

Systematic assessment of intracoronary pressure-flow relationships in patients with severe aortic stenosis and coronary artery disease before and after transcatheter aortic valve implantation

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Declaration of Originality

I hereby declare that the work presented in this thesis is my own.

Dr Yousif Ahmad

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Abstract

Patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) commonly have coronary artery disease, and the optimal treatment of this coexistent coronary disease has not been defined. For patients without severe aortic stenosis, the use of intracoronary physiology has been shown to improve outcomes when compared to an angiographic-guided approach.

The use of intracoronary physiology to guide revascularisation decisions for patients with severe aortic stenosis is contingent on understanding how aortic valvular stenosis affects coronary flow velocity. TAVI permits a unique opportunity to assess the impact of aortic stenosis on the coronary circulation because physiological assessments can be made in the presence of severe aortic stenosis (pre-TAVI) and then in the absence of severe aortic stenosis (post-TAVI) in the same patient.

In the series of mechanistic studies that comprise this thesis, I will utilise such an approach in order to isolate the effect of the stenosed aortic valve on the coronary circulation, minimising the potential effect of any confounding factors. I will utilise combined coronary pressure and flow velocity measurements, both at resting conditions and during hyperaemia, before and after TAVI. I will perform phasic analyses to examine the differential effects of TAVI on coronary flow velocity in different phases of the cardiac cycle, when the valve is either open or closed.

My first set of experiments will determine the acute effects of TAVI on coronary flow velocity over different phases of the cardiac cycle, and its effect on the most common clinically-used indices of coronary stenosis severity (FFR and iFR).

Secondly, I will quantify the effect of severe aortic stenosis on microcirculatory function and determine if this is influenced by coexistent coronary stenoses.

Finally, I will examine the longer-term effects of relieving aortic stenosis on coronary haemodynamics by repeating invasive pressure and flow velocity studies in patients 6-months following TAVI. This will allow me to determine whether acute changes in coronary flow velocity seen immediately after TAVI are sustained, or whether they change at longer-term follow-up, and how this impacts indices of coronary stenosis severity.

Dedication

To my parents, whose enduring support has been vital and whose patience I have tested too much.

Acknowledgments

To my supervisors, mentors, collaborators, colleagues, friends, and patients: my contribution to this work pales next to yours.

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1.Introduction

Aortic stenosis and coronary artery disease

Aortic stenosis is the commonest valvular heart lesion encountered worldwide, and its prevalence increases with age(1). Coronary artery disease and aortic stenosis commonly coexist(2). This is because the two conditions share the same pathogenesis and risk factors(3,4). Half of patients over the age of 70 with aortic stenosis will have concomitant coronary artery disease, and this prevalence also increases with age. For patients undergoing surgical aortic valve replacement who also have coronary artery disease, the standard of care has been coronary artery bypass grafting at the time of valve replacement(5), and this is the approach recommended by international guidelines as a class I recommendation.

This paradigm has now shifted with the advent of transcatheter procedures for the treatment of aortic stenosis, most commonly transcatheter aortic valve implantation (TAVI). This is now the treatment of choice for many patients with severe aortic stenosis at high and intermediate surgical risk. As patients undergoing TAVI are generally older than patients undergoing surgical aortic valve replacement (SAVR), the prevalence of coronary artery disease is even higher in these patients. The framework for treating coexistent coronary artery disease (CAD) in these patients is not directly translatable from SAVR to TAVI.

The rationale and advent of TAVI

Surgical aortic valve replacement (SAVR) has been shown to prolong life and improve symptoms for patients with symptomatic severe aortic stenosis(6,7). Guidelines therefore recommend this as the therapy of choice for these patients(8,9). Unfortunately, a substantial number of patients are not offered SAVR despite having symptomatic severe aortic stenosis due to prohibitive operative risk(10). Without treatment, the prognosis of these patients is dire(11,12). There was therefore an unmet clinical need: a less invasive way to treat severe aortic stenosis which would permit the treatment of patients who are deemed too high risk for surgery and therefore would be denied treatment.

This formed the basis for transcatheter aortic valve implantation (TAVI). This involves the insertion of a bioprosthetic valve using transcatheter techniques, most commonly via the femoral artery. The new valve is implanted within the native valve (which is not replaced, different to SAVR).

The foundational clinical trial evidence for TAVI

The first randomised controlled trial to establish the safety and efficacy of TAVI were the PARTNER trials in 2010. This involved the conduct of two simultaneous trials. One trial randomised patients who were deemed inoperable to either standard therapy or TAVI.

This was designed as a superiority trial. The other trial randomised patients deemed at high-surgical risk to either SAVR or TAVI. This was designed as a non-inferiority trial.

The inoperable cohort formed the PARTNER 1B group(13). This trial included 358 patients with severe aortic stenosis who were deemed unfit for surgery. Patients were then randomised to standard therapy (including balloon aortic valvuloplasty) or TAVI. The primary outcome was all-cause mortality, and all patients were followed for at least one year. Crossover from the standard therapy group to the TAVI group was not permitted. The TAVI device used in this trial was the balloon-expandable Edwards SAPIEN heart-valve system (Edwards Lifesciences, Irvine, California).

At 12-months, the rate of all-cause death in the standard therapy group was 50.7%, compared to 30.7% in the TAVI group (hazard ratio, 0.55; 95% confidence interval [CI], 0.40 to 0.74; $P<0.001$). 83.8% of patients within the standard therapy group underwent balloon aortic valvuloplasty.

This result was durable out to 5 years of follow-up(14). At 5-years the rate of death was 93.6% in the standard therapy group.

My conclusions from the PARTNER 1b (inoperable cohort) trial are:

- The prognosis of patients with severe aortic stenosis who are deemed unfit for surgery is dismal
- Balloon aortic valvuloplasty does not modify the course of the disease (93.6% dead at 5 years)
- TAVI is clearly superior to “standard therapy” in these patients, with a number needed to treat of 5 at the 1-year timepoint

The high-risk cohort formed the PARTNER 1a group(15). This trial randomised 699 patients to TAVI with the Edwards Sapiens valves or SAVR. The primary outcome was all-cause mortality at 12 months and it was designed as a non-inferiority trial. The rates of death at 12 months were 24.2% in the TAVI group and 26.8% in the SAVR group, (p=0.001 for noninferiority).

Subsequent to this was the publication of another randomised trial, this time using the self-expanding bioprosthetic Medtronic CoreValve or Evolut R valve (Medtronic, Minneapolis, Minnesota). This trial differed in that it randomised 795 patients considered at high surgical risk in a 1:1 fashion between TAVI with the CoreValve, and SAVR. The primary outcome was again all-cause mortality. In this trial, the rate of all-cause mortality at 1-year was significantly lower with TAVI than SAVR (14.2% vs. 19.1%, p<0.001 for noninferiority; p = 0.04 for superiority). This result was durable out to 2-years.

My conclusions from the PARTNER 1a high-risk cohort and CoreValve trials are:

- For patients deemed at high-surgical risk, TAVI is at least equivalent to SAVR for reduction in all-cause mortality
- The concept of high-surgical risk is imprecisely defined and ultimately at the discretion of the treating Heart Team

Adoption of TAVI into clinical guidelines

Following the publication of these pivotal trials, TAVI was incorporated into guideline recommendations for the treatment of severe aortic stenosis(16,17). Both the American and European guidelines gave TAVI a class I recommendation for patients who are deemed unsuitable for SAVR, and a class IIa recommendation for patients who are deemed at high surgical risk.

Expansion of TAVI into intermediate risk patients

The initial foundational trials for TAVI established its safety and efficacy, initially in patients who were inoperable, and then in patients at high risk surgical risk. The natural evolution of this would be to then test TAVI in a less extreme risk group. To this end, the PARTNER 2 trial compared TAVI to SAVR in patients deemed at intermediate surgical risk(18). This trial used the next generation Edwards balloon-expandable valve, the Sapiens XT. This

device had lower profile deliverability systems, the larger 29mm valve size, and thinner struts. 2032 patients were randomised between the two competing therapies, with the primary endpoint being a composite of all-cause mortality and disabling stroke measured at 2 years in a non-inferiority design.

The rate of death or stroke was 19.3% with TAVI group and 21.1% with SAVR (HR 0.89; $p=0.25$; $p=0.001$ for non-inferiority). Importantly, in patients who had their TAVI performed via the transfemoral access route (as opposed to the more invasive transapical route), outcomes with TAVI appeared superior to SAVR (HR 0.78; 95% CI, 0.61 to 0.99; $p=0.04$).

As with the high-risk trials, in parallel to the PARTNER 2 trial there was another randomised trial of CoreValve in intermediate risk patients(19). This randomised 1746 intermediate risk patients to TAVI or SAVR. Similarly to PARTNER 2, the primary endpoint was all-cause mortality or disabling stroke at 2 years in a non-inferiority design. There was no difference between TAVI and SAVR for the primary endpoint (12.6% with TAVI and 14.0% with SAVR).

Thus, with the publication of these two trials TAVI has been established as a safe and effective therapy for patients with severe symptomatic aortic stenosis at intermediate surgical risk.

TAVI in low-risk patients

The natural progression for TAVI was now seen as evaluating the technology in clinical trials which recruited patients considered at low-risk for death with surgery. In 2019, two trials were published which set out to answer this question(20,21).

The PARTNER-3 trial (20) randomised 1000 patients to either surgical aortic valve replacement or TAVI via the transfemoral route with the implantation of a Edwards Sapien 3 balloon-expandable valve. The primary end point was a composite of death from any cause, stroke, or rehospitalization at 1 year after the procedure. TAVI was found to be superior to surgery for this outcome (hazard ratio, 0.54; 95% CI, 0.37 to 0.79; $P=0.001$ for superiority).

In parallel, the Evolut Low Risk trial investigators published the results of their trial(21) comparing surgical aortic valve replacement to TAVI with a suprannular self-expanding valve (the Medtronic CoreValve, Evolut R, or Evolut PRO valves). 1468 patients were randomised in this non-inferiority trial, in which the primary endpoint was a composite of death or disabling stroke at 24 months. This incidence of this endpoint was 5.3% in the TAVI group and 6.7% in the surgical group, and the prespecified non-inferiority margin was easily met (although the prespecified criterion for superiority was not met).

A paradigm shift for TAVI

This expansion of TAVI into younger and lower-risk patients has important consequences for how the procedure is viewed and how patients are assessed. During the initial TAVI experience, when patients at extreme risk were being treated, survival was the principal outcome of interest. However, as TAVI is now being demonstrated to be a good option for patients at intermediate risk, patients are surviving for many years after their procedure(22). It is therefore becoming of increasing importance to understand how to assess and treat any coexistent coronary artery disease for these patients who may be living for a decade or longer after their TAVI procedure. Avoiding residual ischaemia or additional revascularisation procedures may become important metrics in the future for TAVI studies, as well as quality of life metrics that may include freedom from angina.

Thus, the presence of CAD, which may have until recently been relegated to a secondary concern amongst TAVI patients, is now a major consideration for this patient group and will only take on greater significance in the coming years.

How common is CAD in patients undergoing TAVI?

Due to the common pathogenesis and risk factors, CAD is frequently seen in patients with severe aortic stenosis undergoing TAVI. The precise incidence, however, is difficult to

ascertain and the quoted values vary substantially between studies from as low as 44.2%(23) to as high as 75.4%(24).

The main reason for the varying incidence rates reported in the medical literature is likely to be due to the varying definition as to what constitutes “coronary artery disease”. Some definitions are centred upon clinical factors such as a history of prior myocardial infarction or a prior revascularisation procedure, and some are based on angiographic criteria (with all attendant limitations of visual or quantitative assessment of coronary stenosis severity(25,26)).

What is the impact of CAD on clinical outcomes for patients undergoing TAVI?

We have learned from the surgical literature that patients undergoing SAVR who have coexistent CAD have worse long-term outcomes(27,28), and that concomitant CABG at the time of valve surgery can improve outcomes in both the acute phase and longer term(28,29), although there is no randomised trial evidence to this effect. It is therefore of interest as to whether the same might be true for patients undergoing TAVI.

The currently available data have not definitively established the impact of CAD in clinical outcomes in patients undergoing TAVI and all such studies have important limitations.

One early observational study suggested that the presence of CAD meant that patients were 10 times more likely to die within 30-days of TAVI(30). As well as representing early clinical experience with devices and techniques which have since evolved significantly, this observational study demonstrated substantial imbalance between the two clinical groups. Patients who had CAD were inherently higher risk, as evidenced by a lower ejection fraction and higher EuroSCORE. Patients in the CAD group were also more likely to be treated via the transapical route, which is known to obviate some of the clinical benefit of TAVI. It is likely, therefore, that the higher mortality in the CAD group in this study is simply a reflection of a higher risk patient cohort treated with a higher risk interventional technique. Other observational studies have shown contrasting results. One registry of 136 patients showed similar survival rates in TAVI patients stratified by the extent of CAD(31). Another French registry (32) demonstrated a similar pattern in terms of patients referred for TAVI with CAD having a higher risk profile (EuroSCORE $31 \pm 18\%$, vs. $23 \pm 11\%$, $p=0.004$), and with the presence of CAD having no impact on survival ($p=0.28$). A meta-analysis of 7 studies and 2472 patients (33) suggested that the presence of CAD did not affect prognosis after TAVI when adjusted in a multivariate analysis. Finally, an Italian registry of 663 patients(34) suggested that while CAD did not affect mortality, patients who were not revascularised were more likely to suffer a myocardial infarction than those who were.

Due to the small number of studies in this field, and the limitations inherent in their observational methodology, there is substantial uncertainty in how CAD should be treated in patient undergoing TAVI.

In some patients with CAD, there may be concern regarding intraprocedural ischaemia during TAVI due to hypotension or rapid ventricular pacing. Conversely, performing PCI is not without risk due to the chronic, calcific nature of the CAD in many patients and the attendant increase in contrast volume required. There are also risks pertinent to the mandated use of dual antiplatelet therapy in these patients with an inherently high bleeding risk.

It is intuitive, therefore, to aim to limit to PCI as much as possible to lesions that are causing significant myocardial ischaemia and where it might be reasonably be assumed that PCI might improve the patient's long-term outcomes. The assessment of CAD in patients undergoing TAVI then becomes increasingly important.

Non-invasive assessments of ischaemia

There is an established role for the use of stress testing in patients with aortic stenosis where there may be some doubt regarding the patient's symptoms or the severity of the aortic stenosis, or to help in the assessment of patients with low-flow low-gradient aortic

stenosis(35). This is, however, a distinct entity from the use of stress testing in the assessment of CAD in patients with aortic stenosis.

The use of stress testing in these patients has been considered limited. This is, essentially, due to the limited specificity of stress tests in patients with severe aortic stenosis. A significant proportion (28-48%) of patients with aortic stenosis and unobstructed coronary arteries will exhibit signs of myocardial ischaemia during stress testing(36). This can be seen as symptoms of chest pain, ECG changes suggestive of ischaemia or regional wall motion abnormalities. Furthermore, there is no prospective data available that supports the use of non-invasive stress testing to determine revascularisation or any consequent impact on clinical outcomes. Finally, there have been potential safety concerns related to the use of pharmacological stress in patients with severe aortic stenosis(37).

Guidelines recommend against the use of non-invasive ischaemia tests to assess for the significance of CAD in patients with severe AS. Due to the limited utility of non-invasive ischaemia testing for guiding revascularisation, particular emphasis has recently turned to the role that intracoronary physiology may play in these patients.

Before outlining the currently available data for coronary physiology in patients with severe aortic stenosis, I will discuss the use of coronary physiology more broadly in

patients with coronary artery disease. Finally, I will discuss the unique haemodynamic profile of patients with aortic stenosis and how this can affect the coronary circulation.

Assessment of coronary stenosis severity

Historically, invasive coronary angiography and visual stenosis assessment has formed the basis of the assessment of coronary stenosis severity and determination of the need for revascularisation. However, this approach has inherent limitations. Firstly, angiography provides only a two-dimensional representation of the internal lumen of a coronary artery(38). Secondly, fluid dynamic mechanisms which underpin the dissipation of coronary blood flow and pressure loss are complex and not captured by angiographic metrics such as percentage reduction in luminal diameter or the length of the stenosis(39). Furthermore, visual estimation of angiographic stenosis severity is subjective and poorly reproducible(25,26). Finally, the appearance of the coronary angiogram is not predictive of the presence of myocardial ischaemia(40), and the presence and severity of myocardial ischaemia has been shown to predict adverse events(41,42) and it is therefore felt that treating ischaemia-producing lesions is linked to better clinical outcomes than when treatment is guided by angiography alone(43).

The need for intracoronary physiology

In view of this above stated importance of identifying ischaemia to guide treatment, patients may undergo non-invasive tests of ischaemia. These tests, however, have limitations. Firstly, they are of limited utility in patients with multivessel disease (due to the phenomenon of balanced ischaemia)(44,45). Secondly, a non-invasive ischaemia test can localise ischaemia to a myocardial territory, but cannot isolate a culprit vessel or lesion(46).

Due to these aforementioned limitations of angiographic assessments and non-invasive assessments, the use of intracoronary physiology has emerged as an invasive assessment of coronary stenosis severity which can be performed during cardiac catheterisation.

I will now discuss the basis of invasive coronary physiology, the development and validation of physiological indices of coronary stenosis severity and finally discuss their role in patients with aortic stenosis.

Coronary flow

A coronary stenosis causes myocardial ischaemia due to a reduction in blood flow. In response to any reduction in blood flow, the coronary microcirculation dilates. This vasodilatation can maintain normal resting coronary blood flow up to very severe degrees

of stenosis (approximately 85% diameter stenosis)(47). Hyperaemic flow, conversely, begins to fall at much lower degrees of stenosis (30-50%)(47).

This formed the physiological basis for the coronary flow reserve (CFR), one of the first indices of invasive coronary stenosis severity. CFR is defined as the ratio of hyperaemic blood flow to resting blood flow within the measured coronary artery(47). This ratio is a reflection of the capability to augment flow, which is a combined function of the epicardial artery and the microcirculation. There is strong prognostic data supporting the use of CFR(48).

Despite this strong prognostic data, and the ability to directly measure coronary flow velocity, the use of flow-based indices has not been integrated into clinical practice. This is primarily due to the technical difficulty associated with measuring coronary blood flow velocity. The Doppler-flow signal can be vulnerable to noise, and requires a large degree of optimisation to obtain an accurate flow trace. Furthermore, the Doppler wires themselves are stiff and difficult to manipulate compared to a standard coronary guidewire. For these reasons, measurements of coronary flow velocity are largely confined to the research setting. Also for this reason, there was renewed interest in the development of pressure-based indices of coronary stenosis severity which has formed the cornerstone of invasive coronary physiology in clinical practice. The use of pressure as a surrogate for flow is predicated on the proportionality of pressure and flow, which is

observed when intracoronary resistance is stable, a relationship analogous to Ohm's law. When this fundamental pre-requisite is achieved, a decrease in pressure across a coronary stenosis reflects a decrease in coronary blood flow to the dependent myocardium.

Resistance and microvascular resistance

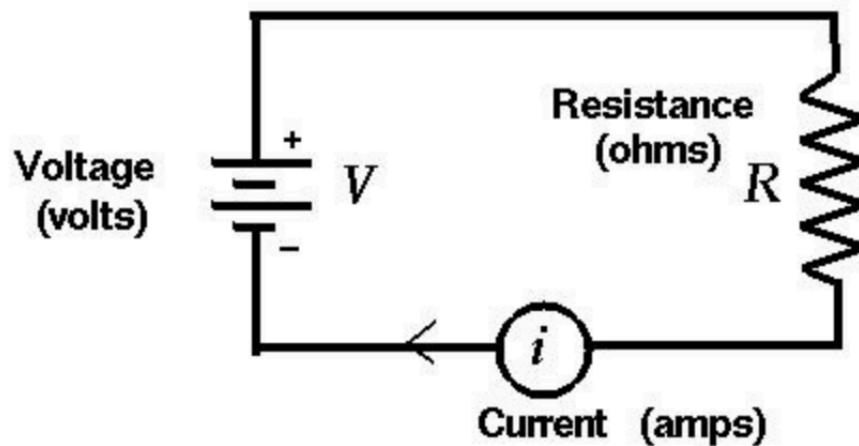
Throughout physics and biology, there is a well-defined concept of resistance which is the *potential difference* required to sustain a *flow*. The formula that defines resistance in all fields is:

Resistance = Potential difference / flow

In electrical engineering, the potential difference is voltage (volts), and flow is current (amps), and the resistance is ohms.



Ohm's Law



$$V = i R$$

In fluid dynamics, the potential difference is a pressure difference (e.g in mmHg). Strictly speaking, flow should be described as a volume per unit time (such as ml/min). This yields a resistance in mmHg/(ml/min). However, it is difficult to measure volume flow rates in the intact human directly. One way to estimate it is to measure the velocity (e.g with Doppler) and multiply this by the cross-sectional area indicative of flow. The latter quantity is itself also a little difficult to measure, however.

Therefore, a proxy for microvascular resistance that is commonly used in coronary physiology research is to set aside the assessment of cross-sectional area and simply

calculate pressure over velocity. This gives a quantity which will rise and fall with microvascular resistance but is not itself microvascular resistance because of the absence of cross-sectional area information. This is commonly termed the 'microvascular resistance' and has been in extensive use in the field(49).

When using an index of microvascular resistance, pressure over velocity, we should be aware that while this reliably detects when resistance changes, in which direction and by which factor, it does not directly give a value for microvascular resistance.

Fractional flow reserve

Fractional flow reserve (FFR) is defined as the ratio of the coronary pressure distal to a stenosis (P_d) relative to the aortic pressure proximal to the stenosis (P_a) under conditions of maximal hyperaemia(50). The induction of maximal hyperaemia is used to achieve a condition of stable intracoronary resistance. This is achieved by the administration of a potent vasodilator drug. Intravenous or intracoronary adenosine is the most commonly used agent, both in clinical practice and in validation studies, and therefore represents the current gold standard for the assessment of FFR(51). The theoretical value for FFR of a normal coronary artery is 1.0, irrespective of vessel or patient. FFR is a vessel-specific index and represents the fraction of maximum blood flow that remains despite the

presence of a coronary stenosis. Accordingly, an FFR value of 0.80 confers a 20% pressure loss across the stenosis.

Clinical trial data for FFR

The prospective, randomised DEFER (Deferral versus performance of PTCA in patients without documented ischaemia) trial⁽⁵²⁾ allocated patients with stable coronary disease and a negative FFR value (>0.75) to either deferral or performance of PCI. The primary end-point, event-free survival, was similar between deferred and performance groups (89% vs. 83%), but was significantly lower in the reference group of patients with a positive FFR undergoing PCI (78%). Subsequent long-term follow-up of the DEFER cohort confirmed that, in patients with stable coronary disease, deferral of coronary stenoses with negative FFR >0.75 was safe and that revascularization of these stenoses did not confer additional symptomatic benefit from angina at 5⁽⁵³⁾ and 15 years⁽⁵⁴⁾. This advocated FFR, with a cut-off value of 0.75, as an accurate tool for identification of coronary stenosis that can safely be managed with medical therapy alone.

The FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial was a prospective, multicentre, randomized study that assigned 1,005 patients with multivessel CAD to coronary revascularization guided either by FFR (using a cutpoint of 0.8) or angiography alone⁽⁴³⁾. The primary endpoint, major adverse cardiac events

(MACE) at 1 year, was significantly lower in the FFR group compared with those assessed with angiography-alone (13.2% vs. 18.3%, respectively; relative risk 0.72; 95% CI 0.54-0.96; $p=0.02$). Furthermore, FFR-guided revascularization was associated with the placement of fewer stents, the use of less contrast, and reduced costs compared with revascularization guided by visual assessment alone. Subsequent published evidence suggested that increased adverse events follow deferral of lesions falling in the 0.75-0.8 range and using 0.8 as the FFR cut-point maintains a specificity of 90%, providing endorsement for the higher value(55).

The DEFER and FAME trials had served to prove that in stable coronary disease, PCI of lesions deemed to be non-ischaemic by FFR was at best, ineffectual, and at worst, likely to be harmful. Subsequently, the FAME 2 (Fractional Flow Reserve guided PCI versus Medical Therapy in Stable Coronary Disease) trial tested the hypothesis that an FFR-guided PCI strategy plus optimal medical therapy (OMT) would be superior to OMT alone for the treatment of patients with stable CAD and functionally significant ($FFR<0.8$) coronary stenoses(56). Recruitment ceased early following a large reduction in the primary composite endpoint in the PCI+OMT versus OMT group (HR 0.32; 95% CI:0.19-0.53; $p<0.001$). On closer inspection, this difference was accountable largely due to an eight-fold decrease in the rate of urgent revascularization in the PCI+OMT arm (1.6% vs 11.1%; HR 0.13; 95% CI 0.06-0.30; $p<0.001$). Notably, the rates of death from any cause, cardiac death and MI were not statistically different between the two groups. This

observation was consistent at 2 and 3 year follow up(57). Finally, a cost-effectiveness analysis of the FAME 2 data demonstrated that an initial strategy of FFR guided PCI was attractive from an economic standpoint(58).

The RCT evidence for FFR is summarised in Table 1.1. As a result of this body of work, FFR has class 1A recommendations from international guideline committees(59,60).

Instantaneous wave-free ratio

Lance Gould's seminal work in 1978(61) identified a period during diastole when coronary resistance was stable, and consequently pressure and flow were proportional. Using wave intensity analysis, it was possible to characterise a specific portion of this period in which the generation of new pressure waveforms is absent, and competing waves that affect coronary blood flow are quiescent(62). This wave-free period therefore offers a window of diastole during which intracoronary resistance was constant. This formed the basis for the instantaneous wave-free ratio (iFR). iFR is defined as the ratio of distal coronary pressure to proximal aortic pressure during the wave free period of diastole:

$$\text{Instantaneous wave – free ratio (iFR)} = \frac{P_{d_{wfp}}}{P_{a_{wfp}}}$$

The diagnostic accuracy of iFR as compared to FFR was tested in the ADVISE study(62), and also subsequently the ADVISE registry(63). Both of these studies demonstrate excellent classification agreement between iFR and FFR for intermediate coronary lesions. iFR was then compared to FFR in a series of studies which used a third-party adjudicator for ischaemia (either invasive or non-invasive). The CLARIFY study(64) demonstrated that iFR and FFR had equivalent agreement classification with hyperaemic stenosis resistance (HSR) which is an invasive measure of the haemodynamic significance of a coronary stenosis. When iFR and FFR were compared to CFR, it was found that iFR had better agreement and closer correlation with CFR than FFR did(65). iFR has also been validated against non-invasive measures of ischaemia(66).

Clinical trial data for iFR

Despite a wealth of validation data, iFR required outcome data to facilitate full adoption into clinical practice. The publication of two recent, large prospective, multicentre, randomized controlled trials has addressed whether iFR-guided revascularisation is equivalent to FFR in patients with intermediate coronary lesions. The main results of DEFINE-FLAIR(67) (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation) and iFR-SWEDEHEART(68) (Evaluation of iFR vs FFR in Stable Angina or Acute Coronary Syndrome) trials were concordant and demonstrated that coronary revascularization guided by iFR was non-inferior to revascularization guided by FFR with

respect to the rate of MACE at one year: DEFINE-FLAIR 6.8% vs. 7.0% respectively, $p < 0.001$ for non-inferiority; SWEDEHEART 6.7% vs. 6.1%, respectively, $p = 0.007$ for non-inferiority.

These trials were intended to have similar designs to permit the synthesis of their results (Table 1.2), thereby producing the largest dataset of physiology-guided coronary revascularization in contemporary practice (4,529 patients in total). Both trials used identical pre-specified single thresholds for treatment ($iFR \leq 0.89$, $FFR \leq 0.80$) and, and the primary endpoint was also identical (MACE, defined as a composite of death from any cause, non-fatal MI, or unplanned revascularization).

In both trials, procedural adverse symptoms and clinical signs were significantly more prevalent in those patients randomised to FFR. DEFINE-FLAIR demonstrated that procedural time was significantly shorter with iFR than with FFR.

The RCT evidence for iFR is summarised in Table 2. On the basis of these results, iFR received a class 1A recommendation from the ESC in 2018(69).

These two trials finally conclusively established iFR as an alternative index to FFR, and successfully challenged the dogma that maximal hyperaemia is required for the assessment of the functional significance of a coronary lesion.

FFR and iFR are continuous variables but they have become adopted as dichotomous tests with a threshold of 0.80 and 0.89 respectively. They have never been tested for sensitivity and specificity for identifying future MI or cardiac death. These indices have become dichotomous indicators of therapy with no assessment of sensitivity and specificity and its proponents recommend it forcefully and with absolute certainty (see below) and they have been adopted uncritically in the guidelines.

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Coronary pressure never lies.

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⊕ Author information

Abstract

Fractional Flow Reserve (FFR), calculated by coronary pressure measurement, is the invasive gold standard to assess the hemodynamic significance of a coronary stenosis. FFR reliably indicates whether a stenosis is responsible for inducible ischemia and if percutaneous coronary intervention is appropriate. False positive or negative FFR is rare. Occasionally, however, a clinical or angiographic condition is encountered in which in first instance the FFR measurement contradicts the intuitive feeling of the interventionalist. Further examination in such cases, however, often reveals a clear physiologic explanation and in this manner FFR "lifts the veil". Two such patients are presented in this case report and the reasons for apparent or actual false positive or negative FFR are discussed.

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iFR and FFR in patients with severe aortic stenosis

As discussed, the use of intracoronary physiology to guide revascularisation provides superior patient outcomes than an angiographic-guided approach. It is therefore logical to see whether such an approach could be applied to patients with severe aortic stenosis

and coexistent CAD. The foundational trials for both FFR and iFR, however, excluded patients with aortic stenosis and their use has never been validated in this cohort. There has been recent interest in utilising physiology in this setting, and some recent data has begun to accumulate in the field.

The majority of the published work on iFR and FFR in patients with severe aortic stenosis has been from the Verona group. Pesarini et al(70) measured FFR in 133 lesions before and TAVI. They reported no overall change in FFR before and after TAVI. However, when their analysis was restricted to vessels with an FFR below the conventional treatment threshold of 0.8, they found a significant change. For these patients, the FFR value declined after TAVI (0.71 ± 0.11 versus 0.66 ± 0.14); they also suggested that lesions with a greater than 50% diameter stenosis reduction saw a decline in FFR after TAVI (0.84 ± 0.12 versus 0.82 ± 0.16 ; $P=0.02$). The authors stated that the indication to treat a coronary lesion only changed in 6% of patients, but this is based on an assumption that the FFR cutpoint of 0.8 is valid in patients with severe aortic stenosis. The overall pattern from this study seemed to emerge that FFR may be overestimated in patients with severe aortic stenosis. This is consistent with previously published work in unobstructed coronary arteries where FFR declined significantly immediately post-TAVI(71).

The same group also published a study aiming to compare the diagnostic accuracy of FFR and iFR in patients with severe aortic stenosis(72). The authors concluded that an iFR

value cutpoint of 0.83 was the best predictor of an FFR value below 0.8. This approach, however, overlooks the fact that the FFR cutpoint of 0.8 was never validated in severe aortic stenosis.

More recently, Scarsini compared diagnostic categorisation of iFR to FFR in 66 patients (145 lesions) before and after TAVI (73). The mean iFR value pre-TAVI across the population was identical to the mean FFR value. iFR pre-TAVI had a negative predictive value of 98.8%. The mean iFR pre-TAVI was identical to the iFR value post-TAVI. There was a 15% categorisation change by iFR after TAVI. Their study highlights 3 important aspects of the assessment of any physiological index in a new clinical context: (1) the need for a valid reference standard; (2) the importance of understanding stenosis distribution when interpreting results; and (3) the need for further studies in this field.

The importance of a valid reference standard

FFR is dependent on maximal hyperaemia. In patients with aortic stenosis this is significantly impaired due to the stenosed aortic valve, the hypertrophied myocardium of the left ventricle, elevated left ventricular end-diastolic pressure, and associated remodelling of the coronary microcirculation(74). These factors result in attenuated hyperaemia.

The identical iFR and FFR values in Scarsini's study elegantly demonstrate this inability of adenosine to increment flow these patients. The inability to achieve maximal hyperaemia invalidates the physical principles upon which FFR depends and therefore calls into question the validity of using this index as a reference standard in patients with aortic stenosis, and certainly the use of the 0.80 cut-point used in this study. The negative and positive predictive values derived in this study should therefore be interpreted cautiously. Indeed, studies using coronary flow velocity as well as pressure have highlighted the sensitivity of hyperaemic indices to aortic stenosis, albeit in patients without coronary lesions(71). Interestingly such studies suggest that hyperaemic parameters are more susceptible to change post-TAVI than resting parameters. This is consistent with Scarsini's results, demonstrating identical average iFR values pre and post-TAVI.

The importance of stenosis distribution

The mean iFR before and after TAVI was identical (0.89). However, it was reported that in 15% of patients iFR categorisation of functional significance changed post-TAVI. The direction of change was unpredictable and higher than the categorisation change with FFR. The authors conclude that iFR should be used in caution in patients with severe aortic stenosis as there was significant variation post-TAVI.

To conclude this, however, fails to appreciate the role of population distribution and the limitations of using a continuous variable dichotomously. This apparent greater classification change is a result of the distribution of iFR values when compared to FFR values. The majority of patients in this study had iFR values that group around the iFR cut-point of 0.89. Any biological variation will therefore lead to treatment reclassification of a large proportion of patients when the inherent variability of iFR causes its value to drop below or climb above the cutpoint. In contrast, the majority of patients had FFR values (mean pre-FFR 0.88) that were significantly further away from the FFR cut-point (due to attenuated hyperaemia). Therefore, the biological variation and numerical changes in FFR resulted in fewer stenosis classification changes. The classification change, or lack of change, is therefore an artefact of using a continuous variable such as FFR or iFR dichotomously, stenosis distribution, and the inadequate hyperaemia seen in these patients.

In such a scenario, the index with a mean value (majority of patients) far away from the cut point can appear to have less categorisation variability despite the same numerical variability (see Figure 1.1). This categorisation variability around the treatment threshold has been defined in FFR. When measured 10 minutes apart in the same patient FFR itself has a categorisation change in 15%, increasing to 50% when FFR values are close to the treatment threshold(75).

