THE PATHOPHYSIOLOGICAL ALTERATIONS IN MYOCARDIAL BLOOD FLOW IN PATIENTS WITH SEVERE AORTIC STENOSIS

PHD DOCTORAL THESIS

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I, Michael Michail, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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ABSTRACT

Regulation of coronary blood flow is maintained through a delicate balance of ventriculoarterial and neurohumoral mechanisms. The aortic valve is integral to the functions of these systems, and disease states that compromise aortic valve integrity have the potential to adversely disrupt coronary blood flow. Aortic stenosis (AS) is the most common cause of valvular heart disease requiring medical intervention, and the prevalence and associated socioeconomic burden of AS is set to increase with population ageing. Valvular stenosis precipitates a cascade of structural, microcirculatory and neurohumoral changes, which all lead to impairment of coronary flow reserve (CFR) and myocardial ischaemia even in the absence of notable coronary stenosis. This is partially due to left ventricular hypertrophy which occurs in response to increased afterload, thus increasing resting myocardial oxygen demand. The presence of coronary disease in these patients further increases their ischaemic potential and impairs CFR. Such patients are therefore at higher risk of mismatch between oxygen supply and demand. The assessment of the physiological impact of coronary stenosis is therefore of growing interest and the methods of doing so are under current evaluation.

This thesis examines several hypotheses. Firstly, that the relief of AS results in immediate, yet partial, resolution of physiological myocardial blood flow. Ongoing improvements in myocardial blood flow are dependent on longer term adaptive changes in relation to endothelial function. Secondly, that physiologically significant coronary artery disease in patients with severe AS undergoing transcatheter aortic valve replacement (TAVR) portend worse outcomes. Finally, with this in mind, and a better understanding of the coronary physiology in AS patients, the final part examines the hypothesis that CT-derived fractional flow reserve can be used to assess the functional significance of coronary artery stenoses in patients with severe AS.

The first part of the thesis looks at the unexplored physiological changes that impact coronary blood flow in patients undergoing TAVR with a specific focus on two areas. Firstly, it looks at the early

changes in proximal aortic physiology and endothelial function; secondly, it looks at the long-term adaptive changes in endothelial function following TAVR. In the first study, invasive data from 54 patients undergoing TAVR enabled aortic reservoir pressure and wave intensity analysis before and immediately after TAVR. This data demonstrated that increases in central aortic pressure following TAVR relate to increased excess pressure and improved transvalvular energy profiles with unchanged reservoir pressure. These haemodynamic changes are likely responsible for the improved myocardial and other organ perfusion. These changes may also explain the apparently protective state of persistent hypertension in patients following TAVR, in contrast to that seen in essential hypertension which is associated with arterial stiffening.

In the second study (eFAST study), early and late changes in endothelial function before and after TAVR were investigated in 27 prospectively recruited patients undergoing TAVR. This data demonstrated that endothelial function in patients with AS improves early following TAVR and that this improvement is sustained at late follow up. There is evidence of ongoing late normalisation of arterial haemodynamics, including lower wall shear stress. The late adaptations likely contribute to the delayed improvements that have been observed in coronary physiology and patient symptoms.

A better understanding of the pathophysiological changes in myocardial blood flow in the context of AS permits better understanding of the impact of abnormal coronary physiology on outcomes in patients undergoing treatment for severe AS. The second part of this thesis explored the physiological impact of coronary stenosis in patients undergoing TAVR and whether non-invasive CT-derived measures of pressure and flow can be used to provide this assessment. In the third study, angiographic CAD scoring tools were used to investigate the prognostic impact of coronary stenosis defined by their anatomical complexity (SYNTAX score) and a physiological scoring system (DILEMMA score). This study demonstrated that whilst both scoring tools could stratify clinical outcomes, only angiographic physiological scoring using DILEMMA score remained independently associated with outcomes when

adjusted for other clinical factors. The increasingly evident importance of correctly identifying functionally significant CAD in this patient group has driven the exploration in the use of invasive pressure wire assessment in this patient group. However, the use of invasive intracoronary wires is associated with risk and given that these are typically older patients with greater frailty left an unmet need for a non-invasive alternative. With this in mind, the fourth study investigated the feasibility and validity of using of CT-derived fractional flow reserve (CT-FFR) in patients with AS. Forty-two patients were prospectively recruited into the CAST-FFR study. Invasive FFR was compared against CT-FFR in 60 vessels. The data demonstrates that CT-FFR is safe and feasible in patients with severe AS. Besides a high yield of interpretable vessels, the data suggests that the diagnostic accuracy of CT-FFR in this cohort is high, despite the abnormal coronary physiology in these patients.

In summary, the work from this thesis adds to the expanding body of evidence which helps our understanding of the abnormal ventriculoaortic, coronary and microcirculatory physiology in patients with severe AS. The work from this thesis also lays important foundations in the use of non-invasive physiological assessment using CT-FFR for coronary evaluation in patients pre-TAVR.

IMPACT STATEMENT

The prevalence of aortic stenosis (AS) increases in older age such that it estimated that up to 3% of individuals above the age of 75 years will have AS at a severity that warrants procedural treatment. Importantly, with an increasingly ageing population, the burden of this disease upon the health service is set to continue to rise.

Transcatheter aortic valve replacement (TAVR) is a percutaneous alternative to surgical aortic valve replacement (SAVR) and has gained popularity over the last decade. It circumvents a sternotomy, can be performed under local anaesthetic, and allows quicker recovery for patients. Besides the advantages to the patient, it has perceived economic advantages given the quicker procedural time, shorter hospital stay and reduced burden on rehabilitation services. It has therefore attracted widespread interest as a feasible alternative to SAVR, not only in those who have prohibitively high surgical risk, but also in lower surgical risk groups. TAVR has revolutionised the treatment for many with severe AS and is radically changing the horizons for healthcare provision and policies. As TAVR transitions to become the new standard of care for the treatment of severe AS, the modality continues to be scrutinised for its effect in restoring premorbid physiology and ultimately improving patient outcomes.

As such, the first half of this thesis explores important questions about the normalisation of physiology following TAVR, including the expected timescale for such recovery. This was examined in the eFAST study and indeed demonstrates that endothelial function recovers early post-TAVR with some ongoing changes which are only observed at longer term follow up. This contributes to the growing body of evidence demonstrating key benefits in TAVR as a minimally invasive option. This study provides a stepping stone to further investigate different conditions which may optimise or hamper this recovery, for example using different device platforms or to better understand patient prosthesis mismatch.

TAVR uniquely involves the deployment of a new aortic valve prosthesis without any notable interruption of normal circulation as is the case with cardiopulmonary bypass. This provided a unique opportunity to assess some of the first changes in physiology – that at the aortic root level. One of the studies in this thesis provides unique insights into the immediate haemodynamic changes from which all the subsequent benefits are expected to originate. This study demonstrated that early hypertensive changes – which are recognised post-TAVR – are due to increased excess pressure, a mechanism which may be responsible for the paradoxical benefit seen in patients who are hypertensive post-TAVR.

The second half of thesis focuses on the assessment and prognostic impact of coronary artery disease in the context of patients undergoing TAVR – an area which has gained considerable interest given the absence of evidence and guidance. The CAST-FFR study explores the feasibility and validity of using CT-FFR in patients with severe AS to assess both coronary anatomy and function pre-TAVR. Importantly, this was integrated into a one-stop-shop cardiac CT as part of patients' standard of care for pre-TAVR assessment which has several potential advantages. Besides shortening patients' pre-TAVR diagnostic journey, it minimises the need for additional invasive diagnostic procedures thus improving patient safety and minimising the use of iodine contrast. This study was presented as a Late-Breaking Clinical Trial at EuroPCR 2020 and the study was picked up medical news outlets. CT-FFR in pre-TAVR patients is now being further investigated in large prospective trials.

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LIST OF PUBLICATIONS

Relevant manuscripts published during the doctoral period:

1. Comella A, **Michail M**, Chan J, Cameron JD, Gooley R, Mathur A, Hughes AD, Brown AJ. Patients with aortic stenosis exhibit early improved endothelial function following transcatheter aortic valve replacement: The eFAST study. *Int J Cardiol.* (2021) DOI: 10.1016/j.ijcard.2021.03.062.
2. Comella A, **Michail M**, Chan J, Thakur U, Gooley R, Ko B, Cameron JD, Brown AJ. Discordance between hyperaemia and non-hyperaemia pressure indices in patients with severe aortic stenosis. *JACC Cardiovasc Interv.* (2021). DOI: 10.1016/j.jcin.2020.10.049.
3. **Michail M**, Ihdayhid AR, Comella A, Thakur U, Cameron JD, McCormick LM, Gooley R, Nicholls SJ, Mathur A, Hughes AD, Ko BS, Brown AJ. Feasibility and validity of CT-derived fractional flow reserve in patients with severe aortic stenosis: the CAST-FFR study. *Circ Cardiovasc Interv.* DOI: 10.1161/CIRCINTERVENTIONS.120.009586.
4. **Michail M**, Thakur U, Mehta OH, Ramzy JM, Comella A, Ihdayhid AR, Cameron JD, Nicholls SJ, Hoole SP, Brown AJ. Non-hyperaemic pressure ratios to guide percutaneous coronary intervention. *Open Heart* (2020) DOI: 10.1136/openhrt-2020-001308
5. Mehta OH, Hay M, Lim RY, Ihdayhid AR, **Michail M**, Zhang MJ, Cameron JD, Wong DTL. Comparison of diagnostic performance between QFR, Non-Hyperemic Pressure Indices and FFR. *Cardiovasc Diagn Ther* (2020). DOI: 10.21037/cdt-20-179
6. Thakur U, Khav N, Comella A, **Michail M**, Ihdayhid AR, Poon E, Nicholls SJ, Ko B, Brown AJ. Fractional flow reserve following percutaneous coronary intervention. J Interv Cardiol (2020) DOI: 10.1155/2020/7467943
7. **Michail M**, Thakur U, Comella A, Lim RY, Gupta V, Tan S, Rashid H, Cameron JD, Nicholls SJ, McCormick LM, Gooley R, Mathur A, Hughes AD, Brown AJ. Angiographic functional scoring of coronary artery disease predicts mortality in patients with severe aortic stenosis undergoing TAVR. *Cardiovasc Revasc Med* (2020) DOI: 10.1016/j.carrev.2020.04.024

8. Cameron JN, Mehta OH, **Michail M**, Chan J, Nicholls SJ, Bennett MR, Brown AJ. Exploring the relationship between biomechanical stresses and coronary atherosclerosis. *Atherosclerosis* (2020) DOI: 10.1016/j.atherosclerosis.2020.04.011

9. **Michail M**, Hughes AD, Comella A, Cameron JN, Gooley R, McCormick LM, Mathur A, Parker KH, Brown AJ, Cameron JD. Acute effects of transcatheter aortic valve replacement on central aortic hemodynamics in patients with severe aortic stenosis. *Hypertension (*2020) DOI: 10.1161/HYPERTENSIONAHA.119.14385

10. Ihdayhid AR, Koh JS, Ramsy J, Kumar A, **Michail M**, Brown AJ, Samady H. The Role of Fractional Flow Reserve and Instantaneous Wave-Free Ratio Measurements in Patients with Acute Coronary Syndrome. *Curr Cardiol Rep* (2019) DOI: 10.1007/s11886-019-1233-6

11. **Michail M**, Ihdayhid AR, Brown AJ, Ko B. Discordance of intracoronary pressure-based indices in severe angiographic stenosis: are we missing the flow? *Cardiovasc Interv Ther. (*2019) DOI: 10.1007/s12928-019-00609-6.

12. **Michail M**, Asrress KN, Cameron JD, Gooley R, McCormick LM, Hughes AD, Brown AJ. Adaptations to coronary physiology in a patient with severe aortic stenosis and complete heart block undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv. (*2019) DOI: 10.1016/j.jcin.2019.01.215.

13. **Michail M**, Dehbi HM, Nerlekar N, Davies JE, Sharp ASP, Talwar S, Cameron JD, Brown AJ, Wong DTL, Mathur A, Hughes AD, Narayan O. Application of the DILEMMA score to improve lesion selection for invasive physiological assessment. *Catheter Cardiovasc Interv. (*2019) DOI: 10.1002/ccd.28054

14. **Michail M**, Cameron JN, Nerlekar N, Ihdayhid AR, McCormick LM, Gooley R, Niccoli G, Crea F, Montone RA, Brown AJ. Periprocedural myocardial injury predicts short and long-term mortality in patients undergoing transcatheter aortic valve implantation. *Circ Cardiovasc Interv. (*2018) DOI: 10.1161/CIRCINTERVENTIONS.118.007106.

15. **Michail M**, Narayan O, Parker KH, Cameron JD. Relationship of aortic excess pressure obtained using pressure-only reservoir pressure analysis to directly measured aortic flow in humans. *Physiol Meas* (2018) DOI: 10.1088/1361-6579/aaca87

16. **Michail M**, Brown AJ. Physiology of the normal heart. *Medicine (*2018) DOI: 10.1016/j.mpmed.2018.05.001

17. **Michail M,** Davies JE, Cameron JD, Parker K, Brown AJ. Pathophysiological coronary and microcirculatory flow alterations in aortic stenosis. *Nat Rev Cardiol.* (2018) DOI: 10.1038/s41569-018-0011-2

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ABBREVIATIONS

AS – aortic stenosis

BCW – backward compression wave

BEW –backward expansion wave

CAD – coronary artery disease

CCS (angina score) – Canadian Cardiovascular Society

CFR – coronary flow reserve

CTA – computed tomography angiography

CT-FFR – CT-derived fractional flow reserve

DS – DILEMMA score

ED – endothelial dysfunction

FMD – flow mediated dilatation

FCW – forward compression wave

FEW – forward expansion wave

FFR – fractional flow reserve

ICA – invasive coronary angiography

iFR – instantaneous wave-free ratio

LAD – left anterior descending artery

LVH – left ventricular hypertrophy

MRI – magnetic resonance imaging

NO – nitric oxide

NPV – negative predictive value

NYHA – New York Heart Association

PCI – percutaneous coronary intervention

PPMI – periprocedural myocardial injury

PPV – positive predictive value

QCA – quantitative coronary angiography

RCA – right coronary artery

TAVR – transcatheter aortic valve replacement

WIA – wave intensity analysis

WSS – wall shear stress

1. BACKGROUND

This chapter is based on the published manuscript:

Michail M, Davies JE, Cameron JD, Parker KH, Brown AJ. Pathophysiological coronary and microcirculatory flow alterations in aortic stenosis. *Nat Rev Cardiol.* (2018) DOI: 10.1038/s41569-018-0011-2.

Contribution:

I performed the literature review. I wrote the manuscript and contributed substantially to the discussions of the manuscript. JDC, JED and KHP contributed to the discussions in the manuscript. AJB contributed to the discussions, edited the manuscript and provided overall supervision.

1.1. INTRODUCTION

The physiology of coronary blood flow is complex and multifaceted, as it is dictated by interactions between ventriculoarterial and neurohumoral systems. These interactions maintain a homeostatic balance during the resting state and enable adaptations to increases in physiological demands, such as are observed during exercise.

The aortic valve is intrinsic to ventriculoarterial coupling, and any impairment in valve function adversely affects the overall balance of this system. Degenerative aortic stenosis (AS) is the most common form of aortic valve disease and is precipitated by progressive calcification of the valve leaflets and annulus[1], which impairs leaflet mobility and compromises the valve orifice area.[2,3] AS is typically a disease of old age; an estimated 3% of individuals aged >75 years in developed countries have AS of sufficient severity to warrant medical intervention.[4,5] Importantly, the global number of patients with severe AS is set to double in the next two decades, which will place an ever-increasing burden on health-care providers.[6] From a haemodynamic perspective, AS leads to reduced blood flow through the narrowed valve, with resultant pressure overload within the left ventricle. This overload causes compensatory pathophysiological and morphological changes within the left ventricle, including hypertrophy and fibrosis. The resultant increase in myocardial mass generates an increased oxygen demand, which requires further mechanical and metabolic adaptations. This sequence of events decouples the balance of ventriculoarterial systems, as well as adversely impacts blood flow in the epicardial coronary vasculature and microcirculation.

These physiological alterations in coronary blood flow in patients with AS raise several important considerations for the clinician. Myocardial ischaemia and angina pectoris are well-described even in patients with AS who have unobstructed coronary arteries.[7] Additionally, 25–50% of patients with severe AS also have coronary artery disease (CAD).[8-11] The presence of symptoms (including angina) in patients with AS has traditionally been associated with a poor prognosis[7]. Moreover, in patients with

AS undergoing surgical aortic valve replacement, some evidence suggests that individuals who do not undergo coronary revascularization at the time of this surgery have inferior outcomes.[12] The implications of incomplete revascularization in patients undergoing percutaneous transcatheter aortic valve replacement (TAVR) are less clear, and no consensus has been reached on the management of concurrent CAD in this setting. This lack of certainty is reflected in the 2017 European Society of Cardiology guidelines, which include only a class IIa recommendation (based on level C evidence) for revascularization in patients undergoing TAVR.[13] Finally, established physiological assessment tools, such as fractional flow reserve (FFR), have not yet been validated in patients with AS, and consequently the assessment of CAD in these individuals requires careful consideration of the scant available evidence from published studies of these tools in AS.

In this chapter, we discuss the key pathophysiological concepts associated with coronary blood flow in patients with high-gradient, high-flow AS through the presentation of contemporary basic science, animal models and human studies. A thorough understanding of these mechanisms is crucial for clinicians managing patients with AS, especially those with concurrent CAD.

1.2. ASSESSMENT OF CORONARY PHYSIOLOGY

The various historical and contemporary models of coronary blood flow provide an insightful, but somewhat incomplete picture of coronary haemodynamics. Yet, a fundamental knowledge of coronary haemodynamics is becoming increasingly important in the management of CAD and is now recognised as vital in guiding treatment strategies in the catheterization laboratory.

Wave intensity analysis, which uses methods initially developed in the field of gas dynamics, provides a means for assessing the net influence of upstream and downstream effects on arterial haemodynamics.[14] Its use in epicardial arteries has increased our understanding of the magnitude and direction of the forces that contribute to coronary blood flow throughout the cardiac cycle.[15,16] These

forces create waves that either accelerate or decelerate coronary blood flow, depending on both their direction (forward waves propagate in a proximal to distal direction, whereas backward waves propagate in a distal to proximal direction) and type (compression or expansion). Six main waves contribute to coronary blood flow (**Figure 1-1**).[17] These waves are not discussed in detail in this Review, as they have been thoroughly reviewed elsewhere.[16] The two dominant waves that contribute to coronary blood flow have been identified as dominant systolic forward compression wave (sFCW) and the dominant diastolic backward expansion wave (dBEW). In systole, propulsion of blood through the aortic valve and aorta creates the sFCW, which increases blood velocity in the proximal segment of the coronary arteries.[16] In diastole, as the ventricle relaxes, the reduction of pressure in the left ventricular cavity decompresses the intramyocardial vessels. This release of downstream pressure creates the dBEW, which accelerates blood flow in the epicardial vessels. Indeed, the dBEW is the largest contributor to coronary flow,[16] as can be demonstrated by comparing flow characteristics between the left and right coronary arteries. The systolic or 'proximally originating' flow velocities are no different between these two vessels, in keeping with the similarity of sFCW measurements.[18] However, diastolic flow velocities are greater in the left main stem than in the right coronary artery, resulting from a stronger dBEW in the left than in the right coronary arteries. The difference in diastolic flow velocity between these vessels is probably attributable to the greater compressive forces exerted by the higher myocardial mass in the left than in the right ventricle, which lead to increases in both recoil and dBEW.

The role of metabolic and vasoactive factors in coronary blood flow regulation has been extensively described[19]. In brief, these autoregulatory factors help to prevent mechanical damage from the two main forces acting on the vascular wall — namely, tensile stress induced by arterial pressure, which causes stretching of the vascular wall, and shear stress, which is the parallel frictional force exerted by blood flow against the vessel endothelium[20]. In response to increased mean arterial pressure and subsequent epicardial vessel wall stretch, myogenic mechanisms help regulate constant

microcirculatory flow with ensuing contraction of afferent arterioles. Flow-induced vasodilatation, by contrast, is an endothelium-dependent process increases vascular diameter and helps to minimize shear stress.

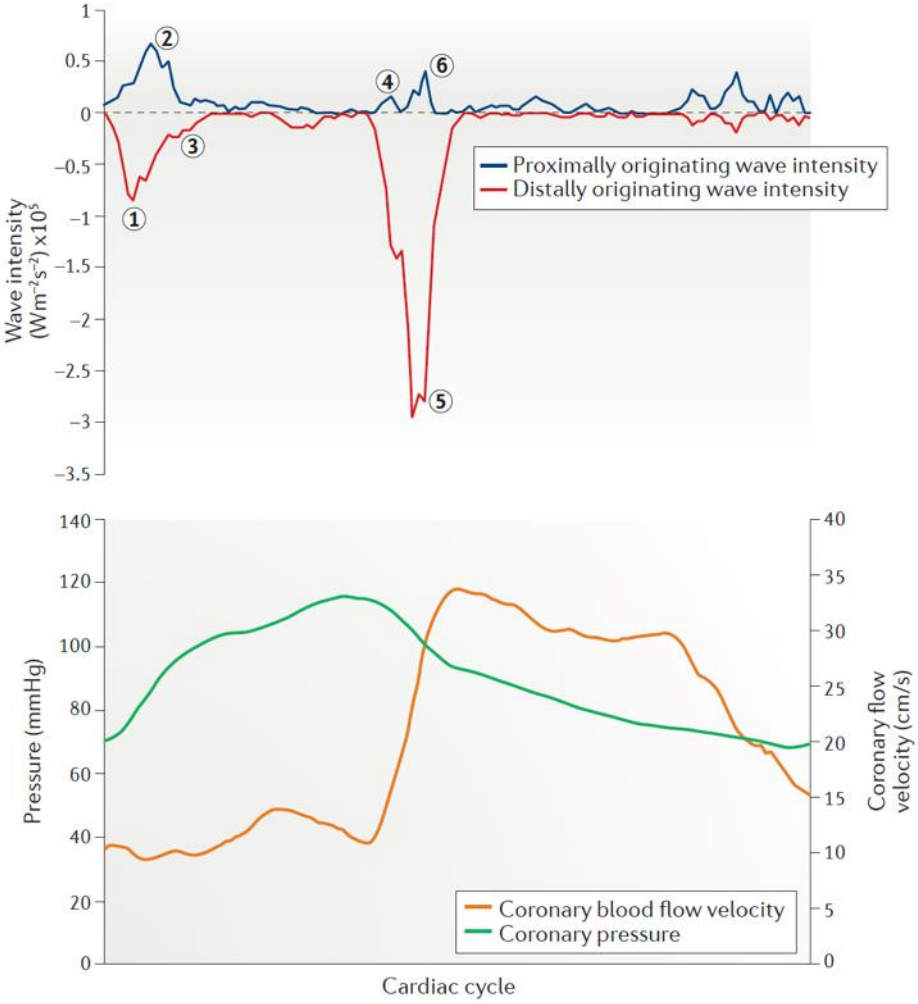


Figure 1-1 | Representative example of coronary pressure and blood flow velocity traces and separated wave intensity profiles measured over a single cardiac cycle Six major waves, labelled 1-6 according to their sequence of arrival, have been identified within the coronary circulation (top panel). These waves are hypothesized to explain the changes in coronary blood pressure and flow velocity observed during the cardiac cycle (bottom panel). The early systolic backward compression wave **(1)** is generated by the compression of peripheral intramyocardial vessels during isovolumic contraction. The dominant systolic forward compression wave **(2)** is generated by the contraction of the left ventricle and is conducted through the open aortic valve into the coronary arteries. The backward systolic wave occurring at the same time **(3)** is generated by continuing compression of the intramyocardial vessels and by reflection of the dominant systolic forward compression wave from sites of impedance mismatch. As the rate of ventricular ejection decreases during late systole, a forward expansion wave **(4)** is generated in the left ventricle that propagates through the still- open aortic valve into the coronary arteries. This wave is opposed by the dominant diastolic backward expansion wave **(5)**, which is generated by recoil of the compressed peripheral intramyocardial vessels as the ventricle relaxes. As the aortic valve closes, a smaller forward compression wave is generated, termed the late forward compression wave **(6)**. Figure reproduced from MonashHeart data; Michail et al, Nat Rev Cardiol

Although coronary angiography remains the gold standard technique for the delineation of luminal obstruction in the assessment of chest pain, it does not provide functional data on the potential for ischaemia conferred by any given stenosis.[21] Coronary blood flow can be measured using invasive tools, most commonly intracoronary Doppler ultrasonography (using a sensor-tipped guidewire) or thermodilution techniques. Both methods require estimation of the vessel's cross-sectional area or internal volume, which limits their usefulness in clinical practice.

Coronary blood flow can be altered mechanically by various pathophysiological changes that affect flow input from the proximal end of the coronary arteries, flow output at the distal end of the coronary arteries (that is, at the microcirculatory level), and any alterations in coronary artery diameter, lesion length or tortuosity (**Figure 1-2**). Conditions that affect flow input include hypotension, left ventricular failure, a suboptimal heart rate and aortopathies; those affecting flow output include conditions such as intrinsic microcirculatory dysfunction, ventricular hypertrophy or diastolic dysfunction. Alterations in coronary artery diameter and lesion length occur primarily as a result of atherosclerosis, and the haemodynamic alterations associated with these changes have been the focus of widespread research and clinical interest. Finally, computational flow dynamics studies have shown that substantial tortuosities within coronary arteries result in greater pressure drops than are observed in less tortuous vessels.[22] In patients with AS, coronary physiology is impacted by the changes in flow input (such as reduced perfusion pressure as a result of the stenotic valve) and flow output (such as the microcirculatory changes as a result of left ventricular hypertrophy). Additionally, AS could indirectly reduce coronary blood flow by worsening CAD and tortuosity.

1.2.1. CORONARY FLOW RESERVE.

Coronary flow reserve (CFR) is defined as the ratio of volumetric blood flow at maximal hyperaemia to that at rest. Maximal hyperaemia can be achieved with vasoactive substances such as adenosine, regadenoson or nitroprusside. CFR is, therefore, an index of the capacity of the coronary circulation

to accommodate increased blood flow in response to increased myocardial oxygen demand. CFR assesses the ability of the whole (micro and macro) circulatory system to upregulate blood flow, but does not identify the exact level of flow limitation.

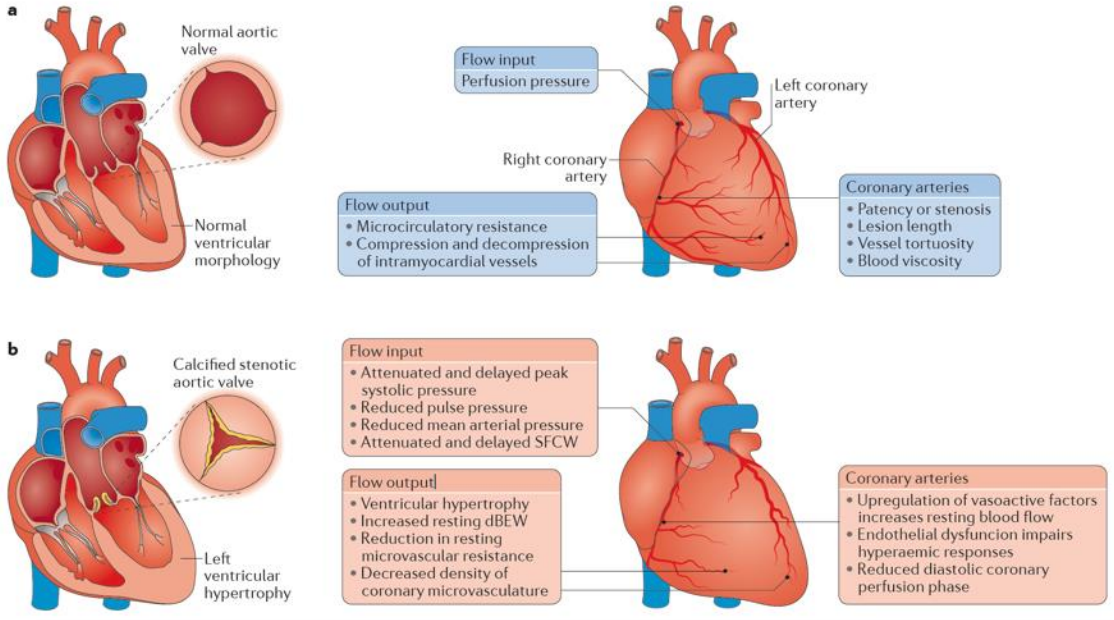


Figure 1-2 | The principal determinants of coronary blood flow.
(a) Coronary blood flow is affected by factors that act at the flow input and flow output levels or within the epicardial arterial circulation (coronary arteries). **(b)** Aortic stenosis adversely affects coronary blood flow through a combination of mechanisms that decrease coronary flow reserve and promote myocardial ischaemia. dBEW, dominant diastolic backward expansion wave; sFCW, dominant systolic forward compression wave. *Figure from Michail et al, Nat Rev Cardiol. 2018.*

1.2.2. FRACTIONAL FLOW RESERVE

FFR is widely recognised as a robust and reproducible tool for assessing flow reduction across an epicardial stenosis.[23] The autoregulation of microvascular resistance facilitates a constant mean blood flow despite variations in central blood pressure. In the hyperaemic state, however, these autoregulatory mechanisms are minimised and coronary blood flow becomes directly proportional to perfusion pressure, thus enabling the use of pressure as a surrogate for flow. FFR is thus defined as the ratio of maximal hyperaemic blood flow across a stenosis to the maximal blood flow in the same vessel in the theoretical absence of stenosis.[24] The applications and limitations of FFR are not discussed in detail here, as they have previously been reviewed elsewhere[25].

1.2.3. INSTANTANEOUS WAVE-FREE RATIO

Instantaneous wave-free ratio (iFR) is an alternative to FFR that does not require the use of a hyperaemic agent.[26] Trans-stenotic measurements are made during a 'wave-free' period in diastole during which the microvascular resistance is minimal and stable, whereby perfusion pressure becomes proportional to flow – similar to the conditions achieved by adenosine. iFR has been demonstrated to be a safe and effective alternative to hyperaemia-dependent indices.[27]

Although both iFR and FFR can provide useful and objective assessments of blood flow reduction across a lesion, the validation studies for these indices specifically excluded individuals with AS, in whom the microcirculatory and microcirculatory environments are altered. Thus, the applicability of these two tools in patients with AS remains to be established.

1.3. ISCHAEMIC POTENTIAL IN AORTIC STENOSIS

The evolution of myocardial hypertrophy in patients with AS results in a cascade of physiological alterations that strive to meet the resultant increase in oxygen demand. A mismatch between oxygen supply and demand might result in angina pectoris even in the absence of coronary artery stenosis. The reported prevalence of angina in patients with severe AS ranges from 38% to 83%,[10,11,28-30] some of which is attributable to the coexistence of CAD. In individuals with AS who do not have CAD, the reported prevalence of angina ranges from 52% to 61%.[10,11,30] Early evidence suggested that once a patient with AS develops angina, their prognosis is poor.[7] An understanding of the mechanisms leading to angina in patients with AS and unobstructed arteries is thus of considerable practical interest.

1.3.1. ATTENUATION OF CORONARY FLOW RESERVE

Early studies in canine models showed that CFR is attenuated in the presence of AS.[31] These findings were corroborated in humans[32-34] and demonstrated in contemporary studies using invasive sensor-equipped guidewires[35-38] and non-invasive imaging.[38-40] Invasive studies showed that baseline blood

flow velocity is almost 18% higher in patients with AS than in unobstructed controls, and that hyperaemic flow velocity was significantly (34%) lower in patients with AS than in controls.[35,36] The increase in baseline blood flow velocity (and therefore increased blood flow) in patients with AS is considered to represent an adaptation to meet the increased oxygen demands of the hypertrophied ventricular myocardium. The increased baseline flow and reduced hyperaemic flow, therefore, results in a reduction in CFR. A blunted CFR has been proposed as one of the principal reasons for exertional angina pectoris in patients with AS who have unobstructed coronary arteries. Mathematical modelling[41] indicates that CFR is markedly reduced when the effective area of the aortic orifice is severely reduced (<1.0 cm^2) and becomes exhausted when the effective orifice area is <0.5–0.6 cm^2.

