showed more improvement in arterial stiffness post-TAVI. This seems plausible, as patients with more severe AS might benefit more from the restoration of the normal hemodynamic flow patterns. This is in agreement with recently published results on carotid stiffness in TAVI patients [24]. Other studies also found that echocardiographic indices including AVA, MPG, and ejection time, as well as patient characteristics like age, BMI, and HR, were the most commonly reported predictors of change in arterial stiffness after TAVI [9,25,26]. Interestingly enough, age did not significantly correlate with change in arterial stiffness, as reported by other authors [9,25]. Overall, this indicates that both hemodynamic factors and CV risk factors might influence changes in arterial stiffness in our study.

Carotid 2DST is a promising new method that is still being investigated in the evaluation of arterial stiffness. Animal sheep models and in-vitro validation had good agreement with reference strain values [27,28]. Literature reference values for CS and CSR are not widely available. So far, in a patient group slightly younger than our study sample, the picture is inhomogeneous with both higher, lower, and similar ranges in CS and CSR [24,29–31]. This wide range of values might be explained by age, comorbidities, and generally high heterogeneity in the patient populations of the studies. CS and CSR values found in this study seem to be comparable to what is reported in the literature, but better data on reference values and their dependence on methods are needed. A comparison of carotid 2DST with PWV and other sonographic markers of arterial stiffness, like intima media thickness and AIx@75, showed a low correlation between 2DST and other markers, but good inter- and intrarater agreement [10]. We observed the same low correlation between 2DST and other markers in our study, especially with the Mobil-O-Graph measurements. AIx@75 and aPWV are markers of central arterial stiffness, and quantify arterial stiffness in a different location of the arterial tree [17]. Correlations between β_{area} and CS and CSR were notably higher. This was to be expected, as the β stiffness index is another local arterial stiffness parameter and was measured at the same location. It is interesting that only CS and CSR significantly changed after TAVI and β_{area} did not. Podgórski et al. compared 2DST of

the CCA and other sonographic markers to PWV and the augmentation index [10]. They found the reliability of 2DST to be higher than that of the β stiffness index, which might also explain the different outcomes in our studies. In a larger sample, the β stiffness index might significantly change after TAVI as well.

Our study shows the following strengths: the variation of the primary outcome variables is limited by the pre- and post-TAVI measurement design. Moreover, the performance of all measurements was conducted by one investigator. Confounders like MAP, HR, age, and sex were accounted for by the adjustment in the models. Still, certain limitations should be acknowledged.

The study sample included 47 patients, but measurements were not always available for all patients due to technical issues and measurement quality. Excluding measurements that did not meet pre-defined criteria was important to achieve high data quality. Studies in larger populations are needed, especially to establish more complex interactions between factors influencing arterial stiffness. It was not possible to blind the investigator to the time point of the measurement. The follow-up period was limited to three days, so long-term data on stiffness parameters are not available for this study. Interestingly, other studies have shown that changes in different arterial stiffness parameters persist after AVR in long-term follow-up [8,32]. However, more studies are needed to determine whether a decrease in arterial stiffness post-TAVI is associated with a better cardiovascular outcome in the long run. Further, the influence of different AVR procedures (e.g., TAVI vs. surgical valve replacement) on arterial stiffness needs to be addressed in the future. The study sample was quite heterogeneous. Men comprised the vast majority of study participants, which could be due to retention bias, as men seemed to agree more frequently to take part in the study. In addition, a larger cohort of men present for TAVI at the hospital, as studies have shown that women are underdiagnosed and the severity of AS symptoms is underestimated in female patients [33]. As expected, patients were also multimorbid. In comparison to patients receiving surgical valve replacement, TAVI patients are commonly older and frailer. This limitation was, however, accounted for by the paired study design. To minimize the influence of atrial fibrillation on the analysis, sufficient data quality in ECG-readings for 2DST had to be reached. Stiffness parameters for patients with and without atrial fibrillation were compared, and no significant differences were found. Atrial fibrillation is a common condition affecting approximately one third of TAVI patients, it is therefore important to take this factor into account [34].

5. Conclusions

In summary, we found a significant improvement in arterial stiffness of the CCA after TAVI, as measured by CS and CSR using 2DST, which is an accessible and readily available method to measure arterial stiffness. Results indicated that these improvements might be associated with a change in MAP, baseline AVA, BMI, ΔMPG, ΔMaxPG, and NT-proBNP for CS and CSR. Future efforts should focus on expanding the understanding of arterial stiffness in different sections of the arterial tree. Moreover, the interchangeability of 2DST with other stiffness parameters, and its additional value for prognostics, risk stratification and treatment decisions, should be addressed. Studies in larger populations and longer follow-up periods are needed to assess whether 2DST of the CCA has prognostic and diagnostic value. Additionally, more complex models investigating the factors influencing the change in both arterial stiffness of the CCA and central arterial stiffness after AVR, as well as the characteristics of patients displaying different degrees of agreement, would be beneficial to identify patients that would most benefit from AS treatment.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm13010222/s1, Table S1: Pearson correlation matrix of stiffness indices circumferential strain (CS, %), strain rate (CSR, 1/s), normalized stiffness index β_{area}, arterial pulse wave velocity (aPWV, m/s), augmentation index normalized to heart rate (AIx@75, %) and patient characteristics, hemodynamic parameters, and laboratory parameters in patients with aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI); Table S2: Mixed linear

regression model with a random intercept for Patient ID and arterial stiffness markers as outcomes variables for patients before and after transcatheter aortic valve transplantation (TAVI); Table S3: Patients with atrial fibrillation (paroxsysmal and permanent) versus patients without atrial fibrillation arterial stiffness markers before transcatheter aortic valve transplantation (TAVI).