The majority of iFR values (left panel) centred around the iFR cut point (0.89); as a result any inherent variability of iFR exposes a large proportion of patients (grey area under curve) either just dropping below or above the treatment threshold. However, a minority of FFR values centred around the FFR cut point (0.80) due to an inability to achieve maximal hyperaemia. As a result, fewer patients (grey area under curve) were reclassified despite the same inherent variability of FFR. Treatment reclassification is therefore dependent on stenosis distribution and the treatment threshold, which is yet to be defined for FFR in this context.

How does the presence of aortic stenosis affect the coronary circulation?

There are two determinants to coronary blood flow: proximal squeezing forces from the aortic end of the coronary artery; and distal suction forces from the microcirculation. This phasic nature of coronary flow is different in a coronary artery when compared to a systemic artery (Figure 1.2).

Coronary flow reserve, as previously discussed in detail, is the ratio of hyperaemic blood flow to resting blood flow. The left ventricle hypertrophies in the presence of severe aortic stenosis as a response to the increased afterload caused by the stenotic valve. This increased myocardial mass by definition necessitates an increase in oxygen demand. To meet this increased demand, patients with severe aortic stenosis have a compensatory

higher resting coronary flow compared to control groups without aortic stenosis(71,76). Simultaneously, there is a reduction in hyperaemic coronary blood flow in patients with severe aortic stenosis(68,73). This is thought to be caused at least in part by external compression of the microvasculature by the hypertrophied ventricle which leads to fixed rise in resistance(77). Patients with severe aortic stenosis also have elevated levels of circulating vasoconstrictors which counteract the effect of hyperaemic agents(78). This increase in resting flow and reduction in hyperaemic flow inevitably leads to a reduction in the coronary flow reserve.

Insights from wave intensity analysis

A wave is defined as a disturbance that propagates from one place to another with time. Wave intensity analysis can be used to identify and quantify these waves and in its simplest form, net wave intensity, is calculated as the product of the change in pressure (dP) and change in flow velocity (dU) at a particular point in the cardiac cycle. Its units are of power ($Ws^{-2}m^{-2}$); with a negative value indicating a backward-travelling wave and a positive value indicating a forward-travelling wave. In the context of coronary arteries, backward-travelling waves originate from the microcirculatory or distal end of the vessel, and forward-travelling waves from the proximal end of the vessel. The two dominant waves that contribute to coronary blood flow have been identified as the systolic forward compression wave (FCW), and diastolic backward expansion wave (BEW).

In a study of 11 patients with severe aortic stenosis and unobstructed coronary arteries, pacing at elevated heart rates was used to increase the demand for coronary blood flow(79). Instead of augmenting when the heart rate rose, the coronary diastolic suction wave was seen to decrease. This maladaptive pattern was reversed immediately after TAVI. This was posited as a potential source of angina in patients with severe aortic stenosis and unobstructed coronary arteries.

In another invasive flow study of 15 patients with severe aortic stenosis and unobstructed coronary arteries(76), the effects of aortic stenosis on the proximal systolic contribution to coronary flow was explored. In this study, patients with severe aortic stenosis had an attenuated forward compression wave, which was partially relieved by TAVI. This is likely a function of the stenotic aortic valve leading to a reduction in forward systolic blood pressure, and therefore a reduction in coronary perfusion pressure which leads to a net reduction in systolic coronary flow.

Aims of thesis

I will conduct a series of experiments which will advance our knowledge of the coronary haemodynamics in patients with severe aortic stenosis and coronary artery disease. These experiments will be centred upon patients undergoing transcatheter aortic valve implantation (TAVI), because this situation will permit me to assess the coronary

circulation in the presence of severe aortic stenosis (pre-TAVI) and in the absence of severe aortic stenosis (post-TAVI) in the same patient. Such an approach will allow me to isolate the effect of the valvular lesion (and its treatment) on the coronary circulation, and minimise the potential effect of any confounding factors. I will assess the haemodynamics both at rest and during hyperaemia, and will perform phasic analyses to examine the differential effects of TAVI on coronary flow in different phases of the cardiac cycle.

My thesis will answer three key questions:

Question 1. In patients with severe AS and CAD, what is the effect of the presence of severe AS on coronary flow velocity, and consequently on FFR and iFR?

Question 2. Does aortic stenosis affect microvascular physiology?

Question 3. Is the effect of aortic stenosis on coronary physiology only short-term, i.e. once the aortic stenosis is removed, there is no further change, or is there a longer-lasting effect?

Firstly, I will perform combined pressure and flow velocity studies before and after TAVI in patients with severe aortic stenosis and coronary artery disease. These measurements will be made in resting conditions and during hyperaemia, and phasic analysis will be

performed to determine the acute effect of TAVI on coronary flow velocity and its effect on the most common clinically-used indices of coronary stenosis severity (FFR and iFR). These studies will all be undertaken within a single catheter-laboratory procedure.

Secondly, I will quantify the effect of severe aortic stenosis on the function of the coronary microcirculation and determine if this is influenced by concomitant coronary disease. I will also study another cohort of patients undergoing PCI for coronary lesions but without severe aortic stenosis, to assess the influence of the coronary lesion – and its treatment – on the microcirculation. This is an exploratory analysis to qualitatively discern the impact of severe AS and coronary stenoses on the microcirculation, and how each responds to treatment.

Finally, I will examine the longer-term effects of TAVI on coronary flow velocity by repeating invasive pressure and flow velocity studies in patients 6-months following TAVI. This will allow me to determine whether the acute changes in coronary flow velocity seen immediately after TAVI are sustained or change at longer-term follow-up.

The overall aim of this thesis is to provide the first systematic assessment of intracoronary pressure-flow velocity relationships in patients with severe aortic stenosis and coronary artery disease before and after transcatheter aortic valve implantation.

Tables

Table 1.1. Summary characteristics of patient outcome FFR trials.

	Question	Subjects	Study population (n)	Primary endpoint	FFR cut- off	Mean FFR	Conclusion
DEFER	Safety of deferral of PCI where FFR>0.75	SCD	325	24 month MACE	≤ 0.75	Defer: 0.87±0.07 (n=91) Performan ce: 0.87±0.06 (n=90) Registry: 0.56±0.16 (n=144)	Deferral of PCI safe where FFR>0.75
FAME	Efficacy of FFR guided PCI vs. PCI based on angiograp hy alone	Multi- vessel SCD / ACS with non culprit stenosis	1005	12 month MACE	≤ 0.75	Overall cohort: 0.71±0.18 Ischaemic lesions: 0.60±0.14 Nonischae mic	FFR guided PCI superior to PCI based on angiography alone

					lesions:	
					0.88±0.05	
FAME 2	FFR	Multi-	1220	MACE (Trial	≤ FFR	FFR guided PCI +
	guided	vessel		halted at 7	0 guided	OMT reduces urgent
	PCI +OMT	SCD		months	. PCI +	revascularisation
	vs OMT			follow up)	8 OMT:	compared to OMT
	alone				0 0.68±0.10	alone
	where				OMT	
	FFR≤0.80				alone:0.68	
					±0.15	

Values are mean ± SD unless otherwise indicated. SCD = Stable coronary disease

Table 1.2. Summary characteristics of patient outcome iFR trials.

	Study population (n)	FFR mean	iFR Mean	Deferred by FFR (%) total assessed)	Deferred by iFR (%) total assessed)	FFR MACE (%)	iFR MACE (%)	p-value for non- inferiority
DEFINE- FLAIR	2,492	0.83±0.09 (n=1,250)	0.91±0.09 (n=1,242)	583 (46.6)	652 (52.5)	7.0	6.8	<0.001
iFR- SWEDE- HEART	2,037	0.82±0.10 (n=1,019)	0.91±0.10 (n=1,018)	438 (43.5)	476 (46.7)	6.1	6.7	0.007

Values are mean ± SD unless otherwise indicated.

Figures

Figure 1.1. The importance of stenosis distribution on treatment categorisation.

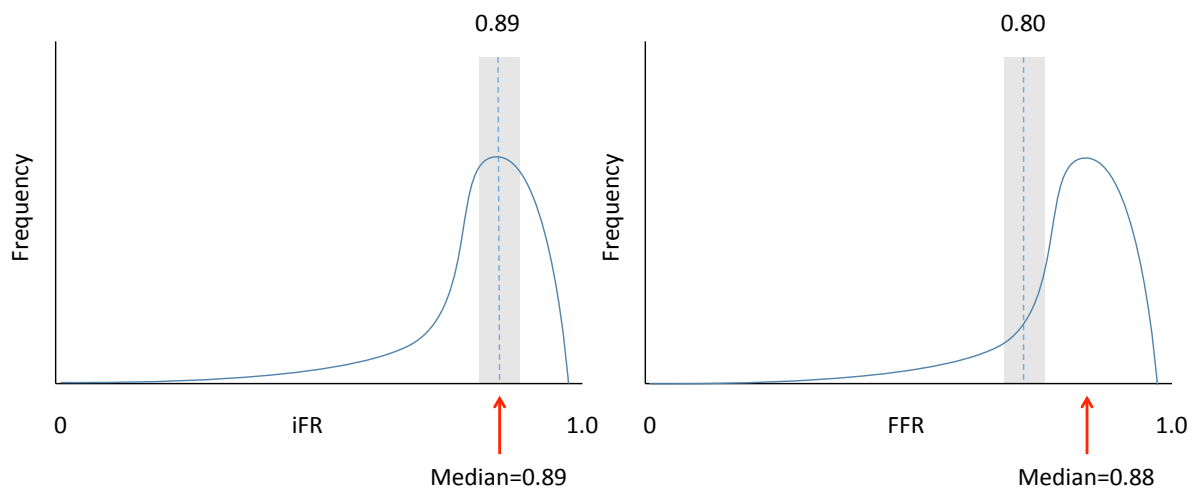
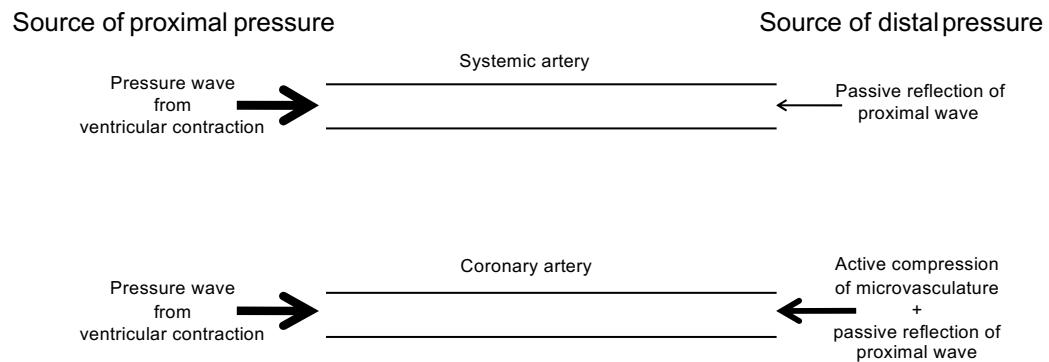
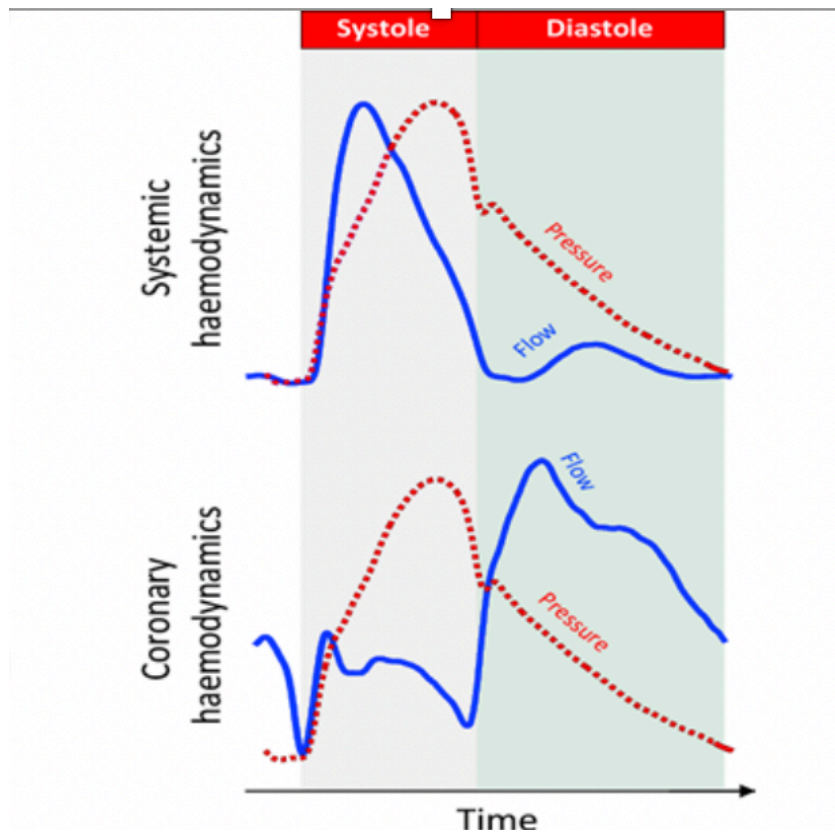


Figure 1.2 The differential natures of coronary flow in systemic and coronary arteries.



The presence of severe aortic stenosis can affect coronary blood flow both at the proximal and distal ends, and makes the coronary physiology of patients with severe aortic stenosis uniquely complex.

Figure 1.3. Pressure and flow relations during different phases of the cardiac cycle in both systemic and coronary vessels.



2.Methods

Participating centres

The vast majority of patients were recruited from The Hammersmith Hospital, Imperial College Healthcare NHS Trust. Some additional patients were recruited from Skane University Hospital, Lund, Sweden; Amsterdam Medical Center, Amsterdam, The Netherlands; and Aarhus University Hospital, Aarhus, Denmark. Raw data from all centres was sent to myself, and I performed all aspects of data processing and each analysis myself.

Patient recruitment and ethical approval

All patients recruited to the studies performed as part of this thesis were scheduled for TAVI as part of their planned clinical care. Patients were identified at the TAVI MDT meetings and TAVI outpatient clinics. After determining suitability, patients were approached during their pre-assessment appointments. All patients were provided with the Patient Information Sheet (see Appendix). Patients were given time (over 24 hours) to consider their participation, and any questions they may have had were answered.

Ethical approval was provided by the Oxford Research Ethics Committee (ref 14/SC/1103).

Inclusion criteria

The inclusion criteria for the study were as follows:

- Symptomatic severe aortic stenosis scheduled for TAVI on clinical grounds by the Heart Team
- Moderate to severe coronary artery disease on angiography

Exclusion criteria

The exclusion criteria for the studies were as follows:

- Known non-viable myocardium in the area of the corresponding coronary artery being studied
- Contra-indication to the administration of adenosine
- Inability to consent
- Weight over 200kg

Cardiac catheterisation

Summary of catheterisation protocol

Cardiac catheterisation and coronary angiography were undertaken via either the transradial or transfemoral route at the operator's discretion, using standard equipment. A guiding catheter was used to intubate the vessel of interest. 5000 units of heparin were administered intra-arterially. A dual pressure and Doppler sensor-equipped 0.014"

guidewire was used for all physiological assessments (ComboWire, Volcano Corp, San Diego). The guidewire signal was normalised in the aorta and then advanced a minimum of three-vessel diameters distal to the stenosed segment. After an optimal and stable flow-velocity signal was obtained, resting pressure and flow measurements were recorded. Hyperaemia was then induced via a 150 µg bolus of intracoronary adenosine, and hyperaemic measurements were made. At the end of each recording, the pressure sensor was returned to the catheter tip to ensure that there was no pressure drift. When drift was identified (≥ 0.01), all measurements were repeated. Left ventricular end diastolic pressure was recorded using a pigtail catheter placed in the LV cavity. The entire protocol was repeated immediately following the deployment of the new aortic valve.

TAVI procedure

All TAVI procedures were undertaken according to standard clinical protocols. All patients were treated under local anaesthetic. The valves used were either the balloon-expandable Edward's Sapien XT/S3 valves (Edwards Lifesciences LCC, Irvine, CA), the self-expandable Medtronic CoreValve/Evolut-R valves (Medtronic Inc, Minneapolis, MN) or the repositionable Lotus valve (Boston Scientific, Natick, MA); valve choice was at the operator's discretion.

ComboMap system

The ComboMap system (see Figure 2.1) processes the information it receives from the guide wire (ComboWire), pressure transducer (from the catheter laboratory table) and other external inputs (ECG). Intravascular blood pressure and/or blood flow velocity measured in the coronary arteries during procedures are displayed real-time on the console.

The ComboMap processes the following data: 1) distal coronary pressure (Pd) and coronary flow velocity measured from the Combowire; 2) the aortic pressure measured from the guiding catheter tip; and 3) the electrocardiogram (ECG) measured from the patient.

The guidewire is connected to the machine via a mobile Pimette which can be placed close to the patient during the invasive study but avoids contact with fluids. Care was taken to maintain sterility throughout. The console is connected directly to the transducer which receives aortic pressure from the catheter. The ECG is optimised to ensure the R-wave is the largest point, and is used to define phases of the cardiac cycle during data processing and analysis.

Recording is selected manually and made prospectively. Recordings are timestamped but separate detailed notes regarding data acquisition are made simultaneously to ensure the robustness and accuracy of the data.

ComboWire XT

The ComboWire is a steerable guidewire which combines two different sensors: pressure and flow velocity (Doppler). The guide wire has a diameter of 0.014" (0.36 mm) and a length of 185 cm; this is the same as a standard coronary guidewire. Wire activation requires flushing with heparinised saline while the wire remains in the packaging. The two connectors (RJ45 type for pressure and multi-pin for flow velocity) are connected to the pimmette. When this is done, the console system will activate the wire and start a calibration system. The wire tip is straight and requires shaping to permit manipulation and steering within the coronary artery. Caution is advised during wire-shaping to avoid damaging the sensors at the tip.

Pressure sensor

The pressure sensor uses the MEMS (MicroElectroMechanicalSystems) technology to form a thin silicon diaphragm over a pressure chamber. Tiny resistors are embedded in the diaphragm, and their resistances change when the diaphragm flexes in response to the

changes in blood pressure. The pressure electronically monitors the resistor values, using factory calibration coefficients to convert the resistance into a pressure reading.

Doppler sensor

The Doppler sensor utilises quartz crystals; when an electric current is applied to these crystals, they change shape rapidly. The vibrations of the crystals produce sound waves that travel outward. Conversely, when sound or pressure waves hit the crystals, they emit electrical currents. Therefore, the same crystals can be used to send and receive sound waves. The transducer can therefore be used both to transmit and receive ultrasound signals. The signal processing electronics uses the pulsed-wave Doppler method, generating waveforms and processing the frequency-shifted echo signals to extract the blood flow velocity information from the received signal.

Catheters

Standard 6 French guiding catheters were used for all cases. The choice of guiding catheter was left at the discretion of the operator. Typically, an Extra Back Up (EBU) or Judkins Left catheter was used for the left coronary artery, with the size determined by each individual patient's anatomy and aortic root dimensions. Typically, a Judkins Right 4.0 was used for the right coronary artery. On occasions, different guiding catheters were required post-TAVI to intubate the coronary arteries after the new valve had been

implanted; in no patients was inability to reintubate the coronary ostia post-TAVI a reason for the protocol not being completed.

Medication

No changes to the patient's usual medical regimen were made pre-procedure. Patients were loaded on antiplatelet therapy pre-TAVI as per local institutional policy. Before the insertion of the ComboWire, 5000 units of heparin were administered. The activated clotting time was checked with a target of 250-300 seconds.

Hyperaemia was induced via the use of adenosine. This was administered as an intracoronary bolus of 150 µg. I elected to avoid giving a prolonged intravenous infusion as I did not want to precipitate perilous drops in systemic blood pressure in patients with severe aortic stenosis. Any safety concerns regarding transient heart block in patients with severe aortic stenosis were mitigated by the fact all patients had a transvenous pacing system in-situ.

Aortic and coronary pressure measurement

Aortic pressure is measured via the fluid-filled hollow guiding catheters. Pressure is transmitted through a fluid column to an external transducer, to which the fluid-filled system is connected. To ensure consistent and accurate data, the distance between the

coronary artery to the pressure transducer was kept to a minimum and the catheter was kept free of bubbles. The pressure transducer was fixed to the catheter table to avoid erroneous readings of pressure due to height changes of the transducer. Before each case, the fluid-filled catheters was zeroed at the right atrial level with the patient supine. Over-engagement of the guiding catheter can cause pressure damping, which is seen as a reduction in the aortic blood pressure and loss of the dichrotic notch. This will lead to a falsely low Pa value which will impact on all physiological pressure measurements (causing artificially higher iFR and FFR values). The aortic pressure waveform was carefully inspected throughout to ensure there was no damping.

The previously discussed ComboWire was used to record distal coronary pressure (Pd). The first step in preparation is flushing the wire with room temperature heparinised saline. Then the wire is connected using the pimmette and calibration of the pressure wire was carried out outside the body, with the wire positioned and rested on the table, through an automated process by the ComboMap. The wire was then removed from the packaging and the tip was shaped to permit steering of the wire.

Whipping artefact can affect Pd readings. This is observed if the pressure sensor is striking the vessel wall. This can be over-come by withdrawing the wire slightly or gentle manipulation. Care was taken to avoid whipping, and other artefacts, throughout all physiological assessments.

Pressure normalisation

All pressures were 'normalised' or 'equalised' at the ostium of the artery. When the wire sensor was introduced into the ostium of the vessel (e.g. left main stem or right coronary artery), the introducer needle was removed and the Y- connector port was firmly closed. If the Y-connector is not closed, then blood leak means the aortic pressure trace is underestimated

After normalisation, the Pd and Pa trace should both be 1.0 and be overlaid over each other with no temporal delay. If any of these criteria were not met, then normalisation was repeated.

Pressure drift

After each measurement, the wire was returned to the vessel ostium to check for "pressure drift". This is observed a Pd/Pa ratio which is not 1.0. This drift can be observed in either the upward or downward direction. The cause of drift is degradation of signal output from the pressure sensor over the time it takes to complete a case.

Although small levels of drift (up to 0.02 units) are considered clinically acceptable, I did

not accept any level of drift for these cases. If any drift was encountered, the wire was normalised again, and the recording was repeated in its entirety.

Flow velocity measurement

Coronary flow velocity is measured using the ComboWire. The Doppler sensor is located approximately 5mm from the tip of the wire. The pulsed Doppler beam angle is 45 degrees and insulates a sample volume approximately 4 mm downstream of the Doppler probe. Fine rotational movements are carried out so that the Doppler beam captures the highest velocity. The instantaneous peak velocity of blood (IPV) is recorded.

The manipulation of the wire to optimise the flow trace can be challenging: the aim is to obtain the highest velocity trace possible with the densest spectral trace. Once a good signal is obtained, effort is concentrated on optimising the digital tracking of the spectral trace. This tracking envelope represents IPV, and it is only this envelope that is available for offline analysis. Adequate tracking is therefore essential.

The first step in optimising the envelope is to alter the scale so that a small, dense signal is obtained. At this point, the IPV threshold is adjusted between 0 and 4 to find the optimal threshold for close tracking. Once good tracking is achieved, the scale can be expanded again. Once good traces and good tracking are achieved, prolonged recordings (60-120

seconds) were made. Meticulous documentation of timings of recordings was taken to facilitate offline analysis of the haemodynamic data.

Data acquisition process

The outputted signals of pressure and velocity taken from the ComboMap connector panel are in analogue form. These signals together with the electrocardiogram signal are fed into a BNC connector box (BNC-2010, National Instruments). A 70 multi-pin output cable was then fed from this connector box into a National Instruments analogue to a digital PCMCIA card (DAQ-Card AI-16E-4) within the PC.

Customized data acquisition software was developed and written using Labview (National Instruments). The hardware and software was developed to be stable at high sampling frequencies (in excess of 10000Hz). However, as the output frequency from the ComboMap console was substantially lower, the sampling frequency was standardized at 1000Hz. Each of Pa, Pd, IPV, APV and ECG were stored in an .SDY file.

Study Manager

The SDY file was exported at the end of the procedure from the ComboMap and opened in a customised software programme, Study Manager (Version 2.2.11.16, Academic

Medical Centre, The Netherlands). Study Manager allows for visualisation of the ECG, pressure traces and flow envelopes (Figure 2.5).

Using the Study Manager software, appropriately marked out segments of data were extracted as .txt files. These were labelled clearly to define when the recording was made i.e. "pre-TAVI, hyperaemia", or "post-TAVI baseline". A minimum of 5 beats of data was required for extraction and further analysis.

Matlab

A bespoke Matlab programme (Mathworks, Inc., Version 6.0.0.88) was written which facilitated phasic analysis of the invasive haemodynamic data. This allowed identification of the whole cardiac cycle, systole, diastole and the wave free period.

The first step would be to select the portion of the recorded traces for analysis (Figure 2.6).

After this, pressure and flow traces were displayed, as well as wave intensity analysis (Figure 2.7).

By selecting appropriate points in the cardiac cycle, phasic analysis was possible. A schematic of how this is performed is shown in Figure 2.8.

At this stage, data for pressure, flow and resistance was outputted for the whole cardiac cycle, systole, diastole, and the wave-free period.

R Studio

Further statistical analysis was performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). This program manipulated the raw .csv data using the 'dplyr' package and plotted the raw data using the 'ggplot2' package.

Overall data collection and synthesis

As described earlier, the majority of patients were recruited from The Hammersmith Hospital, Imperial College Healthcare NHS Trust. There were two principle challenges to data collection:

- 1) Occurrence of intraprocedural complications that precluded completion of the research protocol after valve implantation
- 2) Obtaining high-fidelity Doppler flow traces

In the earlier phases of recruitment, procedural complications occurred relatively more commonly owing to larger sheath sizes, higher risk patients, and being comparatively earlier on in the learning curve of the procedure. For the purposes of the protocol, paired data before and after valve implantation were essential. Therefore, if a procedural complication occurred that precluded further physiological assessment (i.e. haemorrhage, conversion to open surgery) then the data could not be used for analysis.

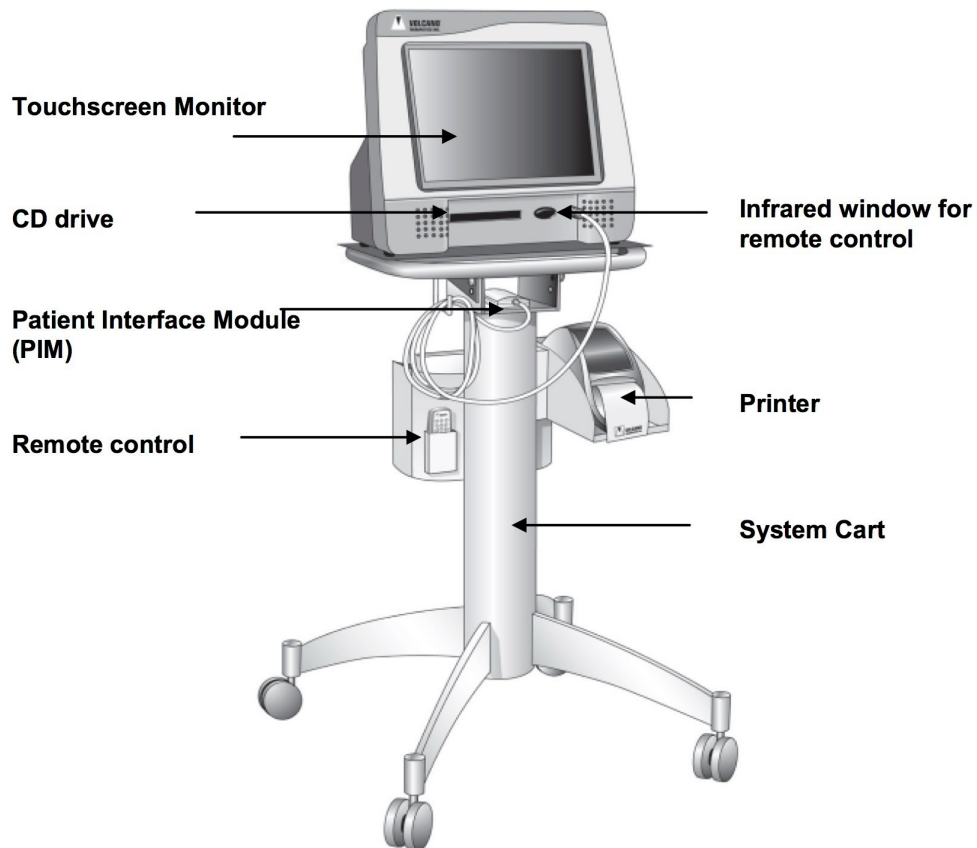
In total, 12 experiments were abandoned with incomplete data due to intraprocedural complications. In order to help mitigate against this loss of data, international collaborators were invited to participate. After appropriate training on the use of the Combowire and the protocol, data was collected from three other centres: Skane University Hospital, Lund, Sweden; Amsterdam Medical Center, Amsterdam, The Netherlands; and Aarhus University Hospital, Aarhus, Denmark. All data collected from international collaborators was sent to Imperial for all aspects of analysis, which were performed by myself with oversight from my primary supervisor. All traces underwent quality control to ensure only the highest fidelity data was used for analysis; 25% of traces sent from other centres were ultimately discarded and not utilised in analysis. A total of 3 patients from Sweden, 6 from Denmark and 8 from The Netherlands were included for analysis; a total of 38 from London were included. I was present for each case performed in London and ensured the protocol was completed accurately, and that high-quality haemodynamic data was obtained. This would often necessitate repeating the protocol

several times to ensure high-quality data was obtained for each condition (resting pre-TAVI data, hyperaemic pre-TAVI data, resting post-TAVI data, hyperaemic post-TAVI data).

The process of taking an invasive haemodynamic study performed in the cardiac catheterisation laboratory to yielding pressure and flow data suitable for analysis and presentation in scientific manuscripts was all performed at Imperial by myself with oversight from my primary supervisor. This process took approximately 20 hours for each individual case, taking into account the multiple steps involved, and that each case needed separate analysis for each separate condition (resting pre-TAVI data, hyperaemic pre-TAVI data, resting post-TAVI data, hyperaemic post-TAVI data).

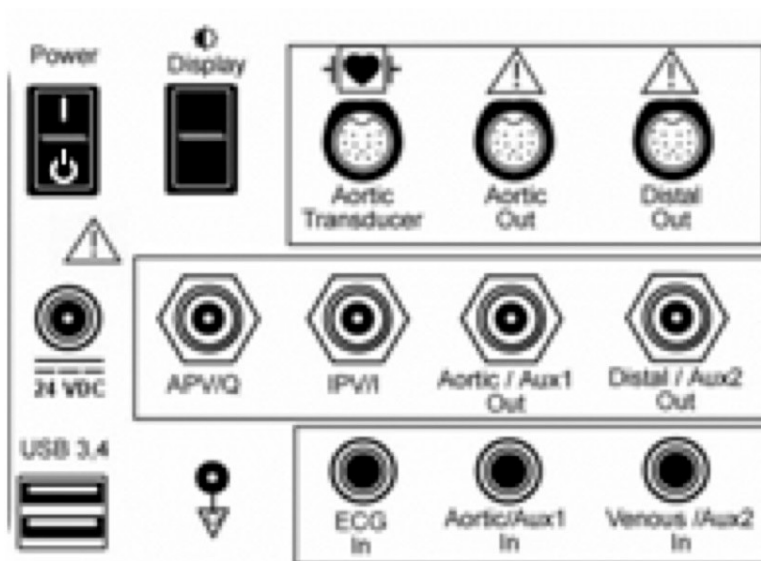
Figures

Figure 2.1. Combomap



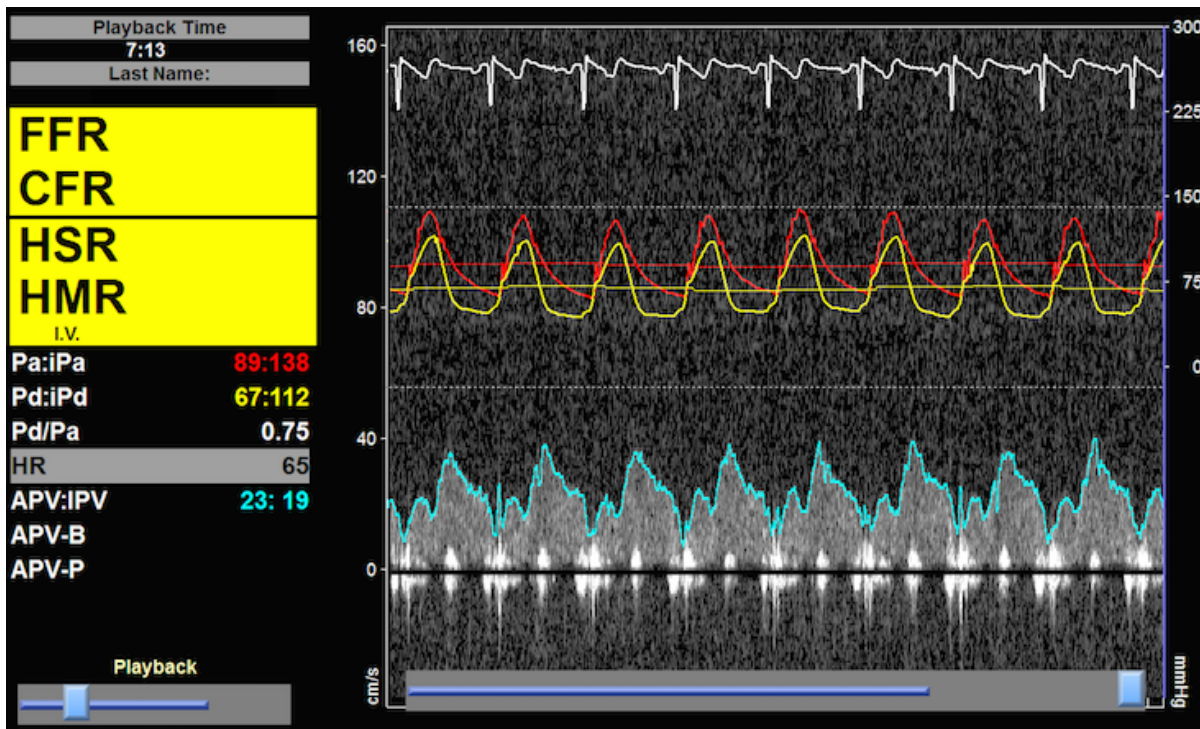
ComboMap console used in the catheter laboratory to collect simultaneous flow velocity and pressure data. Source: ComboMap Operators Manual Version 2.1, Volcano Corporation.