Wave intensity analysis has also been used to investigate CFR in patients with AS. In two studies of patients undergoing TAVR to treat severe AS, CFR was assessed using either incremental pacing[46] or adenosine-induced hyperaemia.[35,42] Incremental pacing indicated a fall in dBEW in patients with AS, a pattern that reversed following the relief of AS with TAVR.[42] Conversely, adenosine-induced hyperaemia revealed an increase in dBEW in patients with AS after TAVR, although this dBEW increase was smaller than that observed in untreated controls.[35] The discrepant results of these two studies might be explained by the vasodilatory effects of adenosine on the microcirculation, which reduce microcirculatory resistance, thereby improving myocardial recoil and suction, and so increasing dBEW. This cascade might not occur with incremental pacing. The ratio of hyperaemic dBEW to at-rest dBEW (termed the dBEW reserve) was highest in control patients and lowest in the AS group[35]. Following TAVR, the AS group demonstrated restoration of the dBEW reserve to control values. The observation of a strong correlation between CFR and dBEW reserve further underscores the important contribution of dBEW to coronary arterial flow.

1.3.2. LEFT VENTRICULAR HYPERTROPHY AND MICROCIRCULATORY CHANGES.

Left ventricular hypertrophy (LVH) is prevalent in a large majority of patients with AS, although some evidence suggests that 10–20% of patients with severe AS are spared.[43-45] LVH is predominantly considered to be the result of adaptive remodelling in response to increased afterload. However, emerging evidence suggests that maladaptive processes also lead to an inappropriate increase in left ventricular mass.[46] Increases in myocardial mass generate an increased oxygen demand. Morphological studies have demonstrated a decreased density of the coronary microvascular bed in animals with AS[47-49], suggesting an inadequate growth of new vessels during hypertrophy. The existing, decreased-density coronary vasculature accommodates this increased oxygen demand (further impairing CFR) via a compensatory increase in resting myocardial blood flow[33,36-38], which is facilitated by autoregulatory factors that drive coronary vasodilatation and reduce microvascular resistance.

Decreased myocardial resistance at rest has been demonstrated in both invasive[36,50] and non-invasive[37] studies in patients with AS. PET scanning demonstrated a reduction in at-rest myocardial resistance by showing an increase in resting total left ventricular blood flow; this increase was directly proportional to ventricular mass.[37] Whereas microvascular resistance at rest was lower in patients with severe AS than in controls, hyperaemic myocardial resistance was similar in both groups.[36,50] An inability to reduce microvascular resistance further in response to increased demand, therefore, contributes to the impaired CFR in patients with AS. In other words, CFR is mediated by the same mechanisms utilised in patients with AS to upregulate coronary blood flow at rest. Such use limits the capacity of these mechanisms to further upregulate blood flow, resulting in a blunted CFR. Similarly, a cardiac MRI study demonstrated that myocardial perfusion reserve — a reliable indicator of microvascular dysfunction[51-53] — was lower in symptomatic patients with severe AS than in either asymptomatic patients with severe AS or a control group.[54]

Wave intensity analysis has provided further insights into the physiological alterations resulting from LVH. dBEW is attenuated in patients with LVH but without AS.[16] By contrast, dBEW is accentuated in patients with both LVH and severe AS (**Figure 1-3**).[35,42] These disparate results suggest that the pathogenesis and morphogenesis of LVH is distinctly different in patients with and without AS. The increased compressive force exerted by the hypertrophied ventricle might generate increased recoil, explaining the accentuated dBEW in patients with AS. However, this mechanism might be absent in patients without AS; in post-mortem morphological studies, individuals with LVH secondary to hypertension had a network of thickened and fibrosed intramyocardial arterioles, findings that were absent in individuals with LVH secondary to AS[55]. Thickening and fibrosis of these vessels might attenuate their elasticity, reducing recoil, and thereby explaining the attenuation of dBEW. Thus, the increase in baseline coronary blood flow in response to increased myocardial oxygen demand in patients with AS is likely to be a product of not only neurohumoral factors, but also, greater vascular recoil, as demonstrated by the increased dBEW.

1.3.3. REDUCED CORONARY PERFUSION PRESSURE.

The role of the sinus of Valsalva in facilitating valve closure was postulated as early as the 16th century by Leonardo da Vinci.[56] In 1968, *in vitro* flow modelling showed that the sinus ridge created vortices in flow patterns within the sinus of Valsalva that facilitated early valve closure without notable regurgitation.[57] Additionally, these models demonstrated that the sinus of Valsalva was crucial for optimising blood flow into the coronary arteries and for preventing plasma skimming. Plasma skimming describes the phenomenon whereby red blood cells are sequestered from plasma at bifurcation sites in the vascular tree. This typically results in a lower haematocrit in the branched vessel compared to the main vessel.[49] These concepts have been demonstrated in contemporary cardiac MRI studies.[58] In *ex vivo* models, AS resulted in a substantial reduction in systolic coronary flow velocity.[59] Similar findings have also been demonstrated in invasive studies; as expected, narrowing of the aortic valve orifice yields reductions in stroke volume, systolic pressures, mean arterial

pressures and, therefore, in coronary perfusion pressure.[35] This decrease in coronary perfusion pressure correlated with a decrease in sFCW on wave intensity analysis (**Figure 1-3**). Additionally, patients with AS demonstrated a delay in the peak sFCW, which correlated with the expected delayed peak aortic pressure seen in severe AS.[35] These changes were partially restored by TAVR-mediated relief of AS.[35] Interestingly, adenosine-induced hyperaemia increased the amplitude of the sFCW[35], whereas the sFCW amplitude decreased with incremental pacing[42] in studies of patients with AS. This discrepancy highlights differences in the effects of adenosine and exercise on the cardiovascular system.

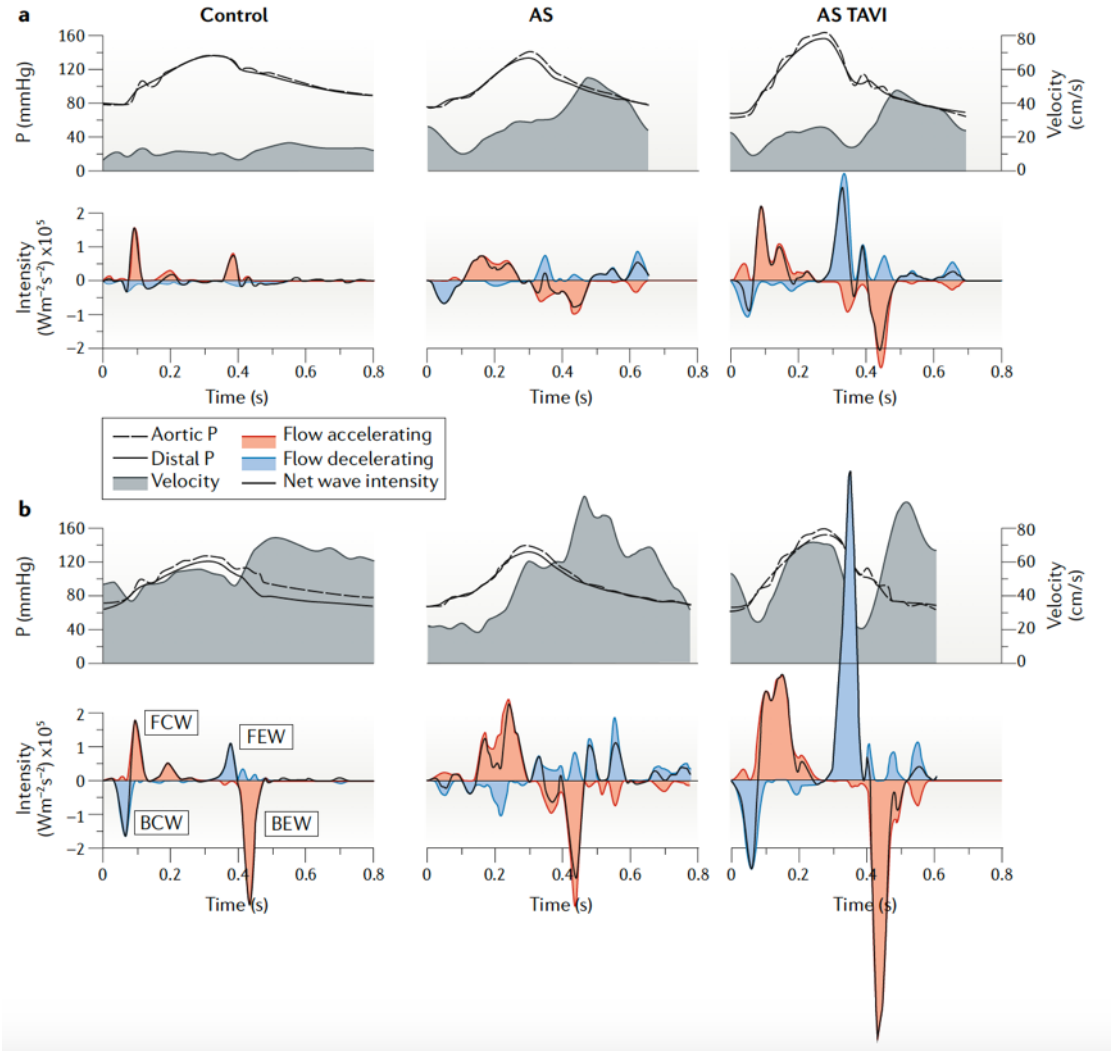


Figure 1-3 | Haemodynamic waveforms and associated coronary wave intensity profiles.

Profiles were obtained while at rest (part a) and during hyperaemia (part b) from a control patient without aortic valve stenosis (AS) (left panel), a patient with severe AS (middle panel), and the same patient with AS after transcatheter aortic valve replacement (TAVR) (right panel). In the patient with AS, the dominant systolic forward compression wave (FCW) is attenuated but is restored following TAVR. The magnitude of the dominant diastolic backward expansion wave (BEW) is increased in the patient with AS. This change is postulated to be the result of increased compression of the hypertrophied ventricle and, therefore, increased recoil, which creates more 'suction'. Following TAVR, the increase in magnitude of the BEW is further accentuated. *Figure from Michail et al, Nat Rev Cardiol. 2018*

1.3.4. REDUCED DIASTOLIC TIME FRACTION

Further ischaemic potential in AS can be attributed to the decreased duration of diastole relative to that of systole in the cardiac cycle, as most coronary perfusion occurs during diastole[60]. The diastolic time fraction also decreases with increasing severity of AS,[37,50] a mechanism that is in part be attributed to the prolongation of left ventricular ejection time. Furthermore, patients with AS have an elevated resting heart rate, which directly shortens the diastolic coronary perfusion time.[61] This high

resting heart rate attenuates the ability of the heart to further accommodate any additional oxygen demand, another factor that contributes to the reduced CFR in patients with AS.

1.3.5. ENDOTHELIAL DYSFUNCTION

The vascular endothelium is a single layer of cells that lines all the vessels of the circulatory system and serves as a semipermeable barrier between the blood and vascular smooth muscle. For many years, the vascular endothelium was considered to act primarily as a physical barrier, but subsequent evidence showed that it is a metabolically active organ with autocrine and paracrine secretory functions[62].

This endothelium also plays a crucial part in the regulation of vascular wall function and coronary blood flow, through a delicate balance of vasoconstricting and vasodilating factors,[19] in particular, nitric oxide[63] and prostaglandins.[64] Endothelial dysfunction is strongly associated with the aetiology and pathogenesis of atherosclerosis[65] and has, therefore, emerged as a key target in the management of CAD. Endothelial dysfunction is characterised by a reduction in the availability of vasodilators, particularly nitric oxide, which impairs endothelium-dependent vasodilatation.[66]

Other cardinal features of endothelial dysfunction include proinflammatory, proliferative and prothrombotic states, which promote the development and progression of atherosclerosis.[65] Besides the ischaemic effects of luminal stenosis and plaque rupture, endothelial dysfunction can also induce ischaemia in unobstructed arteries through vasoconstriction.[67,68] AS was associated with endothelial dysfunction in several studies.[69-71] Flow-mediated dilatation (FMD) is an index of vasomotor function[69,72] that can be assessed non-invasively using ultrasonography. In healthy vasculature, reactive hyperaemia following brachial artery occlusion provokes the endothelium to upregulate nitric oxide release, causing vasodilatation. In one study, patients with AS showed a significant reduction in systemic FMD compared with individuals without valvular disease.[69] The association between AS and

endothelial dysfunction has further been demonstrated by banding the aorta in guinea pigs.[73] Impaired relaxation of coronary arteries was demonstrated in the animals with aortic banding compared to untreated controls. Impaired arterial relaxation and a reduced ability to upregulate blood flow attenuate CFR, and further evidence in support of this relationship is derived from studies of FMD in patients with peripheral artery disease[74,75] or CAD[79].

1.4. EFFECTS OF RELIEF OF AORTIC STENOSIS

1.4.1. IMMEDIATE AND SHORT-TERM CHANGES

As expected, the relief of AS by either surgical aortic valve replacement or TAVR yields improvements in coronary flow but does not prompt the immediate restoration of premorbid physiology. Despite instantaneous relief of the ventricular outflow obstruction, the reversal of structural adaptations (such as ventricular remodelling and coronary angiogenesis) requires additional time.

The relief of valve obstruction with TAVR does not yield immediate changes in baseline coronary flow velocity, an observation that is consistent with findings that microvascular resistance remains unchanged from baseline.[36,42,76] However, significant increases are observed in hyperaemic flow velocity, which suggests that hyperaemic microvascular resistance decreases as a result of improved left ventricular relaxation.[36] Unfortunately, several studies have shown that this change does not result in a clinically meaningful increase in CFR immediately after TAVR, as CFR remains lower in patients with AS after TAVR than in individuals without valvular disease.[35,36,76] Interestingly, however, subgroup analyses in one study of patients after TAVR showed that individuals without post-procedural paravalvular regurgitation had more favourable haemodynamics after TAVR (including better hyperaemic flow velocity and a statistically significant increase in the CFR) than in those with post-procedural paravalvular regurgitation.[35]

Wave intensity analysis demonstrated, as expected, a significant increase in the sFCW following relief of AS with TAVR[35,42], along with increases in stroke volume, systolic pressure, mean arterial pressure and coronary perfusion pressure[77]. Additionally, TAVR reversed the observed pre-treatment delay in the time to peak sFCW,[35] further supporting the trend towards restoration of normal function. The evidence for an immediate effect of TAVR on the dBEW is less clear. Two studies have reported conflicting findings: in the first, the dBEW intensity at rest decreased[42], whereas in the second dBEW increased[35] immediately after valve implantation. We might speculate that the increased contractility (and therefore increased recoil) of a hypertrophied left ventricle in patients with AS results in a greater dBEW than is observed in controls without AS.[35] The increased amplitude of resting dBEW following TAVR seen in the second study[35] could, therefore, represent the improved relaxation (and therefore improved recoil) of the hypertrophied ventricle. A potential explanation for the post-treatment fall in dBEW in the first study[42] is that deployment of balloon-expandable valves, which were predominantly used in this cohort, requires rapid ventricular pacing that might have caused myocardial stunning[78]. An additional finding of the second study was that adenosine-induced hyperaemia resulted in an increase in dBEW after TAVR, to levels comparable with those of controls.[35] Similarly, in the first study, incremental-pacing-induced hyperaemia resulted in an increased dBEW after TAVR.[42]

Whether or not endothelial function improves in patients with AS after TAVR has also been investigated. As previously reported, FMD was impaired in patients with AS compared with controls at baseline, before surgical aortic valve replacement[69,79]. However, FMD had not improved at follow-up (mean 5.3 months), suggesting the persistence of endothelial dysfunction, via a mechanism involving nitric oxide.[79] By contrast, another study showed a statistically significant increase in FMD, 3 months after TAVR, in patients treated for severe AS.[80] These investigators also observed decreases in the levels of circulating endothelial microparticles[80] and markers of compromised endothelial integrity,[81,82] which support the notion that some restoration of endothelial function follows the relief

of aortic valve obstruction. The long-term (that is, more than a few months) effects of aortic valve intervention on the recovery of endothelial function have not been examined.

1.4.2. LONG-TERM ADAPTIVE CHANGES

As expected, the immediate changes in coronary physiology associated with relief of outflow obstruction predominantly involve the systolic driving forces and reflect the substantial increases in perfusion pressure and sFCW. According to the intramyocardial pump model, the dBEW is produced by recoil of the ventricle following contraction. Thus, changes in the dBEW that are a consequence of LVH might continue to evolve after the relief of outflow obstruction, as regression of LVH occurs along with resolution of the microvascular dysfunction. Early clinical data demonstrated marked regression of LVH at a mean of 19 months after aortic valve replacement.[83] This study used biplane angiography to estimate left ventricular mass,[83] and subsequent studies that used echocardiography[84,85] and cardiac MRI[86] for this purpose reported congruent findings on the effects of AS treatment.

The long-term effects of AS relief on CFR were first reported in 1991.[33] At a mean of 30 months after surgical aortic valve replacement, invasive assessment showed that CFR had improved by 34%, and that this change correlated with regression of LVH. These findings were corroborated in subsequent non-invasive[87] and invasive[76] studies in patients undergoing TAVR. Similarly to previous studies, CFR showed no improvement immediately after TAVR, but a repeated invasive assessment at 12 months demonstrated a statistically significant improvement in CFR. A separate follow-up study of patients with AS at 12 months after surgical aortic valve replacement found substantial regression of LVH associated with a reduction in total left ventricular flow, assessed using PET.[88] Of note, this improvement in PET-derived CFR did not directly relate to LVH regression, but instead was related to improvements in other variables, such as aortic valve area and diastolic perfusion time.[88] These findings are consistent with those of a study of cardiac MRI-derived CFR in patients 6 months after surgical aortic valve replacement, which demonstrated that patient–prosthesis mismatch resulting in

an indexed effective orifice area <0.85 cm^2/m^2 led to a decrease in CFR.[89] Additionally, CFR normalised in patients who received stentless valves, which imitate the natural geometry more closely than stented valves do.[89] These data suggest that progressive restoration to normal physiology continues for several months after the relief of AS.[76] Additionally, patients with optimal procedural outcomes (such as those without patient–prosthesis mismatch or paravalvular regurgitation) seem to have more favourable outcomes with regard to coronary physiology.[36,89] Although wave intensity analysis has not yet been used to examine the long-term outcomes of TAVR, we can reasonably speculate that the dBEW will normalize with the regression of LVH, but with less pronounced changes in the sFCW.

1.5. FUNCTIONAL ASSESSMENT OF CORONARY STENOSIS

CAD occurs in 25–50% of patients with AS[8-11] and its incidence increases with advancing age.[90] Traditionally, coronary artery bypass surgery is performed at the time of surgical aortic valve replacement in patients with co-existing coronary disease.[91] Patients with severe CAD who are not revascularised at the time of surgical aortic valve replacement are at an increased risk of adverse short-term and long-term outcomes.[12] Limited evidence has shown that patients undergoing TAVR who have prior revascularization of CAD, have an increased 30-day and overall mortality compared with patients without prior revascularization.[92] However, studies that used anatomical scoring tools to quantify the extent of CAD in patients undergoing TAVR have demonstrated conflicting findings. In 271 patients who had undergone TAVR, those with a high SYNTAX score (≥33) had greater mortality at 30 days and 12 months than those with low (0-22) and intermediate (23-32) scores.[93] However, quantitative coronary angiography (which was also performed in the same cohort, to measure lesion stenosis severity) was unable to discriminate patient outcomes. Another study of 377 patients who had undergone TAVR found no differences in all-cause mortality, stroke, or myocardial infarction between the groups with high (≥33) and low (≤22) SYNTAX scores.[94] In a separate study, Duke Myocardial Jeopardy scores were also unable to stratify patient outcomes after TAVR.[95] The absence

of information on the physiological consequences of CAD severity as assessed by anatomical scoring systems might explain the disparity between these studies.

Visual assessment of stenosis severity is well-recognised to be a poor predictor of physiological indices such as CFR in patients without AS, as blood flow is also highly dependent on other anatomical and physiological variables, such as lesion length.[96,97] In consequence, FFR-guided percutaneous coronary intervention (PCI) is associated with better outcomes than PCI with angiographic guidance alone.[23,98-100] As discussed above, CFR is impaired in patients with AS, even in those with unobstructed coronary arteries; the addition of coronary stenosis is likely to further reduce CFR. We can speculate that CFR would be impaired at a lower threshold of valvular stenosis severity than would be the case for unobstructed arteries.

The evidence for non-invasive functional assessment of CAD in patients with AS is limited, owing to difficulties in reliable image interpretation and safety concerns related to the use of pharmacological stress-inducing agents. However, emerging studies have assessed the feasibility of using imaging modalities such as MRI, echocardiography, SPECT and PET. Overall, although these techniques have high sensitivity for identifying obstructive CAD in patients with AS, specificity was often lower than in patients without AS, again probably because CFR is already decreased in patients with severe AS.[101-104]

Invasive assessment of CAD has also not been fully validated in patients with AS, although data exploring the use of functional indices are accumulating. Adequate assessment of FFR largely relies on the ability to induce maximal hyperaemia and thereby minimize distal resistance, which maximizes the pressure gradient across a lesion. The structural and metabolic changes caused by AS result in a submaximal microvascular vasodilatory response to hyperaemic agents and, therefore lower trans-stenotic pressure gradient, which results in overestimation of FFR readings. In one study of FFR in

patients with severe AS, the initial mean FFR was 0.97, which showed a statistically significant decrease of 0.02 after TAVR.[36] In another study, by contrast, FFR values for 133 coronary lesions in 54 patients showed no overall change after TAVR in patients with severe AS.[105] The findings of this study were, however, particularly interesting for the subgroups of patients with baseline FFR values above and below 0.80 (the indication threshold for PCI). The patients in whom PCI was indicated (FFR ≤0.80) had even lower FFR values after TAVR, whereas those in whom PCI was not indicated (FFR >0.80) had even higher values after TAVR. Moreover, 7 of the 54 patients experienced a change in FFR from below to above the PCI threshold after TAVR, and therefore a change in this indication.[105] These changes in FFR values resulting from the relief of AS alone, without any change in CAD, further suggest that the accuracy of FFR in this population of patients should be carefully considered. However, this study only dealt with changes in coronary physiology immediately after TAVR, and no conclusions can be drawn with regard to any delayed changes that might follow the relief of AS.

Concordance between FFR and iFR values has been studied in patients with severe AS.[106] An iFR cut-off of 0.83 was the best predictor of FFR ≤0.80 — well below the previously validated iFR cut-off of 0.89, which was derived in patients without AS.[107] Of note, lower iFR cut-offs predicting an FFR ≤0.80 in patients with AS was especially relevant to lesions in the left anterior descending artery (LAD), which is usually associated with larger myocardial blood supply and is, therefore, particularly prone to submaximal hyperaemia. This finding further supports the notion that FFR significance in AS maybe underestimated compared with iFR, as the measurement of iFR (unlike FFR) does not rely on pharmacological hyperaemia.[106] Another study reported findings congruent with this contention: the largest shift in FFR in patients with AS after TAVR was seen in the LAD.[105]

Furthermore (and in contrast to the results of the DEFINE-FLAIR[27] and SWEDEHEART[108] studies), the number of lesions considered to result in functional impairment was greater when iFR as opposed to FFR was used, further suggesting that FFR significance is underestimated compared with iFR in

patients with AS.[106] Unlike FFR values, mean iFR values do not change when measured before and after TAVR.[109] However, individual patients can show erratic variations in iFR values, which suggests that caution is needed with the use of this tool in patients with AS[109]. Owing to the lack of high-quality evidence, no consensus has been reached on the assessment and management of CAD in patients with AS, and this controversial topic remains an important focus of research.

1.6. CONCLUSIONS

AS leads to numerous alterations in coronary physiology. In addition to the reduced perfusion pressure resulting from increased energy dissipation by the stenosed valve, left ventricular morphological adaptations alter microcirculatory functions, further modifying the ventriculoarterial balance. In combination with the modulation of vasoactive factors, these changes facilitate the upregulation of coronary blood flow at rest to meet an increased oxygen demand. Impaired CFR occurs in patients with AS even in the absence of CAD, and is the main cause of angina pectoris in this setting.

The physiological consequences of relieving AS yields immediate restoration of some aspects of coronary physiology, however the longitudinal effects of the treatment, with LVH regression and cardiac remodelling are less comprehensively understood. Additionally, limited evidence suggests that improvement in physiological indices post-TAVR seems dependent on specific procedural outcome measures such as the degree of paravalvular regurgitation and patient-prosthesis matching, with these areas a focus for future clinical research.

Finally, studies that explore the effect of coronary disease on patient outcomes following aortic valve intervention have yielded divergent results. Although there is clear potential for functional assessment of lesion-specific ischaemia, the validity of invasively derived indices in patients with AS remains questionable, with evidence suggesting their accuracy is modified by the altered microcirculatory

environment. As such, the method and requirement for functional assessment of coronary stenosis in these patients remains to be defined.

2. RESEARCH AIMS AND OBJECTIVES

2.1. HYPOTHESES

1. Relief of AS results in immediate, yet partial, resolution of physiological myocardial blood flow. Such early changes affecting coronary blood flow include improved aortic haemodynamics and endothelial function.
2. Ongoing improvements in myocardial blood flow are dependent on longer term adaptive changes in relation to endothelial function.
3. Physiologically significant CAD will have adverse outcomes on patients with severe AS undergoing TAVR.
4. CT-derived fractional flow reserve can be used to assess the functional significance of coronary artery stenoses in patients with severe AS.

2.2. AIMS

The first part of the thesis aimed to investigate some of the unexplored immediate and late physiological changes that impact myocardial blood flow in patients with severe AS undergoing TAVR. Specifically, it aimed to determine:

1. The haemodynamic changes in the proximal aorta following AS relief with TAVR.
2. The early and late response in endothelial function post-TAVR.

In better understanding the physiological impact of severe AS upon coronary physiology, the second part of the thesis aimed to determine:

3. The prognostic impact of physiologically significant coronary stenosis in patients undergoing TAVR.
4. The feasibility, safety and validity of CT-derived fractional flow reserve in patients with severe AS.

3. MATERIALS AND METHODS

3.1. STUDY 1: THE ACUTE EFFECTS OF TAVR ON CENTRAL AORTIC HAEMODYNAMICS IN PATIENTS WITH SEVERE AS

Study protocol

This was a retrospective study performed at MonashHeart (Monash Health, Melbourne, Australia). Data was extracted retrospectively from our catheterization hemodynamic recording system. Patients were eligible for inclusion if they underwent TAVR for severe AS at MonashHeart using either self-expandable, balloon expandable or mechanically expandable valves. Simultaneous left ventricular and

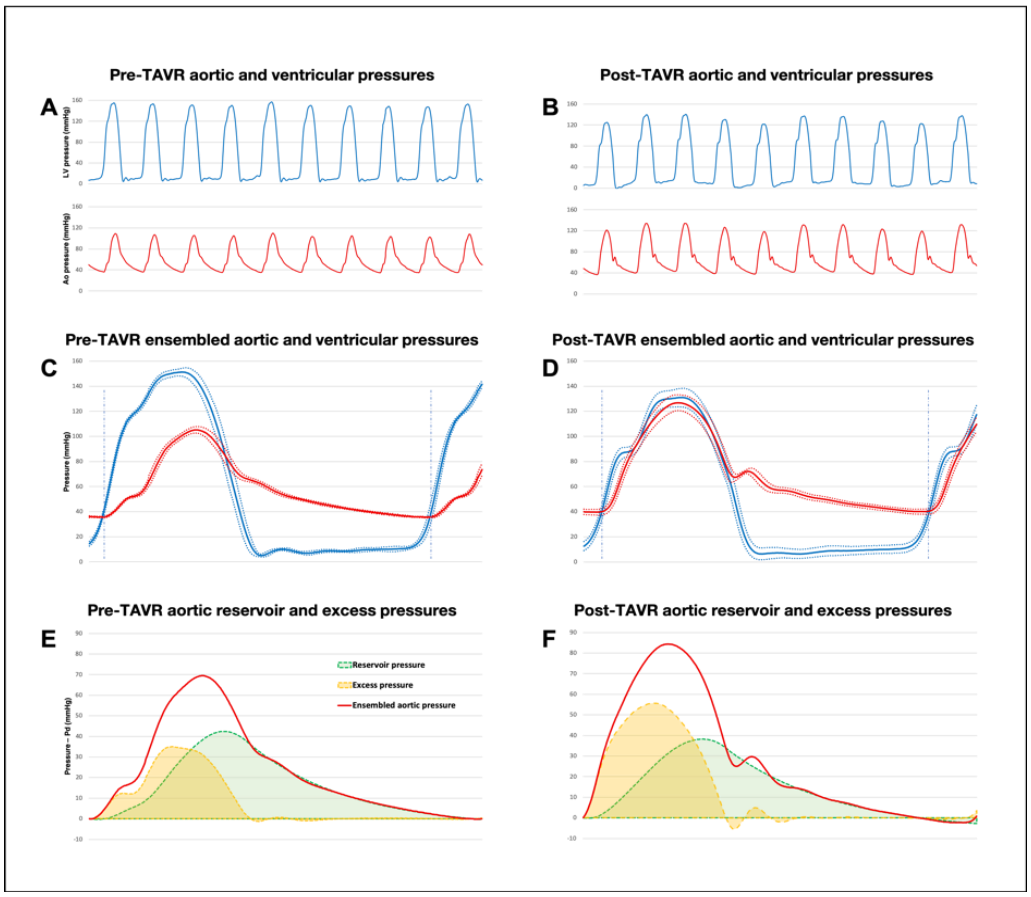


Figure 3-1 | Left ventricular and aortic pressures before and after TAVR

Panels **(A)** and **(B)** presents aortic (red) and ventricular (blue) pressure signals before and after TAVR, respectively. Panels **(C)** and **(D)** presents the ensembled pressure signals with the dotted line representing their standard deviation. Panels **(E)** and **(F)** presents the ensembled aortic pressure (red), excess pressure (yellow) and reservoir pressure (green).

aortic pressures were acquired using 6Fr pigtail catheters with aortic measurements taken approximately 5 cm above the aortic annulus. Measurements were performed at baseline before balloon aortic valvuloplasty (if required) and were repeated typically within five minutes after valve deployment (**Figure 3-1A and 3-1B**). Signals were transduced via a Philips Xper Cardio Physiomonitoring System (Andover, MA, USA). Signals were sampled at 500 Hz with data exported and analysed offline using MATLAB (MathWorks, Inc, Natick, Massachusetts, USA). Two hundred patients were randomly selected for this analysis. Patients were considered for inclusion if their pre- and post-TAVR recorded tracings demonstrated regular R-R intervals and those without significant peri-valve implant hypotension (<90mmHg). Resultant pressure waveforms were carefully evaluated with pressure-damped traces excluded by observers blinded to all other data. The aortic pressure waveforms were ensembled using 5-10 consecutive beats (**Figure 3-1C and 3-1D**), following which, reservoir pressure (**Figures 3-1E and 3-1F)** and wave intensity analysis was performed.

Reservoir pressure analysis

Various models have been proposed to describe the ventriculo-arterial mechanisms responsible for the formation and distal propagation of the central aortic pressure, which is a fundamental prerequisite for the perfusion of tissue and key organs including the heart. Previous studies have demonstrated that the elasticity and compliance of the aorta are key in determining pressure waveform morphology during both systole and diastole.[110] One available approach for the evaluation of central aortic pressures is the 'reservoir pressure model' which proposes that aortic BP can be separated into components representing reservoir and excess pressures.[111] In systole, aortic reservoir pressure is characterised by cyclic volume-related aortic distension (allowing blood storage with associated increase in potential energy) whilst in diastole, elastic recoil results in distal propagation of blood in association with decreased local aortic volume. In comparison, aortic root excess pressure is determined by volume inflow into the proximal aortic segment.[111] We have recently demonstrated that the shape of the excess pressure waveform in the proximal aorta is linearly related to the

measured velocity profile as assessed by continuous Doppler imaging,[112] a finding which enables aortic WIA to be performed using aortic pressure-only waveforms. Insights into the hemodynamic changes in the aorta can also be obtained using wave intensity analysis (WIA), which provides a means for assessing the net influences of upstream (proximal) and downstream (distal) effects on arterial haemodynamics and this has been previously applied in the aorta and coronary arteries.[16,77]

Reservoir pressure analyses were performed using previously described methods from ensembled-averaged pressure waveforms.[111] To calculate reservoir pressure, it is assumed that P_r satisfies overall conservation of mass

$$\frac{dP_r}{dt} + k_d(P_r - P_\infty) = \frac{Q_{in}}{C} \quad (1)$$

Where k_d is the diastolic rate constant (the reciprocal of the diastolic time constant $\tau = RC$, R is the net resistance to flow through the microcirculation and C is the net compliance of the arteries). Q_{in} is the volume flow rate into the aortic root and P_∞ is the asymptote of the diastolic pressure run-off. It is assumed that $Q_{in} = \zeta P_x$, where ζ is a constant related to and of the same units as the characteristic impedance of the aortic root and P_x is excess pressure.

Under these conditions Equation 1 can be written

$$\frac{dP_r}{dt} + k_d(P_r - P_\infty) = k_s(P - P_r) \quad (2)$$

where k_s is the systolic rate constant (the reciprocal of ζC). In this approach the proportionality of P_x to Q is a fundamental requirement.