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data that supports the results are available upon request from the corresponding author (Leonie Arnold: leonie.arnold@med.uni-muenchen.de).

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

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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

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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.

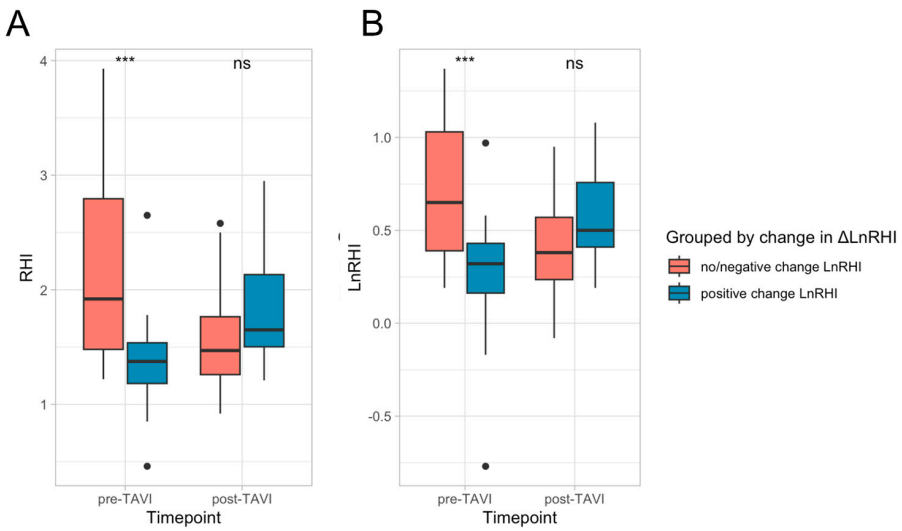

Fig. 1. A) Reactive hyperemia index (RHI) and B) the natural logarithm of the RHI (lnRHI) of patients before and after transcatheter aortic valve implantation (TAVI) grouped by improvement (ΔlnRHI >0) or no/negative change (ΔlnRHI ≤0) of the lnRHI. *t*-test RHI by group: pre-TAVI $p < 0.001$, post-TAVI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

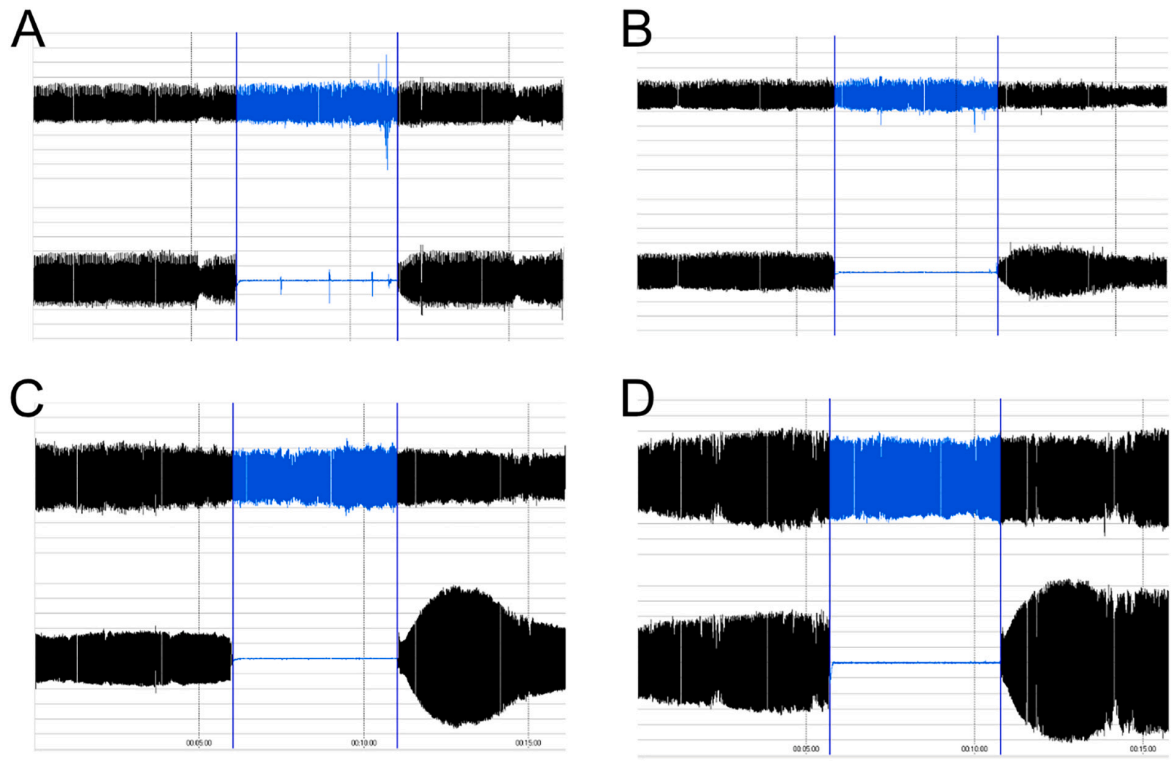

Fig. 2. Recordings of EndoPAT® examination of two patients. Pre-TAVI (A) and post-TAVI (B) examination of a patient with a higher natural logarithm of the reactive hyperemia index (lnRHI) after TAVI, and pre-TAVI (C) and post-TAVI (D) examinations of a patient with a lower lnRHI after TAVI.

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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