Figure 2.2. Array of connectors on the ComboMap console.



Array of connectors on the ComboMap console. The aortic transducer receives directly from the patient and returns a signal to the catheter laboratory haemodynamic system. An analogue ECG signal was also received.

Figure 2.3 Output from the Combomap panel



Three distinct panels are visible. Upper panel: White line - electrocardiogram reading. Middle panel: Red line - proximal aortic pressure trace; Yellow line - distal coronary pressure trace. Lower panel: Doppler spectral trace is in the lower panel. The digital blue tracking trace that superimposes over the spectral trace has been optimised during data acquisition. On the left-hand side parameters are shown if traces have been properly bookmarked during the recording process.

Figure 2.4. Schematic figure demonstrating the features of the ComboWire XT

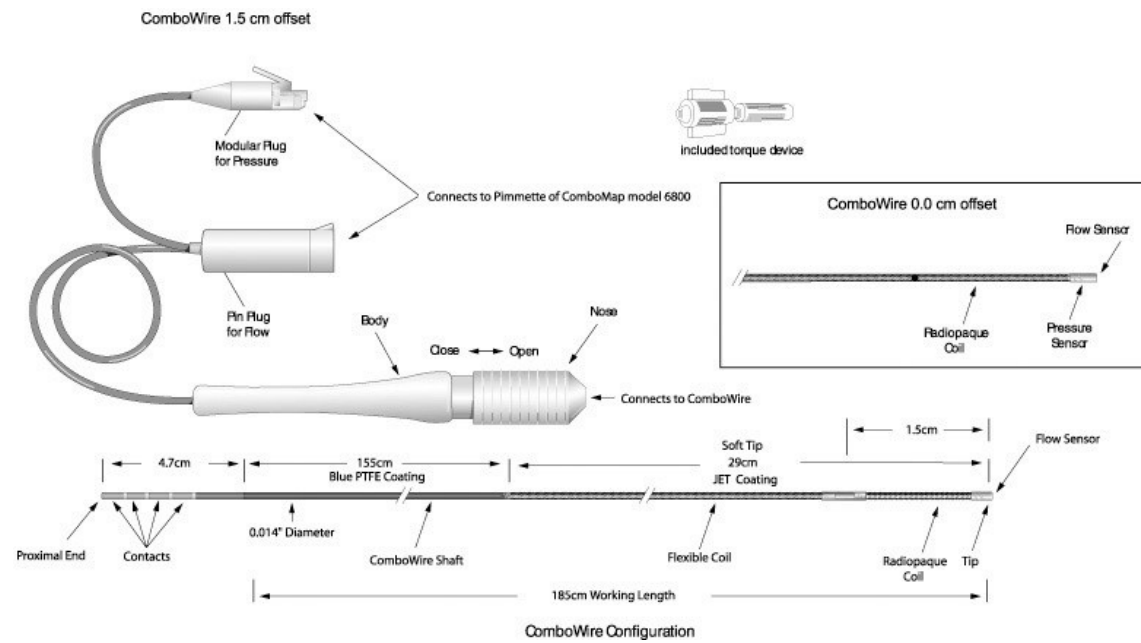
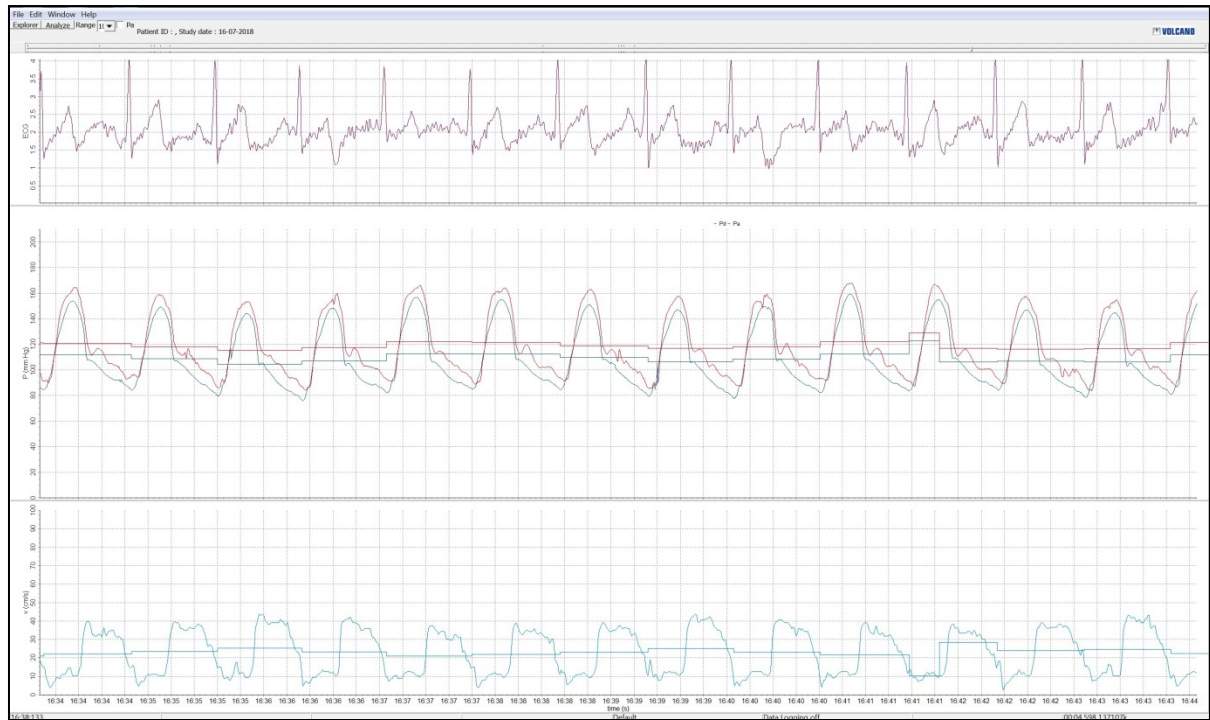
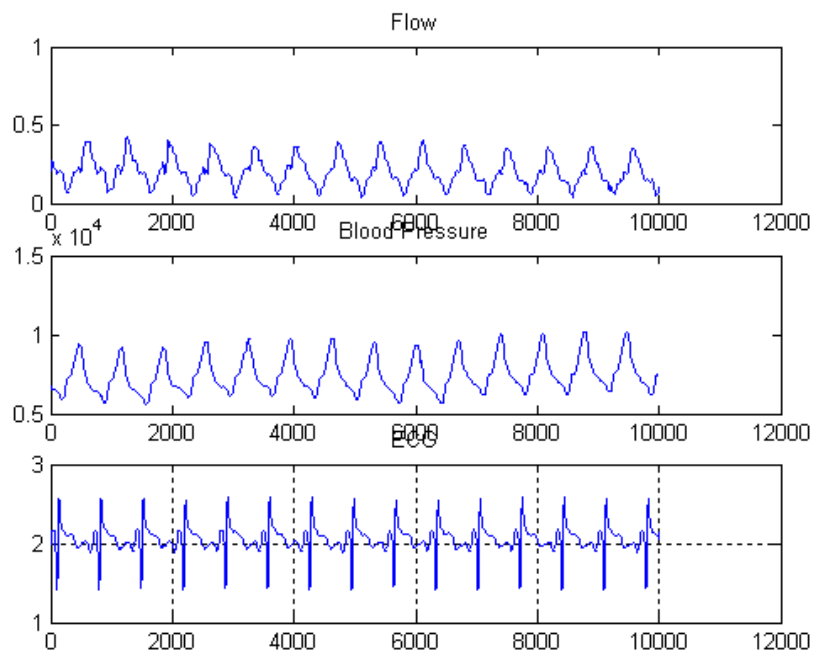


Figure 2.5. Data exported from the Combomap console viewed in the Study Manager software programme.



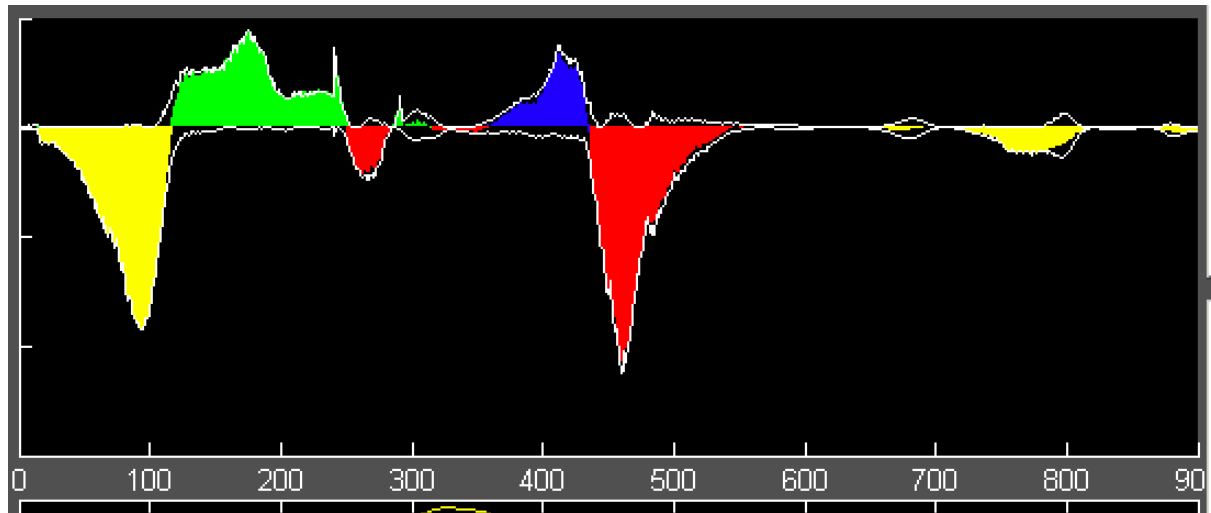
ECG (top panel), coronary and aortic pressure (middle panel) and coronary flow velocity (bottom panel) can be reviewed and selected ('snipped') for subsequent analysis. All data is time aligned (x axis).

Figure 2.6. Data selected for analysis in Matlab



The top panel displays flow velocity, the middle panel displays blood pressure and the bottom panel displays ECG.

Figure 2.7. Wave intensity analysis and pressure and flow traces produced in Matlab



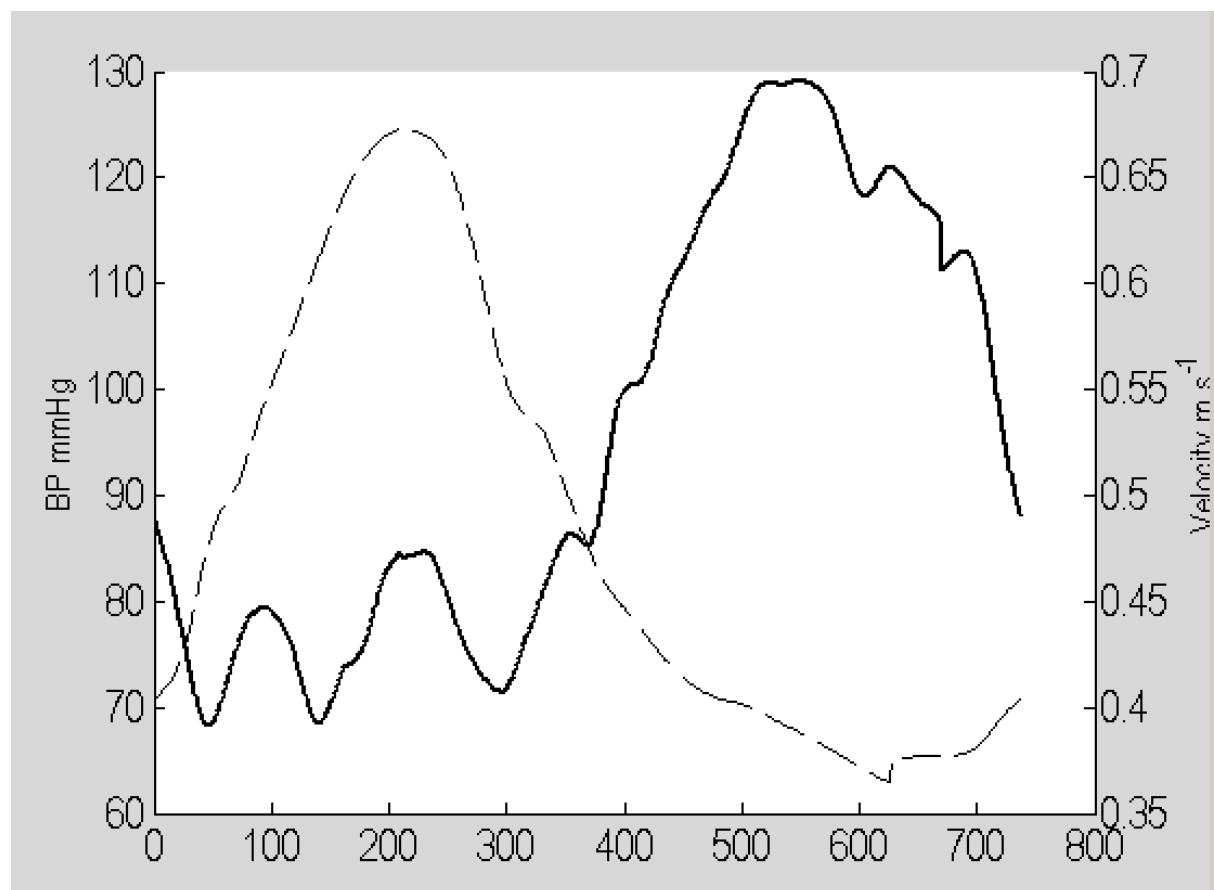
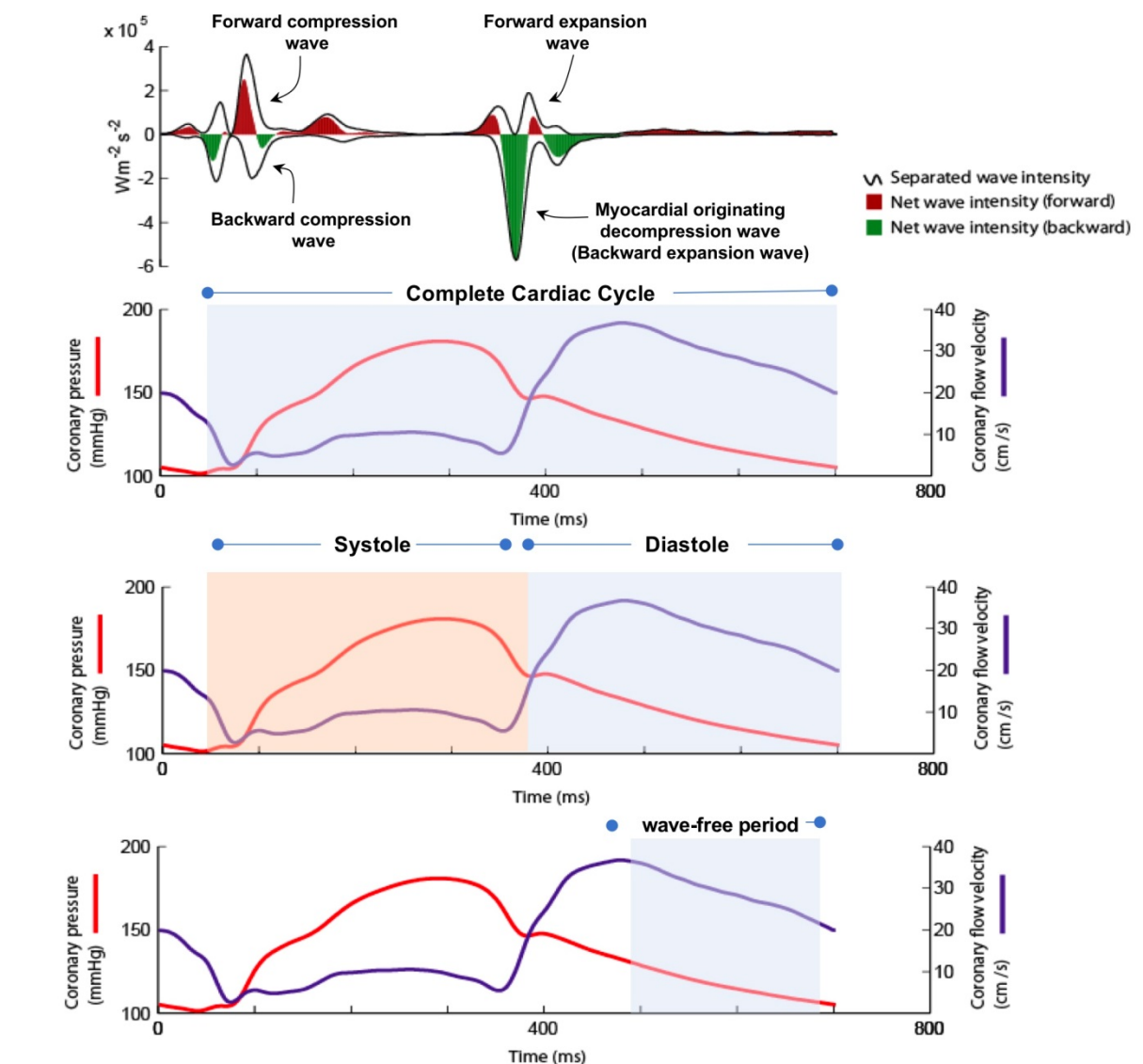


Figure 2.8. Schematic of phasic analysis performed



3.The acute effects of TAVI on coronary pressure and flow in patients with severe aortic stenosis and coronary artery disease: determining how aortic stenosis affects phasic and hyperaemic coronary flow

The experiments and findings of this chapter have been published in:

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.

Ahmad Y, Götberg M, Cook C, Howard JP, Malik I, Mikhail G, Frame A, Petraco R, Rajkumar C, Demir O, Iglesias JF, Bhindi R, Koul S, Hadjiloizou N, Gerber R, Ramrakha P, Ruparel N, Sutaria N, Kanaganayagam G, Ariff B, Fertleman M, Anderson J, Chukwuemeka A, Francis D, Mayet J, Serruys P, Davies J, Sen S.

JACC Cardiovasc Interv. 2018 Oct 22;11(20):2019-2031. doi:

10.1016/j.jcin.2018.07.019.

Abstract

Background

Many patients with severe aortic stenosis (AS) have coexistent coronary artery disease (CAD). The effect of the severe AS on coronary flow velocity in patients with coronary disease has not been studied. This makes it difficult to know how to use guidelines on invasive indices of lesion severity which were explicitly developed in patients without severe aortic stenosis, when those indices are known to be exquisitely sensitive to variations in flow.

In this first study, I conducted a systematic analysis of phasic intracoronary pressure and flow velocity in patients with severe AS and CAD, undergoing TAVI, to determine how aortic stenosis affects: (1) phasic coronary flow velocity; (2) hyperaemic coronary flow velocity; and (3) the most common indices of coronary stenosis severity, iFR and FFR.

Methods

28 patients (30 lesions, 50.0% male, mean age 82.1 ± 6.5 years) with severe aortic stenosis and coronary artery disease were included. Intracoronary physiological assessments were performed at rest and during hyperaemia immediately pre and post-TAVI.

Results

Flow velocity during the wave-free period of diastole was constant after TAVI (29.78 ± 14.9 cm/s versus 30.81 ± 19.6 cm/s, $p=0.64$). Whole-cycle hyperaemic flow velocity increased significantly post-TAVI (33.44 ± 13.4 cm/s pre-TAVI versus 40.33 ± 17.4 cm/s post-TAVI, $p=0.006$); this was secondary to significant increases in systolic hyperaemic flow velocity post-TAVI (27.67 ± 12.1 cm/s pre-TAVI versus 34.15 ± 17.5 cm/s post-TAVI, $p=0.02$). iFR values were constant post-TAVI (0.88 ± 0.09 pre-TAVI versus 0.88 ± 0.09 post-TAVI, $p=0.73$); whereas FFR decreased significantly post-TAVI (0.87 ± 0.08 pre-TAVI versus 0.85 ± 0.09 post-TAVI, $p=0.0008$).

Conclusion

The effect of TAVI on coronary flow velocity varies across the cardiac cycle. Systolic flow velocity is significantly increased after TAVI, but diastolic flow velocity is not. It also varies with the administration of adenosine, with a larger effect from the administration of adenosine seen after TAVI.

Resting flow velocity during diastole is relatively little changed by TAVI, in comparison to the changes seen in flow velocities in systole and with adenosine.

We infer from this that the distorting effect of aortic stenosis on flow-dependent parameters may be lower in the resting diastolic time-window, than in whole-cycle hyperaemic conditions.

Introduction

Many patients with severe aortic stenosis also have coronary artery disease(3,4).

Determining the significance of the coronary artery disease is challenging because we do not know to what extent our invasive indices of ischaemia are affected by the severe aortic stenosis(17). It is difficult to extrapolate clinical research about the relevance of various levels of ischaemia indices, when those trials were conducted in patients without severe aortic stenosis and it is unclear how severe aortic stenosis affects the indices(43)(80).

Invasive indices are measured either during resting or hyperaemic conditions and can be further divided into those that use the complete cardiac cycle (Pd/Pa and fractional flow reserve, FFR(80)) or only a period within diastole (instantaneous wave-free ratio, iFR(62)).

It has been suggested that hyperaemic coronary flow velocity is impeded by severe aortic stenosis(74), but this has never been tested in humans with severe aortic stenosis and coronary artery disease.

Previous researchers have looked purely at pressure (FFR and iFR) in patients before and after TAVI, focusing on the level of agreement between FFR and iFR. None of those researchers measured flow velocity in patients with severe aortic stenosis and coronary artery disease; and therefore they were unable to do anything more than speculate on the underlying reasons for what they found.

In this project, we focused on careful, deliberate measurements of intracoronary flow velocity before and after TAVI. This allows us to study the mechanistic question of whether FFR and iFR may behave differently.

Transcatheter aortic valve implantation (TAVI) provides a unique opportunity to test the effect of severe aortic stenosis on coronary physiology⁽⁷⁹⁾, because it is possible to perform intracoronary physiology assessments immediately before and after valve insertion. Each subject is therefore their own control, maximising the informativeness of the data since many confounders will thereby be balanced.

In this study, I used TAVI to determine the impact of a severely stenotic aortic valve on: (1) phasic coronary flow velocity; (2) hyperaemic coronary flow velocity; and (3) indices of coronary stenosis severity, iFR and FFR.

Methods

Patient population

I included 28 consecutive patients (30 lesions) with severe aortic stenosis planned for TAVI and at least moderate coronary artery disease judged angiographically. Recruiting centres were The Hammersmith Hospital, Imperial College NHS Trust, London, United Kingdom, and Skane University Hospital, Lund, Sweden. TAVI was indicated by international guidelines, and the treatment decision was made at a Heart Team meeting. Exclusion criteria were known non-viable myocardium in the area of the corresponding coronary artery being studied, contra-indication to the administration of adenosine, inability to consent or weight over 200kg. All participants gave written informed consent and the study was given full ethical approval (ref 14/SC/1103).

Cardiac catheterisation protocol

Cardiac catheterisation and coronary angiography were undertaken via either the transradial or transfemoral route at the operator's discretion, using standard equipment. A guiding catheter was used to intubate the vessel of interest. 5000 units of heparin were administered intra-arterially. A dual pressure and Doppler sensor-equipped 0.014" guidewire was used for all physiological assessments (ComboWire, Volcano Corp, San Diego). The guidewire signal was normalised in the aorta and then advanced a minimum of three-vessel diameters distal to the stenosed segment. After an optimal and stable

flow-velocity signal was obtained, resting pressure and flow velocity measurements were recorded. Hyperaemia was then induced via a 150 µg bolus of intracoronary adenosine, and hyperaemic measurements were made. At the end of each recording, the pressure sensor was returned to the catheter tip to ensure that there was no pressure drift. When drift was identified (≥ 0.01), all measurements were repeated. Left ventricular end diastolic pressure was recorded using a pigtail catheter placed in the LV cavity. The entire protocol was repeated immediately following the deployment of the new aortic valve. An example of the invasive pressure and flow velocity traces obtained is shown in Figure 3.1.

TAVI procedure

All TAVI procedures were undertaken according to standard clinical protocols. All patients were treated under local anaesthetic. The valves used were either the balloon-expandable Edward's Sapien XT/S3 valves (Edwards Lifesciences LCC, Irvine, CA), the self-expandable Medtronic CoreValve/Evolut-R valves (Medtronic Inc, Minneapolis, MN) or the repositionable Lotus valve (Boston Scientific, Natick, MA); valve choice was at the Heart team and operator's discretion.

Analysis of haemodynamic data

I processed the hemodynamic signals with the associated instrument console (ComboMap; Volcano Corp, San Diego, CA), which were stored for offline analysis.

Analog output feeds were taken from the pressure-velocity console and ECG, fed into a National Instruments DAQ-Card AI-16E-4, and acquired at 1 kHz with Labview. Data were analyzed offline with a custom software package designed with Matlab (Mathworks, Natick, MA).

FFR (80) and iFR (62) were calculated using standard definitions and equations.

Flow velocity was measured both at rest and during hyperaemia. Phasic analysis was then performed offline to permit analysis of flow velocity over the whole cardiac cycle, during systole, during diastole and during the wave-free period specifically.

The wave-free period was identified using wave-intensity analysis as previously describe(79). A custom-written algorithm in Matlab was used to separate systole, diastole, and the wave-free period to facilitate phasic analysis of haemodynamic data. A schematic outlining how this was performed is shown in Figure 3.2.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) unless otherwise stated. Comparisons before and after TAVI were performed with a Wilcoxon signed-rank test. The threshold for statistical significance was set at 0.05. The Wilcoxon test was chosen as, although the data passed the tests for normality, there were concerns that due to the small sample size only severe deviations from normality would be picked

up. Therefore, it was felt best to use a comparison test of statistical significance that would be valid in both normal and non-normal data.

Results

Patient population and procedural characteristics

28 patients (30 lesions, 50.0% male, mean age 82.1 ± 6.5 years) were included. Baseline clinical characteristics are summarised in Table 3.1. Data regarding quantitative coronary angiography are summarised in Table 3.2. The baseline echocardiographic and procedural characteristics are summarised in Table 3.3. Mean peak aortic valve velocity was 407.18 ± 93.68 cm/sec, mean peak gradient was $70.01 \pm 32/85$ mmHg with a calculated mean aortic valve area of 0.68 ± 0.22 cm² (velocity time integral method).

Coronary flow velocity pre and post-TAVI

A summary of coronary haemodynamics before and after TAVI is shown in Table 3.4. A summary of coronary flow velocity before and after TAVI is shown in Figure 3.4.

Whole cycle haemodynamics

Whole cycle hyperaemic flow velocity increased significantly by $25.0 \pm 3.8\%$ post-TAVI (33.44 ± 13.4 cm/s pre-TAVI versus 40.33 ± 17.4 cm/s post-TAVI, $p=0.004$).

Systolic haemodynamics

Systolic resting flow velocity increased significantly by $36.8 \pm 5.4\%$ post-TAVI (16.48 ± 9.4 cm/s pre-TAVI versus 21.05 ± 13.1 cm/s post-TAVI, $p=0.004$). Systolic

hyperaemic flow velocity increased significantly by $31.2 \pm 5.4\%$ post-TAVI (27.67 ± 12.1 cm/s pre-TAVI versus 34.15 ± 17.5 cm/s post-TAVI, $p=0.01$).

Wave-free period haemodynamics

There was no change in resting flow velocity during the wave-free period of diastole after TAVI (29.78 ± 14.9 cm/s pre-TAVI versus 30.81 ± 19.6 cm/s post-TAVI, $p=0.31$). Hyperaemic flow velocity during the wave-free period of diastole was also unchanged after TAVI (44.01 ± 20.6 cm/s pre-TAVI versus 42.52 ± 18.4 cm/s post-TAVI, $p=0.87$).

Indices of coronary stenosis severity before and after TAVI

iFR values were constant after TAVI (0.88 ± 0.09 pre-TAVI versus 0.88 ± 0.09 post-TAVI, $p=0.94$) (see Figure 3.5). FFR values significantly decreased after TAVI (0.87 ± 0.08 pre-TAVI versus 0.85 ± 0.09 post-TAVI, $p=0.0008$). A summary of the indices of coronary stenosis severity before and after TAVI is shown in Table 3.5.

Discussion

In this study, we found that : 1) resting diastolic flow velocity does not change after TAVI; 2) whole-cycle hyperaemic flow velocity increases significantly after TAVI; 3) this increase in whole-cycle hyperaemic flow velocity is driven by increases in systolic flow velocity; and 4) FFR is reduced by 0.02 units ($p=0.0008$) after TAVI, while there is no significant change in iFR ($p=0.94$).

This study does not on its own indicate that iFR or FFR is a better guide to the need for coronary revascularisation in patients requiring TAVI. Current guidance is that for patients without (current) severe AS, FFR and iFR have approximately equal standing as indicators for guideline-directed coronary intervention. In a patient who no longer has severe AS (through receiving a TAVI), FFR and iFR currently also have equal standing. However, waiting until after the TAVI is carried out to perform the FFR and iFR is not clinically satisfactory because if the indices indicate a need for coronary intervention, it might be preferable to perform PCI prior to TAVI, or even consider CABG and AVR rather than TAVI; and this would only be discovered too late, after the TAVI was already carried out. Interventionalists therefore sometimes use FFR or iFR pre-TAVI in the hope of being able to use them in the place of post-TAVI measurements. This study suggests that if doing so, the iFR pre-TAVI is a better predictor of the iFR post-TAVI than the FFR pre-TAVI is a predictor of the FFR post-TAVI. To put it more concisely, iFR is less modified by the artefact of severe AS than FFR is.

Phasic coronary flow in severe aortic stenosis

Coronary flow is phasic, differing between systole and diastole. Systolic flow is driven by pressure changes at the proximal end of the vessel(81). Diastolic flow is driven by pressure changes at the distal end of the vessel(82-84).

During systole, coronary flow is a function of blood emptying from the left ventricle through the aortic valve; and the opposing compression forces from the contracting myocardium, which blunts systolic flow. In severe aortic stenosis, systolic coronary flow is reduced due to obstruction of ventricular emptying by the stenosed aortic valve and simultaneous compression of the microcirculation from the contracting myocardium opposing flow in the coronary artery due to elevated intraventricular pressure(85,86). This results in reduced coronary flow during systole. Relief of the aortic valvular stenosis by TAVI removes the mechanical obstruction to ventricular emptying, increasing aortic flow, and also reducing intraventricular pressure. The net result of these phenomena is an increase in systolic coronary flow(87). This significant systolic increment in flow velocity after TAVI occurs at rest and during hyperaemia (see Figure 3.6).

Diastolic flow during the wave free period occurs when the myocardium is neither contracting nor actively relaxing(79). During this period, the aortic valve is closed.

Restriction of aortic valve opening, a systolic phenomenon, therefore does not impact on

flow during diastole because regardless of the severity of aortic stenosis, the aortic valve leaflets are closed; and therefore the aortic valve is not actively contributing to coronary flow during this period.

Hyperaemic coronary flow in severe aortic stenosis

Maximal blood flow in a coronary artery is affected by microvascular structure and function, left ventricular end diastolic pressure (LVEDP) and right atrial pressure(88–91). Any condition that affects one of these determinants will affect maximal blood flow. In severe aortic stenosis, left ventricular afterload is increased due to the valvular stenosis(92). This results in raised LVEDP and left ventricular hypertrophy, leading to structural changes in the microcirculation that affect its ability to respond to hyperaemic agents(77). Furthermore, patients with severe aortic stenosis have increased circulating vasoconstrictors as part of a compensatory mechanism to increase vascular tone and maintain systemic blood pressure(78). These vasoconstrictors counteract the effect of administered vasodilators such as adenosine and therefore also attenuate the response of the coronary microcirculation to vasodilatory drugs.

The protocol in this study tested the acute effect of treating a stenosed aortic valve on coronary haemodynamics. This study demonstrates that hyperaemic flow velocity increases significantly post-TAVI. This is driven by a significant increase in the systolic component of flow velocity. In contrast, flow velocity during the wave-free period does

not change during hyperaemia post TAVI; which is consistent with the minimal effect of the aortic valve on coronary flow during this period. Therefore, indices of coronary flow velocity that include the systolic phase of the cardiac cycle will be more susceptible to impact from the presence of severe aortic stenosis than indices using only the diastolic flow velocity.

Indices of coronary stenosis severity in severe aortic stenosis

A significant proportion of patients with severe aortic stenosis also have concomitant coronary artery disease. The studies (43) establishing the clinically-used indices of coronary stenosis severity specifically excluded patients with severe aortic stenosis, and so it is difficult to be confident in extrapolating them to these patients unless it is known how the aortic stenosis affects the indices.

Even though the second 'F' in FFR stands for 'flow', both FFR and iFR are calculated using *only* pressure measurements and not flow. Current practice of using cutoff values of FFR and iFR are based on the principle of a standardised level of flow. For FFR, this is a notional 'maximal hyperaemia'; for iFR, this is a notional 'resting diastolic' state.

If the presence of severe aortic stenosis affects flow, then it will affect FFR and iFR. If they are affected by the presence of severe aortic stenosis, then their values should only be

used for clinical decisions when the patient is in the flow state that corresponds to the clinical study in which these indices were developed, namely no severe aortic stenosis.

This means that any index whose value is modified by severe aortic stenosis should be measured after TAVI rather than before. This is problematic if the indication for measurement of the FFR/iFR is to decide whether a vessel has a haemodynamically significant lesion because it has impact on the choice between AVR and TAVI, or whether revascularization should be generally performed.

In this study we found that resting diastolic flow velocity is relatively little affected by the presence of severe aortic stenosis, whereas hyperaemic whole cycle flow velocity is decreased by severe aortic stenosis.

The valve state after TAVI is much closer to the state of the patients in the studies that developed FFR and iFR for clinical guidelines. Therefore, we believe closest to these post-TAVI values is a desirable feature for pre-TAVI values that may be used in decision-making.