This first-order linear differential equation can be solved as:

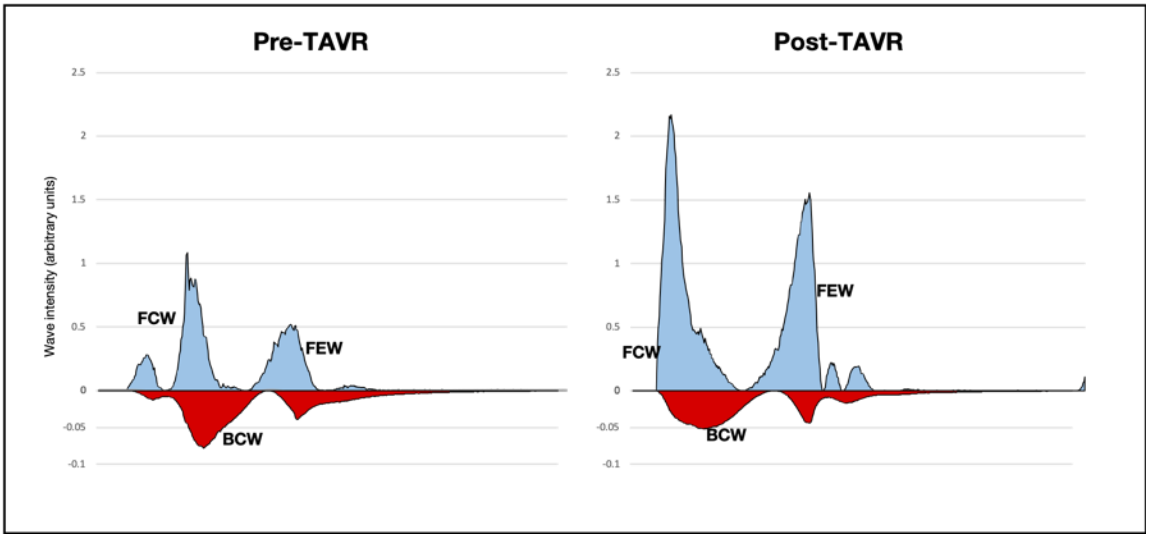
$$P_r = e^{-(k_s+k_d)t} \int_0^t P(t')e^{(k_s+k_d)t'}dt' + \frac{k_d}{k_s + k_d}\left(1 - e^{-(k_s+k_d)t}\right)P_\infty \quad (3)$$

where the diastolic parameters k_d and P_∞ are obtained first by fitting an exponential curve to P during diastole and k_s is obtained by minimising the square error between P and P_r obtained over diastole. All indices of reservoir pressure are reported above the diastolic.

Wave Intensity Analysis

WIA was performed using previously validated methods.[113] Given the previously demonstrated close correlation between the waveform profile of excess pressure and the envelope of Doppler flow velocity in the proximal aorta, this was substituted for the flow waveform in the calculation of wave intensity profiles.[112] The peak wave intensity values represent the peak power density in the wave whilst the area of the waveform represents the energy flux of the wave (energy per unit cross-section of the artery). As excess pressure was used as a surrogate for flow velocity, the units of wave intensity are reported in arbitrary units (a.u., dimensionally equal to pressure squared). We identified the three main aortic waves occurring during the cardiac cycle (**Figure 3-2**)[14,114] being an aortic systolic forward compression wave (FCW) occurring when blood is ejected into the aorta with the rising aortic pressures, followed by an aortic backward compression wave (BCW), caused by reflection of the FCW from sites of higher impedance, and a late aortic systolic forward expansion wave (FEW) representing the separation tensions within the column of blood.

Figure 3-2 | Wave intensity analysis in the aortic root pre- and post-TAVR in one cardiac cycle.
Blue shaded area demonstrates forward traveling waves originating from the left ventricle whilst red-shaded area represents waves originating distally. Forward compression wave (FCW), backward compression wave (BCW) and forward expansion wave (FEW) peak values and energies are seen to increase following transcatheter aortic valve replacement (TAVR). Note the expanded scale for the backwards compression wave.



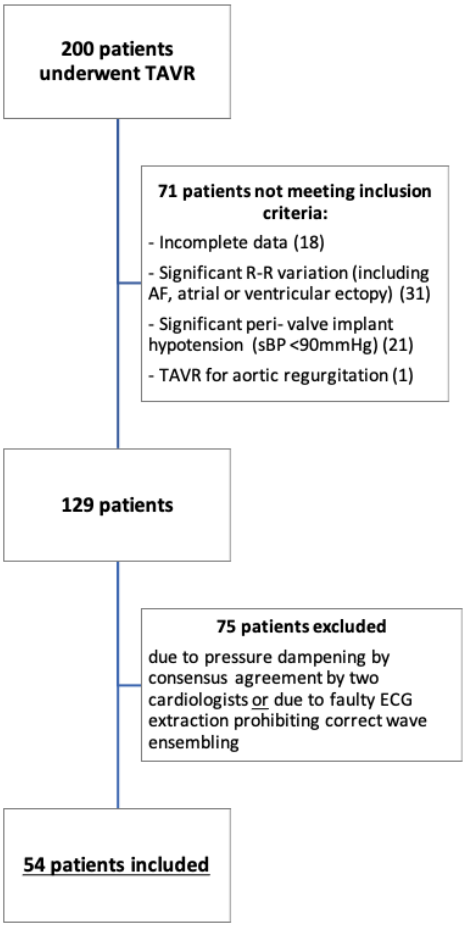
Pressure waveforms were separated into forward (Pf) and reverse going (Pb) components as previously described.[115] Reflection ratio, Pb_{max}/Pf_{max}, was calculated along with the time to peak forward and reverse pressures. Aortic characteristic impendence was calculated from WIA as the initial slope of pressure/flow loop as previously described.[116]

Left ventricular energy balance was estimated using Buckberg's subendocardial viability ratio (SEVR), defined as aortic diastolic pressure-time integral (DPTI) divided by the left ventricular systolic tension time index (TTI, the integral of left ventricular pressure between aortic start systole and start diastole). This represents the ratio between myocardial oxygen demand and supply. In this estimation we have not allowed for left ventricular diastolic pressure and have used directly measured left ventricular systolic pressure rather than the usual surrogate of aortic systolic pressure. This is appropriate in view of the large pressure drop across the aortic valve in the pre-TAVR situation.

Statistical analysis

Data analysis was performed using PRISM (GraphPad Software, Inc., La Jolla, CA, USA). The changes in hemodynamic indices, separated wave pressure parameters and wave intensity were compared using a two-way Student's t-test; non-normally distributed continuous data were tested with a paired Wilcoxon test. Chi-squared tests were used to compare categorical variables. A p value <0.05 was considered statistically significant. All data are presented as pre-TAVR vs. post-TAVR unless specifically stated.

Figure 3-3| Study flow chart



3.2. STUDY 2: PATIENTS WITH AS EXHIBIT EARLY IMPROVED ENDOTHELIAL FUNCTION FOLLOWING TAVR: THE E-FAST STUDY

Study protocol

This was a prospective, single centre study carried out at Monash Medical Centre, Melbourne between February and August, 2019. The study protocol was approved by the institutional research ethics committee (Human Research Ethics Committees Australia reference: HREC/45959/MonH-2018-152246). All recruited patients provided written informed consent.

Patients with severe AS with an indication for TAVR as per international guidelines[13] were screened for eligibility. Exclusion criteria included (1) patients undergoing concomitant coronary revascularisation, (2) stage 5 chronic kidney disease, (3) systemic inflammatory conditions and (4) active malignancy.

FMD assessment was performed at three time points (1) at baseline pre-TAVR; on the day of the procedure, (2) at early follow-up; within 48 hours post-TAVR, and (3) at late follow-up; 4-6 weeks post-TAVR. At each assessment, the patients were graded according to the New York Heart Association (NHYA) class and Canadian Cardiovascular Society (CCS) score for angina pectoris.

TAVR procedure

Prior to the procedure, all patients received 300 mg each of aspirin and clopidogrel. All procedures were performed via femoral artery access and all except one were performed under conscious sedation; one was performed under general anaesthesia and transoesophageal echocardiographic guidance. A temporary pacing wire was sited for all patients via the femoral vein. Patients were implanted with either self-expandable, mechanically-expanded or balloon-expandable valves. Post-procedure valvular regurgitation was assessed on fluoroscopy and if deemed necessary, post-dilation

was performed. Unless anticoagulated for other medical reasons, all patients were discharged on dual antiplatelet therapy for a duration of six months post-TAVR.

Assessment of endothelial function via ultrasonography

FMD was performed in accordance to standardised practice by the same experienced investigator[72]. Prior to assessment, patients fasted and abstained from smoking, coffee and exercise. All tests were conducted in a temperature-controlled environment (21°C). Measurements were taken using a high-resolution linear vascular probe (Mindray L14-6Ns, Mindray, China), placed 1 to 2 cm above the elbow. Duplex recordings were taken for 30 seconds before cuff inflation and then again for 2.5 minutes, beginning 30 seconds before cuff deflation. In order to assess for non-endothelial-dependant vasodilatation, sublingual nitroglycerin was administered after 10 minutes of rest and then the ultrasound measurements were repeated.

Post-processing analysis

Offline analysis was performed on recorded loops to measure brachial artery diameters and the angle-corrected time mean-averaged velocities for WSS calculation. Following cuff-release, the diameter was measured every 4 seconds for the first 20 seconds and then every 10 seconds thereafter as per standard protocol. All diameter measurements were taken at end-diastole and were an average of three separate measurements. FMD was calculated as the percentage change in diameter:

$$\text{FMD (\%)} = \frac{diameter_{(hyperaemia)} - diameter_{(baseline)}}{diameter_{(baseline)}} \times 100$$

WSS was derived using the velocity measurements and vessel diameter using formula:

$$WSS = \frac{8 \times v}{d}$$

Where v is mean blood flow velocity and d is diameter.

Statistical analysis

Our primary end-point was change in FMD at early post-TAVR follow-up. Secondary endpoints included change in brachial WSS and changes in FMD at late post-TAVR follow-up assessment.

All results are reported as mean ± standard deviation (SD). Normality of distribution of FMD measurements was assessed using a Shapiro-Wilk test. Comparison between FMD and WSS values post-TAVR compared to values pre-TAVR in the same individuals using a paired t-test. Correlations between variables were performed using Pearson correlation. Statistical analysis was performed using Python 2.7's statistical packages (scipy.stats and statsmodels), with a p-value <0.05 being deemed significant.

Intra-observer reproducibility was assessed on 15 healthy volunteers. Measurements were taken on two separate occasions at least one week apart. Intraclass correlation coefficient demonstrated excellent reproducibility (ICC = 0.96).

3.3. STUDY 3: ANGIOGRAPHIC FUNCTIONAL SCORING OF CORONARY ARTERY DISEASE PREDICTS MORTALITY IN PATIENTS WITH SEVERE AS UNDERGOING TAVR

Study protocol

We retrospectively screened 320 patients who underwent TAVR for severe AS between November 2008 and October 2016 at MonashHeart, Melbourne. Patients were deemed as having severe AS on echocardiography and met criteria for TAVR as per consensus Heart Team decision. All patients underwent mandated coronary angiography prior to TAVR. Amongst patients with significant CAD, revascularization was undertaken in accordance with Heart Team recommendations, either prior to, or at the time of TAVR. In those patients, the post-revascularization angiograms with residual CAD were used for analysis. Patients were treated with either the Lotus Valve System (Boston Scientific, MA, USA), Medtronic CoreValve or Medtronic Evolut R prostheses (Medtronic, MN, USA). Patients were excluded from analysis if they had (1) prior CABG, (2) tandem coronary stenoses, (3) coronary revascularization during TAVR procedure, or (4) TAVR performed via non-femoral vascular access.

Angiographic assessment for CAD

All angiographic analyses were performed by two experienced readers. Patients with ≥30% angiographic stenosis in at least one artery were considered to have CAD warranting further assessment with DS and SS. SS I scores were calculated using the web-based calculator[117]. Previous studies using SS in patients undergoing TAVR have identified that the majority of patients have a low SS,[118] thus making the conventional thresholds (low SS ≤22, intermediate SS 23-32 and high SS ≥33) unsuitable for stratification. In order to address this, we defined the threshold as the median SS from all the patients with CAD of ≥30% stenosis on visual assessment. DS were calculated by a separate experienced cardiologist blinded to clinical outcomes and SS results.[119] Quantitative coronary angiographic analysis using QAngio (Medis Medical Imaging System BV, Leiden, the Netherlands) was performed to derive minimum luminal diameter (MLD) and lesion length (LL) for each lesion. Bypass Angioplasty Revascularization Investigation Myocardial Jeopardy Index (BARI MJI; percentage of left

ventricular myocardium subtended by a lesion) was derived by assigning an index to all vessels based on length and calibre and dividing the sum of vessel scores distal to the culprit lesion by the sum of all vessel scores. The values for MLD, LL and BARI MJI each receive a score, the total of which represents DS (between 0-12).[119]

Patients were considered to have non-functionally significant disease if lesions had a DS ≤2 as per previous validation studies [119,120]. Patients were classified into two groups: those with functionally significant CAD as evidenced by DS >2 in any of the three epicardial vessels or those with non-functionally significant CAD as defined by DS ≤2.

Study Endpoints and follow up

The primary endpoint for this study was one-year all-cause mortality. Secondary clinical endpoints were 30-day major adverse cardiac and cerebrovascular events (MACCE), comprising spontaneous MI, stroke, TIA, heart failure-related admissions and all-cause death. Outcomes were defined according to the standardised definitions of the Valve Academic Research Consortium-2 consensus (VARC-2) criteria [121].

Statistical analysis

Data was analysed using Stata (Stata Corp LP, College Station, TX). Baseline and procedural characteristics were compared according to CAD severity stratified by DS. Continuous variables are presented as mean ± SD or median ± interquartile range (IQR) according to their distribution. Categorical variables are presented as absolute numbers and percentages. Comparisons were made using t-tests used for continuous variables and $\chi 2$ tests for unpaired categorical variables. The probabilities of death stratified according to CAD severity by DS and SS were plotted using the Kaplan-Meier method. Univariate and multivariate analyses were performed, the latter using a Cox proportional hazards regression model created with variables from univariate analysis with p value ≤

0.2. The proportional hazards assumption for these was satisfied through assessment of both Schoenfeld residuals and log-minus-log survival plots. Hazard ratios (HR) or odds ratios (OR) were reported with 95% confidence intervals. A two-tailed $p<0.05$ was considered statistically significant.

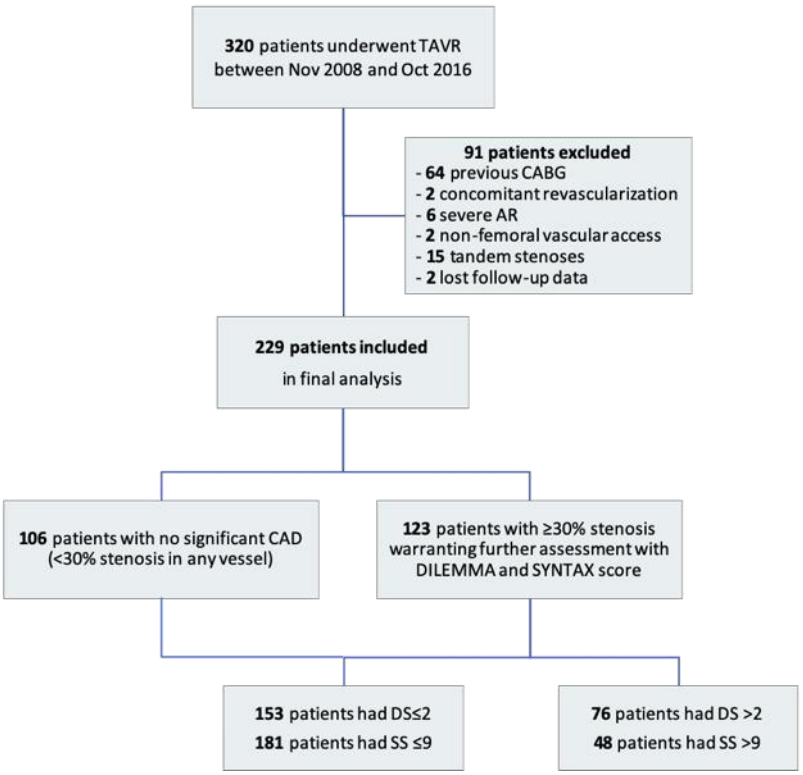


Figure 3-4 | Study flow chart

Patient selection process for this study. Of the 320 patients who were screened, 229 patients were included in the final analysis. AR indicates aortic regurgitation; CABG, coronary artery bypass surgery; CAD, coronary artery disease; TAVR, transcatheter aortic valve replacement.

3.4. STUDY 4: FEASIBILITY AND VALIDITY OF CT-DERIVED FRACTIONAL FLOW RESERVE IN PATIENTS WITH SEVERE AS: THE CAST-FFR STUDY

Study protocol

This was a prospective, single-centre study carried out at Monash Medical Centre, Melbourne between November 2018 and November 2019. The study protocol was approved by the institutional research ethics committee (Human Research Ethics Committees Australia reference: HREC/43524/MonH-2018-67705v1). All recruited patients provided written informed consent.

Patients with severe AS with an indication for TAVR as per international guidelines [13] and underwent pre-procedural ICA were screened for participation. Inclusion criteria were: (1) aged ≥18 years and <90 years old and, (2) patients with ≥30% visual stenosis in at least one coronary artery identified at time of ICA. Exclusion criteria were: (1) severe asthma or resting bradycardia precluding use of adenosine, (2) left ventricular ejection fraction <30%, (3) chronic renal impairment, defined by estimated glomerular filtration rate ≤30ml/min/1.73m^2, (4) myocardial infarction within last 3 months, (5) previous coronary artery bypass surgery (CABG), (6) percutaneous coronary intervention (PCI) in the vessel of interest, (7) >90% visual stenosis in the vessel of interest (8) chronic total occlusions and (9) significant left main coronary disease

Invasive FFR protocol

Cardiac catheterization was performed in accordance to standard practice, via the transfemoral or transradial approach. All patients were anticoagulated using 70-100 IU/kg of unfractionated heparin. Orthogonal plane angiography were acquired at 15 frames per second. Pressure wire assessment was then performed if there was at least one vessel (≥2 mm in diameter) with ≥30% stenosis. Additional vessels were interrogated at operator discretion. The pressure wire (Pressure X, Abbott Vascular, Santa Clara, CA) was calibrated and equalised with aortic pressure before being positioned in the distal

third of the coronary artery (at least 10 mm beyond the maximal stenosis). All patient received intracoronary glyeryl trinitrate (100 mcg) before measurements were performed. Mean distal coronary and mean aortic pressures (Pd and Pa, respectively) were recorded at rest and at hyperaemia, which was induced using intravenous adenosine (140 mcg/kg/min). The intracoronary pressure sensor was subsequently pulled back to the tip of the guiding catheter to assess for potential pressure drift. The FFR reading was categorised as valid if the drift in Pd/Pa was ≤0.02.

The hemodynamic recordings were processed using the QUANTIEN integrated measurement system (Abbott Vascular, CA, US). Anonymised tracings were stored centrally for offline analysis. All aortic and coronary pressure traces were reviewed to ensure FFR readings were taken during a hyperaemic segment in the recording. The traces were once again reviewed to confirm there was no pressure drift at the end of the recording beyond ≤0.02. FFR was calculated by dividing Pd by Pa during maximal hyperaemia.

CT imaging protocol

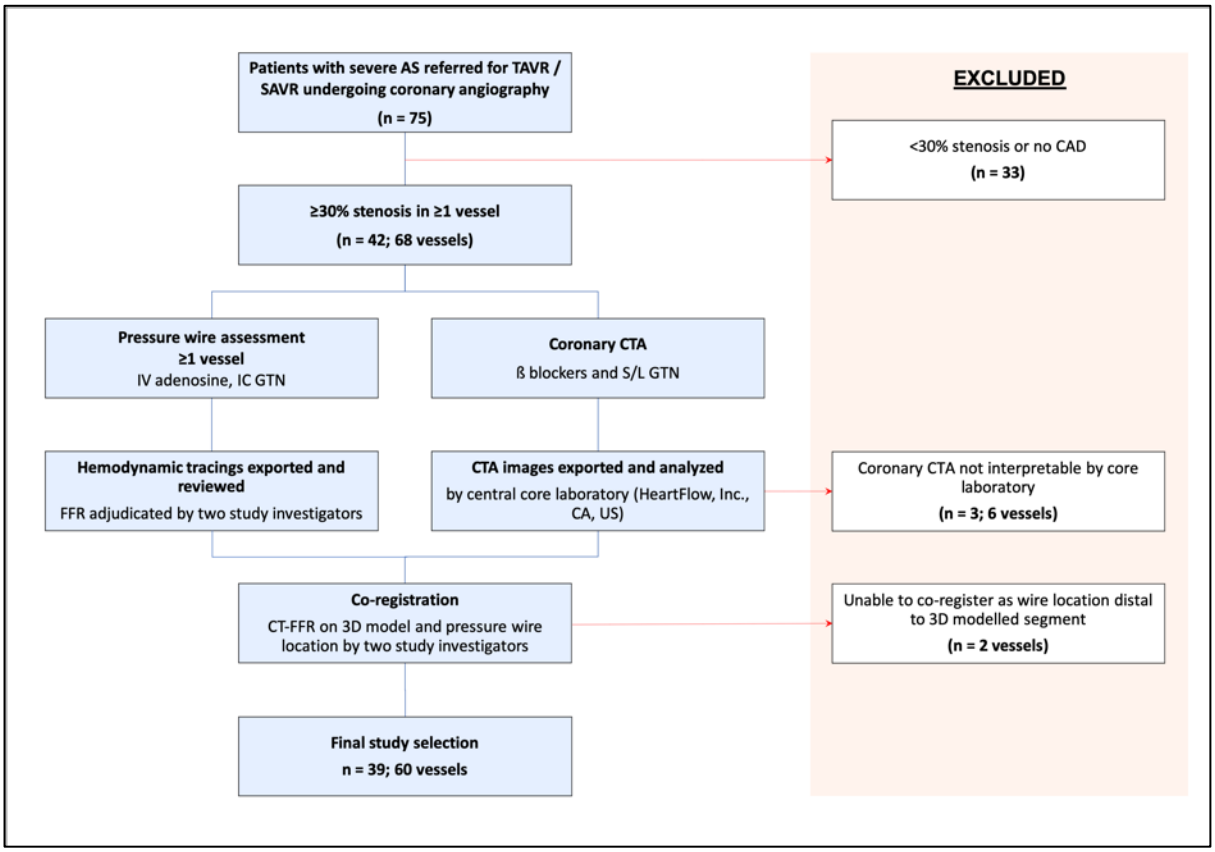
Following cardiac catheterization, patients underwent coronary CTA scanning (mean 7.3 days following ICA) using a 320-row detector CT scanner (Aquilion One Vision; Canon Medical Systems, Otawara, Japan). The scanning protocol was dependent on whether the patients were being considered for TAVR (*cardiac CT protocol A*) or surgical AVR (*cardiac CT protocol B*). Both protocols consisted of a calcium score followed by CTA. All patients received 0.4mg sublingual glyceryl trinitrate with the addition of beta-blockers and/or ivabradine to achieve a pre-scan heart rate of <60 beats/min (protocol adopted from with Society of Cardiovascular Computed Tomography guidelines) [122]. With both protocols, scanning was manually triggered in the arterial phase. Scan parameters for coronary CTA were: detector collimation, 320 $\times$ 0.5 mm; tube current, 300 to 500 mA; tube voltage, 100 to 120 kV; gantry rotation time, 270 ms; and temporal resolution: 135ms. Prospective electrocardiogram gating was used covering 70% to 99% of the R-R interval. In addition to the coronary CTA protocol,

cardiac CT protocol A incorporated the clinically-mandated pre-TAVR scanning protocol which includes the thoracic aorta for annular sizing and peripheral vascular assessment.

Coronary CTA and CT-FFR analysis

Coronary CTA was analysed using a dedicated workstation (Vitrea Fx 6.4, Vital Images, Minnesota, USA) by an experienced CT angiographer (A.J.B), blinded to the results of ICA and FFR. A vessel was considered significantly diseased if there was ≥1 segment that demonstrated >50% luminal stenosis or was non-evaluable due to calcification, motion artefact or extreme tortuosity. CTA images were then analysed for CT-FFR by a central core laboratory (HeartFlow, Inc., Redwood City, California) that were blinded to all invasive FFR and CTA measurements. Electronic 3-dimensional (3D) models of the coronary anatomy containing the CT-FFR data were created for each case. Experienced investigators (M.M. and A.R.I.) identified the locations on the 3D model corresponding to the angiographically

Figure 3-5| Study flow chart



acquired positions of the pressure wire sensor obtained during the FFR recording. Discrepancies were resolved by consensus agreement.

Statistical analysis

The primary endpoint of this study was per vessel diagnostic performance of CT-FFR to predict ischemia, as defined by invasive FFR ≤0.80 using the area under the receiver-operating characteristic curve analysis (ROC AUC). Secondary endpoints included diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for CT-FFR (≤0.80), using FFR ≤0.80 as reference standard. Additional outcomes included the diagnostic performance on a per patient basis, whereby the lowest values of FFR and CT-FFR were used in patients with complete data in more than one vessel. Diagnostic accuracy was also evaluated based on a median split of CT calcium scores to determine the validity of this approach in patients with high calcium scores. The Shapiro-Wilk test was used to assess normality of continuous variables. Continuous variables are expressed as mean ± standard deviation (SD) or median ± interquartile range for skewed data. Categorical variables are provided as frequencies (percentages). The correlation between CT-FFR and invasive FFR was quantified with Pearson's correlation coefficient after assessing the linearity of association. Agreement between the two indices was assessed with a Bland-Altman technique. Statistical analyses were performed with Stata v.14.1 (StataCorp, College Station, TX, USA) and GraphPad Prism v.8.1.2 (La Jolla, CA, USA).

PART 1: PATHOPHYSIOLOGICAL ALTERATIONS OF MYOCARDIAL BLOOD FLOW IN PATIENTS WITH SEVERE AORTIC STENOSIS

4. THE ACUTE EFFECTS OF TRANSCATHETER AORTIC VALVE REPLACEMENT ON CENTRAL AORTIC HAEMODYNAMICS IN PATIENTS WITH SEVERE AORTIC STENOSIS

This chapter is based on the published manuscript:

Michail M, Hughes AD, Comella A, Cameron JN, Gooley R, McCormick LM, Mathur A, Parker KH, Brown AJ, Cameron JD. Acute effects of transcatheter aortic valve replacement on central aortic hemodynamics in patients with severe aortic stenosis. Hypertension (2020) DOI: 10.1161/HYPERTENSIONAHA.119.14385

Contribution:

I conceived the idea and designed the study. I extracted, cleaned and anonymised the data. I performed the data analysis, statistical analysis and wrote the manuscript. AC and JNC assisted with the patient data extraction and analysis. RG, LMM and AM contributed to the discussions. AJB, KHP and ADH contributed to the discussions and editing the manuscript. JDC assisted with the analyses, contributed to the discussions and provided overall supervision.

4.1. ABSTRACT

Background: Severe aortic stenosis (AS) induces abnormalities in central aortic pressure, leading to impaired organ and tissue perfusion. Relief of AS by transcatheter aortic valve replacement (TAVR) is known to be associated with both a short- and long-term hypertensive response. Counterintuitively, patients who are long-term normotensive post-TAVR have worsened prognosis compared with hypertensive patients, yet the underlying mechanisms are not understood. We investigated the immediate changes in invasively measured left ventricular and central aortic pressure following TAVR in patients with severe AS using aortic reservoir pressure, wave intensity analysis (WIA) and indices of aortic function.

Methods: 54 patients (mean age 83.6 ± 6.2 years, 50.0% female) who underwent TAVR were included. We performed both reservoir pressure and WIA on ensembled, invasively acquired pressures waveforms in the ascending aorta and left ventricle immediately pre- and post-TAVR.

Results: Following TAVR, there were increases in systolic, diastolic, mean and pulse aortic pressures (all $p<0.05$). Post-TAVR reservoir pressure was unchanged (54.5±12.4 vs. 56.6±14.0 mmHg, $p= 0.30$) whereas excess pressure increased 47% (29.0±10.9 vs. 42.6±15.5 mmHg, $p<0.001$). WIA (arbitrary units, a.u.) demonstrated increased forward compression wave (64.9±35.5 vs. 124.4±58.9, $x10^3$ a.u., $p<0.001$), backward compression wave (11.6±5.5 vs. 14.4±6.9, $x10^3$ a.u., $p = 0.01$) and forward expansion wave energies (43.2±27.3 vs. 82.8±53.1, $x10^3$ a.u., $p<0.001$). Subendocardial viability ratio was improved with aortic function effectively unchanged post-TAVR.

Conclusions: Increases in central aortic pressure following TAVR relate to increased excess pressure and improved transvalvular energy profiles with unchanged reservoir pressure. These haemodynamic changes are consistent with symptomatic improvement and may be the basis for the association of elevated blood pressure and improved prognosis post-TAVR.

4.2. INTRODUCTION

Degenerative aortic stenosis (AS) is the commonest form of aortic valve disease and is caused by progressive calcification of the valve leaflets, which impairs leaflet mobility and compromises valve orifice area.[1] This leads to restricted blood flow through the stenosed valve, typically leading to narrowed pulse pressure and a delay in peak aortic pressure.[17] Pathophysiological changes in central aortic pressure are known to adversely impact tissue and organ perfusion including that to the myocardium, which may contribute to ischaemia,[123] exertional symptoms and adverse outcomes.

Relief of AS by TAVR has been shown to significantly elevate blood pressure both short- and long-term post-procedure.[124,125] Counterintuitively, several studies have demonstrated that following TAVR, normotensive patients have worse clinical outcomes at short and longer term follow up than those with raised arterial blood pressure (BP)[124-126] however, the mechanisms are not understood. This study presents results of aortic reservoir pressure and WIA immediately before and immediately after the deployment of a TAVR prosthesis, thus demonstrating the immediate impact of the relief of aortic valve obstruction upon central aortic haemodynamics.

We hypothesised that following TAVR, the main central hemodynamic changes would relate to the immediate alterations in the pattern of blood flow into the proximal aorta. This would manifest as an increase and change in the profile of excess pressure as well as increases in the energy and power of the WIA profiles. Conversely, we would expect to see minimal changes in reservoir pressure, which relates predominantly to the global arterial properties and would be expected to be unchanged immediately following valve deployment.

4.3. RESULTS

Of the initial 200 selected patients, 71 did not meet the inclusion criteria. Of the remaining, 75 were excluded due to dampened pressure tracings, inadequate ECG recording prohibiting automated wave-ensembling, or the lack of required identifiable fiducial points for determination of reservoir pressure.

54 patients were included in the final analysis (**Figure 3-3**). The mean age of those with analysable data was 83.6 ± 6.2 years and 50% were female. There were no significant differences between the baseline clinical and demographic data of the 75 excluded and the 54 included patients (**Table 4-1**). All patients underwent TAVR via femoral arterial access and all patients had balloon aortic valvuloplasty prior to valve deployment. The patient baseline and procedural characteristics are presented in **Table 4-2**. The echocardiographic and invasive hemodynamic indices before and after the procedure are presented in **Table 4-3**.

Table 4-1 | Baseline clinical and demographic data of the included and excluded patients			
	Included patients (n=54)	**Excluded patients (n=75)**	**p values**
Age, years	83.6 ± 6.2	82.7±6.4	0.42
Female	27 (50.0%)	33 (44.0%)	0.50
BMI, kg.m^{-2}	27.4 ± 4.9	26.2 ± 5.4	0.22
Hypertension	40 (74.1%)	48 (64.0%)	0.29
Diabetes mellitus	14 (25.9%)	15 (20.0%)	0.63
Dyslipidaemia	34 (63.0%)	37 (49.3%)	0.12
Smoker or ex-smoker	27 (50%)	33 (44%)	0.50
Previous MI	6 (11.1%)	8 (10.7%)	0.94
Previous PCI	11 (20.3%)	11 (14.7%)	0.40
Previous CABG	10 (18.5%)	21 (28.0%)	0.21
Previous Stroke	3 (5.6%)	8 (10.7%)	0.31
PVD	7 (13.0%)	5 (6.7%)	0.22
Chronic kidney disease (eGFR<45)	17 (31.5%)	26 (34.7%)	0.71

Values are mean ± SD or n (%). BMI indicated body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; PVD, peripheral vascular disease.

Following TAVR, there was the expected significant reduction in invasive mean transvalvular gradient (52.0 ± 14.2 vs. 10.5 ± 14.2 mmHg, p <0.001), with a concomitant reduction in peak left ventricular pressure (176.3 ± 25.5 vs. 151.2 ± 28.0 mmHg, p <0.001). There were significant increases in all measures of aortic BP including systolic (128.4 ± 22.0 vs. 144.9 ± 26.6 mmHg, p <0.001), diastolic (52.9 ± 9.8 vs. 56.8 ± 11.2 mmHg, p = 0.03), mean (81.1 ± 13.7 vs. 88.9 ± 15.8 mmHg, p <0.002) and pulse (75.6 ± 18.1 vs. 88.1 ± 20.2 mmHg, p <0.001) pressures. Mean heart rate trended towards an increase (63.6 ± 10.8 vs. 66.4 ± 10.1 beats/min, p = 0.07) whilst diastolic time fraction remained unchanged

following valve deployment (0.625 ± 0.057 vs. 0.633 ± 0.047, p = 0.31). The time to peak systolic LV pressure (expressed as a fraction of the cardiac cycle) was unchanged post-TAVR (0.293 ± 0.136 vs. 0.315 ± 0.132, p = 0.39) whilst the time to peak systolic aortic pressure decreased (0.288 ± 0.048 vs. 0.248 ± 0.032, p <0.001).

Table 4-2 | Patient baseline and procedural characteristics	
Patient demographic data	**(n = 54)**
Age, years	83.6 ± 6.2
Female	27 (50.0%)
BMI, kg/m^2	27.4 ± 4.9
Hypertension	40 (74.1%)
Diabetes mellitus	14 (25.9%)
Dyslipidaemia	34 (63.0%)
Smoker or ex-smoker	27 (50%)
Previous MI	6 (11.1%)
Previous PCI	11 (20.3%)
Previous CABG	10 (18.5%)
Previous stroke	3 (5.6%)
Peripheral vascular disease	7 (13.0%)
Chronic kidney disease (eGFR<45)	17 (31.5%)
Cardiovascular drug therapy	
Statin	38 (70.3%)
ACE or ARB	28 (51.9%)
ß-blocker	25 (46.3%)
α-blocker	0 (0%)
Calcium channel blocker	14 (25.9%)
Diuretics	20 (37.0%)
Procedural characteristics	
General anaesthesia	12 (22.2%)
Femoral	54 (100%)
BAV	54 (100%)
Valve type	
CoreValve	4 (7.4%)
Evolut R	23 (42.6%)
Lotus	16 (29.6%)
Edwards S3	9 (16.7%)
Acurate Neo	2 (3.7%)
Mean valve size, mm	26.9 ± 2.6

Values are mean ± SD or n (%). BAV indicates balloon aortic valvuloplasty; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 4-3 | Echocardiographic and invasive haemodynamic indices pre- and post-TAVR			
Variables	**Pre-TAVR**	**Post-TAVR**	**p value**
Echocardiographic indices			
Peak velocity, ms^{-1}	4.4 ± 0.5	2.2 ± 0.6	<0.0001
Mean gradient, mmHg	47.8 ± 12.8	11.0 ± 6.1	<0.0001
Peak gradient, mmHg	79.0 ± 20.6	20.2 ± 12.03	<0.0001
Aortic valve area, cm^2	0.8 ± 0.2	1.9 ± 0.5	<0.0001
Stroke volume, ml	85.3 ± 18.3	76.4 ± 17.2	0.008
Ejection fraction, %	59.2 ± 14.0	59.8 ± 13.8	0.7
Aortic regurgitation		(transvalvular/paravalvular)	
Mild	17 (31.5%)	5/11 (9.3% / 20.4%)	
Moderate	10 (18.5%)	0/5 (0% / 9.3%)	
Severe	0 (0%)	0 (0% / 0%)	
Intraprocedural invasive indices			
Heart rate, beats/min	63.6 ± 10.8	66.4 ± 10.1	0.07
Systolic aortic BP, mmHg	128.4 ± 22.0	144.9 ± 26.6	<0.001
Diastolic aortic BP, mmHg	52.9 ± 9.8	56.8 ± 11.2	0.03
Mean aortic BP, mmHg	81.1 ± 13.7	88.9 ± 15.8	0.002
Pulse aortic pressure, mmHg	75.6 ± 18.1	88.1 ± 20.2	<0.001
Mean transvalvular gradient, mmHg	52.0 ± 14.2	10.5 ± 5.6	<0.001
Peak left ventricular pressure, mmHg	176.3 ± 25.5	151.2 ± 28.0	<0.001
Diastolic time fraction	0.625 ± 0.057	0.633 ± 0.047	0.31
Time to peak systolic left ventricular pressure as a fraction of the cardiac period	0.293 ± 0.136	0.315 ± 0.132	0.39
Time to peak systolic aortic pressure as a fraction of the cardiac period	0.288 ± 0.048	0.248 ± 0.032	<0.001

Values are mean ± SD. TAVR indicates transcatheter aortic valve replacement; BP, blood pressure.

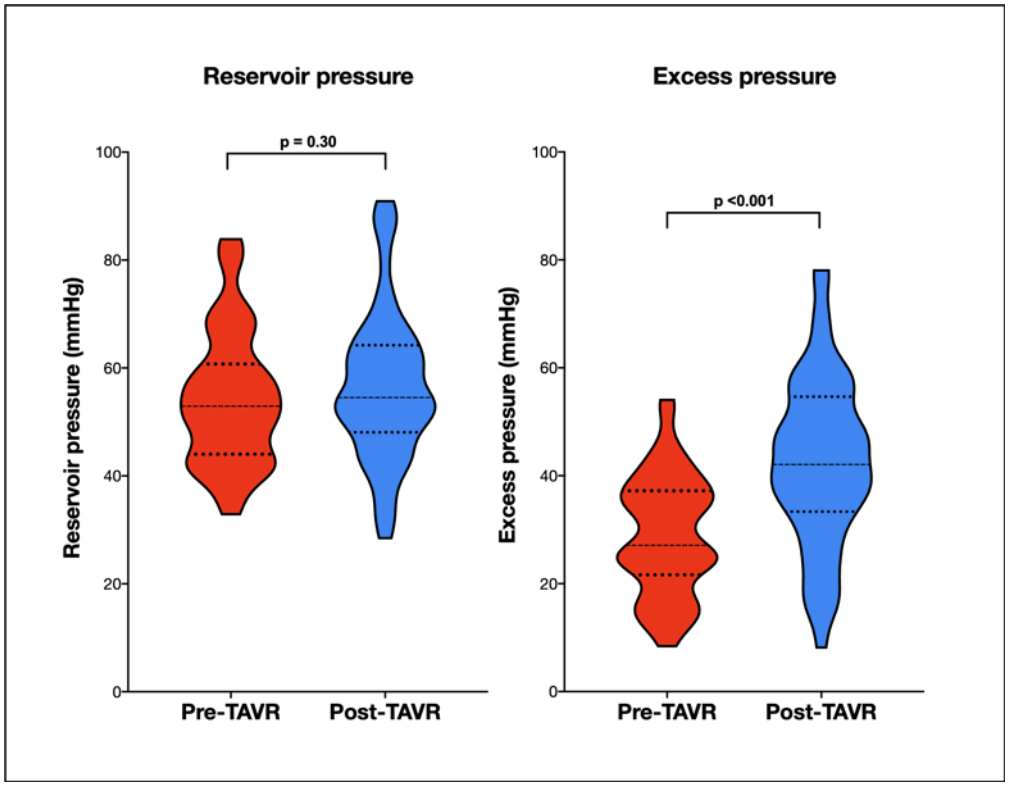
Subendocardial Viability Ratio

DPTI was unchanged post TAVR (42.2 ± 11.4 vs. 42.0 ± 10.7 mmHg.sec, p= 0.91). SEVR was increased post-TAVR (0.97 ± 0.32 vs. 1.25 ± 0.35, p<0.001) predominantly due to decreased LV pressure and consequent TTI (45.1 ± 9.8 vs. 35.0 ± 8.8 mmHg.sec, p< 0.001).

Reservoir pressure analysis

Analysis demonstrated no changes in the aortic reservoir pressure following TAVR (54.5 ± 12.4 vs. 56.6 ± 14.0 mmHg, p = 0.30; **Table 4-4, Figure 4-1**). However, excess pressure increased by 47% following TAVR (29.0 ± 10.9 vs. 42.6 ± 15.5 mmHg, p <0.001). Further analysis demonstrated that the integral of excess pressure – which relates to the total flow during the cardiac cycle[112] – was significantly greater following TAVR (6.66 ± 2.76 vs. 9.36 ± 3.73 mmHg·s, p <0.001). The time to peak reservoir and excess pressure both decreased post-TAVR (p <0.001 for both). There were no differences in the diastolic (18.0±9.6 vs. 14.5±11.6 sec^{-1}, p = 0.052) or systolic (3.9±1.1 vs. 4.2±1.1 sec^{-1}, p = 0.18) rate constants following TAVR.

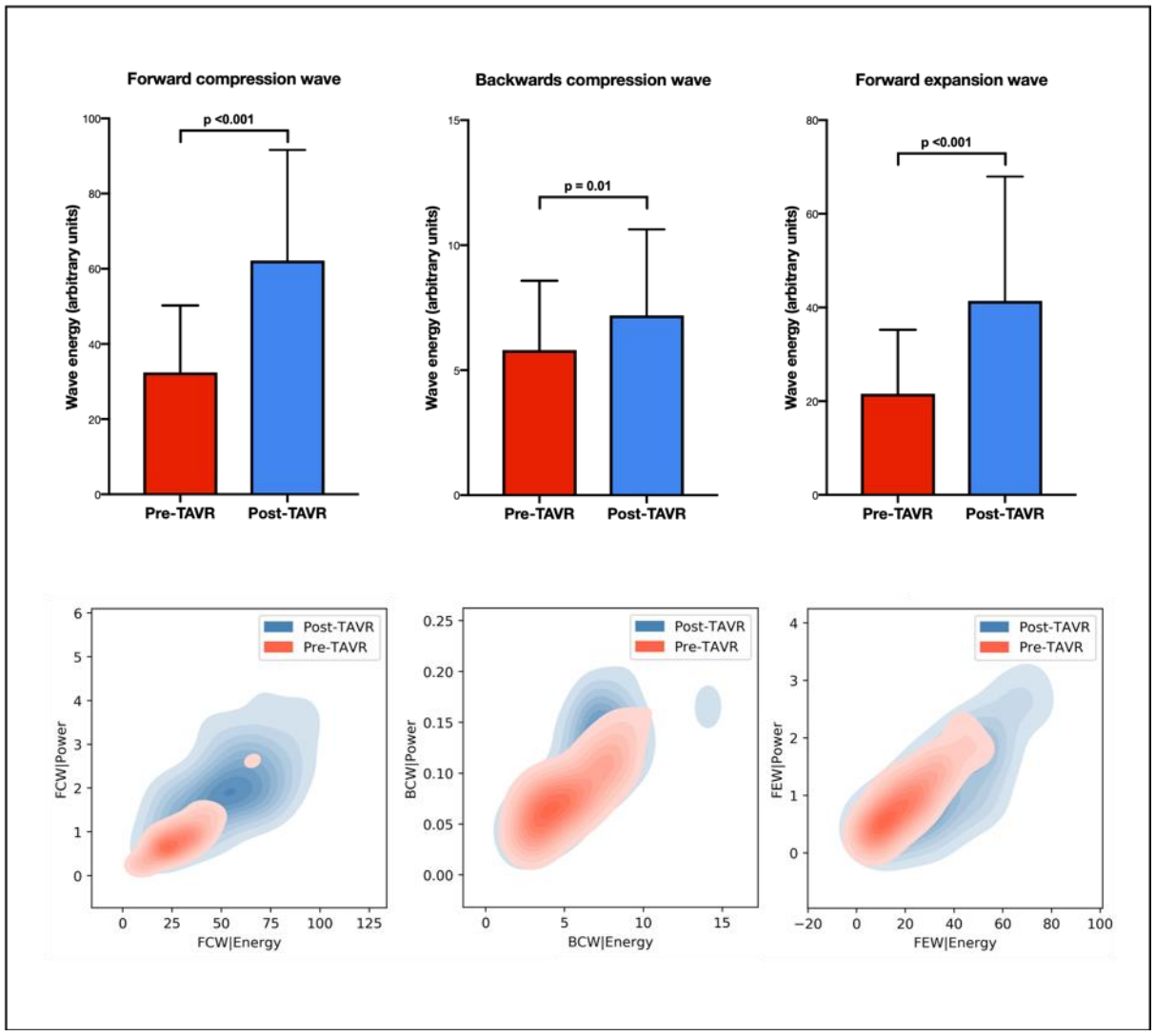
Figure 4-1 | Violin plot demonstrating reservoir and excess pressure before and after TAVR.



Aortic wave intensity analysis

Following TAVR, WIA demonstrated large increases in the peak FCW (1016.3 ± 684.0 vs 2431.1 ± 1304.6 x10^3 a.u., p <0.001; **Table 4-4**; **Figure 4-2**) and FCW energy (64.9 ± 35.5 vs. 124.4 ± 58.9 x10^3 a.u., p<0.001). This was associated with an intensification in the peak BCW (-92.5 ± 52.7 vs. -125.5 ± 76.9 x10^3 a.u, p = 0.01) and increase in BCW energy (11.6 ± 5.5 vs. 14.4 ± 6.9 x10^3 a.u., p = 0.01). Post-TAVR, peak FEW increased (956.0 ± 589.9 vs. 1473.2 ± 1071.9, x10^3 a.u., p <0.001) as did the FEW energy (43.2 ± 27.3 vs. 82.8 ± 53.1 x10^3 a.u., p<0.001).

Figure 4-2 | Changes in wave power and energy in the aortic root pre- and post-TAVR
Following TAVR there are clear increases (shift to the right) in the distribution of forward compression wave (FCW), backward compression wave (BCW) and forward expansion wave (FEW) indicating improved trans-valvular energetics.



Aortic function

There were no changes in aortic characteristic impedance following TAVR (1.01 ± 0.13 vs 1.04 ± 0.10, p= 0.27). Reflection ratio decreased following TAVR (0.56 ± 0.10 vs 0.47 ± 0.13, p<0.001) predominantly driven by an increase in the magnitude of the Pf wave (50.3 ± 13.7 vs 62.8 ± 16.9 mmHg, p <0.001) with no change in the magnitude of the Pb wave (27.2 ± 5.9 vs 28.2 ± 6.9 mmHg, p = 0.64). The time between the peak forward and backward pressures increased following TAVR (0.064 ± 0.019 vs 0.077 ± 0.025 seconds, p<0.001).

Table 4-4 | Reservoir and wave intensity analysis pre- and post-TAVR

Variables	Pre-TAVR	Post-TAVR	p value
Reservoir pressure analysis			
Reservoir pressure (peak), mmHg	54.5 ± 12.4	56.6 ± 14.0	0.30
Excess pressure (peak), mmHg	29.0 ± 10.9	42.6 ± 15.5	<0.001
Excess pressure integral, mmHg.s	6.66 ± 2.76	9.36 ± 3.73	<0.001
Rate constant of systolic aortic filling (k_s), per sec	18.0 ± 9.6	14.5 ± 11.6	0.052
Rate constant of diastolic aortic emptying (k_d), per sec	3.9 ± 1.1	4.2 ± 1.1	0.18
Time to peak reservoir pressure as fraction of cardiac period	0.335 ± 0.052	0.309 ± 0.039	<0.001
Time to peak excess pressure as fraction of cardiac period	0.219 ± 0.053	0.169 ± 0.044	<0.001
Aortic characteristic impedance, a.u.	1.01 ± 0.13	1.04 ± 0.10	0.27
Pf_{max}, mmHg	50.3 ± 13.7	62.8 ± 16.9	<0.001
Pb_{max}, mmHg	27.2 ± 5.9	28.2 ± 6.9	0.64
Pb_{max}/Pf_{max}, reflection ratio	0.56 ± 0.10	0.47 ± 0.13	<0.001
Time between Pf_{max} and Pb_{max} waves, secs	0.064 ± 0.019	0.077 ± 0.025	<0.001
Subendocardial viability ratio			
DPTI, mmHg.sec	42.2±11.4	42.0±10.7	0.91
TTI, mmHg.sec	45.1±9.8	35.0±8.8	<0.001
SEVR	0.97±0.32	1.25±0.35	<0.001
Wave intensity analysis			
FCW energy, $x10^{-3}$, a.u.	64.9 ± 35.5	124.4 ± 58.9	<0.001
FCW (peak), $x10^{-3}$, a.u.	1016.3 ± 684.0	2431.1 ± 1304.6	<0.001
BCW energy, $x10^{-3}$, a.u.	11.6 ± 5.5	14.4 ± 6.9	0.01
BCW (peak), $x10^{-3}$, a.u.	-92.5 ± 52.7	-125.5 ± 76.9	0.01
FEW energy, $x10^{-3}$, a.u.	43.2 ± 27.3	82.8 ± 53.1	<0.001
FEW (peak), $x10^{-3}$, a.u.	956.0 ± 589.9	1473.2 ± 1071.9	<0.001

Values are mean ± SD or n (%).Pf indicates, forward going pressure; Pb, reverse going pressure; FCW, forward compression wave; BCW, backward compression wave; FEW, forward expansion wave; a.u., arbitrary units; SEVR, subendocardial viability ratio; DPTI, diastolic pressure-time integral; TTI, left ventricular systolic tension time index.

4.4. DISCUSSION

This study presents new insights into the immediate physiological changes within the ventriculo-aortic complex in patients with severe AS treated with TAVR. Following TAVR, greater systolic, diastolic, mean and pulse arterial pressures were immediately observed, consistent with previous studies that have shown both immediate and long term increases in aortic BP in patients following TAVR.[77,124-126] Aortic reservoir pressure analysis demonstrates that the increase in total aortic pressure is related to increases in excess pressure without appreciable change in reservoir pressure. Reservoir pressure is recognised to be predominantly dependent on arterial wall properties which is unlikely to change immediately following aortic valve intervention. Left ventricular energetics also improved post-TAVR with an increase in energy supply:demand balance.

Excess pressure, which relates to inflow to the proximal aorta demonstrated significant increases following TAVR. Besides changes in the blood flow profile, this may also be attributable to increased systemic vascular resistance, an observation which has previously been documented post-TAVR.[77] Following TAVR, the prosthetic valve will not only open more briskly, but will have a greater effective orifice area, thus allowing the discharge of greater volume of blood into the aorta earlier in the cardiac cycle, with greater volumetric flow and thus greater momentum. The summation of excess pressure across the full cardiac cycle – a surrogate of the total volumetric flow across the cardiac cycle[112] – increases considerably following TAVR suggesting a potential for increase in stroke volume. The immediate and delayed effects of TAVR on stroke volume however remain unclear,[77,124,125] and our echocardiographic data at a mean of 3.0 days post-TAVR in fact demonstrates a reduction in stroke volume. The immediate changes in excess pressures therefore likely represent changes in the patterns of flow and physiology that would potentially facilitate the upregulation of stroke volume with increasing physiological demands, partially mediated through a combination of reduction of systemic vascular resistance in addition to greater ventricular contractility.

In addition to increases in excess pressure, improvements in flow following TAVR are evidenced by the changes in wave intensity profiles. We observe significant increases in aortic FCW power and energy following TAVR, consistent with previous data[77] suggesting improvement in the transvalvular energy profile following TAVR. Aortic BCW power and energy resulting from reflection of a FCW arriving at sites of impedance mismatch were also greater following TAVR. Contrary to previous findings,[77] our analysis demonstrates increasing aortic FEW power and energy following relief of valvular obstruction.

As hypothesised there were no changes of note in aortic function post-TAVR, as illustrated by no change in characteristic impedance or reservoir pressure (an index of global arterial function) parameters. Additionally, there was no increase in magnitude of any reflected pressure wave, which consequently implies a decreased contribution of aortic impedance to overall increase in central blood pressure post-TAVR. This was predominantly due to an increase in left ventricular-generated forward pressure wave. The slight increase in delay of the backward going pressure wave is consistent with either, or combination of, a pressure-dependent increase in proximal aortic stiffness and/or a peripheral vasodilatation leading to a consequent reduction in, or distal displacement of, any significant impedance mismatch.

Further changes that suggest restoration in central aortic pressure towards premorbid physiology relate to relative timing within the cardiac cycle. Thickened and calcified valves in AS lead to restricted and delayed valvular opening, which manifests clinically with the pathognomonic *pulsus tardus*. It has been demonstrated that the invasively-derived time between the left ventricular and aortic systolic peaks is associated with the severity of AS.[127] Our data shows that following TAVR, there is a decrease in the time to peak systolic aortic, reservoir and excess pressures, which suggests earlier delivery of blood volume into the aorta and partial normalization of aortic flow patterns.

Elevated aortic BP following TAVR can have immediate and long-term implications for patients. Following valve deployment, hypertensive patients pose greater challenges relating to access site haemostasis. Additionally, significant BP surges can lead to neurological events and acute pulmonary oedema.[125] The long-term impact of hypertension following TAVR continues to intrigue clinicians. In non-AS patients, hypertension is typically associated with increased vascular stiffness, altered global arterial properties and poorer prognosis.[128] Conversely, several studies have shown that increased arterial BP (systolic BP thresholds greater than 130 and 140 mmHg) in patients following TAVR paradoxically confers better outcomes compared to lower arterial BP.[124-126] Findings from this study suggest that increases in aortic BP following TAVR relate to improved excess pressure and transvalvular wave energy profiles. The basic mechanism of elevation of central BP post-TAVR is a reduction in the energy loss associated with blood transiting a stenotic aortic valve and therefore this energy is retained to generate increased contained BP in a proximal aortic vessel of unchanged impedance. These hemodynamic changes facilitate improved physiological states at rest and during upregulation for myocardial, cerebral and other organ demand. Maintenance of relatively elevated BP may also indicate an underlying preservation of cardiac function in a proportion of TAVR patients with potential for improvement in symptoms and prognosis in comparison to non-hypertensive post-TAVR patients. It is possible to hypothesise that hypertension post-TAVR is a less deleterious state than underlying poor cardiac function and hence imparts an apparent protective state. Whilst lower BP targets remains desirable in the normal population, optimal thresholds remain unknown in the post-TAVR patient cohort. Further research is required to elucidate the mechanisms, pathophysiology and consequences of hypertension following TAVR to better understand its relationship with improved outcomes.

Limitations of this study include it being a retrospective analysis of data from a single centre. Pressure measurements were acquired from fluid-filled rather than solid state catheters, which can be prone to pressure-dampening, signal attenuation and high frequency information loss. However, potential

error was minimised by blinded adjudication of all pressure traces and there were no differences between the baseline clinical and demographic data for the included and excluded patients. Finally, the rapid ventricular pacing used for balloon aortic valvuloplasty and valve deployment may result in ventricular stunning and has potential to affect immediate post-TAVR aortic pressure readings.[78]

4.5. CONCLUSIONS

In summary, the relief of aortic valvular obstruction following TAVR results in the immediate elevation of central aortic pressure due to increased excess pressure and improved transvalvular energy profiles without changes in reservoir pressure. Persistently higher blood pressure post-TAVR is an apparently protective state. We have shown that acute increases in BP post-TAVR relate to measurable increases in transmitted power and energy to the proximal aorta. If borne out in future studies and shown to predict long-term BP post-procedural, WIA may provide an easily assessable and potentially modifiable biomarker to stratify prognosis post-TAVR.

5. PATIENTS WITH AORTIC STENOSIS EXHIBIT EARLY IMPROVED ENDOTHELIAL FUNCTION FOLLOWING TRANSCATHETER AORTIC VALVE REPLACEMENT: THE E-FAST STUDY

This chapter is based on a manuscript in preparation for publication:

Comella A**, **Michail M****, Chan J, Cameron JD, Gooley R, Mathur A, Hughes AD, Brown AJ. Patients with aortic stenosis exhibit early improved endothelial function following transcatheter aortic valve replacement: The eFAST study. *Int J Cardiol.* (2021) DOI: 10.1016/j.ijcard.2021.03.062.

**joint first author

Contribution:

I conceived the idea and designed the study. I completed the ethics application and co-recruited the patients. I performed the majority of the offline analyses and wrote most of the manuscript with some contribution from AC. AC performed the FMD measurements, some the offline analyses and statistical analysis. JDC, AM and ADH contributed to the discussions. AJB contributed to the discussions and provided overall supervision.

5.1. ABSTRACT

Background: Patients with severe aortic stenosis (AS) exhibit endothelial dysfunction, which can be associated myocardial ischaemia in absence of obstructive coronary disease. Transcatheter aortic valve replacement (TAVR), is used to treat severe AS in patients with high or prohibitive surgical risk. However, it remains unknown whether endothelial function recovers post-TAVR. We therefore sought to assess the early and late changes in endothelial function following TAVR.

Methods: Patients undergoing TAVR for severe AS had ultrasound assessment of endothelial-independent and -dependent flow mediated dilation (FMD). Measurements were performed pre-TAVR, at early follow-up (<48 hours post-TAVR) and late follow-up (4-6 weeks post-TAVR).

Results: 27 patients (mean age 82.0±7.0; 33.3% female) were recruited; 37.0% had diabetes mellitus and 59.3% had hypertension. FMD increased from 4.2±1.6% (pre-TAVR) to 9.7±3.5% at early follow-up ($p<0.0001$). At late follow-up, improvement was sustained (8.7±1.9%, $p<0.0001$ compared with pre-TAVR). Resting brachial arterial flow velocities decreased significantly, but only at late follow-up (11.24±5.16 vs. 7.73±2.79 cm/s, $p=0.003$). Concordantly, at late follow-up, there were decreases in resting wall shear stress (WSS; 14.8±7.8 vs. 10.6±4.8dyne/cm2, $p=0.01$), peak WSS (73.1±34.1 vs. 58.8±27.8dyne/cm2, $p=0.03$) and cumulative WSS (3543±1852 vs. 2504±1089dyne·s/cm^2, $p=0.002$). Additionally, the positive correlation between cumulative WSS and FMD was restored at late follow-up ($r=-0.21$ vs. $r=0.49$).

Conclusion: Endothelial function in patients with AS improves early post-TAVR and this improvement is sustained. This likely occurs as a result of improved arterial haemodynamics, leading to lower localised WSS and release of vasoactive mediators that may also alleviate myocardial ischaemia.

5.2. INTRODUCTION

The underlying disease mechanisms responsible for the development of AS shares common aetiology with coronary atherosclerosis[129]. This includes disturbance in endothelial function, which plays an important role in regulating vascular wall function and organ blood flow[130]; this is mediated by vasoconstriction and vasodilatation through vasoactive factors such as nitric oxide and prostaglandins. Endothelial dysfunction (ED) is characteristic of atherosclerotic disease[131] and has been demonstrated in the early stages of disease in patients with AS[69]. Furthermore, the physiological changes in patients with severe AS result in haemodynamic alterations which further impair normal endothelial wall function[132,133].

ED contributes to the pathophysiological alterations in coronary blood flow in these patients,[17] including impaired coronary flow reserve (CFR)[74,75]. CFR represents the intrinsic ability to upregulate coronary blood flow at times of increased myocardial oxygen demand. The mechanisms for its impairment in AS are multifactorial but include ED-mediated submaximal microcirculatory vasodilatation in hyperaemia and resting secretion of NO causing higher baseline coronary flow velocities[17]. As one of the proposed mechanisms underpinning impaired CFR, ED is likely cornerstone to the exertional symptoms seen in patients with severe AS.

In patients undergoing coronary angioplasty, persistent ED is associated with adverse cardiovascular outcomes.[134] It remains unknown whether ED recovers following TAVR and previous studies have yielded conflicting results[80,135 79,136]. Importantly, it is unknown whether the minimally invasive nature of this procedure allows early recovery, or whether these changes are dependent on other factors which may resolve at a later stage. Importantly, a better understanding of ED recovery may provide insights into the underlying mechanisms in those with persistent symptoms following TAVR.

Endothelial function can be assessed non-invasively by measuring flow-mediated dilatation (FMD) of the brachial artery[72]. Ultrasonography is used to measure changes in the brachial artery during reactive hyperaemia following a period of forearm cuff occlusion. We hypothesised that once the haemodynamic environment is restored to physiological conditions, the improvement in flow pattern down the aorta will induce an improvement in the endothelium. We also hypothesised that improvement in endothelial function is not immediate following TAVR, but may improve after several weeks.

5.3. RESULTS

Twenty-seven patients were included in the study, with all participants undergoing successful assessment of FMD pre-TAVR. Two patients (7.4%) were lost to follow-up at the late post-TAVR assessment. The mean time to early and late follow-up assessments were 1.4 and 40.4 days, respectively.

Table 5-1 | Baseline Demographics

Patient characteristics	Mean ± SD / n (%)
Baseline characteristics	
Age, years	82.0±7.0
Female	9 (33.3)
BMI, kg/m^2	24.8±5.5
Diabetes mellitus	10 (37.0)
Family history of CAD	9 (33.3)
Hypertension	16 (59.3)
Hypercholesterolemia	24 (88.9)
Smokers	3 (11.1)
Ex-smokers	11 (41)
Previous MI	9 (33.3)
Peripheral artery disease	1 (3.7)
Previous stroke	5 (18.5)
Medications	
Beta blockers	10 (37.0)
ACEi/ARB	17 (63.0)
Nitrates	4 (14.8)
Statin	16 (59.2)
Aspirin	13 (48.1)
Warfarin	1 (3.7)
NOAC	7 (25.9)
Calcium channels blockers	10 (37.0)

Values are presented as n (%) or mean±SD. ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; NOAC, novel oral anticoagulants.

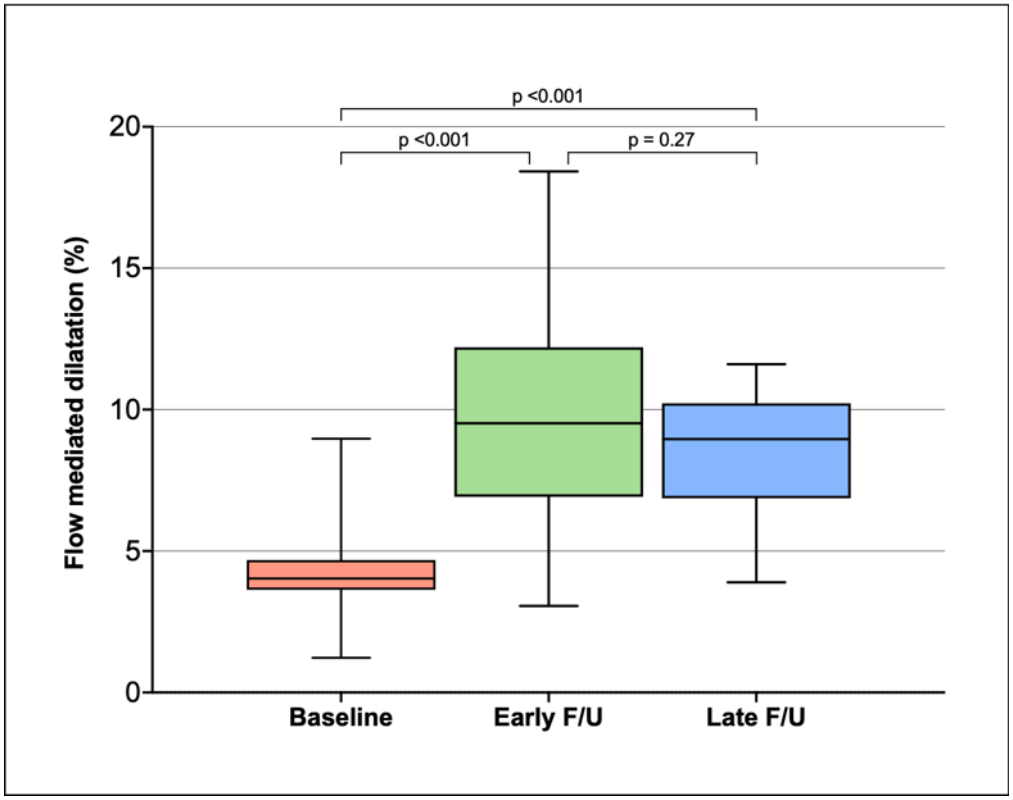
The baseline demographics and pharmacotherapy of this cohort are presented in **Table 5-1**. 10 patients (37.0%) had diabetes mellitus and 16 (59.3%) had hypertension. All TAVR procedures were successful completed with a reduction of mean aortic gradient from 48.8±8.5 to 13.3±6.7 mmHg, ($p<0.0001$). Echocardiographic and symptom data pre- and post-TAVR are presented in in **Table 5-2.**

At baseline only two patients (7.4%) had CCS III angina, with the remainder having no symptoms of chest pain. Twenty-four patients (88.9%) exhibited symptoms of breathlessness prior to TAVR, with 45.8% of these categorised as NHYA class III. Following TAVR, only 1 patient (3.7%) had resolution of breathlessness at early follow-up. At late follow-up, all but two patients (92.0%) were in NYHA class I.