On this basis, the diastolic and resting nature of iFR has the theoretical advantage of permitting measurement of a value pre-TAVI that is not significantly different from the value post-TAVI.

The phenomenon of attenuated hyperaemic whole-cycle flow can also be observed by comparing the results of our study to other studies on indices of coronary stenosis severity in patients without severe aortic stenosis. In the DEFINE-FLAIR and iFR-SWEDEHEART trials, the mean iFR was 0.91 ± 0.09 and 0.91 ± 0.10 , respectively; this is similar to the mean iFR of 0.88 ± 0.09 seen in this study. The mean FFR, however, was 0.83 ± 0.09 in DEFINE-FLAIR and 0.82 ± 0.10 in iFR-SWEDEHEART; these values are lower than those seen in this study (mean FFR 0.87 ± 0.08). This is a function of the attenuated hyperaemia in these patients, due to a blunted effect of adenosine resulting in failure to augment flow velocity sufficiently to produce FFR values similar to those in patients without severe aortic stenosis.

The magnitude of the effect of severe aortic stenosis on FFR averaged only 0.02. This average effect could matter if the patient was close to the cutoff, and of course some patients would have a larger effect. Nevertheless, there would be many patients in whom the clinical dichotomy would not be changed. This change was seen immediately following the TAVI; it is unknown whether the FFR continues to change longer-term after the TAVI.

There is a relative scarcity of available data regarding coronary stenosis assessment in patients with severe aortic stenosis. The existing studies of FFR and iFR have not measured coronary flow velocity (70,72,73).

Pesarini et al studied FFR in 133 coronary lesions in 54 patients before and after TAVI (69). Overall they found no change in FFR values after TAVI, although positive FFR values (classified as lower than 0.80) were observed to decline further after TAVI. This was also somewhat confirmed with the quantitative angiographic data. If the diameter stenosis was >50%, then the FFR value declined significantly after TAVI; if the diameter stenosis was <50% there was no change in FFR value after TAVI. In this study, a diameter stenosis of 30-50% was classified as an 'intermediate lesion', with a diameter stenosis greater than 50% being classified as a severe lesion. The overall diameter stenosis in this cohort was 40%, indicating they recruited patients with a milder form of CAD than those recruited in this current study (mean diameter stenosis in the present study was 56%). Furthermore, this may explain why the overall FFR values did not change; when their analysis was restricted to patients with a greater than 50% diameter stenosis, the mean FFR value dropped from 0.84 to 0.82; this is very similar to the effect observed in the present study within this chapter.

Scarsini et al (71) studied iFR and FFR in 179 lesions in 85 patients with severe aortic stenosis. This was not a study of coronary flow velocity. This was also not a study of patients undergoing TAVI. The aim of the study was to test the diagnostic agreement of iFR and FFR in patients with severe AS, and compare it to patients without severe AS. The diagnostic agreement of iFR and FFR was predicated on the FFR cutoff value of 0.80 and an iFR cutoff value of 0.89. This study concluded that that correlation between FFR and iFR

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in patients with aortic stenosis was similar to the cohort of patients without aortic stenosis. However, the diagnostic agreement between iFR and FFR (using the defined cutoffs that are in place for patients without severe aortic stenosis) was lower in the AS patients (76.3%) when compared to the non-AS patients (86.1%). The optimal iFR cutoff for predicting an FFR of 0.80 was an iFR of 0.83. This is likely simply a mechanism of attenuated hyperaemia meaning that FFR values are falsely elevated in the presence of severe aortic stenosis. The current experiment within this chapter was able to objectively demonstrate that hyperaemic coronary flow velocity was reduced in severe aortic stenosis and increased by TAVI; it is possible that Scarsini and colleagues may have found the same thing had they been able to directly measure flow velocity. Indeed, in the Discussion of their manuscript they note that 'FFR might underestimate substantial CAD in the setting of AS because of the impaired microvascular function'; this is a suggested possible mechanism that is speculative due to the inherent limitations of performing only pressure-gradient assessments (FFR or iFR) in the absence of directly measuring flow velocity. A strength of this current study is the direct measurement of coronary blood flow velocity, and being able to observe directly and clearly that hyperaemic coronary flow velocity is indeed reduced in patients with severe aortic stenosis. Scarsini and colleagues note in this paper that 'extrapolating the same current FFR and iFR thresholds used in CAD patients to AS patients is only hypothesis generating, and its validation warrants further research'. Although the current experiment does not validate any index, it does help provide

mechanistic insights into the behaviour of FFR and iFR in patients with severe aortic stenosis, namely be carefully and directly measuring the coronary flow velocity.

Scarsini and colleagues also compared iFR to FFR in a study 2018 without measuring coronary flow velocity (73). This study evaluated 145 coronary lesions in 66 patients with severe aortic stenosis. FFR and iFR were measured before and after TAVI. The mean iFR values were identical before and after TAVI; this finding is similar to that observed in this current study. Furthermore, the iFR remained identical regardless of the angiographic severity of the coronary stenosis (in contrast to the previous work on FFR in severe aortic stenosis from the same group). Interestingly, the average FFR and iFR values pre-TAVI in this study were the same. This is also likely a function of attenuated hyperaemia. Although once again there was no direct measurement of coronary flow velocity, the FFR value being the same as the iFR likely represents the inability of adenosine to increment flow these patients. This is a finding that was objectively tested and shown in the current study, setting it apart from previous work in the field. The inability to achieve maximal hyperaemia invalidates the physical principles upon which FFR depends and therefore calls into question the validity of using this index as a *reference* standard in patients with aortic stenosis, and the use of a 0.80 cut-point. The diagnostic accuracy of iFR is reported in this study purely in terms of using an FFR of 0.80 as the gold standard, which has not been validated in patients with severe AS. The negative and positive predictive values derived in this study should therefore be interpreted cautiously. Indeed, studies using

coronary flow velocity as well as pressure have highlighted the sensitivity of hyperaemic indices to aortic stenosis, albeit in patients without coronary lesions(71). These studies suggest that hyperaemic parameters are more susceptible to change post-TAVI than resting parameters. This is consistent with Scarsini's results, demonstrating identical average iFR values pre and post-TAVI. This is also consistent with the results of the study that this chapter is based on.

The present study demonstrates that the effect of adenosine is significantly altered in the presence of severe aortic stenosis and this will consequently significantly affect FFR values and therefore any FFR treatment threshold. The significantly blunted effect of adenosine in these patients suggests that the fundamental intracoronary conditions for accurate FFR assessment (maximal hyperaemia) cannot be met in patients with severe aortic stenosis, and therefore questions the role of FFR as an ischaemic gold standard in these patients (93).

Clinical implications

The findings of this study have potential implications for patients with severe aortic stenosis and coronary disease that are undergoing invasive haemodynamic evaluation of coronary lesions with a view to applying guideline-based thresholds to identify vessels requiring treatment. If the clinician wishes to use standard guideline thresholds for necessity of treatment of a vessel, it would be theoretically preferable to use iFR rather

than FFR because the iFR measured pre-TAVI is much more consistent with its value after the aortic stenosis is removed.

The magnitude of the effect of severe aortic stenosis on FFR averaged only 0.02. This average effect could matter if the patient was close to the cutoff, and of course some patients would have a larger effect. Nevertheless, there would be many patients in whom the clinical dichotomy would not be changed. This change was seen immediately following the TAVI; it is unknown whether the FFR continues to change longer-term after the TAVI; this is the subject of Chapter 5 of this thesis.

Further studies are required to determine if there is any significant effect of LVH or its regression on iFR values in this setting. The true role of iFR in patients will only be appreciated with a prospective study comparing an iFR-guided approach to revascularisation to standard angiographically-guided therapy in patients with severe aortic stenosis.

Limitations

This study does not on its own indicate that iFR or FFR is a better guide to the need for coronary revascularisation in patients requiring a TAVI. A cohort study might be a good study design to explore the clinical impact of various levels of iFR and FFR in such

patients. A design for this could be a large cohort recruited from multiple centres, for example across the UK, in which the participants have the measurements but no coronary intervention. Over a period of years, the event rates could be assessed, and it could be established whether pre-TAVI iFR or FFR is a better predictor of subsequent events.

Ultimately, a randomized trial powered for clinical endpoints is the only way to determine whether intervening on lesions in a given range of iFR or FFR is beneficial or not. This would of course be a major undertaking and could be pursued if the observational data described above suggests potential utility.

This study included patients with severe symptomatic aortic stenosis for whom TAVI was decided to be the most appropriate therapy by the Heart Team, in accordance with international guidelines(8). The results cannot therefore be generalised to patients with more mild degrees of aortic stenosis.

Adenosine was administered as an intracoronary bolus and not via intravenous infusion. I cannot therefore exclude the possibility that intravenous adenosine infusion would yield different results. However, intracoronary adenosine is recognised as a valid approach to FFR assessment (94,95) and such assessments have been included in all the large randomised trials of physiology to date(67,68). Intravenous infusion was avoided due to

the recognised potential for a 15% reduction in aortic pressure(96) that could potentially destabilise a patient with severe aortic stenosis.

The prevalence of severe aortic regurgitation (AR) has been significantly reduced with the development of the current generation of TAVI valves (71). This is reflected in the presence of only trivial to mild AR in our dataset compared to other groups that used earlier generation valves(13). It is therefore unlikely that the degree of AR, which was mild at most in these patients, would explain any of the differences seen in coronary flow velocity and other physiological parameters.

The sample size of the study may be considered small, with 30 coronary lesions across 28 patients. However, this is the largest study to date of invasive coronary flow velocity in patients with severe aortic stenosis, and the first to study patients with stenosed coronary arteries. It is also the first study to include phasic analysis, permitting an increase in our understanding of the coronary physiology in this complex haemodynamic condition. This was a mechanistic study, aiming to provide a comprehensive insight to coronary haemodynamics in patients with severe aortic stenosis undergoing TAVI. A decision-making strategy for revascularization in patients with severe aortic stenosis, based on current FFR or iFR data, cannot be made.

Conclusions

The effect of TAVI on coronary flow velocity varies across the cardiac cycle. Systolic flow velocity is significantly increased after TAVI, but diastolic flow velocity is not. It also varies with the administration of adenosine, with a larger effect from the administration of adenosine seen after TAVI.

Resting flow velocity during diastole is relatively little changed by TAVI, in comparison to the changes seen in flow velocities in systole and with adenosine.

Tables

Table 3.1. Baseline clinical characteristics

	n (%)
Age (years)	82.1 (± 6.5)
Male	14 (50.0)
Body mass index (kg/m ²)	27.90 (± 4.8)
Diabetes	7 (25.0)
Hypertension	16 (57.1)
Hyperlipidemia	19 (67.9)
Former smoker	10 (35.7)
Current smoker	0 (0)
Previous myocardial infarction	1 (3.6)
Previous percutaneous coronary intervention	5 (17.9)
Previous coronary artery bypass grafting	1 (3.6)

Table 3.2. Quantitative coronary angiographic data

Target vessel (LAD/Cx/RCA)	16/7/7
Stenosis location (proximal/mid/distal)	12/18/0
Diameter stenosis by QCA (%)	56.11 (± 12.2)
Area stenosis by QCA (%)	79.15 (± 10.7)
Stenosis length (mm)	18.54 (± 5.4)
Minimum luminal diameter (mm)	1.16 (± 0.4)
Minimum luminal area (mm ²)	1.20 (± 0.9)

Table 3.3. Baseline echocardiographic characteristics, and procedural characteristics

	Pre-TAVI	Post-TAVI	p-value
Peak velocity (cm/s)	407.18 (±93.68)	209.58 (±46.0)	<0.001
Peak gradient (mmHg)	70.01 (±32.85)	17.58 (±7.3)	<0.001
Mean gradient (mmHg)	37.64 (±18.48)	8.93 (±4.2)	<0.001
Aortic valve area (cm ²)	0.68 (±0.22)	1.48 (±0.4)	<0.001
LV systolic function			
Normal	20 (71.4)	20 (71.4)	NS
Mildly impaired	3 (10.7)	3 (10.7)	NS
Moderately impaired	2 (7.1)	4 (14.3)	NS
Severely impaired	3 (10.7)	1 (3.6)	NS
Left ventricular end-diastolic pressure (mmHg)	17.63 (±7.9)	15.44 (±6.6)	0.06
Paravalvular leak			
None		15 (53.6)	
Mild		13 (46.4)	
Moderate		0 (0)	
Severe		0 (0)	

Table 3.4. Summary of coronary haemodynamic variables at rest and during hyperaemia pre-TAVI and post-TAVI

	Resting				Hyperaemia		
	Pre-TAVI	Post-TAVI	p value		Pre-TAVI	Post-TAVI	p value
Whole cycle variables							
Flow velocity (cm/s)	22.13±10.3	24.84±12.5	0.1		33.44±13.4	40.33±17.4	0.004*
Aortic pressure (mmHg)	85.85±18.9	92.40±18.9	0.04*		82.99±18.0	88.44±17.1	0.13
Systolic variables							
Flow velocity (cm/s)	16.48±9.4	21.05±13.1	0.004*		27.67±12.1	34.15±17.5	0.01*
Aortic pressure (mmHg)	101.46±22.4	112.11±24.	0.02*		98.87±22.7	110.55±20.7	0.008*
Wave-free variables							
Flow velocity (cm/s)	29.78±14.9	30.81±19.6	0.31		44.01±20.6	42.52±18.4	0.87
Aortic pressure (mmHg)	73.05±15.1	76.41±16.8	0.17		70.13±16.3	70.69±15.0	0.64
Diastolic variables							
Flow velocity (cm/s)	31.67±15.4	33.33±18.6	0.36		46.03±20.5	45.94±18.1	0.92
Aortic pressure (mmHg)	76.76±16.6	78.13±17.0	0.33		71.69±14.9	74.02±15.3	0.34

Table 3.5. Indices of coronary stenosis severity pre and post-TAVI

	Pre-TAVI	Post-TAVI	p-value
Hyperaemic indices			
Fractional flow reserve	0.87 (± 0.08)	0.85 (± 0.09)	0.0008
Resting indices			
Instantaneous wave-free ratio	0.88 (± 0.09)	0.88 (± 0.09)	0.94
Diastolic PdPa	0.88 (± 0.10)	0.89 (± 0.09)	0.75

Figures

Figure 3.1. Figure demonstrating an example of invasive pressure and Doppler flow measurements

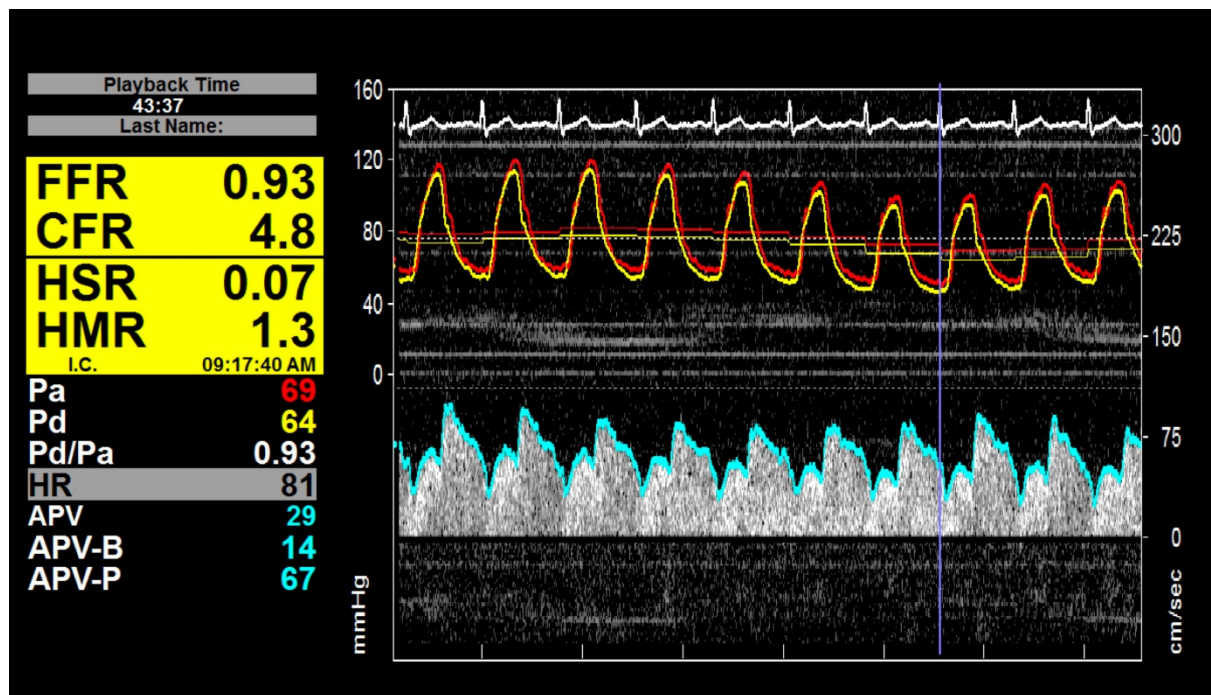


Figure 3.2. Outline of the definitions and calculations used for haemodynamic parameters used in the phasic analysis

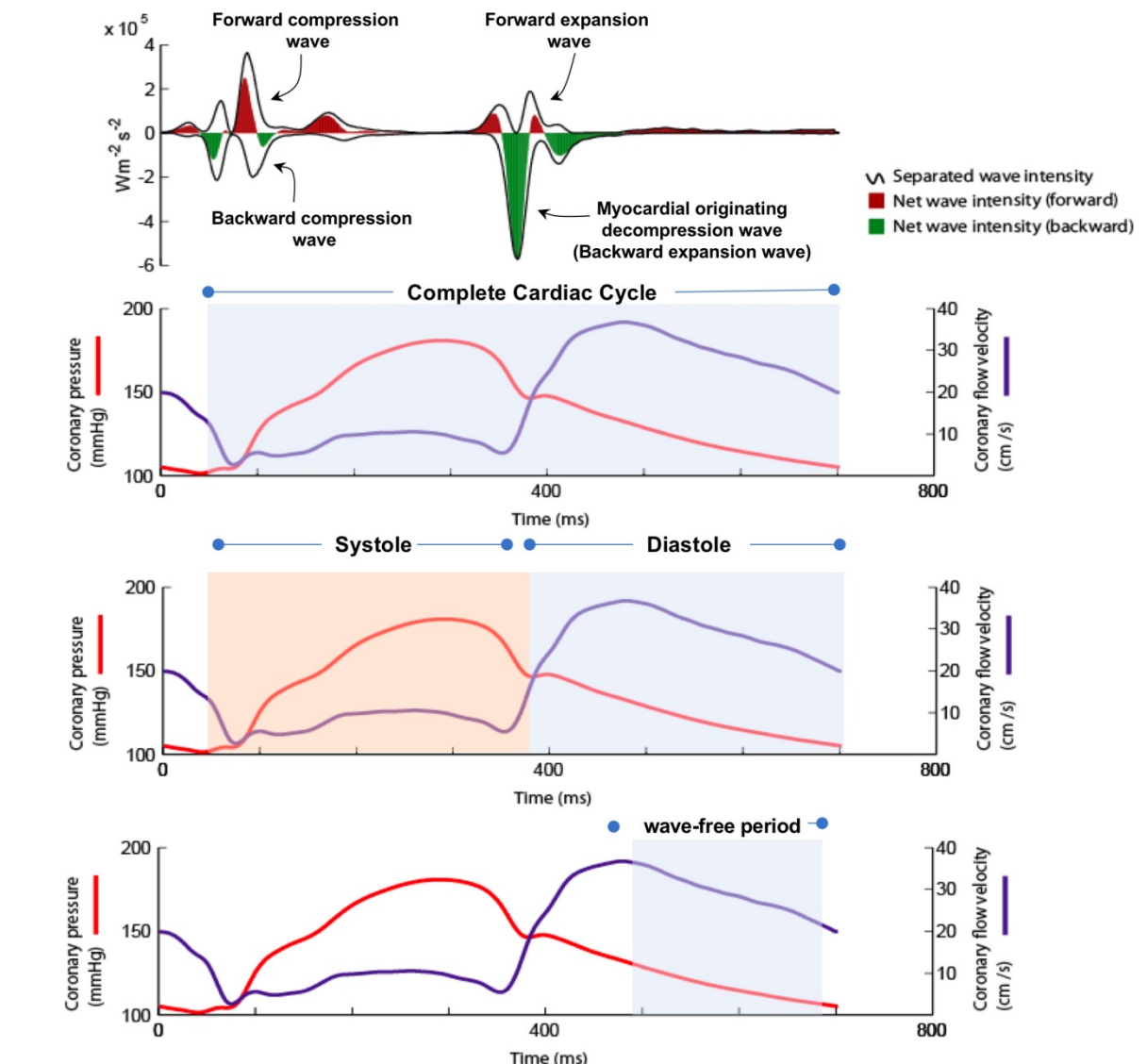


Figure 3.3. Coronary flow velocity pre and post-TAVI

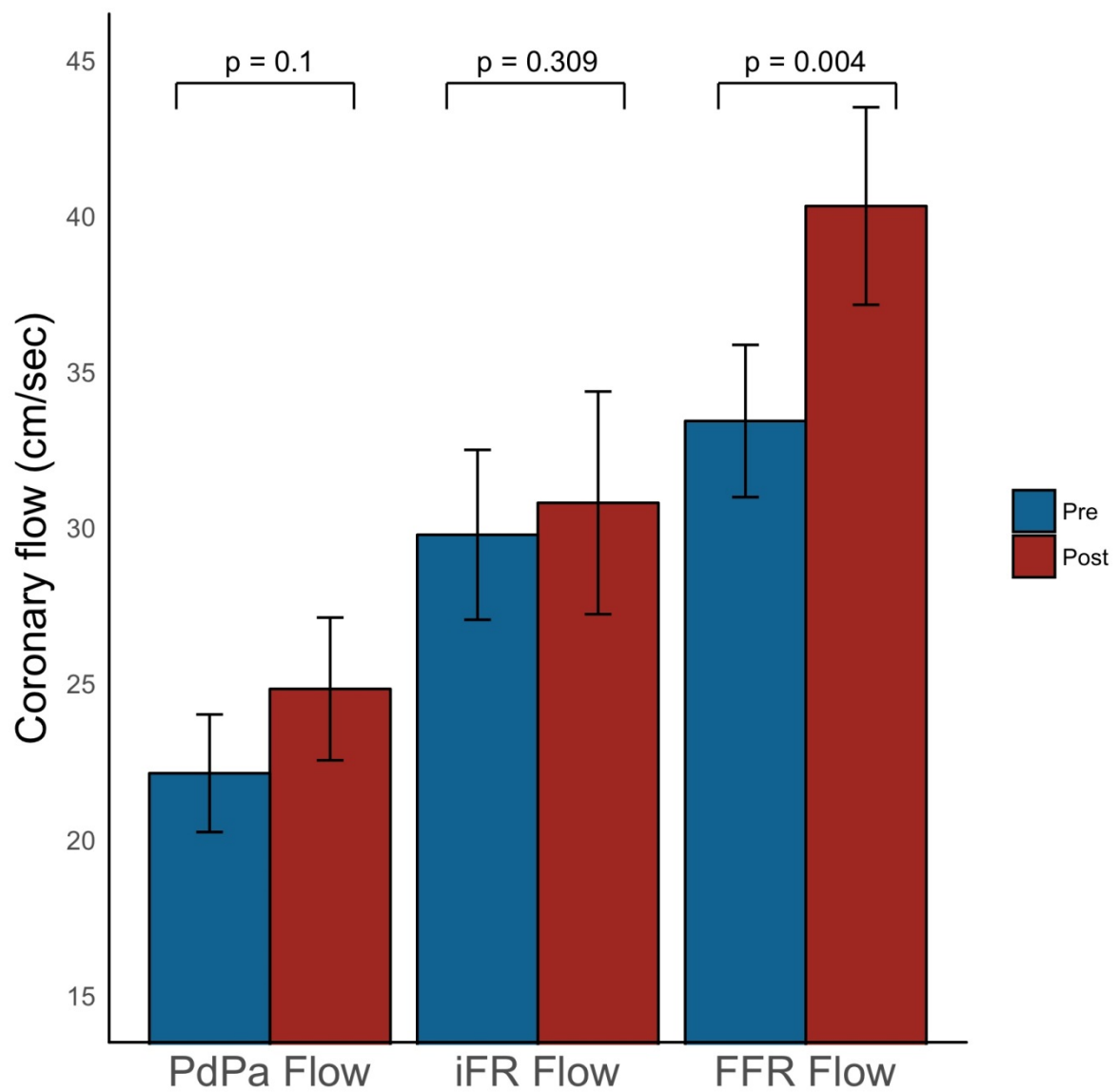


Figure demonstrating the changes in coronary flow before and after TAVI. The left panel (PdPa-flow) is resting flow over the whole cardiac cycle; the middle panel (iFR-flow) is resting flow during the wave-period of diastole; and the right panel (FFR-flow) is

hyperaemic flow over the whole cardiac cycle. Both PdPa-flow and FFR-flow increase significantly more post-TAVI than iFR-flow, which is constant.

The bars denote mean values, with the error bars denoting standard errors.

Figure 3.4. Changes in FFR and iFR seen post-TAVI

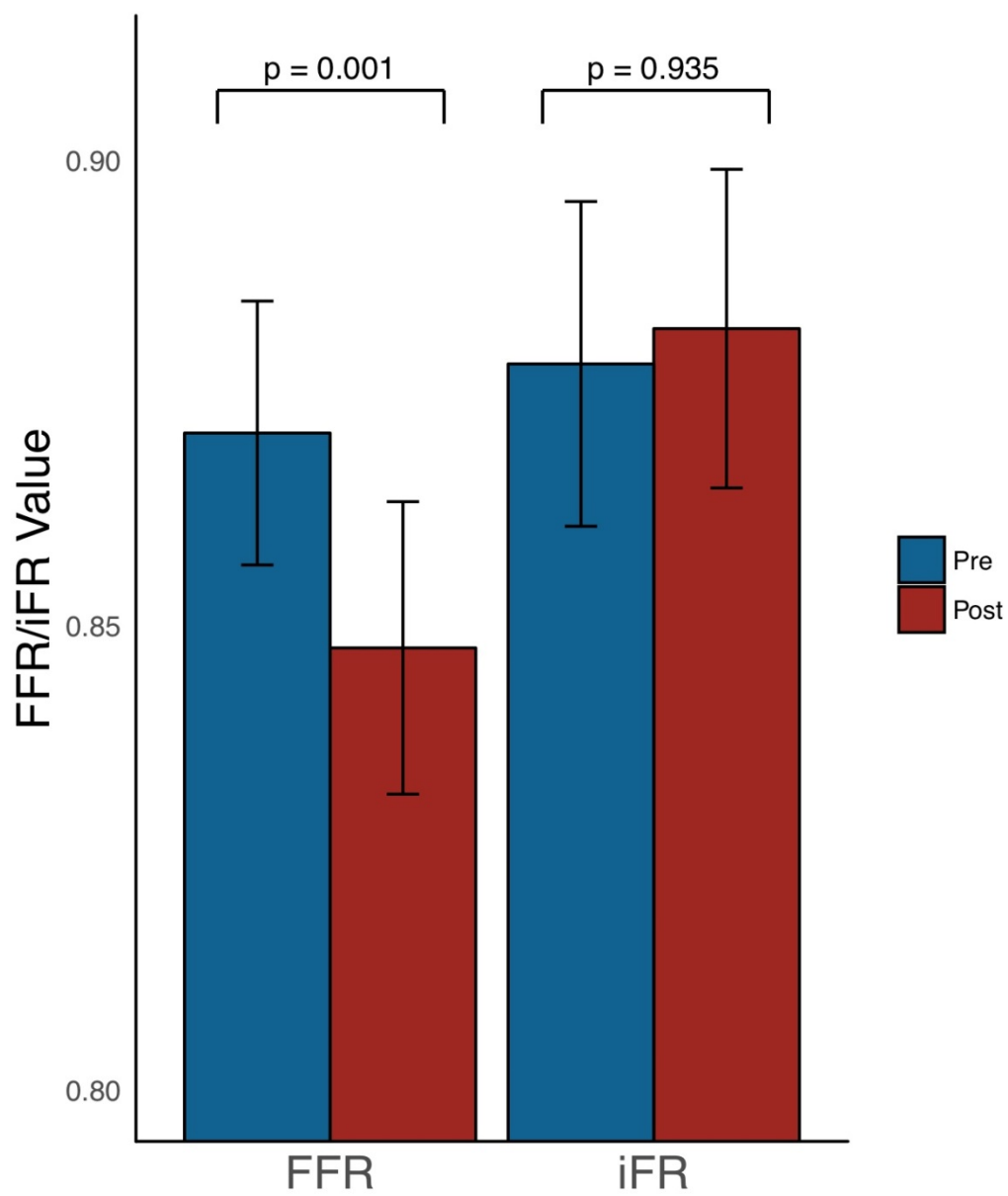
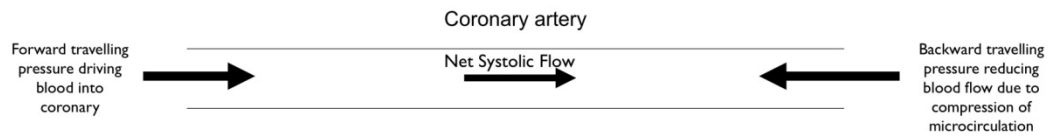


Figure demonstrating the change in FFR and iFR values post-TAVI. FFR decreases significantly, whereas iFR remains constant.

The bars denote mean values, with the error bars denoting standard errors.

Figure 3.5. Changes in systolic coronary flow post-TAVI

A. PRE-TAVI



B. POST-TAVI

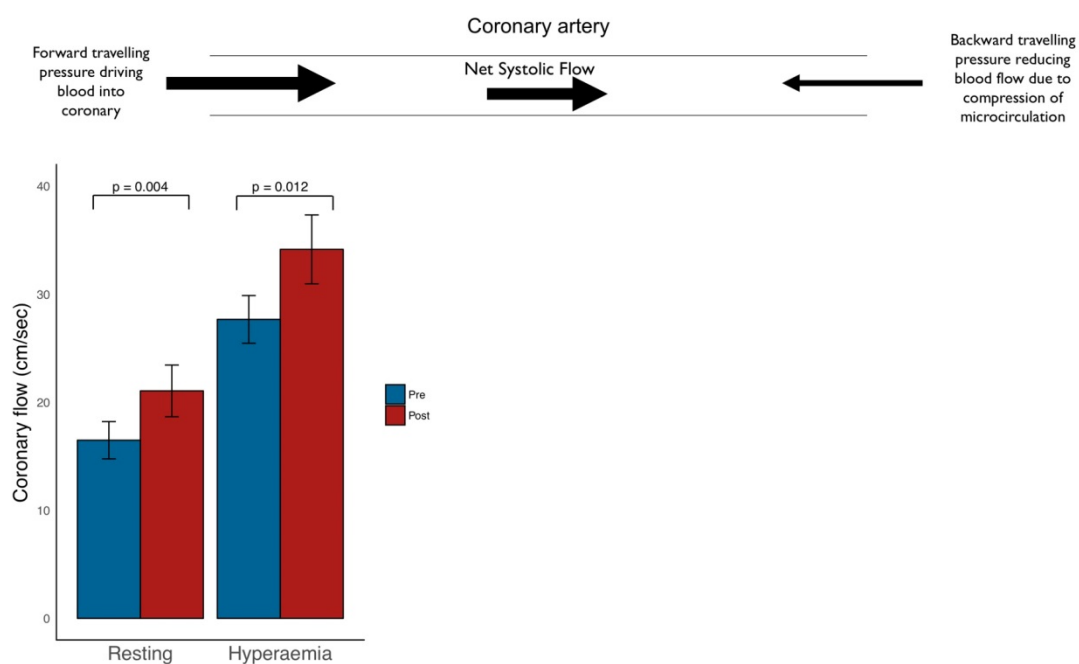


Figure demonstrating the changes in systolic coronary flow post-TAVI. In the top panel there is a schematic, demonstrating that post-TAVI there is increase in the forward travelling systolic pressure, leading to an increase in systolic coronary flow. There is also a reduction in the compressive forces on the microcirculation post-TAVI; these two factors both contribute to a net increase in systolic coronary flow post-TAVI.

The bottom panel demonstrates the statistically significantly increase in systolic coronary-flow seen in our study, both at rest and during hyperaemia.

The bars denote mean values, with the error bars denoting standard errors.

4.The effect of severe aortic stenosis and TAVI on microvascular physiology

The experiments and findings of this chapter have been published in:

Determining the Predominant Lesion in Patients With Severe Aortic Stenosis and
Coronary Stenoses: A Multicenter Study Using Intracoronary Pressure and Flow.

Ahmad Y, Vendrik J, Eftekhari A, Howard JP, Cook C, Rajkumar C, Malik I, Mikhail G,
Ruparelia N, Hadjiloizou N, Nijjer S, Al-Lamee R, Petraco R, Warisawa T, Wijntjens GWM,
Koch KT, van de Hoef T, de Waard G, Echavarria-Pinto M, Frame A, Sutaria N,
Kanaganayagam G, Ariff B, Anderson J, Chukwuemeka A, Fertleman M, Koul S, Iglesias
JF, Francis D, Mayet J, Serruys P, Davies J, Escaned J, van Royen N, Götberg M, Juhl
Terkelsen C, Høj Christiansen E, Piek JJ, Baan J Jr, Sen S.

Circ Cardiovasc Interv. 2019 Dec;12(12):e008263. doi:

10.1161/CIRCINTERVENTIONS.119.008263

Abstract

Background

Both aortic stenosis and coronary lesions influence blood flow to the myocardium and its ability to respond to stress, leading to exertional symptoms. In this chapter, I use the opportunity provided by two cohorts of patients (admittedly different in their characteristics) to explore the potential relative magnitudes of impact of aortic stenosis and coronary stenosis on the microcirculation.

Methods

Group 1: 55 patients with severe aortic stenosis and intermediate coronary lesions who had physiological measurements before and after TAVI. Group 2: 85 patients with intermediate coronary lesions and no aortic stenosis who had physiological measurements before and after PCI. This analysis was exploratory.