Brachial flow-mediated dilatation assessment

Across the cohort, FMD improved from 4.2±1.6% pre-TAVR to 9.7±3.5% at early post-TAVR assessment (p<0.0001). Compared to baseline, the improvement was sustained at late follow-up assessment with mean FMD measuring 8.7±1.9%, p<0.0001 (**Table 5-3, Figure 5-1)**. All patients responded to GTN at baseline resulting in percentage dilation greater than the one induced by the increase in shear (4.2±1.6 vs. 10.9±3.4%, p<0.0001). Time to peak diameter in hyperaemia did not change significantly between pre- and post-TAVR (**Table 5-3**; pre-TAVR 66.4±24.0; early post-TAVR 61.9±25.1, p=0.64; late post-TAVR 55.6±25.3, p=0.10).

Figure 5-1 | Effects of TAVR on flow mediated dilatation.
Improvements in flow mediated dilatation (FMD) are observed at early follow up (F/U), and sustained at late F/U.



Flow-mediated dilatation in the diabetic subgroup

A subgroup analysis was performed on patients with type II diabetes mellitus given the known association with endothelial dysfunction.[137] Despite this, these patients were also found to have a significant improvement in FMD following TAVR, both at early and late follow-up assessments (4.46±2.14% vs. 8.87±4.45% early post-TAVR, p=0.006; vs. 8.89±1.34% late post-TAVR, p= 0.003). Furthermore, there was no convincing evidence that the change in FMD differed between the diabetic and non-diabetic cohorts (ΔFMD at early follow-up for diabetics 4.4±3.9% vs. 7.0±3.1% for non-diabetics, p=0.07; ΔFMD at late follow-up for diabetics 4.1±2.6% vs. 4.6±2.7% for non-diabetics, p = 0.71; overall ΔFMD for diabetics 4.3±3.3% vs. 5.8±3.1% for non-diabetics, p = 0.12; **Figure 5-2**).

Table 5-2 | Echocardiographic and symptom data

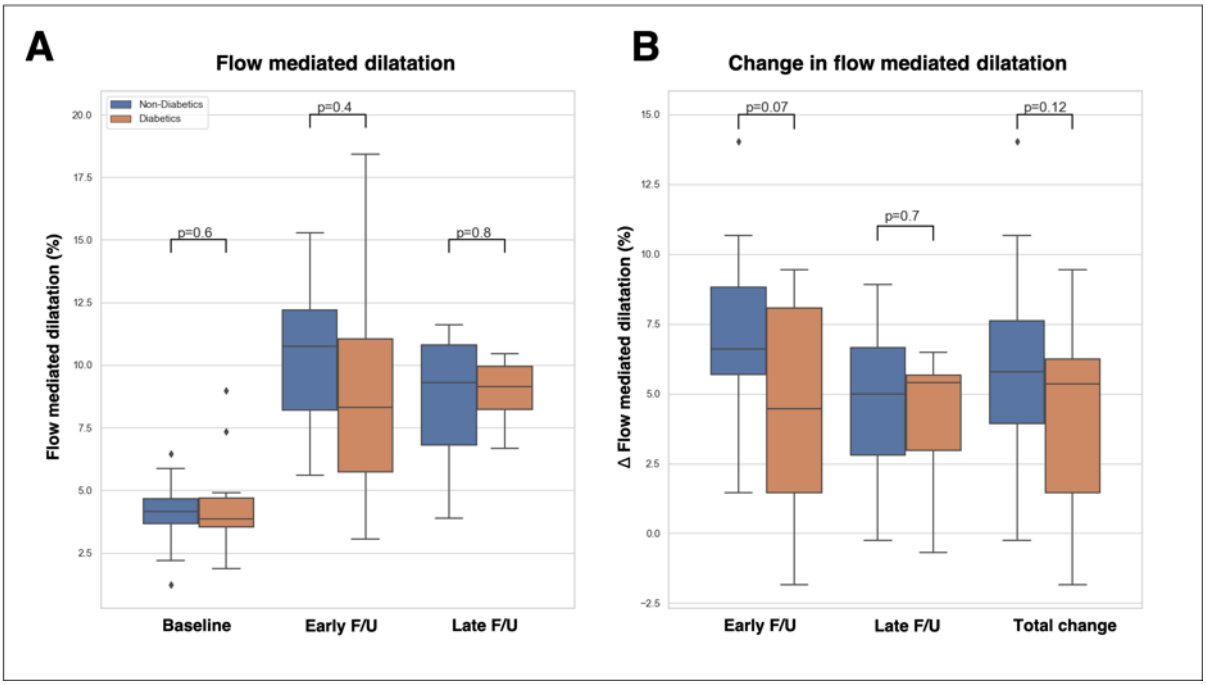
Variable	Pre-TAVR	Early follow-up	Late follow-up	p value
Aortic valve area, cm²	0.78±0.16	1.78±0.58	1.78±0.52	p<0.0001
Mean gradient, mmHg	48.78±8.50	13.33±6.72	12.74±5.89	p<0.0001
Peak gradient, cm/s	81.90±15.56	23.28±12.64	23.36±11.49	p<0.0001
DI	0.21±0.04	0.50±0.13	0.50±0.13	p<0.0001
Ejection fraction, %	59.25±10.91	62.03±11.03*	59.3±9.15**	*p=0.04, **NS
Stroke volume, mL	83.19±17.45	76.10±20.04	84.25±22.65	p>0.05
NYHA class				
I	3	4	23	
II	13	13	0	Not done.
III	11	10	2	
IV	0	0	0	
CCS class				
I	25	25	24	
II	0	0	0	Not done.
III	2	2	1	
IV	0	0	0	

Values are presented as n (%) or mean ± SD. CCS indicates Canadian Cardiovascular Society score for angina pectoris; DI, dimensionless index; NYHA, New York Heart Association score for heart failure. P values are for comparisons with Pre-TAVR.

Flow assessment and wall shear stress

Compared to pre-TAVR, resting brachial arterial flow velocities decreased significantly, but only at late post-TAVR follow-up assessment (11.24±5.16 vs. 7.73±2.79 cm/s, p=0.003). Concordantly, at late post-TAVR follow-up, there were decreases in resting WSS (14.8±7.8 vs. 10.6±4.8 dyne/cm^2, p=0.01; **Figure 5-3A)** and peak WSS (73.1±34.1 vs. 58.8±27.8 dyne/cm^2, p=0.03; **Figure 5-3B**). Whilst a trend was apparent, changes in resting brachial arterial velocities, resting and peak WSS were not statistically significant at early post-TAVR assessment (all p>0.05).

Figure 5-2 | Subgroup analysis of the effects of TAVR on flow mediated dilatation (FMD) in diabetes.
No differences between were found in FMD between the diabetic and non-diabetic patients **(A)** at each timepoint, before and after TAVR. Additionally, there were no differences between the diabetic and non-diabetic patients in **(B)** the change (Δ) in FMD from baseline to early follow up, to late follow up or in the total change.



Similarly, at late post-TAVR follow-up, there were decreases in the cumulative WSS (total area under the curve, AUC; 3543±1852 vs. 2503±1089 dyne·s/cm^2, p=0.002; **Figure 5-3C**) and AUC to peak diameter (2476±1315 vs. 1542±829 dyne·s/cm^2, p=0.001; **Figure 5-3D**). Additionally, there was poor correlation between cumulative WSS with FMD pre-TAVR and this was not restored at early post-TAVR follow-up; however, at late follow-up, the correlation was moderate (total AUC r=0.42, p=0.035; **Figure 5-4**).

Table 5-3 | Changes in brachial flow mediated dilatation and arterial haemodynamics pre- and post-TAVR					
	Pre-TAVR	**Early follow-up**	**p value**	**Late follow-up**	**p value**
FMD, %	4.2±1.6	9.7±3.5	<0.0001	8.7±1.9	<0.0001
Time to peak diameter, s	66.4±24.0	61.9±25.11	0.64	55.6±25.3	0.1
Resting velocities, cm/s	11.24±5.16	11.18±5.93	0.96	7.73±2.79	0.003
Resting WSS, dyne/cm²	14.8±7.8	15.3±9.3	0.74	10.6±4.8	0.01
Peak WSS, dyne/cm²	73.1±34.1	64.1±22.7	0.08	58.8±27.8	0.03
Cumularive WSS (AUC), dyne·s/cm²	3543±1852	3323±1405	0.42	2504±1089	0.002
Cumulative WSS to peak diameter, dyne·s/cm²	2476±1315	2312±917	0.49	1542±829	0.001
Time to peak of resting doppler wave, s	0.09±0.02	0.07±0.02	<0.0001	0.06±0.01	<0.0001
Time to peak of hyperaemic doppler wave, s	0.18±0.04	0.09±0.03	<0.0001	0.09±0.03	<0.0001
Diabetes, FMD, %	4.5±2.14	8.9±4.4	0.006	8.9±1.3	0.003

Values are presented as mean±SD. AUC indicates area under WSS curve; FMD, flow mediated dilation; WSS, wall sheath stress

Further evidence of haemodynamic changes can be observed in the brachial arterial flow pattern. The time to the peak of the resting Doppler wave form decreased at early post-TAVR follow-up, which was sustained at late follow-up (both p≤0.05; **Table 5-3**). Similarly, there was a reduction in the time to the peak of the hyperaemic Doppler wave form at early and late follow-up. The time to peak of the hyperaemic Doppler wave form measured before TAVR correlated well with DI (r=-0.51, p= 0.008). Linear regression revealed that time to peak Doppler wave form was a significant predictor of DI (β = -0.6245, p =0.008, R-squared = 0.26).

Figure 5-3 | Changes in wall shear stress following TAVR.

Whilst there are no appreciable decreases in wall shear stress (WSS) at early follow up post-TAVR, decreases are observed at late follow up in **(A)** resting WSS, **(B)** peak WSS, **(C)** cumulative WSS and **(D)** cumulative WSS to peak diameter.

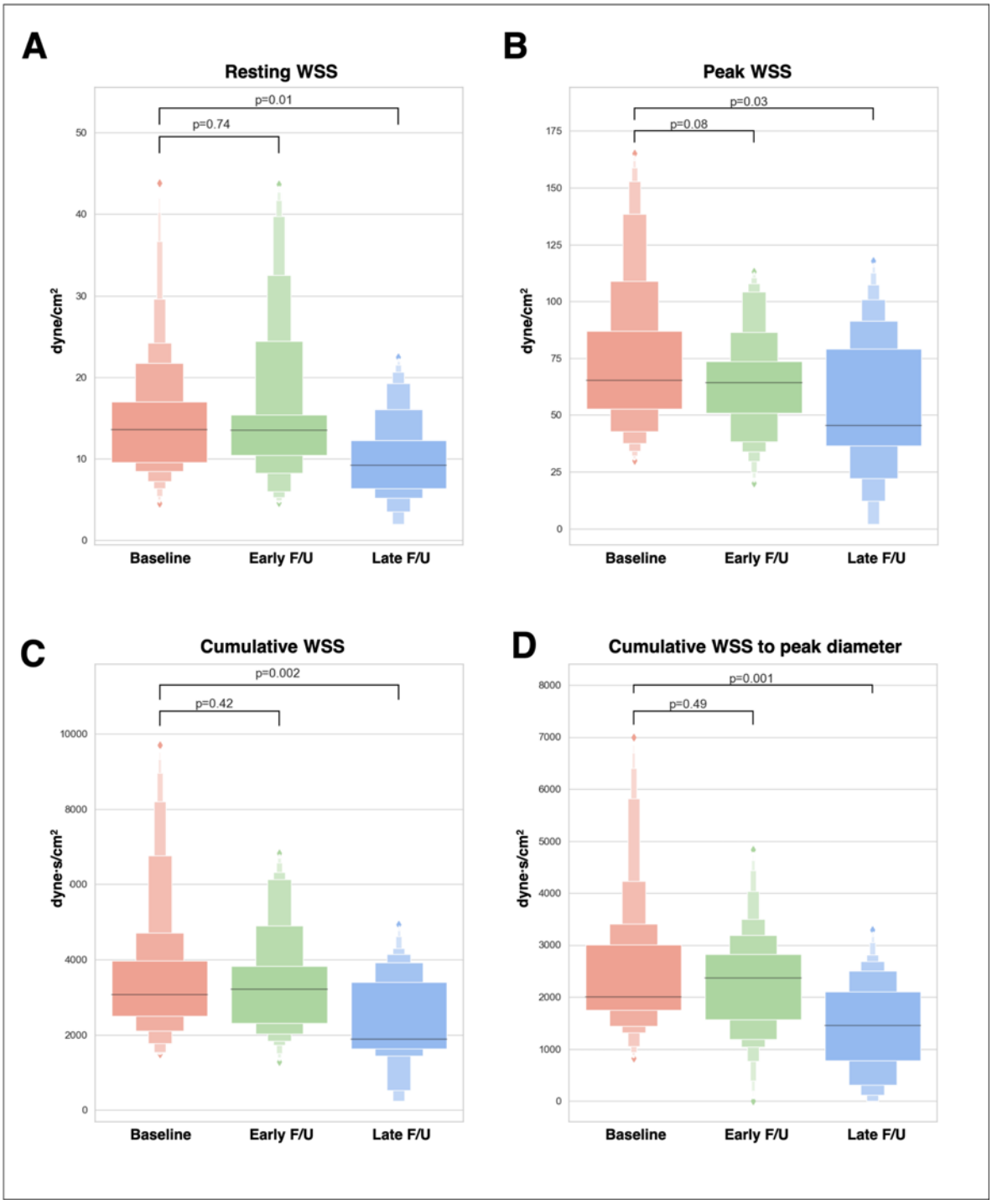
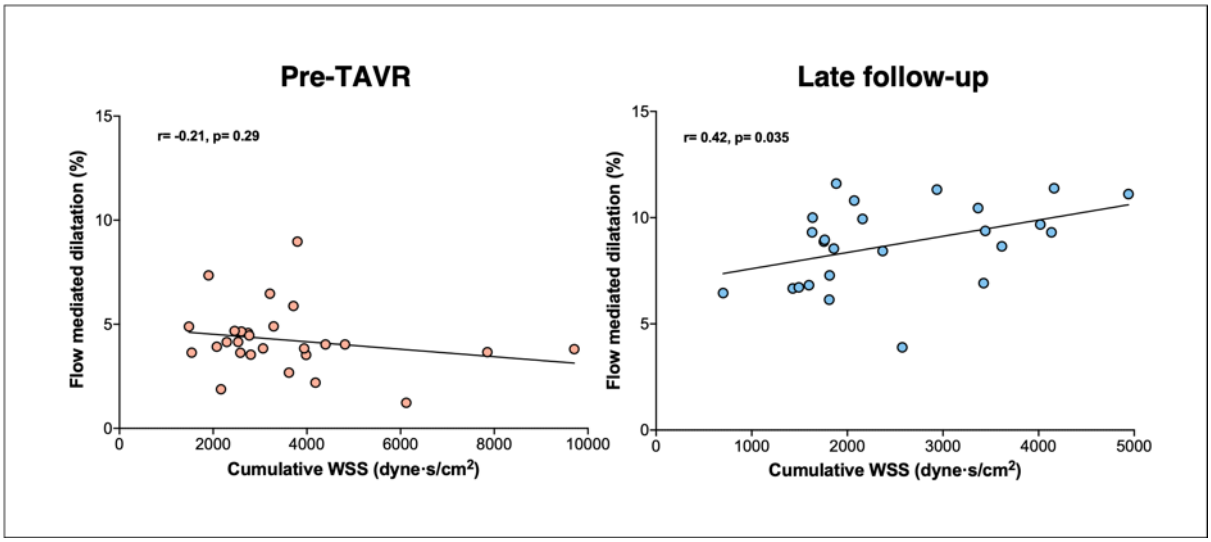


Figure 5-4 | Correlation between flow mediated dilatation (FMD) and cumulative wall shear stress.

Pre-TAVR, there was no correlation between FMD and cumulative wall shear stress (WSS). At late post-TAVR follow up, correlation between the two was restored.



5.4. DISCUSSION

Our study demonstrates improvements in endothelial-dependent FMD following TAVR. These improvements occur early post-TAVR and are sustained at late follow-up. Additionally, there are observed changes post-TAVR in the brachial arterial haemodynamics as evidenced by decreased blood flow velocities and WSS, although some of these changes were only evident at late post-TAVR follow-up.

Early improvements in endothelial function may be a consequence of the early haemodynamic changes associated with the relief of aortic valve obstruction. The time to peak flow velocity decreased at rest and in hyperaemia at early follow-up, likely a manifestation of the central haemodynamic changes[132]. Pre-TAVR, this correlated well with DI, consistent with the prolonged ejection time and delayed peaked velocity associated with AS severity[138,139]. In addition to the haemodynamic changes, the early improvements in FMD may also reflect the quicker global physiological recovery associated with a minimally-invasive approach such as TAVR. This is in contrast to major surgery, which itself can cause early impaired endothelial function, potentially due to factors such as surgical stress, trauma, anaesthesia, pain, hypoxaemia and hypovolaemia[140]. Importantly, patients with comorbidities that are known to impair endothelial function, such as hypertension, diabetes mellitus and smoking were not excluded from this study. This permitted a better reflection of the effect of TAVR on endothelial function in a wider patient demographic with severe AS referred for TAVR. Additionally, the subgroup analysis demonstrated that diabetic patients also benefited from improved endothelial function post-TAVR at early and late follow-up.

Following TAVR there is an observed decrease in brachial WSS, likely representing normalisation of physiology. Whilst early trends were observed, these changes were only detectable at late follow-up, suggesting a slower, adaptive process. Previous evidence has similarly demonstrated that patients with severe AS have high aortic WSS[141] that subsequently decreases following AVR[142,143,144]. Abnormal

vascular WSS in patients with severe AS has been associated with impaired platelet function,[141] which has been shown to resolve following AVR concurrently with decreasing WSS[142]. The mechanisms underlying increases in FMD following TAVR may be partially explained by changes in WSS. In severe AS, high WSS may stimulate eNOS to produce NO[145,146]. This results in vasodilatation, thus increasing resting blood flow as seen in peripheral vessels in this study, but also typically seen in the coronary arteries of such patients.[17] This partial hyperaemic state allows lesser scope for further vasodilatation and upregulation of blood flow due to the partially exhausted mechanisms which results in impaired FMD. Once WSS decreases post-TAVR, resting NO release is reduced, and the brachial artery regains greater scope for vasodilation during hyperaemia and thus restoration of FMD. These explanations are hypothesis-generating and are not conclusive given the presence of other conflicting data which suggests an increase in WSS following relief of AS.[80,147,148] Unusually, these were observed in the absence of changes in blood flow velocities or vessel diameter.

Further evidence of delayed physiological normalisation is observed in the relationship between cumulative WSS (AUC) and FMD. Whilst this normally correlates in healthy subjects[149], this relationship is absent in our study cohort, prior to treatment. Following TAVR, a linear relationship is restored, although this does not occur until late follow-up (when WSS had decreased). Delayed physiological normalisation is similarly observed in myocardial blood flow in patients with severe AS. Resting coronary flow velocities are elevated, with impaired scope for further upregulation (CFR). These abnormalities are not normalised immediately following TAVR. In particular, CFR does not improve immediately post-TAVR[35,76], but rather over a longer time period[76]; this delay may be attributed to factors such as ventricular remodelling and its influence on coronary perfusion[150]. The delays associated with changes in brachial haemodynamics and the reestablishment of the correlation between cumulative WSS and FMD supports the notion whereby some aspects of endothelial function recovery may also be delayed. The slower normalisation of coronary physiology may therefore be dependent on late improvements in endothelial function in addition to ventricular remodelling.

Further studies are required to better understand the mechanisms associated with endothelial function recovery in patients with severe AS. Additionally, further data is required to elucidate whether certain patient or procedural factors are more likely associated with ED; for example, in patients undergoing TAVR under general versus local anaesthetic, or to investigate ED in relation to certain adverse procedural outcomes such as patient-prosthesis mismatch. It is also key to ascertain whether the same improvements in endothelial function can be expected following surgical AVR, or whether recovery is delayed.

Limitations

This is a single-centre study with a limited population size. Nonetheless, the study was adequately powered to demonstrate restoration in endothelial function from the early follow-up. There were no age-matched controls. FMD is an operator-dependant technique and is therefore subject to observer bias. Additionally, it requires experienced operators who are trained in 2D and Doppler ultrasonography[72]. To mitigate, all assessments in this study were performed by the same experienced investigator for consistency. Importantly, there was high reproducibility within a validation cohort.

5.5. CONCLUSIONS

Our data shows that endothelial function in patients with AS improves early following TAVR and that this improvement is sustained. These changes are likely in response to the improved arterial haemodynamics resulting from the relief of AS. There is evidence of ongoing late normalisation of arterial haemodynamics, including lower WSS. These late adaptations likely contribute to the delayed improvements seen in coronary physiology and patient symptoms.

PART 2: THE PROGNOSTIC IMPACT AND ASSESSMENT OF CORONARY STENOSIS IN PATIENTS WITH SEVERE AORTIC STENOSIS UNDERGOING TRANSCATHETER AORTIC VALVE REPLACEMENT

6. ANGIOGRAPHIC FUNCTIONAL SCORING OF CORONARY ARTERY DISEASE PREDICTS MORTALITY IN PATIENTS WITH SEVERE AORTIC STENOSIS UNDERGOING TAVR

This chapter is based on the published manuscript:

Michail M, Thakur U, Comella A, Lim RY, Gupta V, Tan S, Rashid H, Cameron JD, Nicholls SJ, McCormick LM, Gooley R, Mathur A, Hughes AD, Brown AJ. Angiographic functional scoring of coronary artery disease predicts mortality in patients with severe aortic stenosis undergoing TAVR. *Cardiovasc Revasc Med* (2020) DOI: 10.1016/j.carrev.2020.04.024

Contribution:

I conceived the idea and designed the study. I identified the patients for inclusion, performed the analyses, and wrote the manuscript. UT helped with the statistical analysis and collecting follow up data. AC, ST and HR helped collecting follow up data. RYL and VG helped with data extraction and angiographic scoring assessments. JDC, SJN, LMM, RG, AM and ADH contributed to the discussions of the manuscript. AJB assisted with analysis, contributed to the discussions and provided overall supervision.

6.1.1. ABSTRACT

Background: Coronary artery disease (CAD) is common in patients undergoing transcatheter aortic valve replacement (TAVR), although its prognostic significance is questionable. Significant CAD stratified using SYNTAX score (SS) has been associated with greater mortality, yet it is unknown whether the functional impact of CAD also impacts outcomes in this cohort. DILEMMA score (DS) is a validated angiographic functional scoring tool that correlates with fractional flow reserve and instantaneous wave-free ratio.

This study sought to assess the functional impact of CAD on outcomes in patients undergoing TAVR for severe aortic stenosis (AS).

Methods: 229 patients were included in this analysis. Patients underwent angiographic DS and SS and were classified using predefined values. The primary endpoint was one-year all-cause mortality, with secondary endpoints of 30-day major adverse cardiac and cerebrovascular events (MACCE).

Results: The mean age was 83.9±0.5 years (55.0% female), with 11.8% all-cause mortality. CAD defined by ≥30% stenosis in any vessel was not associated with outcomes (HR=1.08, p=0.84). However, the risk of one-year mortality was greater in patients with either SS>9 (20.8% vs. 9.4%, HR 2.34, p=0.03) or DS>2 (18.4% vs. 8.5%, HR=2.28, p=0.03). Both scoring systems were also associated with 30-day MACCE (both p<0.05). After multivariate adjustment, independent predictors of one-year mortality were DS>2 (HR=2.29, p=0.04), left ventricular ejection fraction <50% (HR 2.66, p=0.04) and COPD (HR 2.43, p=0.04).

Conclusion: Our results demonstrate that angiographic functional scoring is independently predictive of both 12-month mortality and 30-day MACCE following TAVR.

6.2. INTRODUCTION

The evolution of TAVR continues to revolutionize the treatment of patients with severe AS. However, the management of concomitant coronary artery disease (CAD) remains controversial. In patients undergoing surgical aortic valve replacement (SAVR), revascularization of significant CAD with coronary artery bypass surgery (CABG) reduces the risk of adverse procedural outcomes[151] and is guideline-recommended[13]. It is therefore of widespread interest whether these same principles should be extrapolated to patients undergoing transcatheter therapies.

The influence of CAD on TAVR outcomes has previously been explored in large registries with conflicting results [152-155]. Given the heterogenous nature of CAD, angiographic complexity using SYNTAX scoring (SS) was explored as an alternative means to stratify outcomes [93,94,156,157]. A pooled analysis of 3107 patients demonstrated that those with higher residual SS were at greater risk of subsequent mortality[118]. Although the mechanisms are unclear, the presence of significant CAD has been associated with periprocedural myocardial injury (PPMI) [158], with PPMI predictive of both 30-day and 1-year mortality [159]. Whilst SS provides an overall assessment of the extent of CAD, it does not assess the prognostic significance of lesion-level or vessel-specific ischemia.

The DILEMMA score (DS) is a validated angiographic scoring tool that strongly correlates with fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) in patients with stable angina and acute coronary syndromes [119,120,160]. DS incorporates minimal luminal diameter, lesion length and Bypass Angioplasty Revascularization Investigation Myocardial Jeopardy Index (reflecting the percentage of myocardium subtended by a lesion). It provides a score ranging from 0 – 12, with a score ≤2 having an excellent negative predictive value for identifying lesions with FFR >0.80 and iFR >0.89.

In this study we sought to assess the prognostic impact of CAD on all-cause mortality following TAVR, stratified by angiographic scoring systems that act as surrogates for anatomical complexity (SS) or lesion physiological significance (DS). Our aim to the try and ascertain whether either metric was more predictive on TAVR outcomes.

6.3. RESULTS

A total of 229 patients were included in the final analysis (**Figure 3-4**). Of those, 123 patients (53.7%) had at least ≥30% stenosis in at least one of the vessels warranting further SS and DS assessment. Stratified by DS, 153 patients (66.8%) had all vessels with DS≤2 whilst 76 (33.2%) had at least one vessel with DS>2. Conventional SS thresholds demonstrated that the majority of patients (98.3%) had a low (0-22), 1.7% had intermediate (22-32) and none had high (≥33) SS. The median SS (excluding all patients with SS of 0) was 9 and this was used as the threshold for analysis. Of the 229 patients, 181 patients (79.0%) had SS ≤9 and 48 patients (21.0%) had SS > 9. Scheduled follow-up was completed in all patients, with a mean follow-up duration of 370 +/- 89 days.

The mean age was 83.9 $\pm$ 0.5 years and 55.0% were female. There were lower rates of previous MI (3.3% vs 10.5%, p = 0.025) and lower rates of previous percutaneous coronary intervention (PCI; 11.1% vs 27.6%, p=0.002) when comparing the DS≤2 vs DS>2 groups. The remainder of the baseline and procedural characteristics remain comparable between groups. The other baseline and procedural characteristics are summarised in **Tables 6-1** and **6-2**.

Table 6-1 | Baseline patient and echocardiographic characteristics							
		DILEMMA score ≤2 (n=153)	**DILEMMA score >2 (n = 76)**	**p value**	**SYNTAX score ≤9 (n=181)**	**SYNTAX score >9 (n=48)**	**p value**
Baseline patient characteristics							
Age, years		83.9 ± 8.5	83.9 ± 5.4	0.98	83.7 ± 8.0	84.5 ± 5.8	0.536
Female Gender		85 (55.6)	41 (53.9)	0.818	106 (58.6)	28 (41.7)	**0.036**
BMI, kg/m²		26.7 ± 5.6	26.8 ± 6.1	0.923	86.8 ± 5.9	26.5 ± 5.4	0.731
Diabetes		28 (18.3)	15 (19.7)	0.793	34 (18.8)	9 (18.8)	0.996
HTN		106 (69.3)	57 (75.0)	0.368	131 (72.4)	32 (66.7)	0.438
AF		47 (30.7)	25 (32.9)	0.738	53 (29.3)	19 (39.6)	0.172
Previous MI		5 (3.3)	8 (10.5)	0.025	8 (4.4)	5 (10.4)	0.110
Previous PCI		17 (11.1)	21 (27.6)	0.002	27 (14.9)	11 (22.9)	0.185
Previous CVA		17 (11.1)	12 (15.8)	0.316	24 (13.3)	5 (10.4)	0.599
COPD		30 (19.6)	21 (27.6)	0.169	39 (21.55)	12 (25.0)	0.609
Creatinine, µmol/L		96.4 ± 44.7	96.2 ± 31.5	0.974	95.6 ± 42.7	99.2 ± 29.4	0.576
Baseline echocardiographic parameters							
Bicuspid valve		2 (1.3)	1 (1.3)	0.996	3 (1.7)	0 (0)	0.996
Valve Area, cm²		0.74 ± 0.2	0.7 ± 0.2	0.245	0.74 ± 0.2	0.68 ± 0.2	0.068
LVEF <50%		20 (13.1)	7 (9.2)	0.394	18 (9.9)	9 (18.8)	0.093
Peak gradient, mmHg		83.0 ± 26.0	81.8 ± 20.9	0.718	82.7 ± 25.0	82.3 ± 22.2	0.922
Mean gradient, mmHg		50.1 ± 16.3	49.0 ± 12.3	0.602	49.8.1 ± 15.6	49.8 ± 13.1	0.983
Aortic Velocity, ms⁻¹		4.4 ± 0.9	4.5 ± 0.5	0.485	4.5 ± 0.8	4.5 ± 0.9	0.683
Dimensionless index		0.22 ± 0.17	0.20 ± 0.05	0.349	0.22 ± 0.15	0.20 ± 0.06	0.315
AR	**None/Mild**	142 (92.8)	73 (96.1)	0.335	168 (92.8)	47 (97.9)	0.190
	Mod/Severe	11 (7.2)	3 (3.9)		13 (7.2)	1 (2.1)	
MR	**None/Mild**	141 (92.2)	67 (88.2)	0.323	167 (92.3)	41 (85.4)	0.144
	Mod/Severe	12 (7.8)	9 (11.8)		14 (7.7)	7 (14.6)	

Values are presented as n (%) or mean ± SD. AF indicates atrial fibrillation; AR, aortic regurgitation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; PCI, percutaneous coronary intervention.