Results

In the aortic stenosis group, microvascular resistance over the wave-free period of diastole increased significantly after TAVI (pre-TAVI 2.71 ± 1.4 mmHg·cm·s⁻¹ vs post-TAVI 3.04 ± 1.6 mmHg·cm·s⁻¹ ($p=0.03$)). Microvascular reserve over the wave-free period of diastole improved significantly after TAVI (pre-TAVI 1.88 ± 1.0 vs. post-TAVI 2.09 ± 0.8 ($p=0.003$)). There was no sign of the severity of the coexistent coronary lesion affecting the pre/post TAVI change in microvascular resistance, across the spectrum of coronary stenosis severity included in this study.

Conclusions

Indices of microcirculatory function improve both after TAVI and after PCI. Approximately similar-sized effects can occur for the two interventions, although it should be remembered that the two groups in this study were in no way matched for other characteristics, so no definitive statement can be made about the exact relative size of this effect.

Introduction

Patients with severe aortic stenosis often have coronary artery disease(97), and both conditions can present with angina or dyspnoea. It is challenging for clinicians to determine which lesion, the valve or the coronary, is predominantly responsible for an individual patient's symptoms.

The cause of chest pain or shortness of breath in these patients is due to inability of the microcirculation to increase blood flow in response to increased demand. The effects of the coronary lesion(98) and the aortic valvular stenosis(71) on the microcirculation have been individually studied; but it is not known how the two interact when they are present in the same patient.

I have previously demonstrated that hyperaemic indices are significantly affected by severe aortic stenosis(99), with hyperaemic flow velocity increasing significantly after TAVI. Resting haemodynamics are less susceptible to this, specifically in the wave-free period of diastole: I previously demonstrated that flow velocity during this period is unchanged after TAVI, as detailed in the previous chapter of this thesis.

In this study, I will use the resting haemodynamics of the wave-free period to determine the effects of transcatheter aortic valve implantation (TAVI) and percutaneous coronary intervention (PCI) on the coronary microcirculation. Microvascular resistance over the

wave-free period has been demonstrated to reflect coronary stenosis severity(64); with low resistance suggesting a more severe stenosis and higher resistance suggesting a less severe stenosis.

In this study, I will (1) quantify the effect of severe aortic stenosis on the coronary microcirculation and determine if this is influenced by concomitant coronary disease and (2) quantifying the effect of a coronary stenosis on the coronary microcirculation in patients without severe aortic stenosis.

Methods

Patient population

Group 1: 55 patients with severe aortic stenosis undergoing TAVI with moderate coronary lesions were recruited from four European centres (The Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom; Amsterdam Medical Center, Amsterdam, The Netherlands; Skane University Hospital, Lund, Sweden; and Aarhus University Hospital, Aarhus, Denmark). All patients had prospectively collected combined coronary pressure and flow velocity measurements, with paired measurements pre and post-TAVI. All patients were scheduled for TAVI on clinical grounds in accordance with clinical guidelines(8), after a decision at a Heart Team meeting, and gave written informed consent for the study protocol. Exclusion criteria were known non-viable myocardium in the area of the corresponding coronary artery being studied, contra-indication to the administration of adenosine, inability to consent or weight over 200kg. All patients had concomitant aortic stenosis and coronary artery disease, and physiological assessments were performed in each patient. There was no PCI performed in this group, after Heart Team decision that it was not required prior to TAVI and enrolment in the study.

Group 2: 85 patients with intermediate coronary lesions undergoing PCI were included from four European centres as part of the IDEAL collaboration(98) (Amsterdam Medical

Center, Amsterdam, The Netherlands; The Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom; Hospital Clinico San Carlos, Madrid, Spain; and VU University Medical Center, Amsterdam, The Netherlands). All patients had combined coronary pressure and flow velocity measurements, with paired measurements pre and post-PCI. All patients recruited were scheduled for elective coronary angiography with physiological stenosis assessment by FFR and gave written informed consent for acquisition of additional physiological data for study purposes. Exclusion criteria were acute myocardial infarction within 48 hours; contraindication to the administration of adenosine; severe valvular heart disease; weight >200 kg; previous coronary artery bypass surgery; vessels with angiographically identifiable myocardial bridging or collateral arteries; and vessels supplying an infarcted territory. All patients in this group underwent PCI as had been determined by the treating clinical team. These patients did not have severe aortic stenosis.

Cardiac catheterisation protocol

In all patients, cardiac catheterisation and coronary angiography were performed via either the transradial or transfemoral route at the operator's discretion. A guiding catheter was used to intubate the target artery. Therapeutic dose heparin was administered. A dual pressure and Doppler sensor-equipped 0.014" guidewire was used for all physiological assessments (ComboWire, Volcano Corp, San Diego). The pressure signals were normalised in the aorta prior to advancing the wire a minimum of three-vessel diameters

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distal to the coronary stenosis. Doppler signals were optimised and stabilised to ensure good tracking profiles. All flow measurements were made by experienced operators; the reproducibility of flow measurements in such hands has been previously demonstrated(100). At this stage, resting pressure and flow measurements were recorded. Hyperaemia was then induced using adenosine, either as an intracoronary bolus of 150 µg or an intravenous infusion of 140 µg/kg/min. Physiological measurements under hyperaemic conditions were then recorded. At the end of each recording, the pressure sensor was returned to the catheter tip to ensure that there was no pressure drift. When drift was identified (≥ 0.01), all measurements were repeated. For TAVI patients, left ventricular pressures were recorded using a pigtail catheter placed in the LV cavity. All patients then either underwent PCI (for patients without aortic stenosis) or TAVI (for patients with aortic stenosis). Subsequent to either intervention, the entire protocol was repeated with the wire sited in the same location as the pre-intervention measurements.

PCI procedures

Drug-eluting stents were used as standard of care. Optimisation using intracoronary imaging and postdilatation were performed at the operator's discretion.

TAVI procedures

All patients were treated under local anaesthesia and conscious sedation. The valves used were either the Edward's Sapien XT/S3 valves (Edwards Lifesciences LCC, Irvine, CA), the Medtronic CoreValve/Evolut-R valves (Medtronic Inc, Minneapolis, MN) or Lotus valve (Boston Scientific, Natick, MA). Valve choice was at the Heart Team and operator's discretion.

Analysis of haemodynamic data

Electrocardiogram (ECG), pressure, and flow velocity signals were processed with the dedicated device console (ComboMap; Volcano Corp, San Diego, CA). Analog output feeds were taken from the pressure-velocity console and ECG, fed into a National Instruments DAQ-Card AI-16E-4, and acquired at 1 kHz with Labview. Data were analysed offline with a custom software package designed with Matlab (Mathworks, Natick, MA) which permitted phasic analysis including that of the wave-free period. The wave-free period was identified using wave-intensity analysis(100) and used to perform phasic analysis. Coronary pressure, flow velocity and resistance were measured during resting conditions and during hyperaemia.

Microvascular reserve was derived as a metric of improvement in coronary haemodynamics after intervention. This was defined as a ratio of hyperaemic microvascular resistance to resting microvascular resistance. Microvascular resistance was defined as distal coronary pressure over flow-velocity, as detailed in the Introduction chapter.

Statistical methods

Continuous variables are presented as mean and standard deviation (SD) unless otherwise stated. Comparisons before and after intervention were performed with a paired t-test, after the data passed tests for normality. The larger sample size of the experiment in this chapter, and the data passing the tests for normality, informed the choice of the paired t-test for comparisons (in contrast to the other studies underpinning the other chapters). The threshold for statistical significance was set at 0.05. Pearson's correlation coefficient was used to assess correlations. All analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient population

TAVI group

55 patients (81.7 ($\pm$ 5.9) years; 49.1% male) were included. Baseline clinical characteristics are shown in Table 4.1. The baseline echocardiographic characteristics are summarised in Table 4.2.

PCI group

85 patients were included (61.3 ($\pm$ 9.4) years; 74.1% male). Baseline clinical characteristics are shown in Table 4.3.

Quantitative coronary angiography

TAVI group

Quantitative coronary angiography for the patients undergoing TAVI is summarised in Table 4.4.

PCI group

Quantitative coronary angiography for the patients undergoing PCI is summarised in Table 4.5.

Physiology pre and post-TAVI

Commonly reported coronary physiological parameters pre and post-TAVI are summarised in Table 4.6. There was a significant decline in FFR immediately after TAVI ($p<0.001$), and a significant increase in CFR immediately after TAVI ($p=0.03$). iFR was unchanged immediately after TAVI ($p=0.80$).

Microvascular resistance over the wave-free period of diastole before and after TAVI

Changes in resistance after TAVI are summarised in Figure 4.1. Resting resistance over the wave-free period of diastole increased significantly after TAVI (pre-TAVI 2.71 ± 1.4 mmHg·cm·s⁻¹ vs post-TAVI 3.04 ± 1.6 mmHg·cm·s⁻¹ ($p=0.03$)). Microvascular reserve over the wave-free period of diastole significantly improved after TAVI (pre-TAVI 1.88 ± 1.0 vs. post-TAVI 2.09 ± 0.8 ($p=0.003$)).

Improvement in resistance achieved by TAVI and PCI stratified by baseline iFR value

Overall, microvascular resistance over the wave-free period improved significantly after PCI. This improvement was dependent on the baseline iFR value: the more severe the coronary stenosis, the greater the improvement in microvascular resistance (see Figure 4.2).

Overall, microvascular resistance over the wave-free period improved significantly after TAVI. This improvement was independent of the baseline iFR value: the improvement in microvascular resistance over the wave-free period post-TAVI is consistent across the spectrum of coronary stenosis severity tested in these experiments (see Figure 4.3).

Discussion

In this study I have shown that: 1) in patients with severe aortic stenosis and intermediate coronary lesions, relief of aortic stenosis acutely results in a significant increase in microvascular resistance; and 2) this increase was consistent across the range of coronary lesions included in this study.

Microvascular reserve and coronary lesions

Microvascular reserve reflects the ability of the microcirculation to increase blood flow to the myocardium in response to increased demand. In patients with coronary artery disease this ability to respond to increased work load is related to (1) the severity of the lesion within the epicardial artery(98) and (2) autoregulation of coronary blood flow(101) and its effect on microvascular resistance. In patients with severe coronary disease, microvascular resistance is relatively lower than in patients with no coronary stenosis (see Figure 4.4).

In a patient with a severe coronary stenosis, the microcirculation is relatively dilated at rest in order to maintain flow. When the need arises to increase coronary flow further, the capacity of the microcirculation to dilate further to increase flow is limited; therefore the difference between resting and hyperaemic flow (microvascular reserve) is small. In patients with no coronary lesion, or after PCI, the opposite is true: the microcirculation is

relatively constricted. Therefore, when the need arises to increase coronary flow further, the capacity of the microcirculation to dilate to increase flow is much greater; and the difference between resting and hyperaemic flow (microvascular reserve) is also greater.

Aortic stenosis and coronary stenosis: the tandem lesion model

In this study I have demonstrated that aortic stenosis also influences coronary microvascular resistance and its ability to respond to stress. In patients with aortic stenosis, microvascular resistance at rest is significantly lower than that observed after relief of the aortic stenosis by TAVI. This suggests that the coronary microcirculation treats aortic stenosis similarly to a coronary stenosis. As the aortic valve becomes more and more stenosed, the microcirculation dilates to maintain coronary flow and microvascular reserve is depleted (see Figure 4.4).

Therefore, in patients with severe aortic stenosis and coronary disease the microcirculation is adapting to two variables that affect blood flow: the stenosed aortic valve and the stenosis in the coronary artery. Resting microvascular resistance and therefore microvascular reserve in these patients is therefore limited by both.

Because the microcirculation treats the two stenoses similarly, determining the predominant lesion is akin to attempting to determine which stenosis is predominant in a coronary artery with tandem lesions. It has been established that this is not possible with

hyperaemia due to both stenoses influencing the blood flow across the other(102).

However, it has been demonstrated to be possible to isolate the significance of a specific lesion with iFR(103).

This finding for tandem lesions can be extrapolated to the TAVI population. In these patients, the tandem lesions are the coronary stenosis and the aortic stenosis. Placing a pressure wire in the vessel distal to the coronary stenosis in a patient with severe aortic stenosis is therefore analogous to placing a pressure wire between two serial lesions in a coronary artery. I have previously demonstrated that hyperaemic flow velocity changes significantly post-TAVI suggesting that hyperaemic indices cannot be used to isolate coronary stenosis severity in patients with aortic stenosis. However, I have demonstrated iFR can accurately isolate the coronary stenosis severity independent to the aortic valve in this setting(99):the iFR pre-TAVI is equivalent to the iFR post-TAVI.

Post-TAVI, resting microvascular resistance increases because one lesion affecting coronary flow velocity has been treated. It does not 'normalise', however, as there is a residual coronary lesion. The change in microvascular resistance observed after TAVI is independent of the underlying coronary stenosis severity, across the severity of lesions tested in this experiment.

Other factors may influence changes in microvascular resistance seen after TAVI, such as advanced age, left ventricular hypertrophy (LVH), and elevated left-ventricular end-diastolic pressure (LVEDP)(91,92).

Clinical implications

It is common for patients with severe aortic stenosis referred for TAVI to have coronary artery disease(4). Both conditions can present with exertional chest pain or shortness of breath. It can be challenging for clinicians to determine which lesion is predominantly responsible for an individual patient's presentation. There is no strong evidence that PCI prior to TAVI improves clinical outcomes(104) but the importance of accurately assessing the functional significance of coronary disease in these patients is increasingly important as TAVI. This study suggests the microcirculation responds to aortic stenosis in a similar way to how it responds to a coronary stenosis.

Limitations

Selection bias is the reason that no quantitative comparison should be made between the TAVI and PCI groups. The patients undergoing TAVI had no reason to be similar in any way to those requiring undergoing PCI, and indeed their baseline characteristics show that they are different in many respects. Even if I were to attempt to compare the FFR and iFR effects between group 1 and group 2, such a comparison would be invalid due to selection bias. For that reason, in this chapter I have focused on pre/post intervention comparisons within each group and only compared the groups qualitatively (e.g to observe that the index of resistance improves after intervention in each group).

The patients undergoing PCI did not have severe aortic stenosis, and there were other baseline differences in the groups, and these differences may underestimate the true effect of TAVI on coronary flow(77,78,88).

I have demonstrated that, in the presence of both aortic stenosis and CAD, TAVI improves microcirculatory function. However, I cannot tell if (1) concomitant treatment of coronary artery stenosis would have afforded additional benefits; (2) or, if in fact treating CAD would have reduced the benefits of TAVI on microcirculation, as it is conceivable that the negative effects of severe aortic stenosis could be more prominent in the presence of concomitant CAD.

A larger proportion of patients in the PCI group had more severe coronary lesions with lower iFR values than in the TAVI group. Nevertheless, the patients were representative of a clinical population with severe AS and CAD who were referred for TAVI.

Conclusions

TAVI improves microcirculatory function across the spectrum of coronary stenosis severity tested in this experiment. Indices of microcirculatory function improve both after TAVI and after PCI. Approximately similar-sized effects can occur for the two interventions, although it should be remembered that the two groups in this study were in no way matched for other characteristics, so no definitive statement can be made about the exact relative size of this effect.

Tables

Table 4.1. Baseline clinical characteristics of TAVI group

	n (%)
Age (years)	81.7 ($\pm$ 5.9)
Male	27 (49.1)
Body mass index (kg/m ²)	27.36 ($\pm$ 5.0)
Diabetes	16 (29.1)
Hypertension	37 (67.3)
Hyperlipidemia	22 (40.0)
Former smoker	20 (36.4)
Previous myocardial infarction	4 (7.3)
Previous percutaneous coronary intervention	8 (14.5)
Previous coronary artery bypass grafting	3 (5.5)

Table 4.2. Baseline echocardiographic characteristics of TAVI group

	Pre-TAVI	Post-TAVI	p-value
Peak velocity (cm/s)	416.73 (±88.44)	218.38 (±47.60)	<0.001
Peak gradient (mmHg)	70.99 (±28.21)	14.41 (±7.6)	<0.001
Mean gradient (mmHg)	41.78 (±17.84)	10.17 (±5.0)	<0.001
Aortic valve area (cm ²)	0.69 (±0.23)	1.48 (±0.3)	<0.001
LV systolic function			0.484
Normal	44 (80.0)	44 (80.0)	
Mildly impaired	6 (10.9)	6 (10.9)	
Moderately impaired	2 (3.6)	4 (7.3)	
Severely impaired	3 (5.5)	1 (1.8)	
Left ventricular end-diastolic pressure (mmHg)	17.43 (±7.4)	15.43 (±6.4)	0.03
Paravalvular leak			
None		28 (50.9)	
Mild		23 (41.8)	
Moderate		4 (7.3)	
Severe		0 (0)	

Table 4.3. Baseline clinical characteristics of PCI group

	n (%)
Age (years)	61.3 ($\pm$ 9.4)
Male	63 (74.1)
Diabetes	22 (25.9)
Hypertension	43 (50.6)
Hyperlipidemia	64 (75.3)
Former smoker	38 (44.7)
Previous myocardial infarction	11 (12.9)

Table 4.4. Quantitative coronary angiographic data for TAVI patients

Target vessel		
LAD		31 (55.5%)
Cx		10 (18.5%)
RCA		14 (26.0%)
Stenosis location		
Proximal		26 (46.3%)
Mid		26 (48.1%)
Distal		3 (5.6%)
Diameter stenosis by QCA (%)		56.11 (± 11.1)
Area stenosis by QCA (%)		79.42 (± 9.7)
Stenosis length (mm)		17.64 (± 9.0)
Minimum luminal diameter (mm)		1.22 (± 0.4)
Minimum luminal area (mm ²)		1.32 (± 0.9)

Table 4.5. Quantitative coronary angiographic data for PCI patients

Target vessel		
LAD		50 (58.8%)
Cx		17 (20.0%)
RCA		18 (21.2%)
Stenosis location		
Proximal		43 (50.6%)
Mid		39 (45.9%)
Distal		3 (3.5%)
Diameter stenosis by QCA (%)		62.69 (± 13.4)
Area stenosis by QCA (%)		85.00 (± 9.9)
Stenosis length (mm)		20.86 (± 11.3)
Minimum luminal diameter (mm)		0.92 (± 0.4)
Minimum luminal area (mm ²)		0.76 (± 0.6)

Table 4.6. Values of common coronary physiological indices pre and post-TAVI

	Pre-TAVI	Post-TAVI	p-value
Fractional flow reserve	0.86 (± 0.08)	0.83 (± 0.09)	<0.001
Instantaneous wave-free ratio	0.87 (± 0.10)	0.87 (± 0.09)	0.80
Coronary flow reserve	1.56 (± 0.50)	1.74 (± 0.50)	0.03
Whole cycle resting flow (PdPa-flow)	22.54 (± 8.86)	23.02 (± 10.45)	0.71
Whole cycle hyperaemic flow (FFR-flow)	33.44 (± 12.69)	38.51 (± 16.31)	0.005
Wave-free period resting flow (iFR-flow)	28.29 (± 12.77)	27.64 (± 16.10)	0.63

Figures

Figure 4.1. Figure outlining the changes in resting resistance, hyperaemic resistance and microvascular reserve pre and post-TAVI.

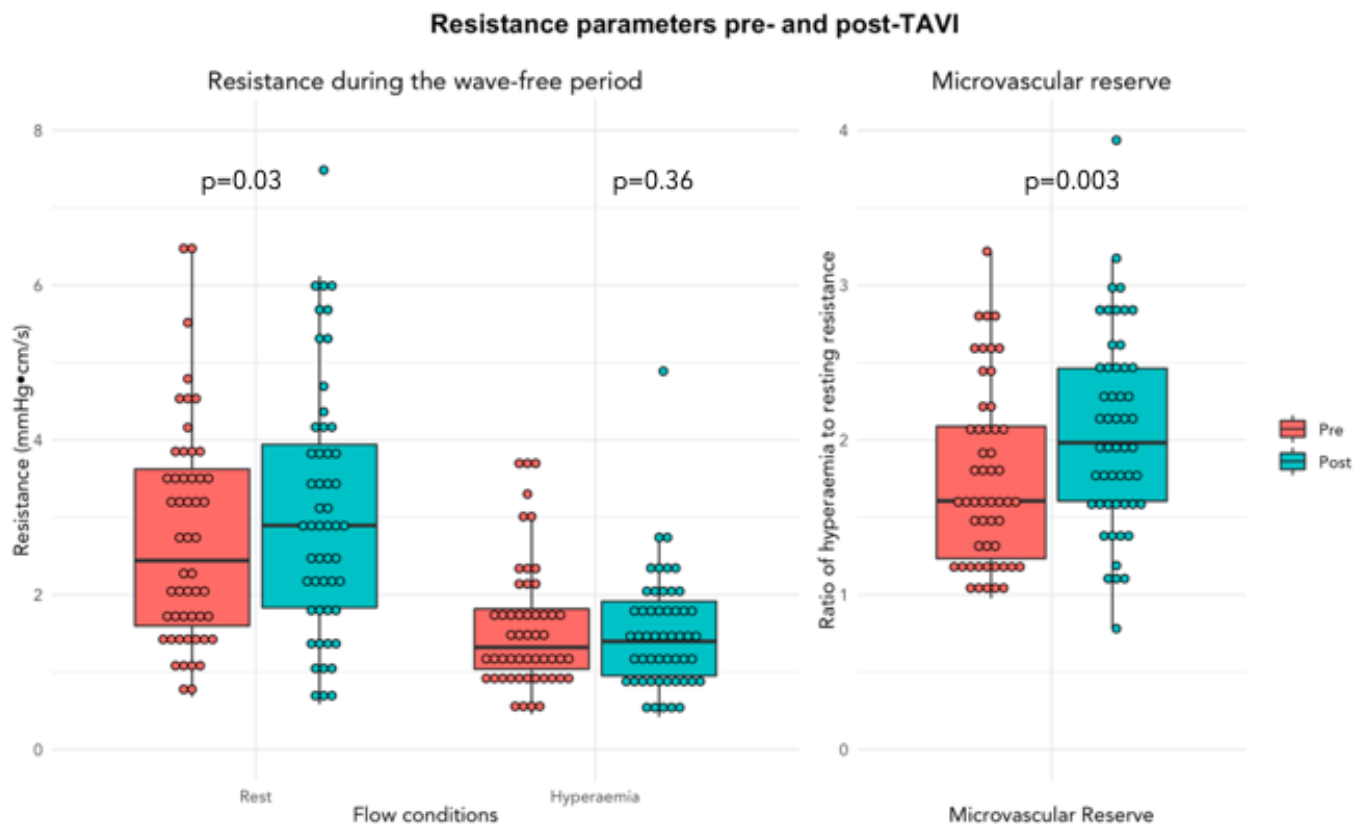


Figure 4.2. Correlation between underlying coronary stenosis severity (baseline iFR value) and improvement in resistance after PCI with a strongly statistically significant association.

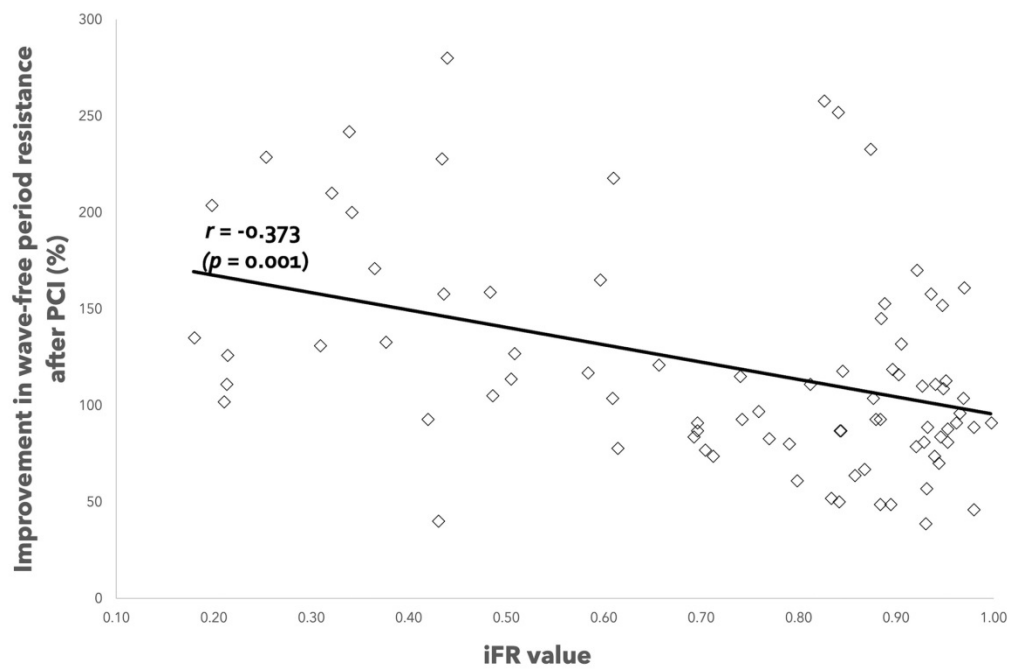


Figure 4.3. Correlation between underlying coronary stenosis severity (baseline iFR value) and improvement in resistance after TAVI with no significant association seen.

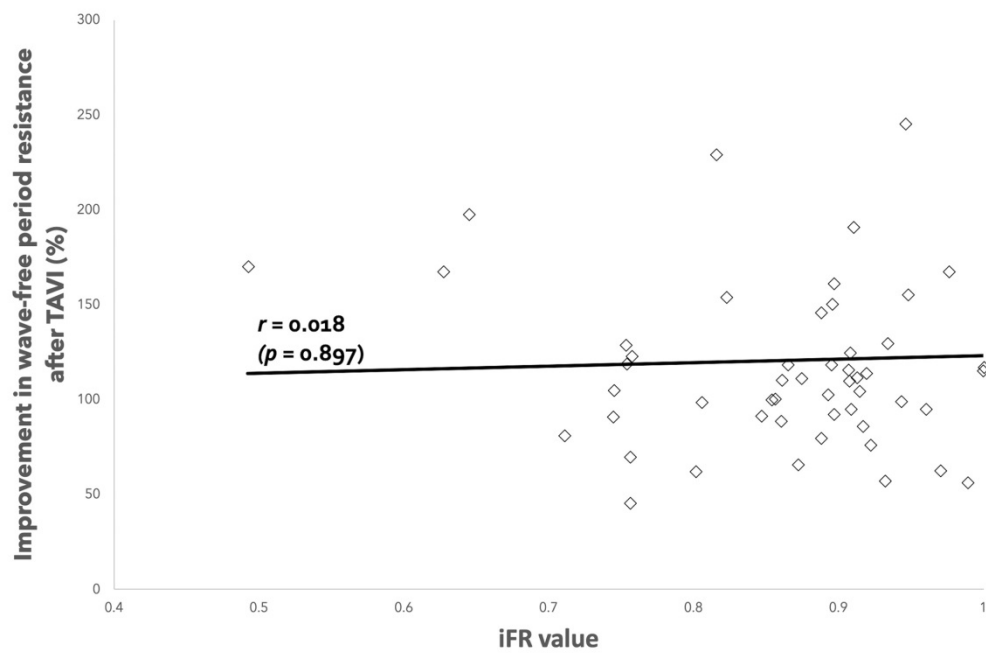
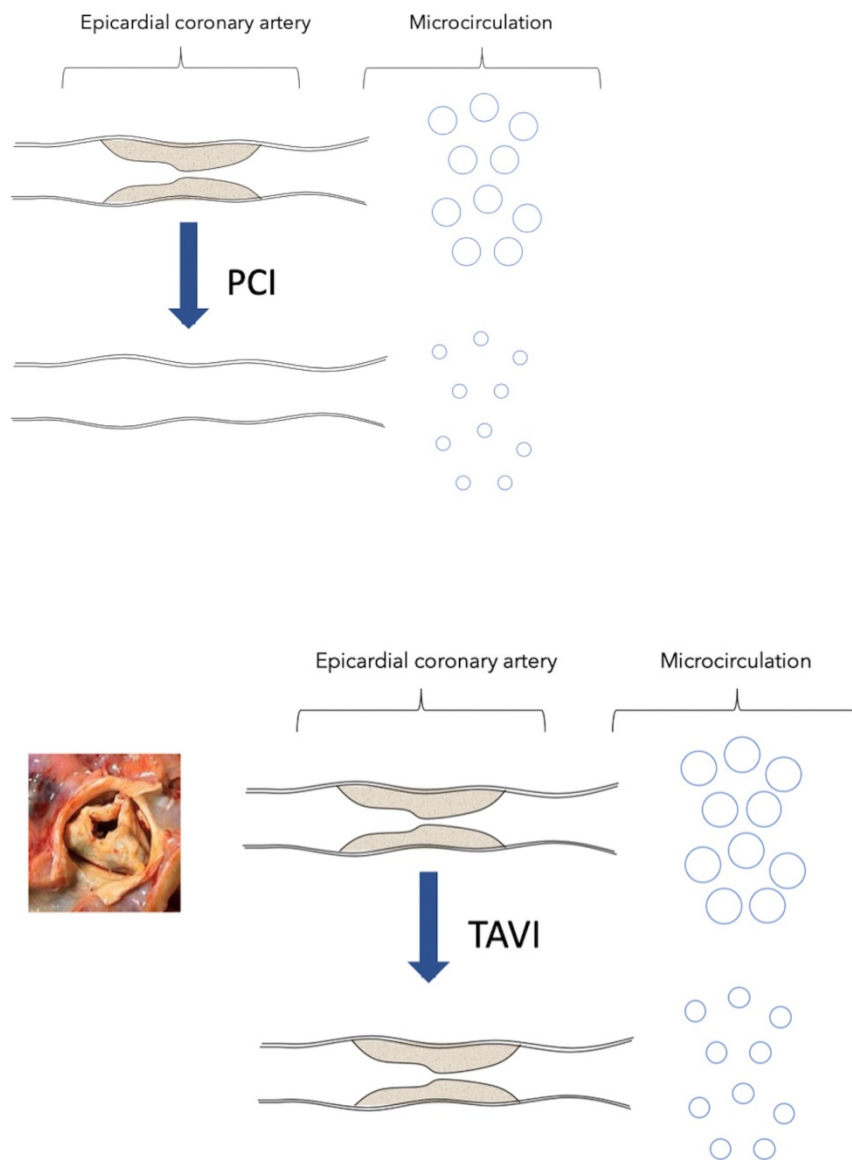


Figure 4.4. Figure outlining coronary autoregulation in patients with coronary stenoses and aortic stenosis.



In the top panel, a patient with a severe coronary stenosis; here, the microcirculation is relatively dilated at rest in order to maintain coronary flow. In these patients when the need arises to increase coronary flow further, the capacity of the microcirculation to dilate further to increase flow is limited; therefore the difference between resting and hyperaemic flow (microvascular reserve) is small. In patients with no coronary stenosis, or after PCI, the opposite is true. In these patients the microcirculation is relatively constricted. Therefore, when the need arises to increase coronary flow further, the capacity of the microcirculation to dilate further to increase flow is large; and the difference between resting and hyperaemic flow (microvascular reserve) is also large, resulting in greater microvascular reserve.

In the bottom panel, a patient with a coronary stenosis and aortic stenosis. As the aortic valve stenoses, so the microcirculation dilates to maintain coronary flow and microvascular reserve is depleted. Therefore, in patients with severe aortic stenosis and coronary disease the microcirculation is adapting to two variables that affect blood flow: the stenosed aortic valve and the stenosis in the coronary artery. Post-TAVI, resting microvascular resistance increases because one lesion affecting coronary flow has been treated. It does not 'normalise', however, as there is a residual coronary stenosis that needs to be accommodated.

5. Longer-term impact of TAVI on coronary haemodynamics in patients with concomitant coronary artery disease and severe aortic stenosis: a 6-month follow-up physiological study

The experiments and findings of this chapter have been published in:

The long-term effects of transcatheter aortic valve implantation (TAVI) on coronary haemodynamics in patients with concomitant coronary artery disease and severe aortic stenosis

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Abstract

Background

For patients with severe aortic stenosis, the assessment and treatment of concomitant coronary artery disease (CAD) is important and it is unknown how TAVI affects coronary flow velocity and other physiological parameters at longer-term follow-up.

Methods

13 patients with severe aortic stenosis referred for TAVI and moderate coronary lesions were included. Patients underwent assessment of coronary haemodynamics in the presence of severe aortic stenosis (pre-TAVI), in the absence of severe aortic stenosis (immediately post-TAVI), and at longer term follow-up (6 months post-TAVI).

Results

Fractional flow reserve (FFR) dropped from 0.85(0.76-0.88) pre-TAVI to 0.79(0.74-0.83) post-TAVI, and then to 0.71 (0.65-0.77) at 6-month follow-up ($p < 0.001$ for all comparisons). Conversely, instantaneous wave-free ratio (iFR) was not significantly different: 0.82(0.80-0.90) pre-TAVI, 0.83(0.77-0.88) post-TAVI, 0.83(0.73-0.89) at 6 months ($p = 0.735$). These changes are explained by the underlying coronary flow velocity.

Hyperaemic whole-cycle coronary flow velocity increased from 26.36(23.82-31.82) cm/sec pre-TAVI to 30.78(29.70-34.68) cm/sec post-TAVI, to 40.20(32.14-50.00) cm/sec at 6-month follow-up ($p < 0.001$ for all comparisons). Resting flow velocity during the wave-free period of diastole was not significantly different: 25.48(21.12-33.65) cm/sec pre-TAVI,

24.54(20.74-27.88) cm/sec post-TAVI, and 25.89(22.57-28.96) cm/sec at 6 months (p=0.500).

Conclusions

TAVI acutely improves whole cycle hyperaemic coronary flow velocity, with ongoing sustained improvements at 6-month follow-up. This enhanced response to hyperaemic stimuli may make FFR assessment less suitable for patients with severe aortic stenosis.

Conversely, resting diastolic flow velocity is not significantly influenced by the presence of severe aortic stenosis.

Introduction

Transcatheter aortic valve implantation (TAVI) has been demonstrated to provide outcomes at least equivalent to surgical aortic valve replacement in high(15), intermediate(18,105) and more recently low-risk(20,21) populations. The appropriate methods of assessment and treatment of concomitant coronary artery disease are unanswered questions in this patient group. Symptomatic assessment is challenging as both severe aortic stenosis and coronary artery disease can commonly cause angina and dyspnoea. Non-invasive tests of ischaemia have also been shown to perform relatively poorly in patients with severe aortic stenosis(74). The role of invasive coronary physiology has yet to be fully elucidated in patients with severe aortic stenosis undergoing TAVI(93).

The acute effect of TAVI on coronary blood flow has previously been described in an earlier chapter of this thesis(71), demonstrating significant reductions in hyperaemic coronary flow velocity and systolic coronary flow velocity in patients with severe aortic stenosis(99). TAVI acutely increased hyperaemic and systolic flow velocity, which subsequently led to an acute reduction in fractional flow reserve (FFR) immediately after TAVI(99).

The longer-term effects of TAVI on invasively measured coronary flow velocity in patients with severe aortic stenosis and concomitant coronary artery disease have yet to be studied. It has been hypothesised that as TAVI leads to longer term regression of left

ventricular mass and remodelling of the ventricle, there will be further longer-term changes in coronary haemodynamics. This hypothesis has never been objectively tested.

In this study, I aim to determine how TAVI affects coronary blood flow velocity and other coronary physiological parameters in patients with severe aortic stenosis and concomitant CAD. I will assess the coronary circulation in the presence of severe aortic stenosis (immediately pre-TAVI), in the absence of severe aortic stenosis (immediately post-TAVI), and after longer-term follow-up (6 months post-TAVI). This will allow me to determine whether the acute changes in coronary flow velocity seen immediately after TAVI are sustained, or whether they change at longer-term follow-up.

Methods

Patient population

Patients with severe, symptomatic aortic stenosis undergoing TAVI with at least moderate coronary lesions were included. All patients were scheduled for TAVI on clinical grounds after a decision at a Heart Team meeting and gave written informed consent for the study protocol. Exclusion criteria were known non-viable myocardium in the area of the corresponding coronary artery being studied, history of coronary artery bypass grafting (CABG), severe renal dysfunction (eGFR <30 ml/min/1.73m²), contra-indication to the administration of adenosine, inability to consent, or weight over 200kg. All patients had prospectively collected combined coronary pressure and flow velocity measurements, with paired measurements immediately pre and post-TAVI, as well as after 6 months follow-up.

TAVI procedures

All patients were treated using local anaesthetic only, via transfemoral access. The used valve types were either the Edward's SAPIEN 3 valves (Edwards Lifesciences LCC, Irvine, CA, USA), or the Medtronic Evolut-R valves (Medtronic Inc., Minneapolis, MN, USA). Valve choice was at the Heart Team and operator's discretion and was decided prior to study inclusion.

Physiological assessment

A dual pressure and Doppler sensor-equipped 0.014" guidewire was used for all physiological assessments (ComboWire, Volcano Corp, San Diego, USA). The pressure signals were normalised in the aorta prior to advancing the wire a minimum of three-vessel diameters distal to the coronary stenosis. Doppler signals were optimised and stabilised to ensure good tracking profiles. At this stage, resting pressure and flow measurements were recorded. Hyperaemia was then induced using an intracoronary bolus of adenosine. Physiological measurements under hyperaemic conditions were then recorded. At the end of each recording, the pressure sensor was returned to the catheter tip to ensure that there was no pressure drift. When drift was identified (≥ 0.01), all measurements were repeated. All patients then underwent the TAVI procedure according to standard clinical protocols. Subsequent to the successful TAVI, the entire protocol was repeated with the wire sited in the same location as the pre-intervention measurements. 6 months following TAVI, patients returned for a follow-up assessment. The entire physiological protocol was repeated in an identical manner to those conducted during the index assessments during the TAVI procedure.

Analysis of haemodynamic data

Electrocardiogram (ECG), pressure, and coronary flow velocity signals were extracted with the dedicated device console (ComboMap; Volcano Corp, San Diego, CA, USA). Analog

output feeds were taken from the pressure-velocity console and ECG, fed into a National Instruments DAQ-Card AI-16E-4, and acquired at 1 kHz with Labview. Data were analysed offline with a custom software package designed with Matlab (Mathworks, Natick, MA, USA).

Coronary pressure and flow velocity were assessed over the whole cardiac cycle and during the wave-free period during the diastolic phase of the cardiac cycle. All measurements were performed during resting conditions and during hyperaemia and were analysed accordingly. The wave-free period was identified using wave-intensity analysis(100) and used to perform phasic analysis.

Definitions of haemodynamic variables were the same as in earlier chapters of this thesis.

Statistical methods

Continuous variables are presented as median and interquartile range ($\pm$ IQR) unless otherwise stated, due to the small sample size of this experiment and concerns that only severe deviations would be detected by tests of normality. Comparisons for pre-TAVI, post-TAVI and longer-term follow-up were performed using the Friedman test. In the first instance, we looked for evidence of an overall significant difference between pre, post and follow-up measurements. In the event that a significant difference was found across all groups, we then compared each individual category in a stepwise fashion, deriving a p

value for each comparison (pre-TAVI versus post-TAVI, pre-TAVI versus follow-up, and post-TAVI versus follow-up). We used the Benjamini-Hochberg procedure to control the false discovery rate. The threshold for statistical significance was set at 0.05. All analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient population

13 patients were included (median age was 77.3 (75.4-80.8) years old). The predicted surgical risk (STS-PROM) was 2.11 (1.97-2.60), depicting a more contemporary lower-risk TAVI population. Baseline clinical characteristics are summarised in Table 5.1. The baseline echocardiographic characteristics are summarised in Table 5.2. 12 patients were treated with the SAPIEN 3 prosthesis, and one patient was treated with the Evolut R prosthesis. Quantitative coronary angiographic data is summarised in Table 5.3.

Coronary haemodynamics

A summary of all coronary haemodynamic data is shown in Table 5.4 and Figures 5.1-5.5.

Indices of coronary stenosis severity

Fractional flow reserve (FFR) dropped from 0.85 (0.76-0.88) pre-TAVI to 0.79 (0.74-0.83) post-TAVI and then to 0.71 (0.65-0.78) at long-term follow-up, with evidence of a significant difference between the groups ($p < 0.0001$). Additional testing showed a significant interaction for each pairwise comparison between the different time points ($p < 0.0001$ for each). Conversely, instantaneous wave-free ratio (iFR) was unchanged pre-TAVI (0.82 (0.80-0.89)), post-TAVI (0.83 (0.77-0.89)) and then at longer-term follow-up (0.83 (0.73-0.93)), with no evidence of a significant difference between the groups

($p=0.735$). Figures depicting the FFR and iFR measurements are shown in figure 5.1 and 5.2.

Coronary flow parameters

Hyperaemic whole-cycle coronary flow velocity increased post-TAVI (26.36.78 cm/sec pre-TAVI vs 30.78 cm/sec post-TAVI), with a further increase at 6-month follow-up to 40.20 cm/sec. There was evidence of a significant difference between the groups ($p=0.012$), with additional testing showing a significant interaction for each pairwise comparison ($p=0.012$ for pre-TAVI versus post-TAVI; $p<0.0001$ for pre-TAVI versus follow-up and post-TAVI versus follow-up).

Resting flow velocity during the wave-free period of diastole was unchanged from pre-TAVI (25.48cm/sec (21.12-33.65) to post-TAVI (24.54cm/sec (20.74-27.88) and then at longer-term follow-up (25.89cm/sec (22.58-28.96), with no evidence of a significant difference between the groups ($p=0.500$). Figures depicting the flow velocity measurements are shown in Figure 5.3 and 5.4.

Coronary flow reserve (CFR) increased from 1.28 (1.10-1.85) pre-TAVI to 1.65 (1.47-1.85) post-TAVI, and then to 1.94 (1.69-2.25) at longer-term follow-up, with evidence of a significant difference between the groups ($p<0.0001$). Additional testing showed a significant interaction for each pairwise comparison ($p<0.0001$ for each).

Clinical events

None of the patients included in this study required coronary revascularisation for angina or acute coronary syndrome up to latest follow-up (6 months).

Discussion

In this study I have shown that: 1) hyperaemic coronary flow velocity increases acutely post-TAVI and continues to rise up to 6-months of follow-up; 2) this rise in flow velocity causes both acute and long-term declines in FFR values, and 3) resting diastolic flow velocity, and consequently iFR, is not affected by severe aortic stenosis and remains unchanged pre-TAVI, post-TAVI and at 6 month follow-up.

Longer-term impact of TAVI on coronary flow velocity

I have previously been shown that TAVI causes acute increases in hyperaemic and systolic flow velocity, leading to an acute reduction in FFR(99).

The longer-term effects of TAVI on coronary flow velocity and indices of coronary stenosis severity, however, have remained unknown and have not previously been studied. In this study it has been demonstrated that there is an ongoing increase in hyperaemic coronary flow velocity out to 6 months, and that this leads to a consequent significant drop in the FFR value. Severe aortic stenosis leads to pathophysiological changes in the left ventricular myocardium, with subsequent hypertrophy and fibrosis(77). These changes cause a fixed compression to the coronary microcirculation, and impedes its ability to vasodilate in response to hyperaemic agents such as adenosine(92). This results in

blunted hyperaemic flow velocity and thus may lead to false-negative FFR values (i.e. the FFR value will be falsely high in patients with severe aortic stenosis).

Following successful treatment of severe aortic stenosis with TAVI, acute changes in the myocardium lead to increases in coronary flow velocity and reductions in FFR directly post-TAVI, as shown by the present and previous studies within this thesis. However, progressive regression of left ventricular mass and other favourable remodelling of the left ventricle may occur far beyond the early phase post-TAVI. This results in further increases in the ability of the microcirculation to respond to hyperaemic stimuli, and, thus in hyperaemic coronary flow velocity (106). This is reflected by our data showing both an increase in hyperaemic coronary flow velocity, as well as a reduction in FFR, up to 6-months of follow-up.

In contrast, resting diastolic flow velocity appears to be unaffected by the presence of severe aortic stenosis. We have previously demonstrated that the aortic valve has minimal impact on coronary flow velocity during diastole. In this study we have now been able to demonstrate that there are also no longer-term changes in resting diastolic flow velocity out to 6 months, and therefore no significant changes in the iFR values. This suggests that left ventricular hypertrophy and elevated left ventricular pressures do not have an important impact on iFR. Such resting indices of coronary stenosis severity are therefore less likely to change after treatment of severe aortic stenosis.

Prior work in the field

Scarsini and colleagues have compared iFR to FFR in a study 2018 without measuring coronary flow velocity (73). This study evaluated 145 coronary lesions in 66 patients with severe aortic stenosis. FFR and iFR were measured before and after TAVI. The mean iFR values were identical before and after TAVI; this finding is similar to that observed in this current study. There was a reported 15% categorisation change by iFR after TAVI. Their study highlights important aspects of the assessment of any physiological index in a new clinical context: (1) the reference standard to which the index is being compared and (2) the importance of understanding stenosis distribution when interpreting results.

The diagnostic accuracy of iFR is reported in this study purely in terms of using an FFR of 0.80 as the gold standard, which has never been validated in patients with severe AS.

Despite the mean iFR before and after TAVI being identical, it was reported in Scarsini's study that in 15% of patients iFR categorisation of functional significance changed post-TAVI. The direction of change was unpredictable and higher than the categorisation change with FFR. The authors conclude that iFR should be used in caution in patients with severe aortic stenosis as there was significant variation post-TAVI.

To conclude this, however, fails to appreciate the role of population distribution and the limitations of using a continuous variable dichotomously. This apparent greater

classification change is a result of the distribution of iFR values when compared to FFR values. The majority of patients in this study had iFR values that group around the iFR cut-point of 0.89. Any biological variation will therefore lead to treatment reclassification of a large proportion of patients when the inherent variability of iFR causes its value to drop below or climb above the cutpoint. In contrast, the majority of patients had FFR values significantly further away from the FFR cut-point (due to attenuated hyperaemia). Therefore, the biological variation and numerical changes in FFR resulted in fewer stenosis classification changes. The classification change, or lack of change, is therefore an artefact of using a continuous variable such as FFR or iFR dichotomously, stenosis distribution, and the inadequate hyperaemia seen in these patients.

This categorisation variability around the treatment threshold has been defined in FFR. When measured 10 minutes apart in the same patient FFR itself has a categorisation change in 15%, increasing to 50% when FFR values are close to the treatment threshold(75).

Clinical implications

For patients undergoing TAVI, the optimal way to assess and treat this concomitant coronary disease has not yet been established. There is currently no clear evidence that PCI prior to TAVI improves clinical outcomes(104), and randomised clinical trials concerning PCI in TAVI-patients are still awaited (i.e. NOTION-3 (NCT03058627) and 172

REVIVAL (NCT03283501)). Large, randomised clinical trials evaluating the use of coronary physiology in these patients will ultimately help to define the optimal treatment strategy. The importance of accurately assessing the significance of coronary disease, and offering PCI if appropriate, is therefore an unanswered question.

I have shown that hyperaemic indices of coronary stenosis severity, such as FFR, may not be able to isolate the functional significance of a coronary lesion in the presence of severe aortic stenosis. They appear to lead to systematic underestimation of coronary lesion severity, and therefore could potentially miss flow-limiting coronary lesions that might benefit from revascularisation.

My findings are also potentially of importance for patients undergoing surgical aortic valve replacement. Pre-operative coronary angiography and FFR measurement, in the presence of severe aortic stenosis, is likely to lead to falsely elevated FFR values and therefore the potential to defer concomitant bypass grafting for a patient who might otherwise benefit from surgical coronary revascularisation.

Limitations

This is a small, prospective, mechanistic study. However, this is the first study to demonstrate longer-term invasive coronary haemodynamic data post-TAVI (with previous

paired measurements immediately before and after TAVI) and is comparable in size to previous physiological studies in the field(79).

Data regarding regression of LV mass was not available. In principle, one might seek a correlation between regression of LV mass and improvement in hyperaemic flow velocity. However, LV mass is vulnerable to noise in its measurement and therefore changes in LV mass over time, which are small changes within a relatively large number, are extremely vulnerable to random noise. While this does not prevent detection of correct direction and approximate magnitude of changes over time in a group, it makes it very difficult to identify a correlation with another variable reliably.

This was a physiological study examining haemodynamic data, and was not intended to look at clinical outcomes, nor powered for this. None of the patients included in this study required coronary revascularisation for angina or acute coronary syndrome up to latest follow-up, and none of them died but in this sample size it is not possible to draw precise general conclusions from this.

A cohort study might be a good future design to explore the clinical impact of various levels of iFR and FFR in such patients. A design for this could be a large cohort recruited from multiple centres, for example across the UK in which the participants have the measurements but no coronary intervention. Over a period of years, the event rates could

be assessed, and it could be established whether pre-TAVI iFR or FFR is a better predictor of subsequent events.

Ultimately, a randomized trial powered for clinical endpoints is the only way to determine whether intervening on lesions in a given range of iFR or FFR is beneficial or not. This would be a major undertaking and could be pursued if the observational data described above suggests potential utility.

My study only included patients with symptomatic severe aortic stenosis referred for TAVI. We do not know how milder forms of aortic stenosis may affect hyperaemic coronary flow and the commonly used indices of coronary stenosis severity. This should, however, be the subject of future research.

Conclusions

TAVI acutely improves whole cycle hyperaemic coronary flow velocity, with ongoing sustained improvements at longer-term follow-up. This enhanced response to hyperaemic stimuli leads to FFR values to drop both acutely after TAVI and further again at 6-month follow-up. Conversely, resting diastolic flow is not significantly influenced by the presence of severe aortic stenosis, with no significant changes immediately after TAVI or out to 6 months of follow-up. iFR was also constant before TAVI, after TAVI and at 6-months of follow-up.

Tables

Table 5.1. Baseline clinical characteristics

Age (years)	77.3 (75.4-80.8)
Male	6 (46.2)
Body mass index (kg/m ²)	27.6 (24.2-31.6)
Diabetes	1 (7.7)
Hypertension	7 (53.8)
Hyperlipidaemia	3 (23.1)
Former smoker	8 (61.5)
Previous myocardial infarction	2 (15.4)
Previous percutaneous coronary intervention	2 (15.4)
History of atrial fibrillation	3 (23.1)
STS-PROM (%)	2.11 (1.97-2.60)
EuroSCORE-II (%)	1.73 (1.55-2.55)
Follow-up duration	166 (122-238)

Table 5.2. Echocardiographic characteristics

	Pre-TAVI	Post-TAVI	Follow-up	p-value
Peak gradient (mmHg)	75 (59-92)	14 (7-20)	22 (17-29)	<0.001/<0.001/0.06
Aortic valve area (cm ²)	0.83 (0.70-0.95)	1.53 (1.46-1.70)	1.57 (1.40-1.68)	<0.001/<0.001/0.76
LV systolic function				
Normal	10 (76.9)	11 (84.6)	11 (84.6)	ns
Mildly impaired	2 (15.4)	2 (15.4)	2 (15.4)	
Moderately impaired	1 (7.7)	0	0	
Severely impaired	0	0	0	
Paravalvular leak				
None	-	10 (76.9)	12 (92)	ns
Mild	-	2 (15.4)	1 (7.7)	
Moderate	-	1 (7.7)	0	
Severe	-	0	0	

Table 5.3. Quantitative coronary angiographic data

Target vessel	
LAD	6 (46.2)
RCx	3 (23.1)
RCA	4 (30.8)
Stenosis location	
Proximal	6 (46.2)
Mid	3 (23.1)
Distal	4 (30.8)
Diameter stenosis by QCA (%)	53.3 (49.04-63.60)
Area stenosis by QCA (%)	78.2 (74.02-86.75)
Stenosis length (mm)	9.97 (8.07-13.34)
Minimum luminal diameter (mm)	1.27 (1.15-1.63)
Minimum luminal area (mm ²)	1.27 (1.03-2.58)

Table 5.4. Coronary haemodynamic data

	Pre-TAVI	Post-TAVI	Follow-up	p-value*
Fractional Flow Reserve (FFR)	0.85 (0.76-0.88)	0.79 (0.74-0.83)	0.71 (0.65-0.77)	<0.001/<0.001/<0.001
Coronary Flow Reserve (CFR)	1.28 (1.10-1.51)	1.65 (1.47-1.85)	1.94 (1.69-2.25)	<0.001/<0.001/<0.001
instantaneous wave Free Ratio (iFR)	0.82 (0.80-0.90)	0.83 (0.77-0.88)	0.83 (0.73-0.90)	0.735
Hyperaemic whole cycle flow (cm/sec)	26.36 (23.82-31.82)	30.78 (29.70-34.68)	40.20 (32.14-50.00)	0.012/<0.001/<0.001
Resting wave-free diastolic flow (cm/sec)	25.48 (21.12-33.65)	24.54 (20.74-27.88)	25.89 (22.57-28.96)	0.500

Figures

Figure 5.1. Boxplot of the FFR values, for all time points. Individual values are depicted as the dots.

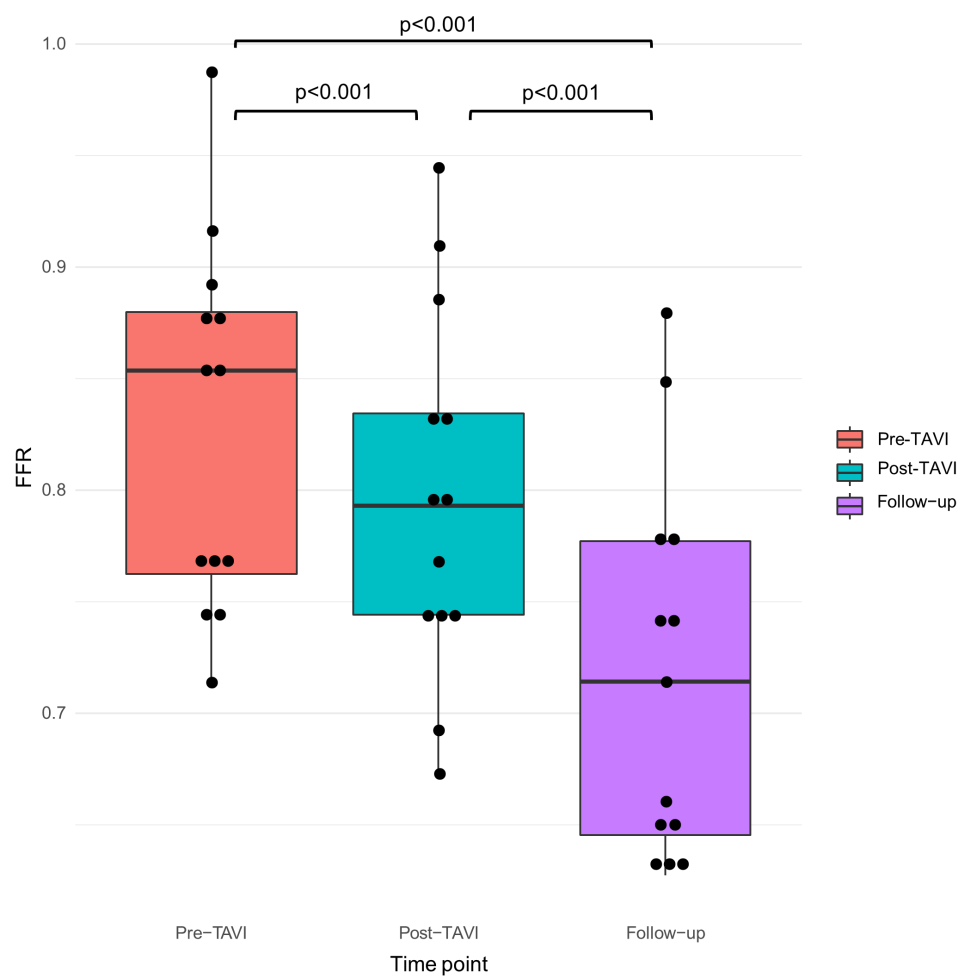


Figure 5.2. Boxplot of the iFR values, for all time points. Individual values are depicted as the dots.

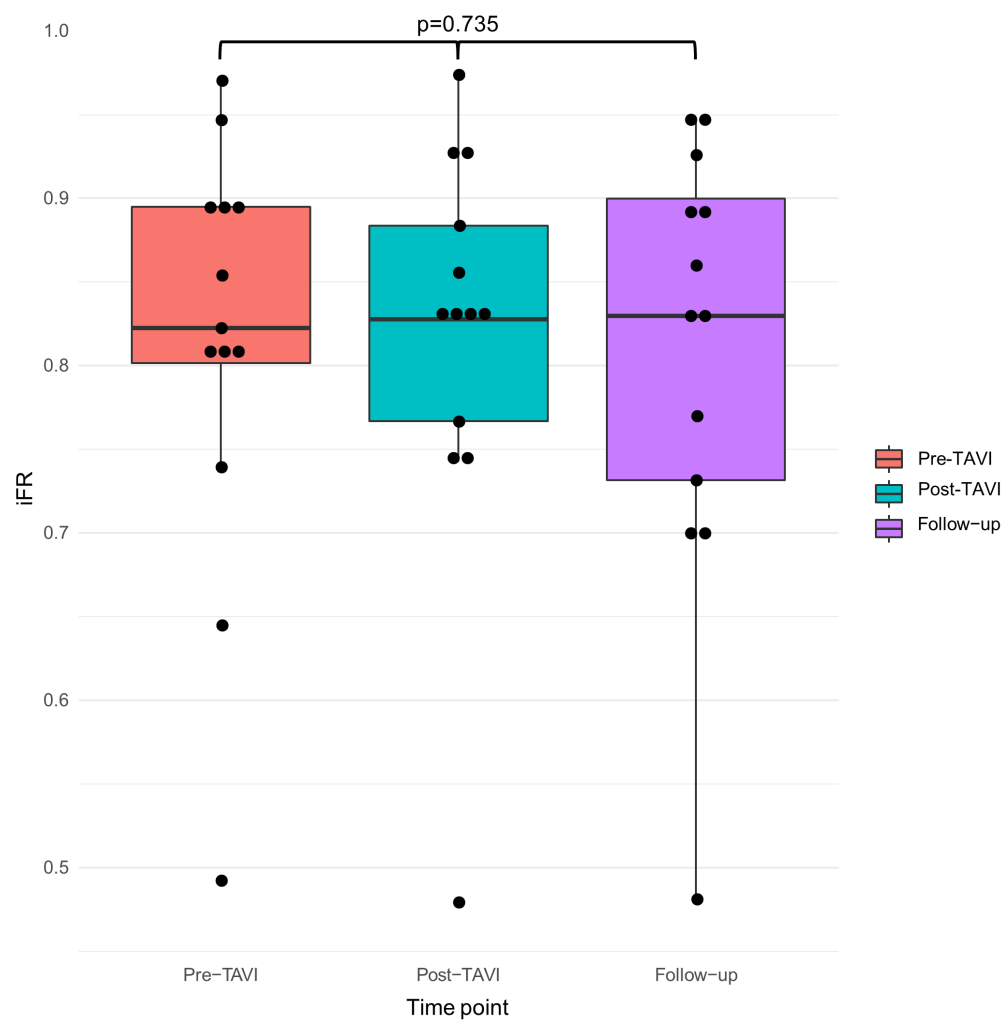


Figure 5.3. Boxplot of the whole-cycle hyperaemic flow values, for all time points.

Individual values are depicted as the dots

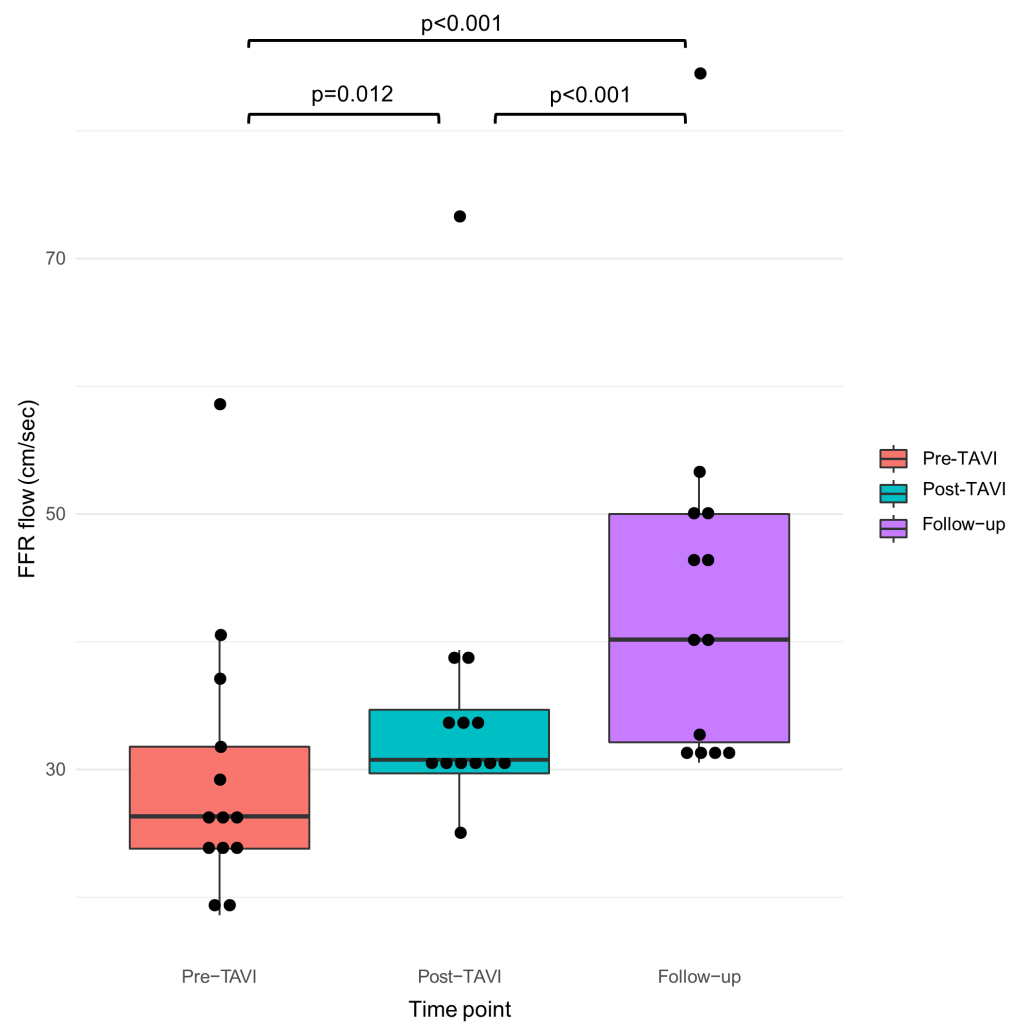


Figure 5.4. Boxplot of the resting wave-free diastolic flow values, for all time points. Individual values are depicted as the dots

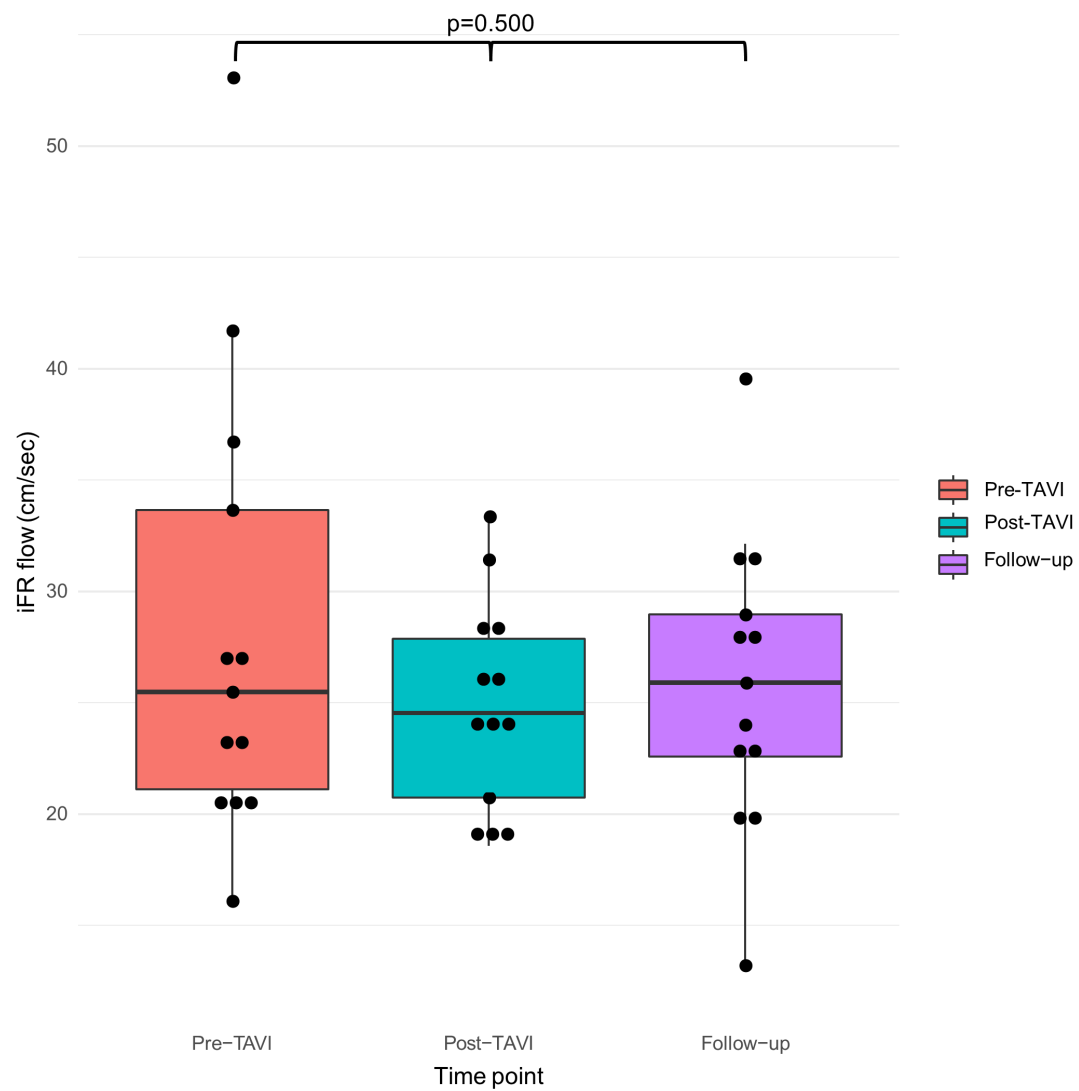
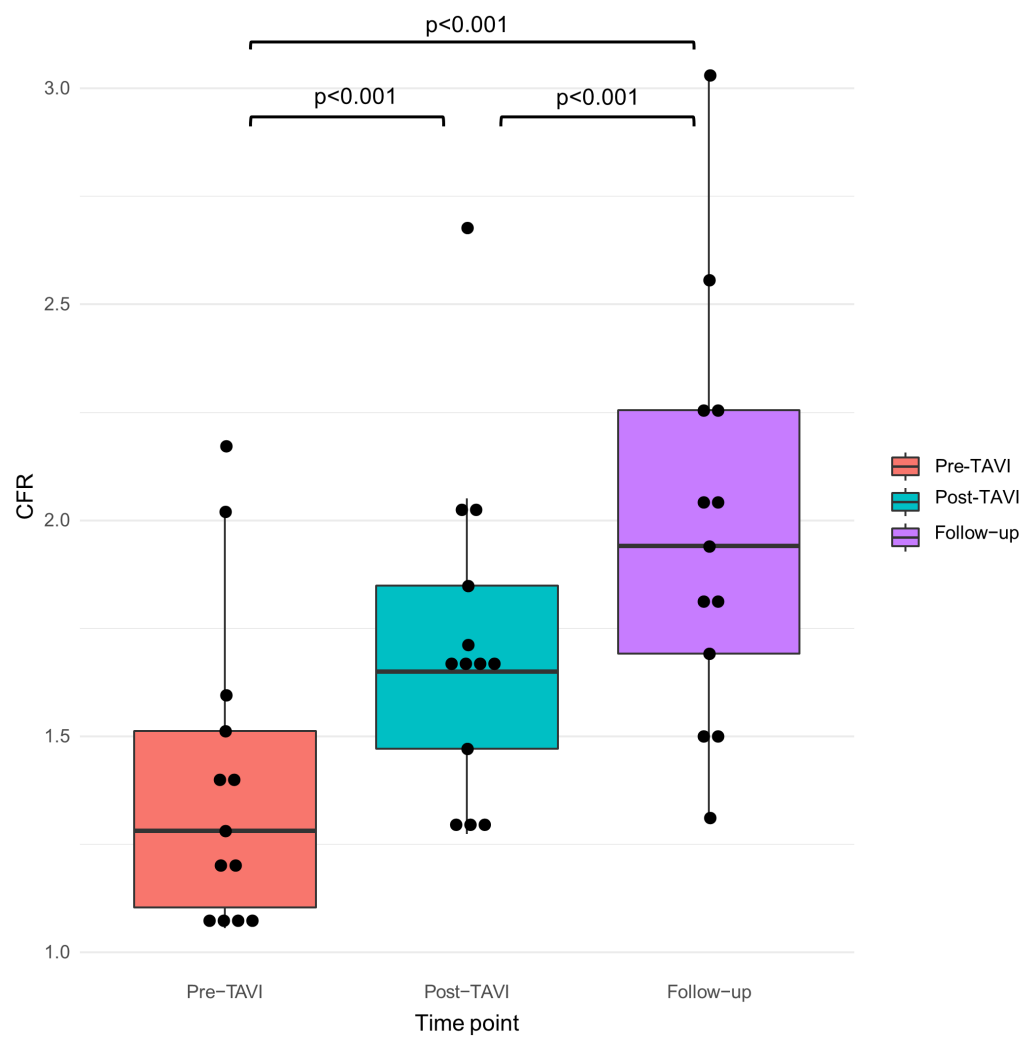


Figure 5.5. Boxplot of the CFR values, for all time points. Individual values are depicted as the dots.