Table 6-2 | Procedural data							
		DILEMMA score ≤2	**DILEMMA score >2**	**p value**	**SYNTAX score ≤9**	**SYNTAX score >9**	**p value**
Self-Expanding Valve		62 (40.5)	30 (39.5)	0.879	72 (39.8)	20 (41.7)	0.813
Length of stay, days		8.6 ± 6.2	9.0 ± 7.1	0.651	8.9 ± 6.8	8.3 ± 5.3	0.605
Bleeding	**VARC 0 or 1**	122 (79.7)	59 (77.6)	0.712	141 (77.9)	40 (83.3)	0.411
	VARC 2 or 3	31 (20.3)	17 (22.4)		40 (22.1)	8 (16.7)	
Vascular complication		39 (25.5)	18 (23.7)	0.766	52 (28.7)	5 (10.4)	0.009
AKI	**No AKI**	134 (87.6)	63 (82.9)	0.702	157 (86.7)	40 (83.3)	0.692
	Stage 1	11 (7.2)	7 (9.2)		14 (7.7)	4 (8.3)	
	Stage 2	4 (2.6)	4 (5.3)		5 (2.8)	3 (6.3)	
	Stage 3	4 (2.6)	2 (2.6)		5 (2.8)	1 (2.1)	
LVEF, <50%		16 (10.5)	14 (18.4)	0.093	16 (8.8)	14 (29.2)	<0.001
Peak gradient, mmHg		22.2 ± 8.7	20.6 ± 11.3	0.248	22.6 ± 10.0	18.3 ± 7.0	0.007
Mean gradient, mmHg		11.7 ± 4.8	10.5 ± 6.3	0.119	11.8 ± 5.6	9.6 ± 3.8	0.012
DI		0.54 ± 0.16	0.52 ± 0.16	0.406	0.53 ± 0.17	0.53 ± 0.13	0.962
AR	**None/Mild**	149 (97.4)	75 (98.7)	0.527	177 (97.8)	47 (97.9)	0.957
	Mod/Severe	4 (2.6)	1 (1.3)		4 (2.2)	1 (2.1)	
MR	**None/Mild**	144 (94.1)	71 (93.4)	0.836	172 (95.0)	43 (89.6)	0.162
	Mod/Severe	9 (5.9)	5 (6.6)		9 (5.0)	5 (10.4)	
New PPM		36 (23.5)	17 (22.4)	0.844	46 (25.4)	12 (25.0)	0.953

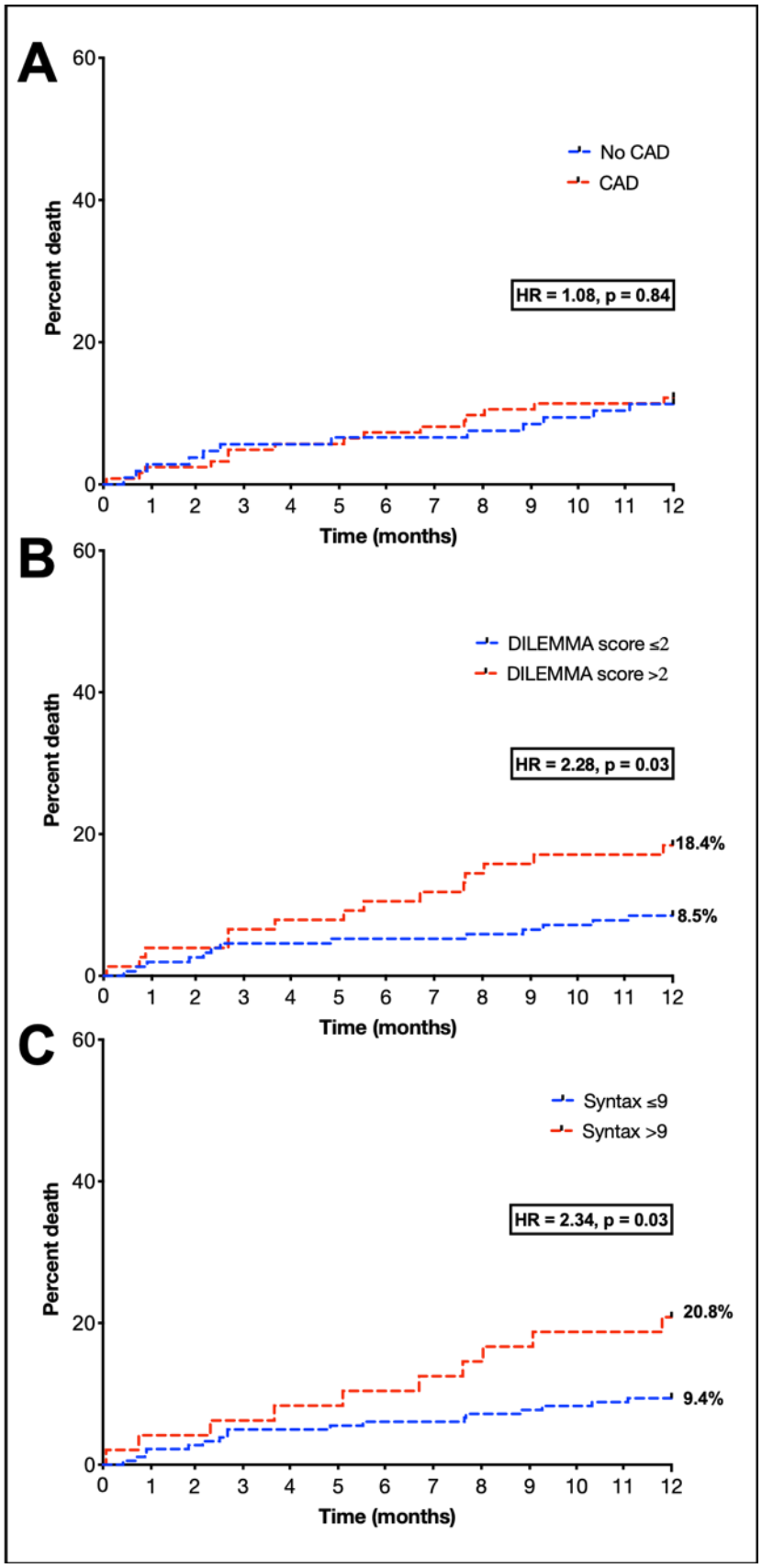
Values are presented as n (%) or mean ± SD. AKI indicates acute kidney injury; AR, aortic regurgitation; DI, dimensionless index; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PPM, permanent pacemaker; VARC, Valve Academic Research Consortium

Primary and secondary endpoints

At 365 days post-TAVR, all-cause mortality was 11.8%. The Kaplan Meier curves demonstrating the differences in mortality stratified by the presence of CAD (defined ≥30% visual stenosis severity in any vessel), DS and SS are presented in **Figure 6-1**. Patients with CAD ≥30% visual stenosis severity in any vessel (not further quantified through angiographic scoring) did not have an increased risk of death (hazard ratio [HR]= 1.08, CI 0.51-2.31, p=0.84; **Figure 6-1A**). However, when stratifying using DS or SS, patients with significant CAD had greater mortality. After 365 days, DS>2 was associated with a significantly increased risk of death compared with DS≤2 (18.4% vs. 8.5%, HR= 2.28, CI 1.07-4.84 p= 0.03; **Figure 6-1B**). Similarly, a SS >9 was associated with a significantly increased risk of death compared with a SS ≤9 (20.8% vs 9.4%, HR 2.34, CI 1.07-5.11, p= 0.03; **Figure 6-1C**). Utilising a

Figure 6-1| Kaplan-Meier curves showing the effects of coronary artery disease (CAD) upon post-TAVR.

This demonstrates mortality as stratified by **(A)** the presence of CAD defined by ≥30% stenosis in ≥1 vessel, **(B)** DILEMMA score and **(C)** SYNTAX score.



multivariate Cox proportional hazards regression model, DS>2 maintained a significant effect on survival after adjusting for age, BMI, gender, previous PCI, LVEF<50% and COPD (adjusted HR 2.29, CI 1.05-4.99 p = 0.04). After multivariate adjustment using the same variables, SS >9 was no longer predictive of mortality (adjusted HR 1.87, CI 0.82-4.22, p= 0.13).

The post-procedural 30-day outcomes are summarised in **Table 6-3**. At 30 days, the unadjusted risk for MACCE was greater for patients whether stratified by DS>2 (OR 2.1, p = 0.03) or by SS >9 (OR 2.8, p = 0.01). Individually, the unadjusted risk for the clinical endpoints of spontaneous MI, stroke, TIA and death were not greater at 30 days when stratified by either SS >9 or DS>2. However, heart failure admissions at 30 days were greater in patients with SS>9 (OR 4.50, CI 1.54-12.9), p<0.001).

Table 6-3 | 30-day outcomes

	DILEMMA score ≤2	DILEMMA score >2	p value	SYNTAX score ≤9	SYNTAX score >9	p value
Spontaneous MI	3 (2.0)	0 (0)	0.219	3 (2.0)	0 (0)	0.370
Stroke and TIA	6 (3.9)	7 (9.2)	0.103	9 (5.0)	4 (8.3)	0.371
Death	3 (2.0)	3 (4.0)	0.375	4 (2.2)	2 (4.1)	0.451
HF admissions	10 (6.5)	10 (13.2)	0.095	10 (5.5)	10 (20.8)	0.001
MACCE	21 (13.7)	19 (25.0)	0.034	25 (13.8)	15 (31.3)	0.005

Values are presented as n (%). Major adverse cardiac and cerebrovascular events (MACCE) included spontaneous myocardial infarction (MI), stroke, transient ischaemic attack (TIA), heart failure (HF) admissions and all-cause death at 30 days.

Other predictors of mortality

The univariate analysis for the covariates associated with adverse outcomes are presented in **Table 6-4** and **Figure 6-2**. Neither diabetes (HR 0.73, CI 0.25-2.1, p= 0.56) nor hypertension (HR 0.94, CI 0.41-2.15, p= 0.89) demonstrated any association with death. There was a trend to increased mortality in patients with LVEF <50% (HR 2.34, CI 0.95-5.81, p = 0.07) and COPD (HR= 2.14, CI 0.98-4.68, p= 0.06) although these did not reach statistical significance. Along with DS >2, both LVEF <50% (HR 2.66, CI 1.03-6.72, p = 0.04) and COPD (HR 2.43, CI 1.04-5.68, p= 0.04) were found to be predictors of mortality

following TAVR after multivariate adjustment. Additionally, within the subgroup of patients with LVEF>50%, those with DS >2 were still at increased risk of mortality (HR= 2.75, CI 1.16-6.54, p=0.02). These findings suggest that mortality was not being driven only by patients with impaired left ventricular function. The subgroup analysis showing the effect of DS >2 and SS >9 on the individual covariates is presented in **Table 6-5**.

Table 6-4 | Univariate analysis			
Variable	**HR**	**CI**	**p value**
[*]Age	1.044	0.97-1.12	0.248
[ɣ]BMI	0.95	0.89-1.01	0.105
Male gender	1.84	0.85-3.96	0.120
Self-Expanding Valve	0.88	0.40-1.92	0.742
Diabetes	0.73	0.25-2.10	0.556
HTN	0.94	0.41-2.15	0.890
Previous CVA	0.54	0.13-2.28	0.402
Previous MI	2.21	0.66-7.33	0.197
Previous PCI	1.13	0.43-2.99	0.800
COPD	2.14	0.98-4.68	0.056
[z]Creatinine	1.00	0.99-1.01	0.447
LVEF <50%	2.34	0.95-5.81	0.066
DS >2	2.28	1.07-4.84	0.033
SS >9	2.34	1.07-5.11	0.033
CAD (≥30% in at least one vessel)	1.08	0.51-2.31	0.840

Independent predictors of post–transcatheter aortic valve replacement mortality. Hazard ratio (HR) and 95% confidence interval (CI). [*]per one-year increase; [ɣ]per 1 kg/cm^2 increase, [z]per 1 µmol/L increase. BMI indicates body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DS, DILEMMA score; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SS, SYNTAX score

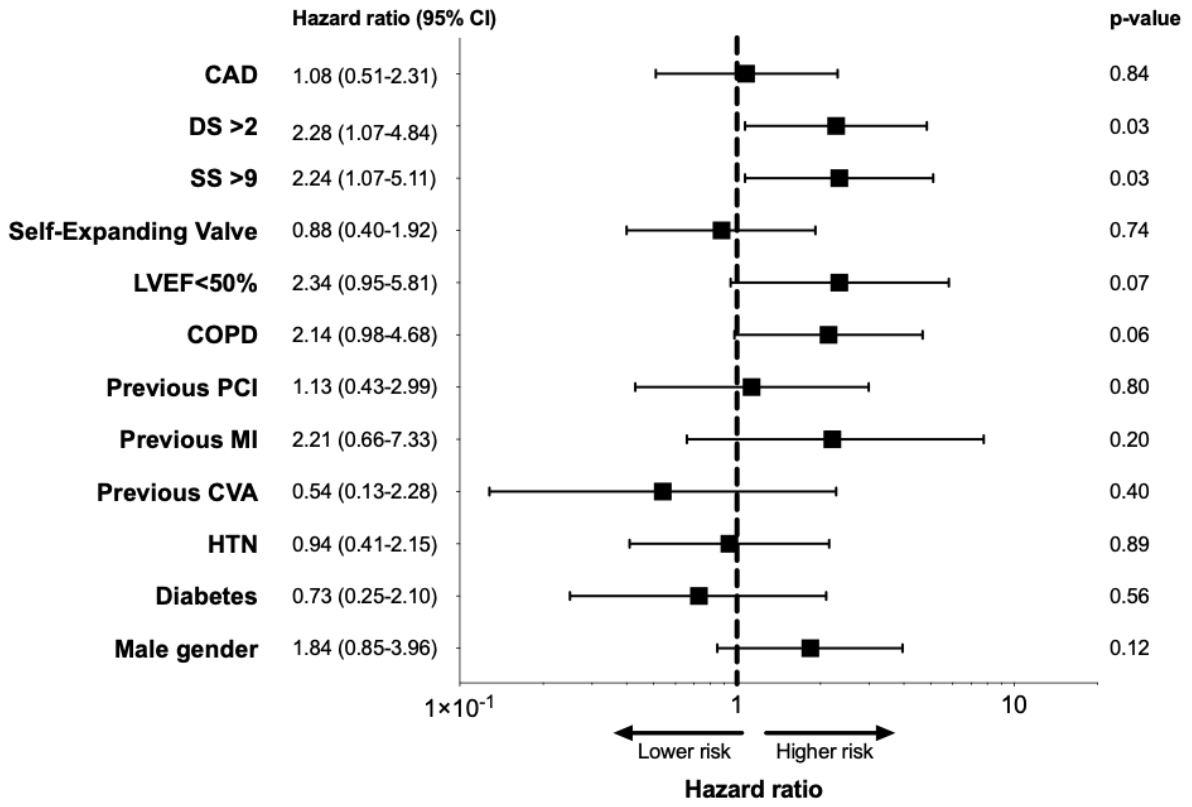


Figure 6-2 | The assessment of independent predictors of mortality following TAVR on univariate analysis.

Left ventricular ejection fraction (LVEF) <30% was the only variable identified to have impacted mortality. CAD indicates coronary artery disease (≥30% in at least one vessel); CI, confidence intervals; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DS, DILEMMA score, HTN, hypertension; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 6-5 | Subgroup analysis

Subgroup	DILEMMA score >2		SYNTAX score >9	
	HR	p value	HR	p value
Age>85	1.53 (CI 0.54-4.38)	0.423	1.27 (CI 0.36-4.50)	0.712
Diabetes Mellitus	1.11 (CI 0.31-3.99)	0.87	1.06 (CI 0.23-5.00)	0.939
Gender	2.35(CI 0.79-7.02)	0.125	1.85 (CI 0.48-7.16)	0.373
Self-expanding valve	2.30 (CI 0.80-6.63)	0.123	0.93 (CI 0.26-3.31)	0.914
BMI*	0.70 (CI 0.16-3.13)	0.640	0.89 (CI 0.77-1.04)	0.154
Hypertension	1.22 (CI 0.34-4.39)	0.77	2.07 (CI 0.44-9.73)	0.359
COPD	2.99 (CI 1.05-8.55)	0.041	2.17 (CI 0.61-7.71)	0.231
LVEF<50%	1.60 (CI 0.36-7.15)	0.538	1.97 (CI 0.51-7.63)	0.325

Subgroup analysis showing the effect of DS >2 and SS >9 on the individual covariates. Hazard ratio (HR) and 95% confidence interval (CI). *per 1 kg/cm^2 increase. BMI indicates body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction.

6.4. DISCUSSION

The findings from this study demonstrate that patients undergoing TAVR with CAD stratified by DS >2 or SS >9 were at greater risk of subsequent mortality. DS >2 remained an independent predictor of mortality even after adjustment for other variables known to predict outcome. Our study also demonstrates that patients stratified by both DS >2 or SS >9 are at higher risk of adverse outcomes as early as 30 days. These results therefore suggest that in patients undergoing TAVR, not only is the angiographic severity of CAD prognostically important, but also the functional significance of lesions. These findings importantly highlight that, similar to non-AS patients, lesions most likely to be ischemia-inducing are prognostically significant.

Whilst SS quantifies the extent and severity of CAD, it provides no information on the functional impact of the disease upon the myocardium it subtends. In patients without AS there is ample data to demonstrate that patients with large burden of ischaemia have worsened prognosis[161,162]. Furthermore, functional testing has a crucial prognostic significance in determining whether revascularization is warranted[163,164]. As such, there has been a paradigm shift from anatomical to functional CAD assessment when making such decisions. This is now superior to angiographic-guided revascularization and is widely acknowledged as gold standard in clinical guidelines.[165]

In patients with severe AS, there are a number of pathophysiological changes that result in greater ischemic potential and impaired coronary flow reserve (CFR), even in the absence of CAD[17]. This includes the evolution of left ventricular hypertrophy in response to increased afterload, which increases resting myocardial oxygen demand. This is met with upregulation of resting coronary blood flow, mediated by decreased microcirculatory resistance. The ability to further increment coronary blood flow in response to additional demands (such as during exertion) is diminished by abnormal ventriculo-aortic physiology. This cascade of events makes patients with severe AS even more susceptible to ischemia than non-AS patients. The presence of functionally significant CAD in this

context further increases myocardial ischemic potential. This places these patients at greater risk of mismatch between oxygen supply and demand at times of physiological stress (type II myocardial infarction), which leads to myocardial necrosis. Various physiological stressors occur during TAVR procedures and can place patients at higher risk of such myocardial ischemic injury. This, for example, includes periods of hypotension during rapid pacing, valve positioning and deployment[166]. Given the known association between PPMI and adverse outcomes[159], it is therefore conceivable that this is one of the principle underlying mechanisms for poorer outcomes in those with higher DS undergoing TAVR as demonstrated herein. This is supported by data which has also shown that the presence of CAD increases the likelihood for PPMI and subsequent mortality in patients undergoing TAVR.[158]

This data suggests that the functional assessment of CAD allows the risk stratification of patients prior to TAVR. Consequently, it raises an important question as to whether revascularisation of functionally significant disease may decrease the risk of adverse events. There are several studies that have demonstrated the feasibility and safety of pressure wire assessment in patients with severe AS[105,109]. Whilst these are promising, there is ongoing debate regarding the most appropriate pressure index in such circumstances[109,167,168]. Several factors need to be considered including the safety of hyperaemic agents in severe AS versus use of non-hyperaemic pressure ratios. Additionally, there may be advantages to using a diastolic-only pressure ratio which may be better suited to the altered physiology[168]. Beyond the validation of these techniques, further research is warranted to investigate whether these technologies can better refine the selection of lesions for upfront revascularization. The NOTION-3 (NCT03058627) and FAITAVI (NCT03360591) randomised trials are currently underway to investigate the outcomes of upstream FFR-guided PCI in patients undergoing TAVR.

Study limitations

This is a single-centre, observational study and whilst we performed multivariate analyses to account for potential confounders, these results will be subject to other unmeasured influences. Despite

endeavours to ensure a completed database, there were some missing data items resulting in the exclusion of patients. Additionally, angiographic scoring tools such as the SS and DS are manually assessed. Nonetheless, in previous validation studies DS demonstrated excellent intra- and inter-operator reproducibility. Whilst SS can be susceptible to variability amongst inexperienced users, these issues were mitigated by using experienced cardiologists who were blinded to the outcomes. Finally, the DS is ultimately a surrogate for FFR and neither are validated in patients with severe AS. As such, further research is required to validate the appropriate conditions and thresholds for invasive pressure indices in this patient cohort.

6.5. CONCLUSIONS

Angiographic scoring tools that assess anatomical complexity and lesion physiological significance predict clinical outcomes following TAVR. However, only angiographic functional scoring remained independently associated with outcomes when adjusted for other clinical factors. Further research is now warranted to validate the use of invasive and non-invasive pressure-based indices in severe AS and their role in guiding upstream revascularisation prior to TAVR.

7. FEASIBILITY AND VALIDITY OF CT-DERIVED FRACTIONAL FLOW RESERVE IN PATIENTS WITH SEVERE AORTIC STENOSIS: THE CAST-FFR STUDY

This chapter is based on the published manuscript:

Michail M, Ihdayhid AR, Comella A, Thakur U, Cameron JD, McCormick LM, Gooley R, Nicholls SJ, Mathur A, Hughes AD, Ko BS, Brown AJ. Feasibility and validity of CT-derived fractional flow reserve in patients with severe aortic stenosis: the CAST-FFR study. *Circ Cardiovasc Interv.* DOI: 10.1161/CIRCINTERVENTIONS.120.009586.

Contribution:

I conceived the idea and designed the study. I completed the ethics application and recruited the patients. I performed a large proportion of the invasive FFR assessments. I performed the data analysis, statistical analysis and wrote the manuscript. The CT-FFR analysis was performed at a central core laboratory (HeartFlow, Inc, US). ARI helped adjudicate the co-registration of the angiographically acquired pressure wire sensor locations to that on the CT-FFR 3D model. AC helped adjudicate the FFR readings from the pressure wire tracings. UT provided assistance with statistical analysis. JDC, LMM, RG, SJN, AM, ADH and BSK contributed to the discussions in the manuscript. AJB assisted with the analyses, contributed to the discussions and provided overall supervision.

7.1. ABSTRACT

Background: Coronary artery disease (CAD) is common in patients with severe aortic stenosis (AS). Computed tomography-derived fractional flow reserve (CT-FFR) is a clinically-utilised modality for assessing CAD, however its use has not been validated in patients with severe AS.

Objectives: To assess the safety, feasibility and validity of CT-FFR in patients with severe AS.

Methods: Prospectively-recruited patients underwent standard-protocol invasive FFR and coronary CT angiography (CTA). CTA images were analysed by a central core laboratory (HeartFlow, Inc., US) for independent evaluation of CT-FFR. CT-FFR data were compared with FFR (ischaemia defined as FFR≤0.80).

Results: 42 patients (68 vessels) underwent FFR and CTA; 39 patients (92.3%) and 60 vessels (88.2%) had interpretable CTA enabling CT-FFR computation. Mean age was 76.2±6.7 years (71.8% male). No patients incurred complications relating to pre-medication, CTA or FFR protocol. Mean FFR and CT-FFR were 0.83±0.10 and 0.77±0.14, respectively. CT calcium score was 1373.3±1392.9. On per vessel analysis, there was strong positive correlation between FFR and CT-FFR (Pearson's R=0.64, p<0.0001). The sensitivity, specificity, positive predictive and negative predictive values were 73.9%, 78.4%, 68.0% and 82.9%, respectively with 76.7% diagnostic accuracy. The area under the receiver-operating characteristic curve (ROC AUC) for CT-FFR was 0.83 (0.72-0.93, p<0.0001), which was significantly higher than that of CTA and QCA (p=0.01 and p<0.001, respectively). Bland-Altman plot showed mean bias between FFR and CT-FFR as 0.059±0.110. On per patient analysis, the sensitivity, specificity, positive predictive and negative predictive values were 76.5%, 77.3%, 72.2% and 81.0% with 76.9% diagnostic accuracy. The per-patient ROC AUC was 0.81 (0.67-0.95, p<0.0001).

Conclusions: CT-FFR is safe and feasible in patients with severe AS. Our data suggests a good diagnostic accuracy of CT-FFR and provides the foundation for future research into the use of CT-FFR for coronary evaluation pre-AVR.

7.2. INTRODUCTION

Approximately 25-50% of patients with severe AS have concomitant CAD [8-11]. Current guidelines recommend revascularization for patients undergoing TAVR with >70% diameter stenosis in proximal coronary segments and it is therefore common practice to perform prior invasive coronary angiography (ICA) [13]. In addition to revascularization decisions, ICA also serves as a means for procedural risk stratification. However, pre-TAVR ICA is associated with inherent risks, particularly in patients with severe AS whom are usually elderly and with comorbidities [169]. Additionally, ICA provides no information on the functional impact of coronary stenosis, which may be important further guiding revascularization decisions prior to TAVR [170]. Given the recognised limitations of ICA in this higher risk cohort, there remains an unmet need for a valid non-invasive alternative that identifies lesion-specific ischaemia.

Coronary computed tomography angiography (CTA) is a well-established non-invasive modality which is used in the diagnosis and management of patients with chest pain of recent onset. Its excellent negative predictive value makes it particularly useful in the assessment of patients with low to intermediate pre-test probability for CAD. Whilst it can provide clinically useful anatomical information regarding the presence and extent of CAD, it does not provide any data on the functional impact of coronary stenosis [171]. CT-derived fractional flow reserve (CT-FFR) is a more recent development which uses computational flow dynamics to simulate invasive fractional flow reserve (FFR) from a standard CTA acquisition [172]. CT-FFR now provides a mean for deriving both anatomy and function from a standard CTA and its high diagnostic performance has led to its adoption in clinical guidelines[173].

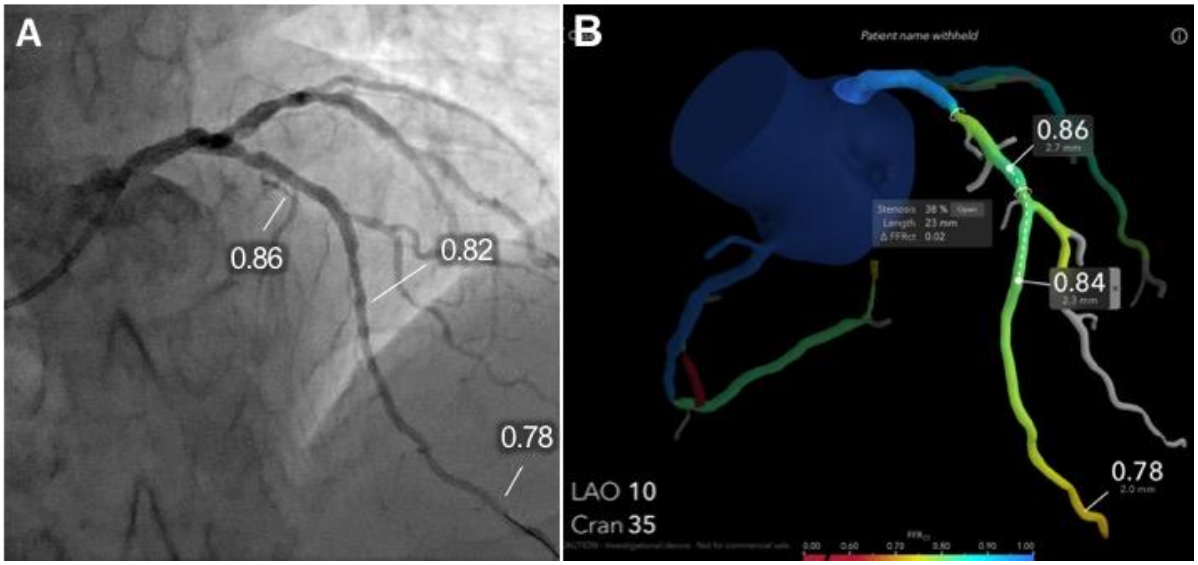
The use of coronary CTA has previously been explored in patients with severe AS [174,175]. However, the application of this technology has been limited by the higher burden of calcium within the coronary vasculature in addition to clinicians' reluctance to use pre-scan medications to optimize image quality

(such as nitroglycerin and beta-blockers). However, recent advances and refinements in image-processing techniques have enabled the use of CTA in patients with higher burden of calcium. Improved imaging acquisition in this cohort also permits the possibility of CT-FFR modelling, which provides incremental functional data. However, CT-FFR has not been previously evaluated in the coronary assessment of patients with severe AS.

We therefore designed and conducted a prospective trial to assess the clinical safety, feasibility and diagnostic performance of CT-FFR in patients with severe AS, compared against invasively derived FFR.

Figure 7-1| A representative case example

(A) invasive coronary angiography with FFR pressure wire assessment of the left anterior descending artery and **(B)** CT coronary angiography with CT-derived FFR co-registered at the same anatomical locations. *Figure from MonashHeart data.*



7.3. RESULTS

42 patients (68 vessels) underwent invasive FFR and CTA assessment (**Figure 3-5**). Of those, 39 patients (92.3%) and 60 vessels (88.2%) had interpretable CTA data enabling CT-FFR computation. Three patients (6 vessels) were not suitable for CT-FFR calculation due to motion artefact on CTA as adjudicated by the central core laboratory. Additionally, 2 vessels were excluded as they could not be

co-registered as the angiographic pressure wire sensor location was distal to the 3D modelled segment. The patient and echocardiographic characteristics are presented in **Table 7-1**. The mean age was 76.2 ± 6.7 years of whom 71.8% were male, 69.2% had hypertension, 53.8% had diabetes mellitus and 12.8% had previous myocardial infarction. Mean aortic valve gradient, aortic valve area and left ventricular ejection fraction were 45.1 ± 9.5mmHg, 0.89 ± 0.25 cm2 and 62.9 ± 10.7%, respectively. Mean patient CT calcium score was 1373.3 ± 1392.9 Agatston units.

Table 7-1 | Patient and echocardiographic characteristics	
Patient characteristics (n = 39)	
Age, yrs	76.2 ± 6.7
Male	28 (71.8)
Body mass index, kg/m²	28.6 ± 6.7
Diabetes mellitus	21 (53.8)
Hypertension	27 (69.2)
Atrial fibrillation	4 (10.3)
Previous MI	5 (12.8)
Dyslipidemia	26 (66.7)
Previous CVA or TIA	5 (12.8)
Smoking	
Current smoker	2 (5.1)
Former smoker	14 (35.9)
Creatinine, mmol/L	90.5 ± 27.2
Total patient calcium score (Agatston units) **Mean ± SD** **Median**	 1373.3 ± 1392.9 1027
Pre-procedural echocardiographic parameters	
LVEF, %	62.9 ± 10.7
Peak gradient, mmHg	75.3 ± 15.9
Mean gradient, mmHg	45.1 ± 9.5
Valve Area, cm²	0.89 ± 0.25
Dimensionless index	0.23 ± 0.04

Values are presented as n (%) or mean ± SD; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

The CT scanning characteristics are presented in **Table 7-2**. All patients received 0.4mg sublingual glyceryl trinitrate. Two-thirds of patients received additional pre-scan medications in order to optimize their heart rate. Mean pre-CTA scan heart rate was 54.2 ± 6.6 beats/min. No patients incurred complications relating to the pre-medication, CTA or invasive FFR protocol.

Table 7-2 | CT scan acquisition characteristics	
CT characteristics	**(n = 39)**
Heart rate, beats/min	54.2 ± 6.6
Nitrates administered	39 (100)
Pre-scan beta-blocker use	
Oral	26 (66.7)
Intravenous	1 (2.6)
Beta-blocker dose, mg (SD)	
Oral metoprolol	78.8 ± 49.3
Intravenous metoprolol	20 ± 0
Ivabradine (10 mg) use	16 (41.0)
Tube voltage, kV	
100	12 (30.8)
120	27 (69.2)
Tube current, mA	663.3 ± 123.1
Radiation exposure (mSv), (SD)	13.1 ± 8.3
CT protocol A (n=23)	17.1 ± 6.7
CT protocol B (n=16)	7.3 ± 6.8

Values are presented as n (%) or mean ± SD

The vessel characteristics are presented in **Table 7-3**. Of the vessels assessed, 36 were left anterior descending arteries, 5 were diagonal, 13 were circumflex or obtuse marginal, 1 was a ramus and 5 were right coronary arteries. On quantitative coronary angiography (QCA), 10.0% of vessels and 15.4% of patients had diameter stenosis ≥50%. On coronary CTA analysis, 35.0% of vessels and 41.0% of patients had CTA diameter stenosis ≥50%. Mean FFR and CT-FFR were 0.83 ± 0.10 and 0.77 ± 0.14, respectively. 38.3% of vessels had an FFR ≤0.80 whilst 41.7% of vessels had CT-FFR ≤0.80.

Per vessel analysis

The diagnostic performance of QCA, coronary CTA and CT-FFR against FFR are presented in **Table 7-4**. On a per vessel basis, there was a strong positive correlation between FFR and CT-FFR (Pearson's rank R=0.64, p<0.0001, **Figure 7-2**). Sensitivity, specificity, positive predictive and negative predictive values were 73.9%, 78.4%, 68.0% and 82.9%, respectively with overall diagnostic accuracy of 76.7% (**Figure 7-3**). The ROC AUC for CT-FFR was 0.83 (95% confidence interval [CI] 0.72-0.93, p<0.0001). The Bland-Altman plot showed the mean bias ± standard deviation between FFR and CT-FFR was 0.059 ± 0.110 (**Figure 7-4**). The ROC AUC for CT-FFR to predict invasive FFR was greater than that of coronary CTA and QCA (both p<0.05).

Table 7-3 | Vessel characteristics	
Variable	
Vessels studied	
LAD or diagonal	41 (68.3)
Cx or OM	13 (21.7)
Ramus intermedius	1 (1.7)
RCA, PDA or R-PLV	5 (8.3)
QCA	
Mean diameter stenosis, %	33.8 ± 12.0
Mean area stenosis, %	54.8 ± 14.2
Number of vessels with diameter stenosis ≥50%	6/60 (10.0)
Number of patients with diameter stenosis ≥50%	6/39 (15.4)
Number of vessels with area stenosis ≥50%	35/60 (58.3)
Number of patients with area stenosis ≥50%	26/39 (66.7)
Coronary CTA	
Number of vessels with CTA maximum stenosis ≥50%	21 (35.0)
Number of patients with CTA maximum stenosis ≥50%	16 (41.0)
Mean FFR	0.83 ± 0.10
Vessels with FFR ≤0.80	23/60 (38.3)
Patients with FFR ≤0.80	17/39 (43.6)
Mean CT-FFR	0.77 ± 0.14
Vessels with CT-FFR ≤0.80	25/60 (41.7)
Patients with CT-FFR ≤0.80	18/39 (46.1)

Values are presented as n (%) or mean ± SD; CTA, CT computed tomography angiography; CT-derived fractional flow reserve; Cx, circumflex; FFR, fractional flow reserve; LAD, left anterior descending; OM, obtuse marginal; PDA, posterior descending artery; QCA, quantitative coronary angiography; RCA, right coronary artery; R-PLV, right posterior left ventricular.