6.Synthesis

This thesis has investigated coronary haemodynamics in patients with severe aortic stenosis and coronary artery disease, performing the first systematic assessment of invasively measured coronary flow velocity before and after transcatheter aortic valve implantation (TAVI) in patients with coexistent CAD. The novel aspects of this thesis pertain to the invasive measurement of coronary flow velocity, which permits a better mechanistic understanding of how commonly used indices of coronary stenosis severity (FFR and iFR) behave in severe aortic stenosis.

This thesis has answered the following 3 key questions:

Question 1. In patients with severe AS and CAD, what is the effect of the presence of severe AS on coronary flow velocity, and consequently on FFR and iFR?

Question 2. Does aortic stenosis affect microvascular physiology?

Question 3. Is the effect of aortic stenosis on coronary physiology only short-term, i.e. once the aortic stenosis is removed, there is no further change, or is there a longer-lasting effect?

In this series of studies, I have demonstrated the acute effect of TAVI on coronary flow velocity. I have identified that both systolic coronary flow and hyperaemic coronary flow

velocity are attenuated in patients with severe aortic stenosis, and are immediately augmented by TAVI; therefore I have been able to identify what appear to be the most appropriate conditions to assess coronary stenoses in patients with severe aortic stenosis: in resting conditions (non-hyperaemic), and during diastole (when the aortic valve is closed). I then quantified the effect of TAVI on the coronary microcirculation in patients with coronary stenoses and severe aortic stenosis, and examine how the severity of the coronary lesion affects improvements in microcirculatory function achieved by TAVI. Finally, I studied the longer-term effects of TAVI on coronary haemodynamics. In this study, I was able to assess the coronary circulation in the presence of severe aortic stenosis (pre-TAVI), in the absence of severe aortic stenosis (post-TAVI), and at longer-term follow-up (6 months post-TAVI). This identified that hyperaemic coronary flow velocity is increased acutely by TAVI , and continues to rise out to 6 months. This increase in hyperaemic flow velocity is accompanied by a concordant drop in FFR values. Conversely, resting diastolic flow velocity, and consequently iFR, is not affected by severe aortic stenosis and remains constant out to 6 months of follow-up.

The flow velocity findings of this study are truly novel as invasive flow velocity has not previously been studied in patients with severe aortic stenosis and coexistent coronary lesions. This advances our understanding of the complex haemodynamic situation seen in patients with severe aortic stenosis and coronary artery disease. I will now discuss some

of these findings in more detail, and place them in context in terms of the previous literature, and identify potential areas for future study.

The importance of measuring coronary flow velocity

Myocardial ischaemia is the result of a reduction in coronary blood flow so that oxygen requirements cannot be met. For purely pragmatic purposes, physiological assessment of coronary stenoses in clinical practice is performed by measuring coronary pressure, rather than directly measuring coronary flow.

Using coronary pressure as a surrogate of flow is contingent on there being a direct linear relationship between coronary pressure and coronary flow. This linear relationship exists when resistance is both stable and minimal. Stable and minimal resistance can be achieved either by the administration of vasodilators (inducing hyperaemia, most commonly by giving adenosine), or by restricting measurements of pressure-gradients to periods of the cardiac cycle when resistance is naturally stable and minimal (the wave-free period of diastole). These two principles underpin the two most commonly used indices of coronary stenosis severity: FFR (measured during hyperaemia, over the whole cardiac cycle), and iFR (measured during resting conditions, during the wave-free period of diastole). Through a series of validation studies and clinical trials, it has been demonstrated that in patients without severe aortic stenosis, both FFR and iFR can be

used as pressure-based indices of coronary stenosis severity and act as a surrogate for coronary flow.

In order to understand how these indices perform in patients with severe aortic stenosis, we must measure coronary flow; furthermore, we must understand how a stenosed aortic valve affects coronary flow. TAVI allows us to assess coronary flow velocity immediately before and after a stenosed aortic valve is treated, and therefore to truly isolate the effect of the valve on coronary haemodynamics; this approach minimises the influence of potential confounding factors.

There is, overall, scarce data on coronary physiology in patients with severe aortic stenosis and coronary artery disease. Every existing study (prior to those included in this thesis) has only examined coronary pressure (FFR and iFR)(70,73); furthermore, these studies have classified coronary stenoses as functionally significant or not based on cutoff values of iFR or FFR that have been established and validated in patients without severe aortic stenosis(72). Another approach has been to compare invasive coronary physiological indices with non-invasive assessments of myocardial ischemia(107).

These approaches have several limitations. To compare an invasive physiological index with a non-invasive approach assumes the non-invasive method is the gold standard. In patients with severe aortic stenosis, non-invasive measures of ischaemia can be

unreliable(74). Secondly, to measure coronary pressure without measuring coronary flow (and using the same cutpoints as in patients without severe aortic stenosis) makes the central assumption that coronary flow is unaffected by severe aortic stenosis.

This work within the context of prior work in the field

The majority of the previous published work in the field of coronary physiology in patients with severe aortic stenosis has come from the Verona group. Pesarini et al studied FFR in 133 coronary lesions in 54 patients before and after TAVI (69). This particular study did not include iFR, and did not include any measure of coronary flow velocity. Overall they found no change in FFR values after TAVI, but a more nuanced reading of the data permits a more refined interpretation. Lesions with functionally significant FFR values (classified as lower than 0.80) were observed to decline after TAVI. This was also seen with quantitative angiographic data. If the diameter stenosis was >50%, then the FFR value declined significantly after TAVI; if the diameter stenosis was <50% there was no change in FFR value after TAVI. The overall diameter stenosis in this cohort was 40%, indicating they recruited patients with a milder form of CAD than those recruited in the series of experiments that comprise this thesis. The average diameter stenosis in the experiments contained within this thesis was approximately 55%. This is consistent with the severity of stenosis examined in clinical trials of coronary physiology in patients without severe aortic stenosis (average diameter stenosis 60% in FAME; average diameter stenosis 48% in the

deferral and performance groups in DEFER, and 57% in the reference group of FFR <0.75 in DEFER). Furthermore, this may help explain why the overall FFR values did not change in Pesarini's study; in fact, when their analysis was restricted to patients with a greater than 50% diameter stenosis, the mean FFR value dropped from 0.84 to 0.82. This is an effect very similar to that observed in the first experiment that formed chapter 3 of this thesis.

Scarsini et al (71) from the same group then studied iFR and FFR in 179 lesions in 85 patients with severe aortic stenosis. This study also did not include any assessment of coronary flow velocity, highlighting a key difference of the work that has formed the basis of this thesis. It is important to note that this was not a study of patients undergoing TAVI, which involved physiological assessments before and after valve intervention. The aim of the study was to test the diagnostic agreement of iFR and FFR in patients with severe AS, and compare it to the diagnostic accuracy of a control group without severe AS. The diagnostic agreement of iFR and FFR was predicated on the FFR cutoff value of 0.80 and an iFR cutoff value of 0.89. This study concluded that that correlation between FFR and iFR in patients with aortic stenosis was similar to the cohort of patients without aortic stenosis. However, the diagnostic agreement between iFR and FFR (using the defined cutoffs that are in place for patients without severe aortic stenosis) was lower in the AS patients (76.3%) when compared to the non-AS patients (86.1%). The optimal iFR cutoff for predicting an FFR of 0.80 was an iFR of 0.83. This is likely simply a mechanism of attenuated hyperaemic flow velocity meaning that FFR values are falsely elevated in the

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presence of severe aortic stenosis. This hypothesis could not be tested in Scarsini's study as there was no measurement of flow velocity.

The experiments that comprise this thesis are able to show that hyperaemic coronary flow velocity was reduced in severe aortic stenosis and improved by TAVI. This mechanism is hinted at in the Discussion of their manuscript: 'FFR might underestimate substantial CAD in the setting of AS because of the impaired microvascular function'; this is a suggested possible mechanism that is speculative due to the inherent limitations of performing only pressure-gradient assessments (FFR or iFR) in the absence of directly measuring flow velocity.

A strength of the current series of studies within this thesis is the direct measurement of coronary blood flow velocity, and being able to observe directly and clearly that hyperaemic coronary flow velocity is indeed reduced in patients with severe aortic stenosis. Scarsini and colleagues note in this paper that 'extrapolating the same current FFR and iFR thresholds used in CAD patients to AS patients is only hypothesis generating, and its validation warrants further research'. Their findings are not at all in conflict with the results of the studies within this thesis, but they are an artefact of using an FFR cutpoint of 0.8 as a gold-standard ischaemic reference to which another index is compared.

Wiegernick and colleagues performed an assessment of invasive coronary flow velocity in patients with severe aortic stenosis before and after TAVI in 2015 (71). It is important to note that this study included only patients with unobstructed coronary arteries, which is a key difference from the work contained within this thesis. Furthermore, all analyses were restricted to the left coronary artery. This study included a control group without severe aortic stenosis: the main aim of this study was to evaluate the effects of severe aortic stenosis on coronary haemodynamics as compared with a cohort of patients without AS. This study did show that hyperaemic flow velocity was lower in patients with severe AS when compared to controls, as was CFR. These findings helped inform the design of the series of experiments within this thesis, where we sought to evaluate coronary flow velocity in patients with severe aortic stenosis and coronary artery disease, before and after TAVI.

Scarsini and colleagues subsequently compared iFR to FFR in a study 2018 (73). This study evaluated 145 coronary lesions in 66 patients with severe aortic stenosis. FFR and iFR were measured before and after TAVI. This was a study of pressure-gradients without assessments of flow velocity.

The mean iFR values were identical before and after TAVI; this finding is similar to that observed in the experiments that comprise this thesis. The mean iFR value was also very

similar to the mean FFR value before TAVI in this study. This is again similar to the results of the experiments within this thesis.

Therefore, Scarsini's results do not appear to be in conflict to my own. A key difference and advance that this thesis represents, is the measurement of flow velocity to permit mechanistic insights that explain the behaviour of iFR and FFR in severe aortic stenosis. For example, the similar pre-TAVI iFR and FFR values in Scarsini's study are likely to be a function of impaired hyperaemic flow velocity in severe aortic stenosis leading to higher FFR values. However, this hypothesis could not be tested in Scarsini's study. This is a finding, however, that was objectively tested and shown in this thesis, setting it apart from previous work in the field. The inability to achieve maximal hyperaemia challenges the physical principles upon which FFR depends and therefore calls into question the validity of using this index as a *reference* standard in patients with aortic stenosis, and particularly the use of a 0.80 cut-point. The diagnostic accuracy of iFR is reported in this study purely in terms of using an FFR of 0.80 as the gold standard, which was validated in patients without severe AS. The negative and positive predictive values derived in this study should therefore be interpreted cautiously. There was also a reported 15% categorisation change by iFR after TAVI. This finding is an artefact of the distribution of iFR values close to the cutpoint, in contrast to the FFR values. The majority of patients in this study had iFR values that group around the iFR cutpoint of 0.89. Any biological variation will therefore lead to treatment reclassification when the inherent variability causes the iFR value to

cross the cutpoint. In contrast, the majority of patients had FFR values significantly further away from the FFR cutpoint (due to the attenuated hyperaemia detailed previously).

Therefore, the biological variation and numerical changes in FFR will lead to less reclassification. The classification change, or lack of change, is therefore a function of: 1) using a continuous variable such as FFR or iFR dichotomously; 2) stenosis distribution and 3) attenuated hyperemia.

In fact, this categorisation variability around the treatment threshold has previously been defined in FFR. When measured 10 minutes apart in the same patient FFR itself has a categorisation change in 15%, increasing to 50% when FFR values are close to the treatment threshold(75).

What is the optimal period of the cardiac cycle to assess coronary lesions in patients with severe aortic stenosis?

Coronary haemodynamic assessment can be made over the whole cardiac cycle, or be restricted to certain periods of the cardiac cycle; the series of studies contained within this thesis use wave-intensity analysis to isolate systole, diastole, and the wave-free period as well as the entire cardiac cycle.

Coronary flow is phasic, meaning it occurs differently within systole and diastole. Changes in pressure at the aortic (or proximal) end of the vessel generally drive systolic flow, whereas diastolic flow is a reflection of the contracting and relaxing myocardium (i.e. at the distal end of the vessel). During systole, coronary flow is a result of the emptying of blood from the ventricle through the aortic valve, and the opposing compression forces from the contracting myocardium. In severe aortic stenosis, systolic coronary flow is impaired due to the mechanical obstruction of ventricular emptying by the stenosed valve.

Conversely, diastolic coronary flow occurs while the aortic valve is closed. Therefore, restricted opening of a stenosed aortic valve is not relevant (this only has an impact during systole). This means that diastolic flow is unaffected by the presence of severe aortic stenosis.

TAVI is seen to lead to acute increases in systolic flow; diastolic flow is constant before and after TAVI. It is intuitive, therefore, that indices that include systole (i.e. all whole-cycle indices) may be more likely to change after valve treatment than diastolic variables.

The fallacy of achieving maximal hyperaemia in patients with severe aortic stenosis

FFR is predicated on the achievement of maximal hyperaemia, typically by the administration of potent vasodilators such as adenosine. Maximal blood flow can be affected by myriad conditions, including right atrial pressure, left-ventricular mass, left ventricular pressure, the presence of circulating vasoconstrictors and microvascular function and structure. Any state that affects one of these variables will therefore affect maximal blood flow.

Patients with severe aortic stenosis typically have elevated right-sided pressures, elevated left-ventricular end-diastolic pressures, left ventricular hypertrophy, increase in the presence of vasoconstrictors, and altered microcirculatory function and structure. This combination of factors means that hyperaemia is attenuated in patients with severe aortic stenosis. This can be seen when you examine the average FFR values in large-scale trials of patients without severe aortic stenosis, which are typically around 0.82-0.83(56,67,68); in both this series of studies and in others in patients with severe aortic stenosis(72,108), the average FFR values are significantly higher (around 0.86-0.87); this is a reflection of attenuated hyperaemia, not being able to augment flow sufficiently to cause a pressure drop and decline in FFR value.

I was able to directly measure hyperaemic coronary flow velocity in this study and demonstrate that relief of aortic stenosis immediately leads to acute increases in hyperaemic flow velocity; and that these increases continue out to 6 months. These increases in hyperaemic flow velocity are accompanied by drops in FFR values.

If FFR is predicated on achieving maximal hyperaemia, and maximal hyperaemia is impossible to achieve in patients with severe aortic stenosis, then it stands to reason that FFR may not be a suitable metric to use for these patients.

A parallel situation? Surgical treatment

TAVI is a new procedure, and the literature and evidence base is inherently limited by this. There are potential lessons that can be learned from the surgical literature which is by definition more extensive and historical.

The first factor to consider is the different profile of a patient with isolated severe AS versus one with severe AS and CAD. A 2013 study(27) of almost 4000 patients demonstrated that those with AS and CAD were older, more symptomatic and had poorer ventricular function. It is this group that is likely most analogous to the TAVI population, where patients are more likely to be older and more likely to have coexistent CAD. Patients undergoing AVR and CABG had worse 10-year prognosis than those with

isolated AS undergoing AVR (10-year survival 43% versus 59%). This pattern of increased risk of AVR and CABG versus AVR alone was also seen in a large German registry of 13,860 patients(109). In-hospital mortality was 2.1% after isolated AVR but 4.5% after AVR and CABG combined. These results, however, are likely a reflection of the higher-risk patient group who required combined surgery, rather than purely a hazard of the procedure itself. Put more simply, the patients having isolated AVR did not have CAD and therefore were inherently lower risk. Performing additional CABG in addition to AVR does, however, increase the surgical time and time spent on bypass, and therefore the attendant complexity and risk of the operation.

A more nuanced understanding can be gained from other historical surgical studies. Data published in 1987 compared outcomes for patients undergoing surgical AVR who were stratified into four groups: those without CAD, those with CAD who did not undergo CABG, those with CAD who did undergo CABG, and those who did not undergo angiography. Focusing on the patients who had CAD, 30-day mortality was 10.3% in patients who did not undergo CABG versus 6.3% in those who did (and 4.5% in those without CAD). This pattern continued out to 10-years: those who did not undergo CABG had a 10-year survival of 36%, compared to 49% for those who did undergo CABG (and 63% for those who did not have CAD). Another historical study conducted from 1975 to 1986 showed a similar pattern(28): both early and late survival were worst in patients with CAD not undergoing CABG, compared to either patients with no CAD or those who

underwent CABG. One study stratified by CAD severity angiographically(29), where one group of patients had lesions >60% bypassed and another had lesions of 40-60% bypassed. Bypassing the milder lesions did not appear beneficial, whereas complete revascularisation of the more severe lesions was associated with reduced late coronary events and better long-term survival. Finally, another historical cohort study(110) demonstrated that late cardiac deaths in patients who had undergone AVR were more common in patients with CAD, and those with CAD which was not bypassed were more likely to have sudden cardiac death.

The surgical domain has no randomized data comparing concomitant revascularization with CABG versus no revascularization for patients with severe AS undergoing AVR. In the absence of randomised data proving superiority of concomitant CABG, there are still conclusions that can be drawn from the surgical experience. First, that the presence of CAD is an adverse prognostic factor for patients with severe AS undergoing AVR. Second, that the combined operation of AVR and CABG is more complex than isolated AVR, and that these patients have poorer outcomes than those who did not undergo CABG (likely through a combination of not having CAD, and having simpler and shorter operations). Finally, observational data suggests that patients with CAD have better outcomes when undergoing CABG than those with unbypassed CAD – although this last statement is the least secure due to the confounded nature of the observational data.

It seems attractive, therefore, to limit performing combined CABG and AVR to situations where it is truly necessary. The benefits of a simpler operation must be balanced against the risks of ischaemia which may impede the patient getting off of cardiopulmonary bypass and their initial progress in-hospital. The decision of whether to bypass CAD is currently performed on angiographic basis, with non-invasive ischemia tests actively discouraged by guidelines in the presence of severe valvular heart disease(8). Current guideline recommendations are class I for concomitant CABG for stenoses greater than 70%, although the low level of evidence (C) reflects the limitations of this data described above. For patients with 50-70% stenoses, the recommendation is IIa. It may be that physiologically-guided revascularization can help provide this 'balance' of limiting revascularisation to haemodynamically significant lesions while avoiding the potential pitfalls of leaving residual ischaemia that might lead to haemodynamic instability that hampers the patient's recovery.

The field of TAVI has the opportunity to generate higher-quality data than that which currently supports surgical practice. There are a number of ongoing randomised trials which will may to answer the unanswered questions regarding the optimal management of PCI in TAVI patients. The ACTIVATION trial(111) aims to enrol 310 patients who are planned for TAVI, and have significant CAD. Significant CAD is defined as $\geq 70\%$ stenosis in a major epicardial coronary or $\geq 50\%$ in a vein graft or protected left main stem. The primary endpoint is a composite of mortality and rehospitalisation at 12 months. This trial

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has a non-inferiority design: the overall aim, therefore, could be said to be proving that it is safe to treat coexistent CAD medically in patients undergoing TAVI.

The NOTION 3 trial (NCT03058627) aims to enrol 452 patients and compare FFR-guided complete revascularisation to medical therapy in patients undergoing TAVI with coexistent CAD. The conventional 0.8 FFR cutpoint will be used. The primary endpoint is a composite of all-cause mortality, MI, and urgent revascularisation at 1-year. Finally, the FAITAVI trial (NCT03360591) aims to enrol 320 patients, and will again utilise FFR and the 0.8 cutpoint. The control group will, however, not be medical therapy but be angiographic guided PCI, with stenting of all stenoses with diameter stenoses >50% by visual estimation. The primary endpoint will be a composite of all-cause death, MI, stroke, major bleeding and target-vessel revascularisation at 12-months.

Future frontiers

The work in this thesis will underpin several areas of ongoing study. I have identified the following domains, related to this thesis, which would warrant further research:

- **Prospective cohort study.** Such a study design could enrol patients with severe aortic stenosis undergoing TAVI and with coexistent CAD not undergoing PCI. Clinically-used coronary physiological parameters (iFR and

FFR) could be measured before and after TAVI. Patients could then be followed-up longitudinally and clinical events such as myocardial infarction or clinically-indicated revascularisation could be recorded. Such a study could then examine if a threshold of iFR or FFR values is predictive of future events.

- **More moderate forms of aortic stenosis.** The final study in this thesis highlights why studying more moderate forms of aortic stenosis would be of value. I demonstrated that in patients with severe aortic stenosis, hyperaemic coronary flow velocity is attenuated, and acute increases in this achieved by TAVI are maintained and continue to rise out to 6 months. The continued long-term increases are likely due to remodelling of the left ventricle and regression of left ventricular mass. Measuring coronary flow velocity in patients with moderate (or even mild) aortic stenosis, when there is likely to be less marked LVH, may be informative. If hyperaemic indices such as FFR are unreliable in severe aortic stenosis, are they reliable in more moderate forms? Is it possible to identify a threshold of severity of aortic stenosis beyond which FFR loses its accuracy?
- **Other forms of valvular heart disease.** Utilising the model of transcatheter intervention, as used in this series of studies, in other valvular lesions will permit further insights into the interplay between valvular heart disease and

coronary haemodynamics. Similar protocols could be designed for patients undergoing transcatheter mitral valve replacement for mitral regurgitation, or indeed transcatheter aortic valve therapies for aortic regurgitation.

- **Clinical trials of physiological-guided coronary revascularisation in patients with severe aortic stenosis.** This work was a physiological and mechanistic series of studies examining haemodynamic data, and was not intended to look at clinical outcomes. Ultimately, large, prospective randomised trials powered for clinical endpoints will be required to fully elucidate the role of coronary physiology in guiding the treatment of severe aortic stenosis.
- **Patients undergoing surgical treatment for aortic stenosis.** The studies in this thesis were limited to patients undergoing TAVI, which was an essential factor in the design of these studies. However, expanding this work into the surgical domain would have potential value. The ability to isolate the functional significance of a coronary stenosis in the context of aortic stenosis will allow clinicians to determine in which patients the valve alone can be treated, and which patients need concomitant revascularisation, which for surgical patients would be via coronary artery bypass grafting. Using a physiological-guided

approach may provide superior outcomes to the current standard,
angiographic-guided approach.

7. Conclusions

Systolic coronary flow velocity and hyperaemic coronary flow velocity are both significantly attenuated by severe aortic stenosis. The acute relief of severe aortic stenosis by TAVI leads to immediate increases in both systolic and hyperaemic coronary flow velocity. These increases continue out to 6-months. Conversely, resting diastolic flow velocity is unaffected by severe aortic stenosis and remains constant immediately post-TAVI and out to 6 months. Resting diastolic indices of coronary stenosis severity (such as iFR) are therefore less likely to change after valve treatment than whole-cycle hyperaemic indices (such as FFR). Further areas of research that could lead on from this thesis include the study of more moderate forms of aortic stenosis, patients with other forms of valvular heart disease (particularly being treated with transcatheter interventions, to facilitate the adoptions of similar research protocols as utilised in this thesis), and prospective clinical trials of physiological-guided revascularisation in patients with severe aortic stenosis (being treated either with TAVI or surgically).

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Undergoing Transcatheter Aortic Valve Replacement: Implications for Clinical Indices of Coronary Stenosis Severity. *JACC Cardiovasc Interv.* 2018 Oct 22;11(20):2019–31.

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9. Appendix

9.1 First author publications arising from this thesis and during PhD studies

The long-term effects of transcatheter aortic valve implantation (TAVI) on coronary haemodynamics in patients with concomitant coronary artery disease and severe aortic stenosis

Ahmad Y, Vendrik J, Eftekhari A, Howard JP, Wijntjens GWM, Stegehuis VE, Christopher Cook, Terkelsen CJ, Christiansen EH, Koch KT, Piek JJ Sen S, Baan jr. J

J Am Heart Assoc. 2020 [In Press]

Determining the Predominant Lesion in Patients With Severe Aortic Stenosis and Coronary Stenoses: A Multicenter Study Using Intracoronary Pressure and Flow.

Ahmad Y, Vendrik J, Eftekhari A, Howard JP, Cook C, Rajkumar C, Malik I, Mikhail G, Ruparel N, Hadjiloizou N, Nijjer S, Al-Lamee R, Petraco R, Warisawa T, Wijntjens GWM, Koch KT, van de Hoef T, de Waard G, Echavarria-Pinto M, Frame A, Sutaria N, Kanaganayagam G, Ariff B, Anderson J, Chukwuemeka A, Fertleman M, Koul S, Iglesias JF, Francis D, Mayet J, Serruys P, Davies J, Escaned J, van Royen N, Götberg M, Juhl Terkelsen C, Høj Christiansen E, Piek JJ, Baan J Jr, Sen S.

Circ Cardiovasc Interv. 2019 Dec;12(12):e008263. doi:

10.1161/CIRCINTERVENTIONS.119.008263.

A case report of the clinical effect of chronic total occlusion recanalization on the instantaneous wave-free ratio in the donor artery.

Ahmad Y, Al-Lamee R, Davies J, Sen S.

Eur Heart J Case Rep. 2018 Mar 21;2(2):1-4. doi: 10.1093/ehjcr/ty014.

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.

Ahmad Y, Götzberg M, Cook C, Howard JP, Malik I, Mikhail G, Frame A, Petraco R, Rajkumar C, Demir O, Iglesias JF, Bhindi R, Koul S, Hadjiloizou N, Gerber R, Ramrakha P, Ruparel N, Sutaria N, Kanaganayagam G, Ariff B, Fertleman M, Anderson J, Chukwuemeka A, Francis D, Mayet J, Serruys P, Davies J, Sen S.

JACC Cardiovasc Interv. 2018 Oct 22;11(20):2019-2031. doi: 10.1016/j.jcin.2018.07.019.

Reply to: Assessing the quality of evidence supporting patent foramen ovale closure over medical therapy after cryptogenic stroke.

Ahmad Y, Howard J, Arnold A, Shun-Shin M, Cook C, Francis D, Sen S.

Eur Heart J. 2018 Oct 14;39(39):3620. doi: 10.1093/eurheartj/ehy498.

Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials.

Ahmad Y, Howard JP, Arnold A, Shin MS, Cook C, Petraco R, Demir O, Williams L, Iglesias JF, Sutaria N, Malik I, Davies J, Mayet J, Francis D, Sen S.
Eur Heart J. 2018 May 7;39(18):1638-1649. doi: 10.1093/eurheartj/ehy12

Optimal antiplatelet strategy after transcatheter aortic valve implantation: a meta-analysis.

Ahmad Y, Demir O, Rajkumar C, Howard JP, Shun-Shin M, Cook C, Petraco R, Jabbour R, Arnold A, Frame A, Sutaria N, Ariff B, Kanaganayagam G, Francis D, Mayet J, Mikhail G, Malik I, Sen S.
Open Heart. 2018 Jan 26;5(1):e000748. doi: 10.1136/openhrt-2017-000748.

Aortic Stenosis in Dialysis Patients.

Ahmad Y, Bellamy MF, Baker CSR.
Semin Dial. 2017 May;30(3):224-231. doi: 10.1111/sdi.12582.

Resolving the paradox of randomised controlled trials and observational studies comparing multi-vessel angioplasty and culprit only angioplasty at the time of STEMI.

Ahmad Y, Cook C, Shun-Shin M, Balu A, Keene D, Nijjer S, Petraco R, Baker CS, Malik IS, Bellamy MF, Sethi A, Mikhail GW, Al-Bustami M, Khan M, Kaprielian R, Foale RA, Mayet J, Davies JE, Francis DP, Sen S.

Int J Cardiol. 2016 Nov 1;222:1-8. doi: 10.1016/j.ijcard.2016.06.106.

A new method of applying randomised control study data to the individual patient: A novel quantitative patient-centred approach to interpreting composite end points.

Ahmad Y, Nijjer S, Cook CM, El-Harasis M, Graby J, Petraco R, Kotecha T, Baker CS, Malik IS, Bellamy MF, Sethi A, Mikhail GW, Al-Bustami M, Khan M, Kaprielian R, Foale RA, Mayet J, Davies JE, Francis DP, Sen S.

Int J Cardiol. 2015 Sep 15;195:216-24. doi: 10.1016/j.ijcard.2015.05.109.

Intra-aortic Balloon Pump Therapy for Acute Myocardial Infarction: A Meta-analysis.

Ahmad Y, Sen S, Shun-Shin MJ, Ouyang J, Finegold JA, Al-Lamee RK, Davies JER, Cole GD, Francis DP.

JAMA Intern Med. 2015 Jun;175(6):931-939. doi: 10.1001/jamainternmed.2015.0569.

9.2 Co-author publications arising from this thesis and during PhD studies

Dobutamine Stress Echocardiography Ischemia as a Predictor of the Placebo-Controlled Efficacy of Percutaneous Coronary Intervention in Stable Coronary Artery Disease: The Stress Echocardiography-Stratified Analysis of ORBITA.

Al-Lamee RK, Shun-Shin MJ, Howard JP, Nowbar AN, Rajkumar C, Thompson D, Sen S, Nijjer S, Petraco R, Davies J, Keeble T, Tang K, Malik I, Bual N, Cook C, **Ahmad Y**,

Seligman H, Sharp ASP, Gerber R, Talwar S, Assomull R, Cole G, Keenan NG,

Kanaganayagam G, Sehmi J, Wensel R, Harrell FE Jr, Mayet J, Thom S, Davies JE, Francis DP.

Circulation. 2019 Dec 10;140(24):1971-1980. doi:

10.1161/CIRCULATIONAHA.119.042918.

Cardiac Rhythm Device Identification Using Neural Networks.

Howard JP, Fisher L, Shun-Shin MJ, Keene D, Arnold AD, **Ahmad Y**, Cook CM, Moon JC, Manisty CH, Whinnett ZI, Cole GD, Rueckert D, Francis DP.

JACC Clin Electrophysiol. 2019 May;5(5):576-586. doi: 10.1016/j.jacep.2019.02.003.

Physiological Pattern of Disease Assessed by Pressure-Wire Pullback Has an Influence on Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance.

Warisawa T, Cook CM, Howard JP, **Ahmad Y**, Doi S, Nakayama M, Goto S, Yakuta Y, Karube K, Shun-Shin MJ, Petraco R, Sen S, Nijjer S, Al Lamee R, Ishibashi Y, Matsuda H, Escaned J, di Mario C, Francis DP, Akashi YJ, Davies JE.

Circ Cardiovasc Interv. 2019 May;12(5):e007494. doi: 10.1161/CIRCINTERVENTIONS.

Association Between Physiological Stenosis Severity and Angina-Limited Exercise Time in Patients With Stable Coronary Artery Disease.

Cook CM, **Ahmad Y**, Howard JP, Shun-Shin MJ, Sethi A, Clesham GJ, Tang KH, Nijjer SS, Kelly PA, Davies JR, Malik IS, Kaprielian R, Mikhail G, Petraco R, Warisawa T, Al-Janabi F, Karamasis GV, Mohdnazri S, Gamma R, de Waard GA, Al-Lamee R, Keeble TR, Mayet J, Sen S, Francis DP, Davies JE.

JAMA Cardiol. 2019 Jun 1;4(6):569-574. doi: 10.1001/jamacardio.2019.1139

Fractional flow reserve derived from microcatheters versus standard pressure wires: a stenosis-level meta-analysis.

Seligman H, Shun-Shin MJ, Vasireddy A, Cook C, **Ahmad Y**, Howard J, Sen S, Al-Lamee R, Nijjer S, Chamie D, Davies J, Mayet J, Francis DP, Petraco R.

Open Heart. 2019 Mar 25;6(1):e000971. doi: 10.1136/openhrt-2018-000971.

Right ventricular pacing for hypertrophic obstructive cardiomyopathy: meta-analysis and meta-regression of clinical trials.

Arnold AD, Howard JP, Chiew K, Kerrigan WJ, de Vere F, Johns HT, Churlilov L, **Ahmad Y**, Keene D, Shun-Shin MJ, Cole GD, Kanagaratnam P, Sohaib SMA, Varnava A, Francis DP, Whinnett ZI.

Eur Heart J Qual Care Clin Outcomes. 2019 Oct 1;5(4):321-333. doi: 10.1093/ehjqcco/qcz006.

Clinical Events After Deferral of LAD Revascularization Following Physiological Coronary Assessment.

Sen S, **Ahmad Y**, Dehbi HM, Howard JP, Iglesias JF, Al-Lamee R, Petraco R, Nijjer S, Bhindi R, Lehman S, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Härle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Silva PC, Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbanda RK, Patel MR, Serruys P, Escaned J, Davies JE.

J Am Coll Cardiol. 2019 Feb 5;73(4):444-453. doi: 10.1016/j.jacc.2018.10.070.

Instantaneous wave-free ratio: an adenosine-independent index to guide coronary revascularisation.

Iglesias F, Degrauwe S, **Ahmad Y**, Nijjer S, Davies J, Sen S.

Cardiovasc Med. 2018;21(0708):181-190.

Impact of Percutaneous Revascularization on Exercise Hemodynamics in Patients With Stable Coronary Disease.