Per-patient analysis

On a per-patient analysis, there again was a strong positive correlation between FFR and CT-FFR (Pearson's rank 0.70, p<0.0001). Sensitivity, specificity, positive predictive and negative predictive values were 76.5%, 77.3%, 72.2% and 81.0% with overall diagnostic accuracy of 76.9%. On a per-patient analysis, the ROC AUC for CT-FFR was 0.81 (CI 0.67-0.95, p = 0.001). The Bland-Altman plot showed the mean bias ± standard deviation between FFR and CT-FFR was 0.064 ± 0.110.

Figure 7-2 | Correlations of CT-FFR vs FFR on a per-vessel and per-patient basis

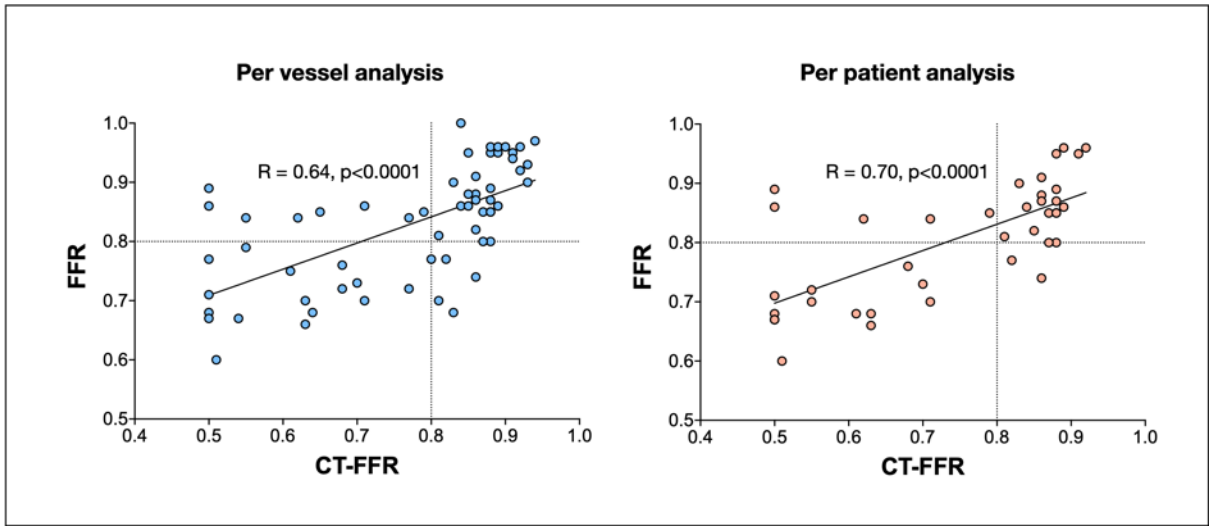


Figure 7-3 | Diagnostic performance on a per-vessel and per -patient basis

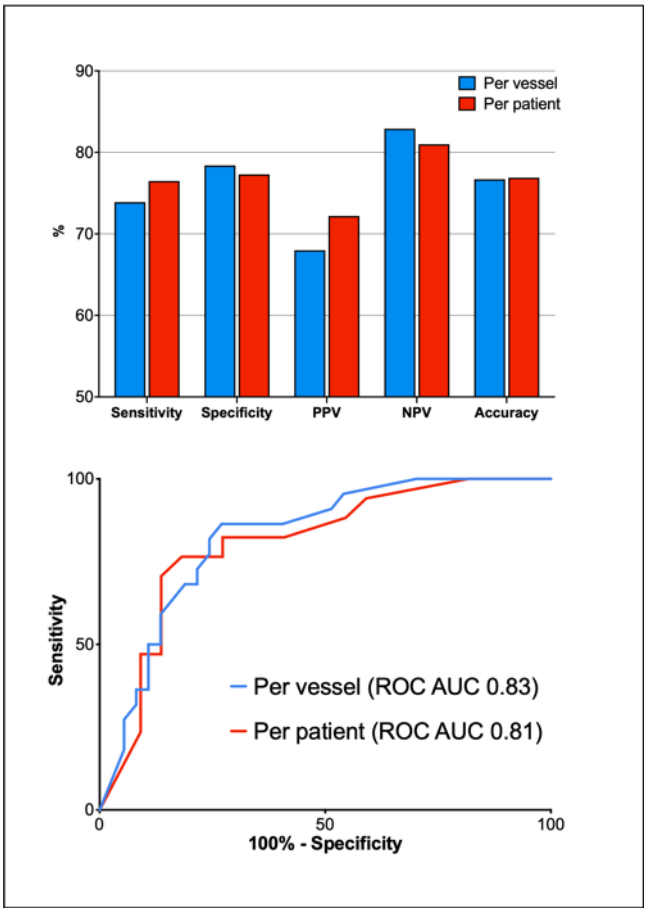
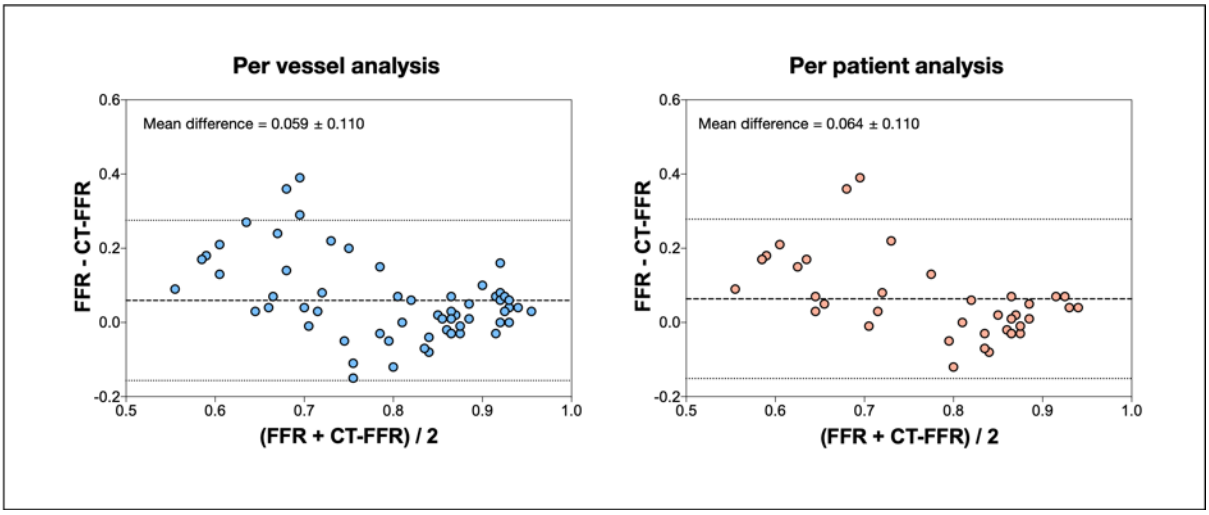


Table 7-4 | Diagnostic performance of CT-FFR, coronary CTA and QCA against invasive FFR				
	Per vessel analysis			Per patient analysis
	CT-FFR	CCTA (>50%)	QCA (>50%)	CT-FFR
Pearson's correlation coefficient	0.64, p<0.0001	N/A	N/A	0.70, p<0.0001
True positive	17	12	4	13
False positive	8	9	2	5
True negative	29	28	35	17
False negative	6	11	19	4
Sensitivity %	73.9	52.2	17.4	76.5
Specificity %	78.4	75.7	94.6	77.3
PPV %	68.0	57.1	66.7	72.2
NPV %	82.9	71.8	64.8	81.0
Accuracy %	76.7	66.7	65.0	76.9
ROC AUC (95% CI) Comparison against ROC AUC for CT-FFR to predict FFR	0.83 (0.72-0.93)	0.64 (0.51.-0.76) p = 0.01	0.56 (0.47-0.65) p <0.001	0.81 (0.67 to 0.95)
Bland-Altman analysis (mean bias ± SD)	0.059 ± 0.110 (-0.16-0.27)	N/A	N/A	0.064 ± 0.110 (-0.15-0.28)

Values are presented as n (%) or mean ± SD. CCTA, coronary computed tomography angiography; NPV, negative predictive value; PPV, positive predictive value; ROC AUC, area under the receiver-operating characteristic curve

Figure 7-4 | Bland-Altman (difference versus average) of FFR vs CT-FFR



Subgroup analysis

A subgroup analysis was performed to look at the diagnostic performance of CT-FFR according to the magnitude of the CT-derived calcium score. This was on a per vessel and per patient basis and the results are presented in **Tables 7-5** and **7-6**, respectively and in **Figure 7-5**. In the per vessel subgroup analysis, the mean vessel calcium scores in the low and high groups were 123.1 ± 94.2 and 735.3 ± 566.5 Agatston units, respectively. The correlation between CT-FFR and FFR in the low calcium score group was stronger (r = 0.85 vs 0.61), however there was no difference between the ROC AUC for CT-FFR between the two groups (0.83 vs 0.82, p = 0.94). In the per patient 2277.1 ± 1518.7, respectively. Similarly, the correlation between CT-FFR and FFR was stronger in the low calcium score group (r=0.85 vs r=0.61), however with no difference between the ROC AUC for CT-FFR between the two groups (0.77 vs. 0.80, p = 0.84).

Figure 7-5 | Subgroup analysis of diagnostic performance of CT-FFR according to CT calcium score

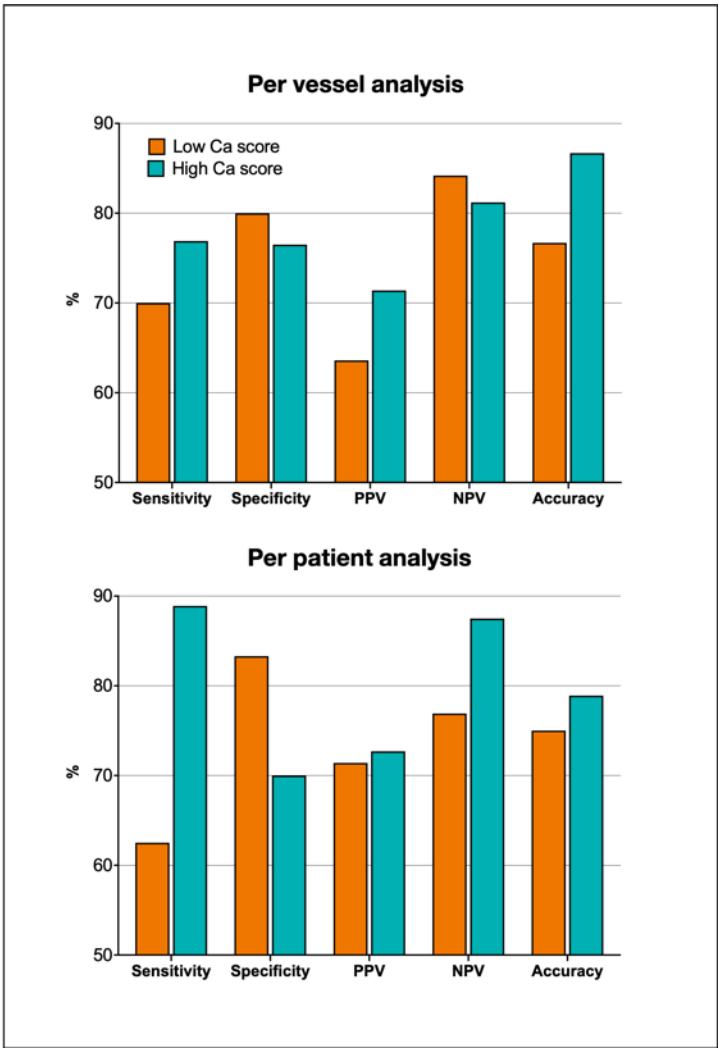


Table 7-5 | Per vessel subgroup analysis of the diagnostic performance CT-FFR according to CT calcium score			
	Low calcium score	**High calcium score**	**p value**
n	**30**	**30**	
Mean calcium score, Agatston units	123.1 ± 94.2	735.3 ± 566.5	
Pearson's rank	0.85, p<0.0001	0.61, p = 0.0004	
True positive	7	10	
False positive	4	4	
True negative	16	13	
False negative	3	3	
Sensitivity %	70.0	76.9	
Specificity %	80.0	76.5	
PPV %	63.6	71.4	
NPV %	84.2	81.2	
Accuracy %	76.7	86.7	
ROC AUC (95% CI)	0.83 (0.67-0.98)	0.82 (0.66-0.99)	0.94

Values are presented as n (%) or mean ± SD. NPV; negative predictive value; PPV, positive predictive value; ROC AUC, area under the receiver-operating characteristic curve.

Table 7-6 | Per patient subgroup analysis of diagnostic performance of CT-FFR according to total CT Ca score			
	Low calcium score	**High calcium score**	**p value**
n	**20**	**19**	
Mean calcium score, Agatston units	514.8 ± 320.3	2277.1 ± 1518.7	
Pearson's rank	0.82 p<0.0001	0.63, p = 0.0037	
True positive	5	8	
False positive	2	3	
True negative	10	7	
False negative	3	1	
Sensitivity %	62.5	88.9	
Specificity %	83.3	70.0	
PPV %	71.4	72.7	
NPV %	76.9	87.5	
Accuracy %	75.0	78.9	
ROC AUC (95% CI)	0.77 (0.52-1.0)	0.80 (0.58-1.0)	0.84

Values are presented as n (%) or mean ± SD. NPV; negative predictive value; PPV, positive predictive value; ROC AUC, area under the receiver-operating characteristic curve.

7.4. DISCUSSION

Our findings demonstrate that coronary CTA and CT-FFR is safe, feasible and has a high diagnostic accuracy in patients with severe AS. These results represent significant progress in the non-invasive assessment of the CAD in patients with severe AS. Despite the well-recognised limitations of using coronary CTA in older patient cohorts with greater burden of coronary vascular calcification, we have demonstrated that in this cohort – older and with a notably high average calcium score – a high diagnostic accuracy can be attained using CT-FFR using the protocols described. Importantly, 93% of our cohort had interpretable data highlighting the potential for future translation into clinical practice.

Several strategies were devised in order to achieve these results. Besides the use of a 320-slice detector CT scanner, we utilised CT-FFR modelling for better characterization and assessment of the vessels to overcome the inherent limitations in the diagnostic performance of CTA alone in the presence of calcified disease. Additionally, we adhered to a strict pre-scanning medication protocol in order to optimize image quality. This approach has traditionally been avoided in patients with severe AS due to concerns with hypotension and circulatory collapse. In our study, we ensured all patients were well hydrated prior to drug administration. Nitroglycerin was administered both prior to coronary CTA and invasive FFR measurements. Beta-blockers and ivabradine were used pre-CTA to attain a heart rate of <60 beats/min, which was achieved in 79% of patients. During invasive FFR, intravenous adenosine was used in all patients and there were no adverse effects relating to medication protocols used in our cohort. Whilst complete atrioventricular block remains a greater risk with adenosine in this patient group, a previous report demonstrated preserved coronary haemodynamics despite systemic hypotension in a patient with severe AS [166]. Despite no adverse outcomes in our cohort, we are unable to quantify the risk for every patient with severe AS and this would need evaluation in further studies, comparing this strategy against the risk of invasive procedures currently used as standard of care.

The use of coronary CTA in patients with severe AS undergoing TAVR has previously been investigated in two retrospective studies [174,175]. In these studies, drugs for vasodilatation and chronotropic control were not used due to concerns about safety. These medications are otherwise recommended for improving the diagnostic performance of CTA, particularly in older patients with significant and calcified CAD [176]. In one of these studies, 18% of the patients underwent ICA as they were deemed to have significant or uninterpretable disease (excluding those who had undergone ICA for another indication) [175]. Of those, more than half the patients had no significant disease on ICA with only a proportion of the remainder (4.5% of the study cohort) undergoing subsequent revascularization. In the second study, all patients underwent ICA following CTA [174]. Whilst the diagnostic accuracy of CTA was 91% in patients with Agatston scores of <400, the overall accuracy was only 66% in those with Agatston scores >1000. These two studies concluded that the use of coronary CTA in this setting is potentially acceptable in patients with lower calcium scores, with CTA acting as a possible gatekeeper for ICA. Notably, these two studies evaluate CTA diagnostic performance against ICA rather than invasive FFR. In our study, the diagnostic performance of CTA (compared with invasive FFR) demonstrates that the use of this technology – even with strict pre-scanning medication protocols – may be inadequate, even as a gatekeeper for ICA. The use of CT-FFR modelling provides an increment in diagnostic performance and, importantly, this is maintained in both the lower and higher calcium score groups.

It is key to acknowledge that the overall diagnostic performance of CT-FFR in this severe AS cohort remains lower than that in previously published literature in non-AS, stable CAD cohorts [177,178]. Compared to our participants, patients in previous studies were younger and with less coronary calcification. However, the performance of CT-FFR is acceptable in those with high calcium scores and this alone is unlikely to account for all the discrepancy observed. Another contributing factor may be the altered coronary and microcirculatory pathophysiology that occurs in patients with severe AS [17].

Valvular stenosis results in pressure overload within the left ventricle and resultant left ventricular hypertrophy. The greater myocardial mass of patients with AS results in increased resting myocardial oxygen demand which is matched with greater resting coronary blood flow. AS patients also exhibit an impaired coronary hyperaemic response. This blunted response is not currently accounted for using standard CT-FFR modelling approaches. These factors may explain the relative overestimation of translesional gradients by CT-FFR compared with invasive FFR. Further work is now required in describing the abnormal coronary physiology in differing patient cohorts, with the aim of improving the accuracy of CT-FFR and other techniques that use computational fluid dynamic approaches.

The ability to use coronary CTA and CT-FFR to appropriately delineate the anatomy opens the opportunity to using CT as a 'one-stop-shop' assessment for patients referred for TAVR. Currently, these patients routinely undergo CTA for pre-TAVR procedural planning for assessment of the left ventricular outflow tract, annulus, ascending and descending aorta and peripheral vasculature [179]. Routinely incorporating coronary assessment within this scan would permit comprehensive pre-TAVR assessment in a single scan, which has clear potential benefit for patients. This would potentially include, (1) completely removing the procedural risks associated with ICA, (2) reducing the risk of nephropathy associated with the additional contrast load of ICA, (3) reducing the discomfort associated with invasive procedures, (4) shortening the diagnostic journey for patients ahead of TAVR and (5) health-economic advantages associated with fewer invasive tests. Hopefully our data acts as a stimulus for definitive clinical trials that assess the use CT-FFR in procedural planning for patients undergoing TAVR.

Limitations

This a single-centre study designed to assess the safety, feasibility and early validity of a non-invasive CT-FFR approach in and ongoing validation in a larger, multi-centre study is required. With a mean age of 76.2 years, our cohort represents a younger age group than that would currently be undergoing

TAVR and it is unclear whether these results can be extrapolated into very elderly patients (>90yrs). However, with expanding indications of TAVR in low and intermediate surgical risk groups, our results may still apply in future patient cohorts. In addition, our subgroup analysis demonstrated that the diagnostic performance of this technology was maintained in patients with higher calcific burden although. Our trial also excludes patients who have had previous revascularization (either by CABG or PCI) and LV dysfunction, which represent a sizeable group of patients undergoing TAVR. Finally, the results from this study relate to one commercially available CT-FFR technique and the validity of other non-invasive techniques remains unknown.

7.5. CONCLUSIONS

Our results demonstrate that CT-FFR is feasible and safe in patients with severe AS. These preliminary data suggest a good diagnostic accuracy of CT-FFR, compared with invasive FFR. These data should act as the foundation for future research into use of CT-FFR during procedural planning for patients with severe AS undergoing valve replacement.

8. SUMMARY

8.1. SUMMARY OF FINDINGS

The studies in this thesis present several key findings.

- Firstly, the implantation of valve prostheses during TAVR results in the immediate elevation of central aortic pressures. This is predominantly due to increased excess pressure and is consistent with improved transvalvular energy profiles seen on wave intensity analyses. These haemodynamic changes are likely responsible for improved organ and myocardial perfusion.
- Other previously identified factors contributing to myocardial ischaemia in severe AS include endothelial dysfunction. The eFAST study demonstrates that endothelial function in patients with severe AS improves early following TAVR and this improvement is sustained at late follow up. Whilst these changes are likely in response to immediate improved arterial haemodynamics from relieving valvular obstruction, there is also evidence of late normalisation of physiology including lowering of WSS. These changes likely contribute to alleviating myocardial ischaemia.
- Myocardial ischaemia in patients with severe AS is further exacerbated by CAD. In patients undergoing TAVR, angiographic scoring tools that assess anatomical complexity and lesion physiological significance can predict clinical outcomes following TAVR. Importantly, only angiographic physiological scoring remained independently associated with mortality when adjusted for other clinical factors. This suggests that functionally significant CAD is important for risk stratification but may offer a therapeutic focus for improving outcomes via upstream revascularisation.
- The CAST-FFR study demonstrates that the use of CT-FFR in patients with severe AS provides a novel, feasible and safe method for assessing the coronary vasculature in patients under consideration for TAVR. Besides the ability to delineate anatomy, this technique provides data on the functional impact of coronary disease. Importantly, this technique is non-invasive, and can be incorporated into current standard-of-care pre-TAVR CT assessments to provide a one-stop-shop

scan. This study provides the foundation for future research into use of CT-FFR during procedural planning for patients with severe AS undergoing valve replacement.

8.2. FUTURE DIRECTIONS

As treatments for AS continue to evolve, ongoing research aims to better understand the disease itself and therapies for the disease. The ongoing validation of CT-FFR in patients with severe AS undergoing TAVR is essential to provide the requisite data that may allow its routine clinical use. This validation is required in a larger clinical trial to evaluate outcomes against the current standard of care.

Central haemodynamics and blood pressure post-TAVR remain a largely unexplored area. Increased blood pressure post-TAVR is common and, as demonstrated, likely related to increased excess pressure and improved transvalvular energy profiles. It is increasingly evident that persistent hypertension post-TAVR offers a beneficial physiological state, yet these patients are often managed with conventional blood pressure targets. Further work is now required to explore the ideal blood pressure targets in patients post-TAVR.

The effects of TAVR on the normalisation of physiology continues to be of interest within the research community. Our ongoing study in this area includes the 'Evaluation of COronary blood flow in patients with severe Aortic Stenosis treated with Transcatheter aortic valve replacement' (COAST study; (Australian New Zealand Clinical Trials Registry number ACTRN12618000403235). This multicentre study uses multimodality assessment in patients pre- and post-TAVR. The study follows up patients six months post-TAVR and aims to identify the determinants of CFR recovery with long term follow up.

A better understanding of the physiology in AS and post-TAVR may provide insights into important clinical conundrums, such as non-responders to treatment. Additionally, it may provide the required knowledge to better refine the technologies and outcomes. For example, it has been suggested that

the use of supra-annular valves reduces the chances of patient-prosthesis mismatch compared to intra-annular prostheses. However, their effect on post-TAVR coronary blood flow remain unexplored.

Further research needs to account for evolving methods and patient safety. Non-invasive physiological surrogates such as FMD, reservoir pressure analyses and pressure-only derived wave intensity analyses provide alternatives to traditional invasive methods such as directly measured intracoronary indices. Additionally, the evolving acquisition and image-processing techniques within cardiac CT and cardiac MRI provide novel and non-invasive methods to carry out such research.

8.3. CONCLUSIONS

Progressive AS results in maladaptations which contribute to abnormal ventriculoaortic physiology. These adversely impact coronary physiology and which impairs the ability its ability to upregulate coronary flow in response to increased demands, thus contributing to symptoms. TAVR is an increasingly used treatment modality which can provide relief of valvular obstruction. Its effects on organ, and particularly myocardial perfusion have been described in this thesis. Whilst many of these treatment benefits are observed early, normalisation to premorbid physiology may take several weeks, and potentially months. It is increasingly evident that CAD adversely impacts outcomes in these cohorts, and the hence, the validation of CT-FFR in patients with severe AS in the CAST-FFR trial provides an important foundation for further trials evaluating its use in pre-TAVR assessment.

9. REFERENCES

1 Bertazzo, S. *et al.* Nano-analytical electron microscopy reveals fundamental insights into human cardiovascular tissue calcification. *Nat Mater* **12**, 576-583, doi:10.1038/nmat3627 (2013).

2 Otto, C. M., Kuusisto, J., Reichenbach, D. D., Gown, A. M. & O'Brien, K. D. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. *Circulation* **90**, 844-853 (1994).

3 O'Brien, K. D. *et al.* Apolipoproteins B, (a), and E accumulate in the morphologically early lesion of 'degenerative' valvular aortic stenosis. *Arterioscler Thromb Vasc Biol* **16**, 523-532 (1996).

4 Ramos, J. *et al.* Large-scale assessment of aortic stenosis: facing the next cardiac epidemic? *Eur Heart J Cardiovasc Imaging*, doi:10.1093/ehjci/jex223 (2017).

5 Nkomo, V. T. *et al.* Burden of valvular heart diseases: a population-based study. *Lancet* **368**, 1005-1011, doi:10.1016/S0140-6736(06)69208-8 (2006).

6 Iung, B. & Vahanian, A. Degenerative calcific aortic stenosis: a natural history. *Heart* **98 Suppl 4**, iv7-13, doi:10.1136/heartjnl-2012-302395 (2012).

7 Ross, J., Jr. & Braunwald, E. Aortic stenosis. *Circulation* **38**, 61-67 (1968).

8 Exadactylos, N., Sugrue, D. D. & Oakley, C. M. Prevalence of coronary artery disease in patients with isolated aortic valve stenosis. *Br Heart J* **51**, 121-124 (1984).

9 Ortlepp, J. R., Schmitz, F., Bozoglu, T., Hanrath, P. & Hoffmann, R. Cardiovascular risk factors in patients with aortic stenosis predict prevalence of coronary artery disease but not of aortic stenosis: an angiographic pair matched case-control study. *Heart* **89**, 1019-1022 (2003).

10 Rapp, A. H., Hillis, L. D., Lange, R. A. & Cigarroa, J. E. Prevalence of coronary artery disease in patients with aortic stenosis with and without angina pectoris. *Am J Cardiol* **87**, 1216-1217; A1217 (2001).

11 Vandeplas, A., Willems, J. L., Piessens, J. & De Geest, H. Frequency of angina pectoris and coronary artery disease in severe isolated valvular aortic stenosis. *Am J Cardiol* **62**, 117-120 (1988).

12 Lund, O., Nielsen, T. T., Pilegaard, H. K., Magnussen, K. & Knudsen, M. A. The influence of coronary artery disease and bypass grafting on early and late survival after valve replacement for aortic stenosis. *J Thorac Cardiovasc Surg* **100**, 327-337 (1990).

13 Baumgartner, H. *et al.* 2017 ESC/EACTS Guidelines for the management of valvular heart disease: The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*, doi:10.1093/eurheartj/ehx391 (2017).

14 Parker, K. H. & Jones, C. J. Forward and backward running waves in the arteries: analysis using the method of characteristics. *J Biomech Eng* **112**, 322-326 (1990).

15 Sun, Y. H., Anderson, T. J., Parker, K. H. & Tyberg, J. V. Wave-intensity analysis: a new approach to coronary hemodynamics. *J Appl Physiol (1985)* **89**, 1636-1644 (2000).

16 Davies, J. E. *et al.* Evidence of a dominant backward-propagating "suction" wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation* **113**, 1768-1778, doi:10.1161/CIRCULATIONAHA.105.603050 (2006).

17 Michail, M., Davies, J. E., Cameron, J. D., Parker, K. H. & Brown, A. J. Pathophysiological coronary and microcirculatory flow alterations in aortic stenosis. *Nat Rev Cardiol* **15**, 420-431, doi:10.1038/s41569-018-0011-2 (2018).

18 Hadjiloizou, N. *et al.* Differences in cardiac microcirculatory wave patterns between the proximal left mainstem and proximal right coronary artery. *Am J Physiol Heart Circ Physiol* **295**, H1198-H1205, doi:10.1152/ajpheart.00510.2008 (2008).

19 Komaru, T., Kanatsuka, H. & Shirato, K. Coronary microcirculation: physiology and pharmacology. *Pharmacol Ther* **86**, 217-261 (2000).

20 Brown, A. J. *et al.* Role of biomechanical forces in the natural history of coronary atherosclerosis. *Nature reviews. Cardiology*, doi:10.1038/nrcardio.2015.203 (2016).

21 Gould, K. L., Lipscomb, K. & Hamilton, G. W. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol* **33**, 87-94 (1974).

22 Vorobtsova, N. *et al.* Effects of Vessel Tortuosity on Coronary Hemodynamics: An Idealized and Patient-Specific Computational Study. *Ann Biomed Eng* **44**, 2228-2239, doi:10.1007/s10439-015-1492-3 (2016).

23 Tonino, P. A. *et al.* Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* **360**, 213-224, doi:10.1056/NEJMoa0807611 (2009).

24 Pijls, N. H. *et al.* Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation* **92**, 3183-3193 (1995).

25 van de Hoef, T. P. *et al.* Fractional flow reserve as a surrogate for inducible myocardial ischaemia. *Nat Rev Cardiol* **10**, 439-452, doi:10.1038/nrcardio.2013.86 (2013).

26 Sen, S. *et al.* Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol* **59**, 1392-1402, doi:10.1016/j.jacc.2011.11.003 (2012).

27 Davies, J. E. *et al.* Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med* **376**, 1824-1834, doi:10.1056/NEJMoa1700445 (2017).

28 Mandal, A. B. & Gray, I. R. Significance of angina pectoris in aortic valve stenosis. *Br Heart J* **38**, 811-815 (1976).

29 Basta, L. L., Raines, D., Najjar, S. & Kioschos, J. M. Clinical, haemodynamic, and coronary angiographic correlates of angina pectoris in patients with severe aortic valve disease. *Br Heart J* **37**, 150-157 (1975).

30 Hakki, A. H. *et al.* Angina pectoris and coronary artery disease in patients with severe aortic valvular disease. *Am Heart J* **100**, 441-449 (1980).

31 Alyono, D., Anderson, R. W., Parrish, D. G., Dai, X. Z. & Bache, R. J. Alterations of myocardial blood flow associated with experimental canine left ventricular hypertrophy secondary to valvular aortic stenosis. *Circ Res* **58**, 47-57 (1986).

32 Marcus, M. L., Doty, D. B., Hiratzka, L. F., Wright, C. B. & Eastham, C. L. Decreased coronary reserve: a mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. *N Engl J Med* **307**, 1362-1366, doi:10.1056/NEJM198211253072202 (1982).

33 Eberli, F. R. *et al.* Coronary reserve in patients with aortic valve disease before and after successful aortic valve replacement. *Eur Heart J* **12**, 127-138 (1991).

34 Julius, B. K. *et al.* Angina pectoris in patients with aortic stenosis and normal coronary arteries. Mechanisms and pathophysiological concepts. *Circulation* **95**, 892-898 (1997).

35 Rolandi, M. C. *et al.* Transcatheter Replacement of Stenotic Aortic Valve Normalizes Cardiac-Coronary Interaction by Restoration of Systolic Coronary Flow Dynamics as Assessed by Wave Intensity Analysis. *Circ Cardiovasc Interv* **9**, e002356, doi:10.1161/CIRCINTERVENTIONS.114.002356 (2016).

36 Wiegerinck, E. M. *et al.* Impact of Aortic Valve Stenosis on Coronary Hemodynamics and the Instantaneous Effect of Transcatheter Aortic Valve Implantation. *Circ Cardiovasc Interv* **8**, e002443, doi:10.1161/CIRCINTERVENTIONS.114.002443 (2015).

37 Rajappan, K. *et al.* Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries. *Circulation* **105**, 470-476 (2002).

38 Gutierrez-Barrios, A. *et al.* Invasive assessment of coronary flow reserve impairment in severe aortic stenosis and ecochadiographic correlations. *Int J Cardiol* **236**, 370-374, doi:10.1016/j.ijcard.2017.01.150 (2017).

39 Bozbas, H. *et al.* Coronary flow reserve is impaired in patients with aortic valve calcification. *Atherosclerosis* **197**, 846-852, doi:10.1016/j.atherosclerosis.2007.07.036 (2008).

40 Nemes, A. *et al.* How can coronary flow reserve be altered by severe aortic stenosis? *Echocardiography* **19**, 655-659 (2002).

41 Garcia, D. *et al.* Impairment of coronary flow reserve in aortic stenosis. *J Appl Physiol (1985)* **106**, 113-121, doi:10.1152/japplphysiol.00049.2008 (2009).

42 Davies, J. E. *et al.* Arterial pulse wave dynamics after percutaneous aortic valve replacement: fall in coronary diastolic suction with increasing heart rate as a basis for angina symptoms in aortic stenosis. *Circulation* **124**, 1565-1572, doi:10.1161/CIRCULATIONAHA.110.011916 (2011).

43 Seiler, C. & Jenni, R. Severe aortic stenosis without left ventricular hypertrophy: prevalence, predictors, and short-term follow up after aortic valve replacement. *Heart* **76**, 250-255 (1996).

44 Dellgren, G. *et al.* Angiotensin-converting enzyme gene polymorphism influences degree of left ventricular hypertrophy and its regression in patients undergoing operation for aortic stenosis. *Am J Cardiol* **84**, 909-913 (1999).

45 Antonini-Canterin, F. *et al.* Symptomatic aortic stenosis: does systemic hypertension play an additional role? *Hypertension* **41**, 1268-1272, doi:10.1161/01.HYP.0000070029.30058.59 (2003).

46 Mureddu, G. F., Cioffi, G., Stefenelli, C., Boccanelli, A. & de Simone, G. Compensatory or inappropriate left ventricular mass in different models of left ventricular pressure overload: comparison between patients with aortic stenosis and arterial hypertension. *J Hypertens* **27**, 642-649, doi:10.1097/HJH.0b013e32831cec98 (2009).

47 Holtz, J., Restorff, W. V., Bard, P. & Bassenge, E. Transmural distribution of myocardial blood flow and of coronary reserve in canine left ventricular hypertrophy. *Basic Res Cardiol* **72**, 286-292 (1977).

48 Rembert, J. C., Kleinman, L. H., Fedor, J. M., Wechsler, A. S. & Greenfield, J. C., Jr. Myocardial blood flow distribution in concentric left ventricular hypertrophy. *J Clin Invest* **62**, 379-386, doi:10.1172/JCI109139 (1978).

49 Bache, R. J., Vrobel, T. R., Ring, W. S., Emery, R. W. & Andersen, R. W. Regional myocardial blood flow during exercise in dogs with chronic left ventricular hypertrophy. *Circ Res* **48**, 76-87 (1981).

50 Lumley, M. *et al.* Coronary Physiology During Exercise and Vasodilation in the Healthy Heart and in Severe Aortic Stenosis. *J Am Coll Cardiol* **68**, 688-697, doi:10.1016/j.jacc.2016.05.071 (2016).

51 Panting, J. R. *et al.* Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* **346**, 1948-1953, doi:10.1056/NEJMoa012369 (2002).

52 Lanza, G. A. *et al.* Relation between stress-induced myocardial perfusion defects on cardiovascular magnetic resonance and coronary microvascular dysfunction in patients with cardiac syndrome X. *J Am Coll Cardiol* **51**, 466-472, doi:10.1016/j.jacc.2007.08.060 (2008).

53 Mahmod, M. *et al.* Myocardial perfusion and oxygenation are impaired during stress in severe aortic stenosis and correlate with impaired energetics and subclinical left ventricular dysfunction. *J Cardiovasc Magn Reson* **16**, 29, doi:10.1186/1532-429X-16-29 (2014).

54 Ahn, J. H. *et al.* Coronary Microvascular Dysfunction as a Mechanism of Angina in Severe AS: Prospective Adenosine-Stress CMR Study. *J Am Coll Cardiol* **67**, 1412-1422, doi:10.1016/j.jacc.2016.01.013 (2016).

55 Schwartzkopff, B. *et al.* Morphometric investigation of human myocardium in arterial hypertension and valvular aortic stenosis. *Eur Heart J* **13 Suppl D**, 17-23 (1992).

56 Robicsek, F. Leonardo da Vinci and the sinuses of Valsalva. *Ann Thorac Surg* **52**, 328-335 (1991).

57 Bellhouse, B. J. & Bellhouse, F. H. Mechanism of closure of the aortic valve. *Nature* **217**, 86-87 (1968).

58 Kvitting, J. P. *et al.* Flow patterns in the aortic root and the aorta studied with time-resolved, 3-dimensional, phase-contrast magnetic resonance imaging: implications for aortic valve-sparing surgery. *J Thorac Cardiovasc Surg* **127**, 1602-1607, doi:10.1016/j.jtcvs.2003.10.042 (2004).

59 Bellhouse, B. J., Bellhouse, F. H. & Reid, K. G. Fluid mechanics of the aortic root with application to coronary flow. *Nature* **219**, 1059-1061 (1968).

60 Heusch, G. Heart rate in the pathophysiology of coronary blood flow and myocardial ischaemia: benefit from selective bradycardic agents. *Br J Pharmacol* **153**, 1589-1601, doi:10.1038/sj.bjp.0707673 (2008).

61 Greve, A. M. *et al.* Resting heart rate and risk of adverse cardiovascular outcomes in asymptomatic aortic stenosis: the SEAS study. *Int J Cardiol* **180**, 122-128, doi:10.1016/j.ijcard.2014.11.181 (2015).

62 Dzau, V. J. & Gibbons, G. H. Autocrine-paracrine mechanisms of vascular myocytes in systemic hypertension. *Am J Cardiol* **60**, 99I-103I (1987).

63 Joannides, R. *et al.* Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. *Circulation* **91**, 1314-1319 (1995).

64 Okahara, K., Sun, B. & Kambayashi, J. Upregulation of prostacyclin synthesis-related gene expression by shear stress in vascular endothelial cells. *Arterioscler Thromb Vasc Biol* **18**, 1922-1926 (1998).

65 Ludmer, P. L. *et al.* Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med* **315**, 1046-1051, doi:10.1056/NEJM198610233151702 (1986).

66 Bonetti, P. O. *et al.* Simvastatin preserves myocardial perfusion and coronary microvascular permeability in experimental hypercholesterolemia independent of lipid lowering. *J Am Coll Cardiol* **40**, 546-554 (2002).

67 Zeiher, A. M., Krause, T., Schachinger, V., Minners, J. & Moser, E. Impaired endothelium-dependent vasodilation of coronary resistance vessels is associated with exercise-induced myocardial ischemia. *Circulation* **91**, 2345-2352 (1995).

68 Hasdai, D., Gibbons, R. J., Holmes, D. R., Jr., Higano, S. T. & Lerman, A. Coronary endothelial dysfunction in humans is associated with myocardial perfusion defects. *Circulation* **96**, 3390-3395 (1997).

69 Poggianti, E. *et al.* Aortic valve sclerosis is associated with systemic endothelial dysfunction. *J Am Coll Cardiol* **41**, 136-141 (2003).

70 Diehl, P. *et al.* Increased levels of circulating microparticles in patients with severe aortic valve stenosis. *Thromb Haemost* **99**, 711-719, doi:10.1160/TH07-05-0334 (2008).

71 Schumm, J. *et al.* In patients with aortic stenosis increased flow-mediated dilation is independently associated with higher peak jet velocity and lower asymmetric dimethylarginine levels. *Am Heart J* **161**, 893-899, doi:10.1016/j.ahj.2011.02.015 (2011).

72 Corretti, M. C. *et al.* Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* **39**, 257-265 (2002).

73 McGoldrick, R. B., Kingsbury, M., Turner, M. A., Sheridan, D. J. & Hughes, A. D. Left ventricular hypertrophy induced by aortic banding impairs relaxation of isolated coronary arteries. *Clin Sci (Lond)* **113**, 473-478, doi:10.1042/CS20070136 (2007).

74 Pellegrino, T. *et al.* Relationship between brachial artery flow-mediated dilation and coronary flow reserve in patients with peripheral artery disease. *J Nucl Med* **46**, 1997-2002 (2005).

75 Oz, F., Elitok, A., Bilge, A. K., Mercanoglu, F. & Oflaz, H. Relationship Between Brachial Artery Flow-Mediated Dilation, Carotid Artery Intima-Media Thickness and Coronary Flow Reserve in Patients With Coronary Artery Disease. *Cardiol Res* **3**, 214-221, doi:10.4021/cr219w (2012).

76 Camuglia, A. C. *et al.* Invasively assessed coronary flow dynamics improve following relief of aortic stenosis with transcatheter aortic valve implantation. *J Am Coll Cardiol* **63**, 1808-1809, doi:10.1016/j.jacc.2013.11.040 (2014).

77 Yotti, R. *et al.* Systemic vascular load in calcific degenerative aortic valve stenosis: insight from percutaneous valve replacement. *J Am Coll Cardiol* **65**, 423-433, doi:10.1016/j.jacc.2014.10.067 (2015).

78 Axell, R. G. *et al.* Rapid Pacing-Induced Right Ventricular Dysfunction Is Evident After Balloon-Expandable Transfemoral Aortic Valve Replacement. *J Am Coll Cardiol* **69**, 903-904, doi:10.1016/j.jacc.2016.12.011 (2017).

79 Chenevard, R. *et al.* Persistent endothelial dysfunction in calcified aortic stenosis beyond valve replacement surgery. *Heart* **92**, 1862-1863, doi:10.1136/hrt.2006.087437 (2006).

80 Horn, P. *et al.* Improved endothelial function and decreased levels of endothelium-derived microparticles after transcatheter aortic valve implantation. *EuroIntervention* **10**, 1456-1463, doi:10.4244/EIJY14M10_02 (2015).

81 Dignat-George, F. & Boulanger, C. M. The many faces of endothelial microparticles. *Arterioscler Thromb Vasc Biol* **31**, 27-33, doi:10.1161/ATVBAHA.110.218123 (2011).

82 Rautou, P. E. *et al.* Microparticles, vascular function, and atherothrombosis. *Circ Res* **109**, 593-606, doi:10.1161/CIRCRESAHA.110.233163 (2011).

83 Kennedy, J. W., Doces, J. & Stewart, D. K. Left ventricular function before and following aortic valve replacement. *Circulation* **56**, 944-950 (1977).

84 Ikonomidis, I. *et al.* Four year follow up of aortic valve replacement for isolated aortic stenosis: a link between reduction in pressure overload, regression of left ventricular hypertrophy, and diastolic function. *Heart* **86**, 309-316 (2001).

85 Walther, T. *et al.* Prospectively randomized evaluation of stentless versus conventional biological aortic valves: impact on early regression of left ventricular hypertrophy. *Circulation* **100**, II6-10 (1999).

86 La Manna, A. *et al.* Left ventricular reverse remodeling after transcatheter aortic valve implantation: a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* **15**, 39, doi:10.1186/1532-429X-15-39 (2013).

87 Hildick-Smith, D. J. & Shapiro, L. M. Coronary flow reserve improves after aortic valve replacement for aortic stenosis: an adenosine transthoracic echocardiography study. *J Am Coll Cardiol* **36**, 1889-1896 (2000).

88 Rajappan, K. *et al.* Functional changes in coronary microcirculation after valve replacement in patients with aortic stenosis. *Circulation* **107**, 3170-3175, doi:10.1161/01.CIR.0000074211.28917.31 (2003).

89 Bakhtiary, F. *et al.* Impact of patient-prosthesis mismatch and aortic valve design on coronary flow reserve after aortic valve replacement. *J Am Coll Cardiol* **49**, 790-796, doi:10.1016/j.jacc.2006.10.052 (2007).

90 Akins, C. W. *et al.* Cardiac operations in patients 80 years old and older. *Ann Thorac Surg* **64**, 606-614; discussion 614-605 (1997).

91 Vahanian, A. *et al.* Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* **42**, S1-44, doi:10.1093/ejcts/ezs455 (2012).

92 Dewey, T. M. *et al.* Effect of concomitant coronary artery disease on procedural and late outcomes of transcatheter aortic valve implantation. *Ann Thorac Surg* **89**, 758-767; discussion 767, doi:10.1016/j.athoracsur.2009.12.033 (2010).

93 Khawaja, M. Z. *et al.* The effect of coronary artery disease defined by quantitative coronary angiography and SYNTAX score upon outcome after transcatheter aortic valve implantation (TAVI) using the Edwards bioprosthesis. *EuroIntervention* **11**, 450-455, doi:10.4244/EIJY14M05_09 (2015).

94 Paradis, J. M. *et al.* Impact of Coronary Artery Disease Severity Assessed With the SYNTAX Score on Outcomes Following Transcatheter Aortic Valve Replacement. *J Am Heart Assoc* **6**, doi:10.1161/JAHA.116.005070 (2017).

95 Masson, J. B. *et al.* Impact of coronary artery disease on outcomes after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* **76**, 165-173, doi:10.1002/ccd.22501 (2010).

96 Iguchi, T. *et al.* Impact of lesion length on functional significance in intermediate coronary lesions. *Clin Cardiol* **36**, 172-177, doi:10.1002/clc.22076 (2013).

97 Brosh, D., Higano, S. T., Lennon, R. J., Holmes, D. R., Jr. & Lerman, A. Effect of lesion length on fractional flow reserve in intermediate coronary lesions. *Am Heart J* **150**, 338-343, doi:10.1016/j.ahj.2004.09.007 (2005).

98 Gould, K. L. *et al.* Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision-making. *J Am Coll Cardiol* **62**, 1639-1653, doi:10.1016/j.jacc.2013.07.076 (2013).

99 Pijls, N. H. *et al.* Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol* **56**, 177-184, doi:10.1016/j.jacc.2010.04.012 (2010).

100 Tonino, P. A. *et al.* Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol* **55**, 2816-2821, doi:10.1016/j.jacc.2009.11.096 (2010).

101 Burgstahler, C. *et al.* Adenosine stress first pass perfusion for the detection of coronary artery disease in patients with aortic stenosis: a feasibility study. *Int J Cardiovasc Imaging* **24**, 195-200, doi:10.1007/s10554-007-9236-6 (2008).

102 Maffei, S. *et al.* Preoperative assessment of coronary artery disease in aortic stenosis: a dipyridamole echocardiographic study. *Ann Thorac Surg* **65**, 397-402 (1998).

103 Patsilinakos, S. P. *et al.* Adenosine stress myocardial perfusion tomographic imaging in patients with significant aortic stenosis. *J Nucl Cardiol* **11**, 20-25, doi:10.1016/j.nuclcard.2003.10.003 (2004).

104 Cremer, P. C. *et al.* Stress positron emission tomography is safe and can guide coronary revascularization in high-risk patients being considered for transcatheter aortic valve replacement. *J Nucl Cardiol* **21**, 1001-1010, doi:10.1007/s12350-014-9928-y (2014).

105 Pesarini, G. *et al.* Functional Assessment of Coronary Artery Disease in Patients Undergoing Transcatheter Aortic Valve Implantation: Influence of Pressure Overload on the Evaluation of Lesions Severity. *Circ Cardiovasc Interv* **9**, doi:10.1161/CIRCINTERVENTIONS.116.004088 (2016).

106 Scarsini, R. *et al.* Coronary physiology in patients with severe aortic stenosis: Comparison between fractional flow reserve and instantaneous wave-free ratio. *Int J Cardiol* **243**, 40-46, doi:10.1016/j.ijcard.2017.05.117 (2017).

107 Petraco, R. *et al.* Classification performance of instantaneous wave-free ratio (iFR) and fractional flow reserve in a clinical population of intermediate coronary stenoses: results of the ADVISE registry. *EuroIntervention* **9**, 91-101, doi:10.4244/EIJV9I1A14 (2013).

108 Gotberg, M. *et al.* Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med* **376**, 1813-1823, doi:10.1056/NEJMoa1616540 (2017).

109 Scarsini, R. *et al.* Physiologic Evaluation of Coronary Lesions Using Instantaneous Wave-free Ratio (iFR) in Patients with Severe Aortic Stenosis Undergoing Trans-catheter Aortic Valve Implantation. *EuroIntervention*, doi:10.4244/EIJ-D-17-00542 (2017).

110 Parker, K. H., Alastruey, J. & Stan, G. B. Arterial reservoir-excess pressure and ventricular work. *Med Biol Eng Comput* **50**, 419-424, doi:10.1007/s11517-012-0872-1 (2012).

111 Wang, J. J., O'Brien, A. B., Shrive, N. G., Parker, K. H. & Tyberg, J. V. Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. *Am J Physiol Heart Circ Physiol* **284**, H1358-1368, doi:10.1152/ajpheart.00175.2002 (2003).

112 Michail, M., Narayan, O., Parker, K. H. & Cameron, J. D. Relationship of aortic excess pressure obtained using pressure-only reservoir pressure analysis to directly measured aortic flow in humans. *Physiol Meas* **39**, 064006, doi:10.1088/1361-6579/aaca87 (2018).

113 Parker, K. H. An introduction to wave intensity analysis. *Med Biol Eng Comput* **47**, 175-188, doi:10.1007/s11517-009-0439-y (2009).

114 Jones, C. J., Sugawara, M., Kondoh, Y., Uchida, K. & Parker, K. H. Compression and expansion wavefront travel in canine ascending aortic flow: wave intensity analysis. *Heart Vessels* **16**, 91-98 (2002).

115 Davies, J. E. *et al.* The arterial reservoir pressure increases with aging and is the major determinant of the aortic augmentation index. *Am J Physiol Heart Circ Physiol* **298**, H580-586, doi:10.1152/ajpheart.00875.2009 (2010).

116 Aguado-Sierra, J. *et al.* Separation of the reservoir and wave pressure and velocity from measurements at an arbitrary location in arteries. *Proc Inst Mech Eng H* **222**, 403-416, doi:10.1243/09544119JEIM315 (2008).

117 Sianos, G. *et al.* The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* **1**, 219-227 (2005).

118 Witberg, G., Zusman, O., Codner, P., Assali, A. & Kornowski, R. Impact of Coronary Artery Revascularization Completeness on Outcomes of Patients With Coronary Artery Disease Undergoing Transcatheter Aortic Valve Replacement. *A Meta-Analysis of Studies Using the Residual SYNTAX Score (Synergy Between PCI With Taxus and Cardiac Surgery)* **11**, doi:10.1161/circinterventions.117.006000 (2018).

119 Wong, D. T. *et al.* A novel coronary angiography index (DILEMMA score) for prediction of functionally significant coronary artery stenoses assessed by fractional flow reserve: A novel coronary angiography index. *Am Heart J* **169**, 564-571 e564, doi:10.1016/j.ahj.2014.11.017 (2015).

120 Michail, M. *et al.* Application of the DILEMMA score to improve lesion selection for invasive physiological assessment. *Catheter Cardiovasc Interv*, doi:10.1002/ccd.28054 (2019).

121 Kappetein, A. P. *et al.* Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg* **42**, S45-60, doi:10.1093/ejcts/ezs533 (2012).

122 Abbara, S. *et al.* SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: A report of the society of Cardiovascular Computed Tomography Guidelines Committee: Endorsed by the North American Society for Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr* **10**, 435-449, doi:10.1016/j.jcct.2016.10.002 (2016).

123 Leung, M. C., Meredith, I. T. & Cameron, J. D. Aortic stiffness affects the coronary blood flow response to percutaneous coronary intervention. *Am J Physiol Heart Circ Physiol* **290**, H624-630, doi:10.1152/ajpheart.00380.2005 (2006).

124 Lindman, B. R. *et al.* Blood Pressure and Arterial Load After Transcatheter Aortic Valve Replacement for Aortic Stenosis. *Circ Cardiovasc Imaging* **10**, doi:10.1161/CIRCIMAGING.116.006308 (2017).

125 Perlman, G. Y. *et al.* Post-procedural hypertension following transcatheter aortic valve implantation: incidence and clinical significance. *JACC. Cardiovascular interventions* **6**, 472-478, doi:10.1016/j.jcin.2012.12.124 (2013).

126 Klinkhammer, B. J., Dyke, C. M. & Haldis, T. A. The development or worsening of hypertension after transcatheter aortic valve replacement (TAVR) improves short-term and long-term patient outcomes. *Heart Asia* **10**, e010994, doi:10.1136/heartasia-2017-010994 (2018).

127 Sato, K. *et al.* Association of Time Between Left Ventricular and Aortic Systolic Pressure Peaks With Severity of Aortic Stenosis and Calcification of Aortic Valve. *JAMA Cardiol*, doi:10.1001/jamacardio.2019.1180 (2019).

128 Chobanian, A. V. *et al.* Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* **42**, 1206-1252, doi:10.1161/01.HYP.0000107251.49515.c2 (2003).

129 Pohle, K. *et al.* Progression of aortic valve calcification: association with coronary atherosclerosis and cardiovascular risk factors. *Circulation* **104**, 1927-1932 (2001).

130 Lerman, A. & Burnett, J. C., Jr. Intact and altered endothelium in regulation of vasomotion. *Circulation* **86**, III12-19 (1992).

131 Brown, A. J. *et al.* Role of biomechanical forces in the natural history of coronary atherosclerosis. *Nat Rev Cardiol* **13**, 210-220, doi:10.1038/nrcardio.2015.203 (2016).

132 Michail, M. *et al.* Acute Effects of Transcatheter Aortic Valve Replacement on Central Aortic Hemodynamics in Patients With Severe Aortic Stenosis. *Hypertension*, HYPERTENSIONAHA11914385, doi:10.1161/HYPERTENSIONAHA.119.14385 (2020).

133 Gimbrone, M. A., Jr., Topper, J. N., Nagel, T., Anderson, K. R. & Garcia-Cardena, G. Endothelial dysfunction, hemodynamic forces, and atherogenesis. *Ann N Y Acad Sci* **902**, 230-239; discussion 239-240, doi:10.1111/j.1749-6632.2000.tb06318.x (2000).

134 Kubo, M. *et al.* Prognostic significance of endothelial dysfunction in patients undergoing percutaneous coronary intervention in the era of drug-eluting stents. *BMC Cardiovasc Disord* **15**, 102, doi:10.1186/s12872-015-0096-z (2015).

135 Takata, M. *et al.* Brachial artery diameter has a predictive value in the improvement of flow-mediated dilation after aortic valve replacement for aortic stenosis. *Heart Vessels* **30**, 218-226, doi:10.1007/s00380-014-0475-x (2015).

136 Moscarelli, M. *et al.* The effect of surgical versus transcatheter aortic valve replacement on endothelial function. An observational study. *Int J Surg* **63**, 1-7, doi:10.1016/j.ijsu.2019.01.014 (2019).

137 Avogaro, A., Albiero, M., Menegazzo, L., de Kreutzenberg, S. & Fadini, G. P. Endothelial dysfunction in diabetes: the role of reparatory mechanisms. *Diabetes Care* **34 Suppl 2**, S285-290, doi:10.2337/dc11-s239 (2011).

138 Ben Zekry, S. *et al.* Flow acceleration time and ratio of acceleration time to ejection time for prosthetic aortic valve function. *JACC Cardiovasc Imaging* **4**, 1161-1170, doi:10.1016/j.jcmg.2011.08.012 (2011).

139 Gamaza-Chulian, S. *et al.* Acceleration Time and Ratio of Acceleration Time to Ejection Time in Aortic Stenosis: New Echocardiographic Diagnostic Parameters. *J Am Soc Echocardiogr* **30**, 947-955, doi:10.1016/j.echo.2017.06.001 (2017).

140 Ekeloef, S. *et al.* Endothelial dysfunction in the early postoperative period after major colon cancer surgery. *Br J Anaesth* **118**, 200-206, doi:10.1093/bja/aew410 (2017).

141 O'Brien, J. R., Etherington, M. D., Brant, J. & Watkins, J. Decreased platelet function in aortic valve stenosis: high shear platelet activation then inactivation. *Br Heart J* **74**, 641-644, doi:10.1136/hrt.74.6.641 (1995).

142 Francis, J. L. Platelet dysfunction detected at high shear in patients with heart valve disease. *Platelets* **11**, 133-136, doi:10.1080/095371000403062 (2009).

143 Bollache, E. *et al.* Perioperative evaluation of regional aortic wall shear stress patterns in patients undergoing aortic valve and/or proximal thoracic aortic replacement. *The Journal of thoracic and cardiovascular surgery* **155**, 2277-2286 e2272, doi:10.1016/j.jtcvs.2017.11.007 (2018).

144 Bissell, M. M. *et al.* Differential flow improvements after valve replacements in bicuspid aortic valve disease: a cardiovascular magnetic resonance assessment. *J Cardiovasc Magn Reson* **20**, 10, doi:10.1186/s12968-018-0431-5 (2018).

145 Cheng, C. *et al.* Shear stress affects the intracellular distribution of eNOS: direct demonstration by a novel in vivo technique. *Blood* **106**, 3691-3698, doi:10.1182/blood-2005-06-2326 (2005).

146 Zhang, Y. *et al.* Shear stress regulates endothelial cell function through SRB1-eNOS signaling pathway. *Cardiovasc Ther* **34**, 308-313, doi:10.1111/1755-5922.12199 (2016).

147 Farag, E. S. *et al.* Transcatheter aortic valve replacement alters ascending aortic blood flow and wall shear stress patterns: A 4D flow MRI comparison with age-matched, elderly controls. *Eur Radiol* **29**, 1444-1451, doi:10.1007/s00330-018-5672-z (2019).

148 Irace, C. *et al.* Arterial remodeling of the common carotid artery after aortic valve replacement in patients with aortic stenosis. *Stroke* **33**, 2446-2450, doi:10.1161/01.str.0000032103.59213.bc (2002).

149 Harris, R. A., Nishiyama, S. K., Wray, D. W. & Richardson, R. S. Ultrasound assessment of flow-mediated dilation. *Hypertension* **55**, 1075-1085, doi:10.1161/HYPERTENSIONAHA.110.150821 (2010).

150 Broyd, C. J. *et al.* Regression of left ventricular hypertrophy provides an additive physiological benefit following treatment of aortic stenosis: Insights from serial coronary wave intensity analysis. *Acta Physiol (Oxf)* **224**, e13109, doi:10.1111/apha.13109 (2018).

151 Mullany, C. J. *et al.* Coronary artery disease and its management: influence on survival in patients undergoing aortic valve replacement. *J Am Coll Cardiol* **10**, 66-72, doi:10.1016/s0735-1097(87)80161-4 (1987).

152 Ludman, P. F. *et al.* Transcatheter aortic valve implantation in the United Kingdom: temporal trends, predictors of outcome, and 6-year follow-up: a report from the UK Transcatheter Aortic Valve Implantation (TAVI) Registry, 2007 to 2012. *Circulation* **131**, 1181-1190, doi:10.1161/CIRCULATIONAHA.114.013947 (2015).

153 Singh, V. *et al.* Comparison of Outcomes of Transcatheter Aortic Valve Replacement Plus Percutaneous Coronary Intervention Versus Transcatheter Aortic Valve Replacement Alone in the United States. *Am J Cardiol* **118**, 1698-1704, doi:10.1016/j.amjcard.2016.08.048 (2016).

154 Linke, A. *et al.* Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study. *Eur Heart J* **35**, 2672-2684, doi:10.1093/eurheartj/ehu162 (2014).

155 Ussia, G. P. *et al.* Impact of coronary artery disease in elderly patients undergoing transcatheter aortic valve implantation: insight from the Italian CoreValve Registry. *Int J Cardiol* **167**, 943-950, doi:10.1016/j.ijcard.2012.03.089 (2013).

156 Witberg, G. *et al.* The Prognostic Effects of Coronary Disease Severity and Completeness of Revascularization on Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement. *JACC. Cardiovascular interventions* **10**, 1428-1435, doi:10.1016/j.jcin.2017.04.035 (2017).

157 Stefanini, G. G. *et al.* Coronary artery disease severity and aortic stenosis: clinical outcomes according to SYNTAX score in patients undergoing transcatheter aortic valve implantation. *Eur Heart J* **35**, 2530-2540, doi:10.1093/eurheartj/ehu074 (2014).

158 Koskinas, K. C. *et al.* Post-Procedural Troponin Elevation and Clinical Outcomes Following Transcatheter Aortic Valve Implantation. *J Am Heart Assoc* **5**, doi:10.1161/jaha.115.002430 (2016).

159 Michail, M. *et al.* Periprocedural Myocardial Injury Predicts Short- and Long-Term Mortality in Patients Undergoing Transcatheter Aortic Valve Replacement. *Circulation: Cardiovascular Interventions* **11**, e007106, doi:10.1161/CIRCINTERVENTIONS.118.007106 (2018).

160 Beton, O., Kaya, H., Turgut, O. O. & Yilmaz, M. B. Prediction of fractional flow reserve with angiographic DILEMMA score. *Anatol J Cardiol* **17**, 285-292, doi:10.14744/AnatolJCardiol.2016.7379 (2017).

161 Hachamovitch, R., Hayes, S. W., Friedman, J. D., Cohen, I. & Berman, D. S. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* **107**, 2900-2907, doi:10.1161/01.CIR.0000072790.23090.41 (2003).

162 Dorbala, S. *et al.* Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. *JACC. Cardiovascular imaging* **2**, 846-854, doi:10.1016/j.jcmg.2009.04.009 (2009).

163 Tonino, P. A. L. *et al.* Fractional flow reserve versus angiography for guideing percutaneous coronary intervention. *N Engl J Med* **360**, 213-224 (2009).

164 De Bruyne, B. *et al.* Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* **367**, 991-1001, doi:10.1056/NEJMoa1205361 (2012).

165 Neumann, F.-J. *et al.* 2018 ESC/EACTS Guidelines on myocardial revascularization. *European Heart Journal*, ehy394-ehy394, doi:10.1093/eurheartj/ehy394 (2018).

166 Michail, M. *et al.* Adaptations to Coronary Physiology in a Patient With Severe Aortic Stenosis and Complete Heart Block Undergoing Transcatheter Aortic Valve Replacement. *JACC. Cardiovascular interventions* **12**, 687-689, doi:10.1016/j.jcin.2019.01.215 (2019).

167 Yamanaka, F. *et al.* Instantaneous Wave-Free Ratio for the Assessment of Intermediate Coronary Artery Stenosis in Patients With Severe Aortic Valve Stenosis: Comparison With Myocardial Perfusion Scintigraphy. *JACC. Cardiovascular interventions* **11**, 2032-2040, doi:10.1016/j.jcin.2018.07.027 (2018).

168 Ahmad, Y. *et al.* Coronary Hemodynamics in Patients With Severe Aortic Stenosis and Coronary Artery Disease Undergoing Transcatheter Aortic Valve Replacement: Implications for Clinical Indices of Coronary Stenosis Severity. *JACC. Cardiovascular interventions* **11**, 2019-2031, doi:10.1016/j.jcin.2018.07.019 (2018).

169 Tavakol, M., Ashraf, S. & Brener, S. J. Risks and complications of coronary angiography: a comprehensive review. *Glob J Health Sci* **4**, 65-93, doi:10.5539/gjhs.v4n1p65 (2012).

170 Lunardi, M. *et al.* Physiological Versus Angiographic Guidance for Myocardial Revascularization in Patients Undergoing Transcatheter Aortic Valve Implantation. *J Am Heart Assoc* **8**, e012618, doi:10.1161/JAHA.119.012618 (2019).

171 Danad, I. *et al.* Comparison of Coronary CT Angiography, SPECT, PET, and Hybrid Imaging for Diagnosis of Ischemic Heart Disease Determined by Fractional Flow Reserve. *JAMA Cardiol* **2**, 1100-1107, doi:10.1001/jamacardio.2017.2471 (2017).

172 Min, J. K. *et al.* Noninvasive Fractional Flow Reserve Derived From Coronary CT Angiography: Clinical Data and Scientific Principles. *JACC. Cardiovascular imaging* **8**, 1209-1222, doi:10.1016/j.jcmg.2015.08.006 (2015).

173 *National Institute for Health and Care Excellence. HeartFlow FFRCT for estimating fractional flow reserve from coronary CT angiography. NICE Medical technologies guidance [MTG32]. 2017 Available from: https://www.nice.org.uk/guidance/mtg32 [Published date: February 2017].*

174 Rossi, A. *et al.* CT angiography to evaluate coronary artery disease and revascularization requirement before trans-catheter aortic valve replacement. *J Cardiovasc Comput Tomogr* **11**, 338-346, doi:10.1016/j.jcct.2017.06.001 (2017).

175 Chieffo, A. *et al.* Routine Screening of Coronary Artery Disease With Computed Tomographic Coronary Angiography in Place of Invasive Coronary Angiography in Patients Undergoing Transcatheter Aortic Valve Replacement. *Circ Cardiovasc Interv* **8**, e002025, doi:10.1161/CIRCINTERVENTIONS.114.002025 (2015).

176 Raff, G. L. *et al.* SCCT guidelines on the use of coronary computed tomographic angiography for patients presenting with acute chest pain to the emergency department: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* **8**, 254-271, doi:10.1016/j.jcct.2014.06.002 (2014).

177 Norgaard, B. L. *et al.* Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). *J Am Coll Cardiol* **63**, 1145-1155, doi:10.1016/j.jacc.2013.11.043 (2014).

178 Ko, B. S. *et al.* Noninvasive CT-Derived FFR Based on Structural and Fluid Analysis: A Comparison With Invasive FFR for Detection of Functionally Significant Stenosis. *JACC. Cardiovascular imaging* **10**, 663-673, doi:10.1016/j.jcmg.2016.07.005 (2017).

179 Jilaihawi, H. *et al.* Cross-sectional computed tomographic assessment improves accuracy of aortic annular sizing for transcatheter aortic valve replacement and reduces the incidence of paravalvular aortic regurgitation. *J Am Coll Cardiol* **59**, 1275-1286, doi:10.1016/j.jacc.2011.11.045 (2012).