Cook CM, **Ahmad Y**, Howard JP, Shun-Shin MJ, Sethi A, Clesham GJ, Tang KH, Nijjer SS, Kelly PA, Davies JR, Malik IS, Kaprielian R, Mikhail G, Petraco R, Al-Janabi F, Karamasis GV, Mohdnazri S, Gamma R, Al-Lamee R, Keeble TR, Mayet J, Sen S, Francis DP, Davies JE. J Am Coll Cardiol. 2018 Aug 28;72(9):970-983. doi: 10.1016/j.jacc.2018.06.033.

Fractional Flow Reserve and Instantaneous Wave-Free Ratio as Predictors of the Placebo-Controlled Response to Percutaneous Coronary Intervention in Stable Single-Vessel Coronary Artery Disease.

Al-Lamee R, Howard JP, Shun-Shin MJ, Thompson D, Dehbi HM, Sen S, Nijjer S, Petraco R, Davies J, Keeble T, Tang K, Malik IS, Cook C, **Ahmad Y**, Sharp ASP, Gerber R, Baker C, Kaprielian R, Talwar S, Assomull R, Cole G, Keenan NG, Kanaganayagam G, Sehmi J, Wensel R, Harrell FE, Mayet J, Thom SA, Davies JE, Francis DP.

Circulation. 2018 Oct 23;138(17):1780-1792. doi: 10.1161/CIRCULATIONAHA.118.033801.

Assessing coronary disease in patients with severe aortic stenosis: the need for a 'valid' gold standard for validation studies?

Sen S, **Ahmad Y**, Davies J.

EuroIntervention. 2018 Jan 20;13(13):1499-1502. doi: 10.4244/EIJV13I13A240.

Fractional Flow Reserve/Instantaneous Wave-Free Ratio Discordance in Angiographically Intermediate Coronary Stenoses: An Analysis Using Doppler-Derived Coronary Flow Measurements.

Cook CM, Jeremias A, Petraco R, Sen S, Nijjer S, Shun-Shin MJ, **Ahmad Y**, de Waard G, van de Hoef T, Echavarria-Pinto M, van Lavieren M, Al Lamee R, Kikuta Y, Shiono Y, Buch A, Meuwissen M, Danad I, Knaapen P, Maehara A, Koo BK, Mintz GS, Escaned J, Stone GW, Francis DP, Mayet J, Piek JJ, van Royen N, Davies JE.

JACC Cardiovasc Interv. 2017 Dec 26;10(24):2514-2524. doi: 10.1016/j.jcin.2017.09.021.

Acute myocardial infarction and stroke secondary to valve thrombosis following transcatheter aortic valve replacement-what can happen when antiplatelet agents are stopped.

Lam MC, Kanaganayagam G, **Ahmad Y**, Fertleman M, Ariff B.

Quant Imaging Med Surg. 2017 Oct;7(5):605-607. doi: 10.21037/qims.2017.10.04.

Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial.

Al-Lamee R, Thompson D, Dehbi HM, Sen S, Tang K, Davies J, Keeble T, Mielewczik M, Kaprielian R, Malik IS, Nijjer SS, Petraco R, Cook C, **Ahmad Y**, Howard J, Baker C, Sharp A, Gerber R, Talwar S, Assomull R, Mayet J, Wensel R, Collier D, Shun-Shin M, Thom SA, Davies JE, Francis DP; ORBITA investigators.
Lancet. 2018 Jan 6;391(10115):31-40. doi: 10.1016/S0140-6736(17)32714-9.

Diagnostic Accuracy of Computed Tomography-Derived Fractional Flow Reserve : A Systematic Review.

Cook CM, Petraco R, Shun-Shin MJ, **Ahmad Y**, Nijjer S, Al-Lamee R, Kikuta Y, Shiono Y, Mayet J, Francis DP, Sen S, Davies JE.
JAMA Cardiol. 2017 Jul 1;2(7):803-810. doi: 10.1001/jamacardio.2017.1314.

Congenital epicardial coronary artery to bilateral internal mammary artery fistulae.

Ghosh AK, Mak SM, **Ahmad Y**, Malik I, Nihoyannopoulos P, Gopalan D.
BJR Case Rep. 2016 Nov 2;2(4):20160014. doi: 10.1259/bjrcr.20160014.

Quantification of the Effect of Pressure Wire Drift on the Diagnostic Performance of Fractional Flow Reserve, Instantaneous Wave-Free Ratio, and Whole-Cycle Pd/Pa.

Cook CM, **Ahmad Y**, Shun-Shin MJ, Nijjer S, Petraco R, Al-Lamee R, Mayet J, Francis DP, Sen S, Davies JE.

Circ Cardiovasc Interv. 2016 Apr;9(4):e002988. doi:

10.1161/CIRCINTERVENTIONS.115.002988.

9.3. List of prizes and awards during PhD studies

American College of Cardiology Young Author Achievement Award, American College of Cardiology Scientific Sessions, 2019 **(Winner)**

American Heart Association Samuel A. Levine Young Clinical Investigator Award, American Heart Association Scientific Sessions, 2018 **(Winner)**

Best Abstract/Young Investigator Award (PCR's Got Talent), EuroPCR, 2018 **(Winner)**

Top 5 Most Read Articles, JACC Cardiovascular Interventions, 2018

Top 5 Most Read Articles, European Heart Journal, 2018

President's Medal, Royal Society of Medicine, 2018 (Finalist)

Top Scoring Abstract, British Cardiovascular Society, 2016 **(Winner)**

Patient Information Leaflet

(Patients scheduled for TAVI with moderate to severe coronary artery disease on angiography)

Exploring the pressure-flow velocity characteristics of coronary stenoses pre and post Transcatheter Aortic Valve Insertion (TAVI)

Chief Investigator: Dr Sayan Sen

Version 1.3

18.04.2014

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Thank you for reading this.

What is the purpose of the study?

You are due to undergo a procedure to relieve a narrowing in your aortic valve that has led to symptoms of chest pain, shortness of breath or blackouts. You have also been found to have narrowings in your heart arteries, which can also cause chest pain or shortness of breath. Determining if the artery or the valve is the cause of the patients symptoms is currently not possible; as a result both are treated and this may increase the risk of complications, such as bleeding, heart attacks and stroke.

This study aims to use special sensor tipped wires that can measure how blood flows in a heart artery to try and determine if the severity of the narrowings in the heart arteries can be assessed independently from the valve. This may allow us to identify if the arteries or the

valve is the cause of the symptoms and therefore only treat the responsible condition, thereby reducing the risk of complication.

Why have I been chosen?

You have been chosen because you are scheduled to have a procedure to relieve the narrowing in your aortic valve and have also been found to have narrowings of your heart arteries. As a normal part of this procedure, tubes will be inserted into the main artery in the groin. This means that at the time of your procedure, we can use this tube to pass our sensor-tipped wires into your heart arteries and safely take measurements in your heart's blood vessels. These measurements will provide us with data regarding how severe the heart artery narrowings are and whether they are being affected by the narrowing in the aortic valve.

Do I have to take part?

No. Your decision to participate in this study is entirely voluntary. You have the right to refuse as well as to withdraw your participation at any time (even if you agree today) without giving a reason. If you decide not to participate or to withdraw, it will not affect the quality of your care or treatment, nor the relationship you have with your doctor and nursing team.

What will happen to me if I take part?

The tubes placed into your main blood vessel in the groin will occur as usual. Our wires will be passed into the heart arteries via the tube already in the leg and we will take measurements both before and after the aortic valve narrowing has been treated.

During the measurements a drug to open up the small vessels may need to be infused. This can be injected via a tube already in the vein in the leg or the drug can be injected directly into the coronary artery. In total the process will add 15 minutes to the procedure. The measurements will not prolong your recovery from the procedure. At the end of the procedure the wires and tubes will be removed.

What are the possible side effects, risks and disadvantages of taking part?

We do not expect you to experience any significant side effects as a result of participating in this study. During the measurements we will be administering medications to open up the small blood vessels in the heart. These are routinely used every day in the cardiac catheter laboratory. The risk of using such drugs are very low, and you will not experience any discomfort as you will be anaesthetised as part of your aortic valve procedure. Other side effects include lowering of blood pressure and slowing of the heart rate which are again short-lived. You will be continually monitored throughout the investigation. We will administer the medications and take the measurements using tubes which are already sited as a routine clinical part of your procedure.

There is a very low risk (less than 1 in 1000) that the wire used to make the measurements will cause any damage to your blood vessels. This risk is minimised as the measurements are performed by an experienced senior Consultant Cardiologist. We will place the wires under x-ray guidance; the mean effective dose from this procedure is equivalent to 4.4 years of natural background radiation.

What are the possible benefits of taking part?

You will not directly benefit from this study, but the information we gain will give a much better understanding of whether there is a need to treat heart artery narrowings at the same time as narrowing of the aortic valve and whether it is possible to determine which problem is causing the symptoms and therefore which problem needs to be treated. In the future, this may have the potential to significantly reduce the complications of these cardiac procedures.

What if something goes wrong?

Imperial College London holds insurance policies which apply to this study. If you experience serious and enduring harm or injury as a result of taking part in this study, you may be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Dr Sayan Sen 020 7594 1264). The normal National Health Service complaint mechanisms are also available to you. If you are still not satisfied with the response, you may contact the Imperial AHSC Joint Research Office.

Will my taking part in this study be kept confidential?

If you agree to take part, data collected about you will be entered onto a computer. However, all data entered will be in an anonymous format and any information obtained from this investigation that can be identified will remain confidential. Relevant sections of your medical notes & data collected during the study may be looked at by individuals from Imperial College, from regulatory authorities or from Imperial NHS trust, where it is relevant to you taking part in this research. We will ask for your permission for these individuals to have access to your records. Your GP will be informed that you are participating in this study.

What will happen to the results of the research study?

Scientific data from this study may be presented at meetings and published so that the information can be used to help others, but your participation in the study will not be made known and will be kept strictly confidential. If you wish, we will give you a summary of the results.

Who is sponsoring the study?

The study will be sponsored by Imperial College London.

Who is funding the research?

The study will be funded by Imperial College London.

Who has reviewed the study?

This study has been reviewed and given a favourable ethical opinion by the Outer London Research Ethics Committee.

If you have any further questions please do not hesitate to contact:

Dr Sayan Sen on 0207 594 1264, sayan.sen@imperial.ac.uk, or Dr Yousif Ahmad on 0207 594 1264 y.ahmad@imperial.ac.uk.

Thank you for taking the time to consider participating in this study

9.5 Ethical approval



Health Research Authority

NRES Committee South Central - Oxford B

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Telephone: 0117 342 1333
Fax: 0117 342 0445

21 July 2014

Dr Sayan Sen
NIHR Clinical Lecturer
Imperial College London
59-61 North Wharf Road
Paddington
London

Dear Dr Sen

Study title: Exploring the pressure-flow velocity characteristics of coronary stenoses pre and post Transcatheter Aortic Valve Insertion (TAVI)
REC reference: 14/SC/1103
IRAS project ID: 155543

Thank you for your letter of 16th July 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 14 July 2014

Documents received

The documents received were as follows:

Document	Version	Date
Covering letter on headed paper		16 July 2014
Participant consent form	1.1	14 July 2014
Participant information sheet (PIS)	1.1	14 July 2014

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	Version	Date
Covering letter on headed paper		16 July 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		29 July 2013
GP/consultant information sheets or letters	1.0	28 May 2014



Health Research Authority

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14 July 2014

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REC reference: 14/SC/1103
IRAS project ID: 155543

The Research Ethics Committee reviewed the above application at the meeting held on 08 July 2014. Thank you for attending, along with Dr Ahmed Yousif, to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager Mr Thomas Fairman, nrescommittee.southcentral-oxfordb@nhs.net.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

PIS

1. Please use a shorter, which is written in lay language, on the PIS and all other participant documentation.

9.6 Response to Examiner Comments

Very broadly it was felt an absolute priority to establish

- Which parts of the work were novel
- Which parts were confirmatory
- Which parts remain inconclusive

There was insufficient recognition, attribution and discussion of the work of others.

Candidate response (in red throughout): Thank you for the opportunity to clarify these points, and to provide more extensive critical appraisal of prior work in the field which has now been expanded significantly both within the chapters based around each experiment, and also as a whole in the Synthesis.

There was insufficient description of the personal contribution versus contribution of collaborators. The total number of experiments, including those where accurate data could not be obtained, the challenges of use of the Doppler wire, would add to an understanding of the body of work that constituted this thesis.

Again, I am grateful for the opportunity to clarify this, as was discussed during the Viva. These aspects have also now been clarified further in the Methodology chapter, as highlighted below:

"Overall data collection and synthesis

As described earlier, the majority of patients were recruited from The Hammersmith Hospital, Imperial College Healthcare NHS Trust. There were two principle challenges to data collection:

- 3) Occurrence of intraprocedural complications that precluded completion of the research protocol after valve implantation
- 4) Obtaining high-fidelity Doppler flow traces

In the earlier phases of recruitment, procedural complications occurred relatively more commonly owing to larger sheath sizes and being comparatively earlier on in the learning curve of the procedure. For the purposes of the protocol, paired data before and after valve implantation were essential. Therefore, if a procedural complication occurred that precluded further physiological assessment (i.e. haemorrhage, conversion to open surgery) then the data could not be used for analysis.

In total, 12 experiments were abandoned with incomplete data due to intraprocedural complications. In order to help mitigate against this loss of data, international collaborators were invited to participate. After appropriate training on the use of the Combowire and the protocol, data was collected from three other centres: Skane University Hospital, Lund, Sweden; Amsterdam Medical Center, Amsterdam, The Netherlands; and Aarhus University Hospital, Aarhus, Denmark. All data collected from

international collaborators was sent to Imperial for all aspects of analysis, which were performed by myself with oversight from my primary supervisor. All traces underwent quality control to ensure only the highest fidelity data was used for analysis; 25% of traces sent from other centres were ultimately discarded and not utilised in analysis. A total of 3 patients from Sweden, 6 from Denmark and 8 from The Netherlands were included for analysis; a total of 38 from London were included. I was present for each case performed in London and ensured the protocol was completed accurately, and that high-quality haemodynamic data was obtained. This would often necessitate repeating the protocol several times to ensure high-quality data was obtained for each condition (resting pre-TAVI data, hyperaemic pre-TAVI data, resting post-TAVI data, hyperaemic post-TAVI data).

The process of taking an invasive haemodynamic study performed in the cardiac catheterisation laboratory to yielding pressure and flow data suitable for analysis and presentation in scientific manuscripts was all performed at Imperial by myself with oversight from my primary supervisor. This process took approximately 20 hours for each individual case, taking into account the multiple steps involved, and that each case needed separate analysis for each separate condition (resting pre-TAVI data, hyperaemic pre-TAVI data, resting post-TAVI data, hyperaemic post-TAVI data)."

There was insufficient forensic discussion of the potential pitfalls in the experiments described, their design and their outcomes. Issues of selection bias needed to be further discussed. Possible other designs (cohort study)

The important issue of selection bias, particularly in Chapter 4, has now been addressed and discussed. Other study designs have also been discussed, particularly with regards to a cohort study.

"This study does not on its own indicate that iFR or FFR is a better guide to the need for coronary revascularisation in patients requiring a TAVI. A cohort study might be a good study design to explore the clinical impact of various levels of iFR and FFR in such patients. A design for this could be a large cohort recruited from multiple centres, for example across the UK in which the participants have the measurements but no coronary intervention. Over a period of years, the event rates could be assessed and it could be established whether pre-TAVI iFR or FFR is a better predictor of subsequent events."

"Selection bias is the reason that no quantitative comparison should be made between the TAVI and PCI groups. The patients undergoing TAVI had no reason to be similar in any way to those requiring undergoing PCI, and indeed their baseline characteristics show that they are different in many respects. Even if I were to attempt to compare the FFR and iFR effects between group 1 and group 2, such a comparison would be invalid due to selection bias. For that reason, in this chapter I have focused on pre/post

intervention comparisons within each group and only compared the groups qualitatively (e.g to observe that the index of resistance increases in each group)."

There was insufficient breadth of discussion eg the parallel situation of surgical AVR (and the evidence, or lack of, for management of concomitant CAD in SAVR)

I agree this is a very important point, which has now been extensively explored in the Synthesis section.

"A parallel situation? Surgical treatment

TAVI is a new procedure, and the literature and evidence base is inherently limited by this.

There are potential lessons that can be learned from the surgical literature which is by definition much more extensive and historical.

The first factor to consider is that different patient profile of one with isolated severe AS versus one with severe AS and CAD. A 2013 study(27) of almost 4000 patients demonstrated that those with AS and CAD were older, more symptomatic and had poorer ventricular function. It is this group that is likely most analogous to the TAVI population, where patients are more likely to be older and more likely to have coexistent CAD.

Patients undergoing AVR and CABG worse 10-year prognosis than those with isolated AS

undergoing AVR + CABG (10-year survival 43% versus 59%). This pattern of increased risk of AVR and CABG versus AVR alone was also seen in a large German registry of 13,860 patients(109). In-hospital mortality was 2/1% after isolated AVR but 4.5% after AVR and CABG combined. These results, however, are likely a reflection of the higher-risk patient group who required combined surgery, rather than purely a hazard of the procedure itself. Put more simply, the patients having isolated AVR did not have CAD and therefore were inherently lower risk. Performing additional CABG in addition to AVR does, however, increase the surgical time and time spent on bypass, and therefore the attendant complexity and risk of the operation.

A more nuanced understanding can be gained from other historical surgical studies. Data published in 1987 compared outcomes for patients undergoing surgical AVR who were stratified into four groups: those without CAD, those with CAD who did not undergo CABG, those with CAD who did undergo CABG, and those who did not undergo angiography. Focusing on the patients who had CAD, 30-day mortality was 10.3% in patients who did not undergo CABG versus 6.3% in those who did (and 4.5% in those without CAD). This pattern continued out to 10-years: those who did not undergo CABG had a 10-year survival of 36%, compared to 49% for those who did undergo CABG (and 63% for those who did not have CAD). Another historical study conducted from 1975 to 1986 showed a similar pattern(28): both early and late survival were worst in patients with CAD not undergoing CABG, compared to either patients with no CAD or those who

underwent CABG. One study stratified by CAD severity angiographically(29), where one group had lesions >60% bypassed and another had lesions of 40-60% bypassed. Bypassing the milder lesions did not appear beneficial, whereas complete revascularisation of the more severe lesions was associated with reduced late coronary events and better long-term survival. Finally, another historical cohort study(110) demonstrated that late cardiac deaths in patients who had undergone AVR were more common in patients with CAD, and those with CAD which was not bypassed were more likely to have sudden cardiac death.

The surgical data has no randomized data comparing concomitant revascularization with CABG versus no revascularization for patients with severe AS undergoing AVR. In the absence of randomised data proving superiority of concomitant CABG, there are still conclusions that can be drawn from the surgical experience. First, that the presence of CAD is an adverse prognostic factor for patients with severe AS undergoing AVR. Second, that the combined operation of AVR and CABG is more complex than isolated AVR, and that these patients have poorer outcomes than those who did not undergo CABG (likely through a combination of not having CAD, and having simpler and shorter operations). Finally, observational data suggests that patients with CAD have better outcomes when undergoing CABG than those with unbypassed CAD - although this last statement is the least secure due to the confounded nature of the observational data.

It seems attractive, therefore, to limit performing combined CABG and AVR to situations where it is truly necessary. The benefits of a simpler operation must be balanced against the risks of ischaemia which may impede the patient getting off of cardiopulmonary bypass and their initial progress in-hospital. The decision of whether to bypass CAD is currently performed on angiographic basis, with non-invasive ischemia tests actively discouraged by guidelines in the presence of severe valvular heart disease(8). Current guideline recommendations are class I for concomitant CABG for stenoses greater than 70%, although the low level of evidence (C) reflects the limitations of this data described above. For patients with 50-70% stenoses, the recommendation is IIa. It may be that physiologically-guided revascularization can help provide this 'balance' of limiting revascularisation to haemodynamically significant lesions while avoiding the potential pitfalls of leaving residual ischaemia that might lead to haemodynamic instability that hampers the patient's recovery."

There was insufficient scepticism about the use of parameters and secondary derived parameters (eg of microvascular resistance). While it was a key part of the thesis that 'flow measurement' was a gold standard relative to 'pressure', flow was derived from Doppler measurements with its own assumptions and limitations

This is also an important element, which has been discussed in the Methodology chapter. I have clarified throughout that flow *velocity* was quantifiably measured in this Thesis, and have also discussed the derivation of microvascular resistance.

"Resistance and microvascular resistance

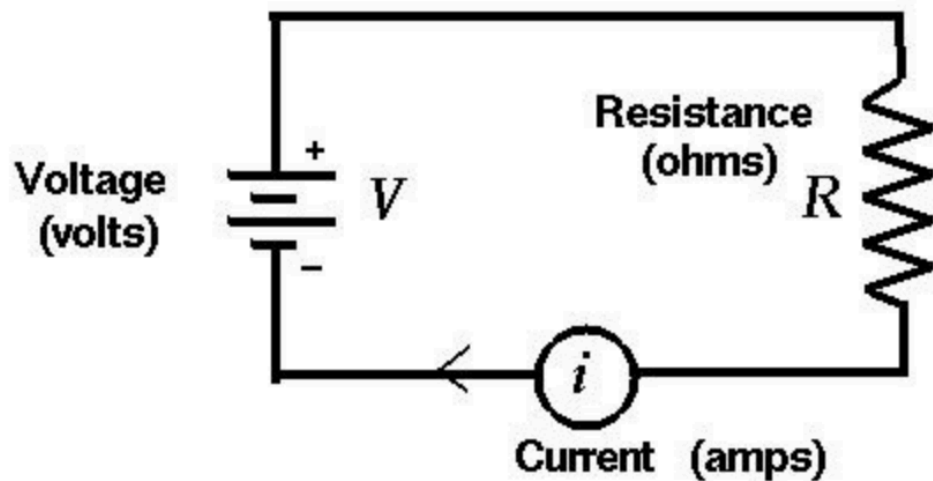
Throughout physics and biology, there is a well-defined concept of resistance which is the *potential difference* required to sustain a *flow*. The formula that defines resistance in all fields is:

$$\text{Resistance} = \text{Potential difference} / \text{flow}$$

In electrical engineering, the potential difference is voltage (volts), and flow is current (amps), and the resistance is ohms.



Ohm's Law



$$V = i R$$

In fluid dynamics, the potential difference is a pressure difference (e.g in mmHg). Strictly speaking, flow should be described as a volume per unit time (such as ml/min). This yields a resistance in mmHg/(ml/min). However, it is difficult to measure volume flow rates in the intact human directly. One way to estimate it is to measure the velocity (e.g with Doppler) and multiply this by the cross-sectional area indicative of flow. The latter quantity is itself a little difficult to measure, however.

Therefore, a proxy for microvascular resistance that is commonly used in coronary physiology research is to set aside the assessment of cross-sectional area and simply calculate pressure over velocity. This gives a quantity which will rise and fall with microvascular resistance but is not itself microvascular resistance because of the absence of cross-sectional area information. This is commonly termed the 'microvascular resistance' and has been in extensive use in the field(49).

When using an index of microvascular resistance, pressure over velocity, we should be aware that while this reliably detects when resistance changes, in which direction and by which factor, it does not directly give a value for microvascular resistance."

There was insufficient clarity in distinguishing 'accuracy' versus 'consistency'

I was grateful for the opportunity to clarify this point during this Viva, and particularly in Chapter 3 my phrasing has been modified to be more precise and avoid this confusion.

"The effect of TAVI on coronary flow velocity varies across the cardiac cycle. Systolic flow velocity is significantly increased after TAVI, but diastolic flow velocity is not. It also varies with the administration of adenosine, with a larger effect from the administration of adenosine seen after TAVI.

Resting flow velocity during diastole is relatively little changed by TAVI, in comparison to the changes seen in flow velocities in systole and with adenosine. We infer from this that

the distorting effect of aortic stenosis on flow-dependent parameters may be lower in the resting diastolic time-window, than in whole-cycle hyperaemic conditions."

There was inaccuracy and inconsistency in the use of terms such as 'significance / significantly' "increased / reduced/ did not change" unsupported by statistical testing and the choice of tests was not always clearly described or justified.

I apologise for the some of the imprecision of language used, and this has now been corrected throughout the thesis.

There was insufficient linkage to clinically relevant parameters, without justification. Eg. what is the association between Microvascular Resistance and clinical outcomes?

The phrase 'This chapter is part of the following publication' is used but it seems more accurate to say 'The experiments and findings of this chapter have been published in ...

This has now been modified throughout the Thesis to adopt the exact phrasing suggested by the examiners.

Specific Comments

Chapter 3:

Main issues:

1.iFR values remained constant pre/post TAVI but this does not mean iFR is necessarily accurate or a clinically useful measurement? The FFR change is small and of uncertain clinical relevance.

Specific points

P.85 Abstract: "Effect of coronary pressure, flow and indices of coronary severity not been studied".

Candidate needs to accept/acknowledge that coronary pressure and indices of coronary severity have been studied pre/post TAVI some year ago (Italian group). Doppler measure of flow is new, although the technology is not. Focus on what this new element is expected to add as justification for study.

I am grateful for this comment and have changed the wording to help emphasise that flow velocity assessment is the truly novel aspect of this study.

"It has been suggested that hyperaemic coronary flow velocity is impeded by severe aortic stenosis(74), but this has never been tested in humans with severe aortic stenosis and coronary artery disease.

Previous researchers have looked purely at pressure (FFR and iFR) in patients before and after TAVI, focusing on the level of agreement between FFR and iFR. None of those

researchers measured flow velocity in patients with severe aortic stenosis and coronary artery disease; and therefore they were unable to do anything more than speculate on the underlying reasons for what they found.

In this project, we focused on careful, deliberate measurements of intracoronary flow velocity before and after TAVI, which has never been done before in patients with coronary artery disease. This allows us to study the mechanistic question of whether FFR and iFR may behave differently.

Transcatheter aortic valve implantation (TAVI) provides a unique opportunity to test the effect of severe aortic stenosis on coronary physiology⁽⁷⁹⁾, because it is possible to perform intracoronary physiology assessments immediately before and after valve insertion. Each subject is therefore their own control, maximising the informativeness of the data since many confounders will thereby be balanced.”

P.85 Abstract Conclusion

“Flow during the wave-free period of diastole does not change post-TAVI; suggesting that indices calculated during this period are less vulnerable to the confounding effect of the stenotic aortic valve”.

Just because iFR remains constant, does this make it more accurate (less confounded)

I have revised the Abstract conclusion entirely in accordance with this comment:

"The effect of TAVI on coronary flow velocity varies across the cardiac cycle. Systolic flow velocity is significantly increased after TAVI, but diastolic flow velocity is not. It also varies with the administration of adenosine, with a larger effect from the administration of adenosine seen after TAVI.

Resting flow velocity during diastole is relatively little changed by TAVI, in comparison to the changes seen in flow velocities in systole and with adenosine. We infer from this that the distorting effect of aortic stenosis on flow-dependent parameters may be lower in the resting diastolic time-window, than in whole-cycle hyperaemic conditions."

p.85 Pressure and flow assessments.

There is a need to examine relationship/correlation between pressure-derived flow and doppler-derived flow and show whether they are reasonably interchangeable as suggested on p95. Candidate says he has these data and could present them.

I apologise for using unclear terminology. There is no such thing as 'pressure-derived flow'. I have reworded the terminology throughout to be clearer.

P.87

"Intro: In order to validate whether an invasive index is accurate in determining lesion significance in patients with severe aortic stenosis, an understanding of how aortic valve stenosis affects coronary flow is required."

Validation requires a different study design: a cohort study with clinical outcomes and assessment of screening performance (detection rates for a range of false positive rates). Candidate's study design can not, a priori, validate use of the invasive indices measures.

I completely agree with this comment and I apologise for the sloppiness in my language here. The introduction has been entirely rewritten, and now does not contain the word 'validate' which was not used appropriately.

Methods

P.89 "Moderate-severe CAD "is inconsistent with patient characteristics in Table where QCA is less than 60%

Clarification is needed. If these patients were selected to have mod/severe CAD then inclusion criteria not met.

I apologise for the imprecision of language here. Moderate-severe was meant to indicate 'moderate or severe' or 'at least moderate'. I have amended this wording. The QCA data in this study is in keeping with other published studies of intermediate coronary lesions

undergoing physiological assessment (mean diameter stenosis 48.5% in the IDEAL study, 48% in the defer and perform groups of the DEFER study, 57% in the reference group in the DEFER study, 60% in the FAME study).

P.91 Concern that some of the measurements are user defined and of uncertain clinical meaning.

Eg. Microvascular Resistance (MVR) is a ratio of pressure and velocity, then given the name (MVR). How do we really know that p/v is measuring MVR? Is this an artificial man-made construct based on different mathematical permutations of pressure and velocity or a metric that has been tested against some other gold standard of microvascular resistance?

Concern that the measurements may be interdependent, correlations not given, and multiple measurements could generate a positive value by chance if you use enough of them.

Thank you for raising the point that resistance, across all of physics, biology and medicine, is pressure divided by *flow*, and not pressure divided by velocity. I have been lax with the terminology as I have used pressure over velocity rather than pressure over flow, although in my defence this is a common shorthand used in coronary physiology research.

However I fully agree it would be better to be accurate with terminology. I have therefore added a section to the Introduction explaining why I use an *index of* microvascular resistance to detect changes in microvascular resistance.

For this specific experiment that underpins this chapter, I have removed references to microvascular resistance entirely, in accordance with the examiner's comments.

Below is the added section to the Introduction clarifying the use of resistance:

"Resistance and microvascular resistance

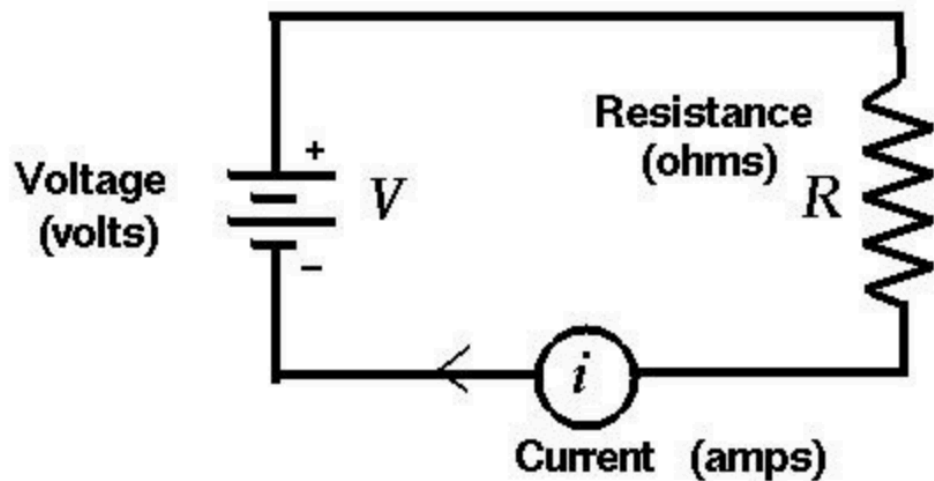
Throughout physics and biology, there is a well-defined concept of resistance which is the *potential difference* required to sustain a *flow*. The formula that defines resistance in all fields is:

Resistance = Potential difference / flow

In electrical engineering, the potential difference is voltage (volts), and flow is current (amps), and the resistance is ohms.



Ohm's Law



$$V = i R$$

In fluid dynamics, the potential difference is a pressure difference (e.g in mmHg). Strictly speaking, flow should be described as a volume per unit time (such as ml/min). This yields a resistance in mmHg/(ml/min). However, it is difficult to measure volume flow rates in the intact human directly. One way to estimate it is to measure the velocity (e.g with Doppler) and multiply this by the cross-sectional area indicative of flow. The latter quantity is itself a little difficult to measure, however.

Therefore, a proxy for microvascular resistance that is commonly used in coronary physiology research is to set aside the assessment of cross-sectional area and simply calculate pressure over velocity. This gives a quantity which will rise and fall with microvascular resistance but is not itself microvascular resistance because of the absence of cross-sectional area information. This is commonly termed the 'microvascular resistance' and has been in extensive use in the field(49).

When using an index of microvascular resistance, pressure over velocity, we should be aware that while this reliably detects when resistance changes, in which direction and by which factor, it does not directly give a value for microvascular resistance."

P.93 Overall there was no significant difference in ejection fraction or heart rate post-TAVI....with a strong trend for reduction in LVEDP ($p=0.06$, Figure 3.3 and Table 3.3). This is not a strong trend. It was not statistically significant and no trend value is given.

I again apologise for the sloppy language and this has been removed.

P.93 Following TAVI, 15 patients (53.6%) had no paravalvular leak, 13 patients (46.4%) had trivial to mild paravalvular leak and no patients had mild to moderate, moderate or severe paravalvular leak (Table 3.3).

It is unclear why this is being given as a result. Is EF and leak relevant in this study? These were not pre-specified aims/outcomes?

I fully agree, and this was not pre-specified. This information was requested by a reviewer during peer-review for publication, and was therefore provided. This has now been removed.

P.95 Whole cycle resting microvascular resistance (BMR) was unchanged post-TAVI (4.20 ± 1.9 mmHg·cm·s⁻¹ pre-TAVI versus 4.14 ± 2.1 mmHg·cm·s⁻¹ post-TAVI, $p=0.81$). Whole cycle hyperaemic microvascular resistance (HMR) decreased by 7.7% post-TAVI (2.42 ± 0.9 mmHg·cm·s⁻¹ pre-TAVI versus 2.14 ± 0.9 mmHg·cm·s⁻¹ post-TAVI, $p=0.03$).

Why report Microvascular Resistance when this was not a prespecified aim? Should this have been an aim? If so need to consider why and what the real meaning of MVR is and its limitations.

I agree and have now removed this.

Systolic haemodynamics

Systolic resting MVR decreased numerically post-TAVI (7.54 ± 3.8 mmHg·cm·s⁻¹ pre-TAVI versus 6.60 ± 3.5 mmHg·cm·s⁻¹ post-TAVI, $p=0.17$). Systolic hyperaemic MVR did not change post-TAVI (3.73 ± 1.6 mmHg·cm·s⁻¹ pre-TAVI versus 3.45 ± 1.6 mmHg·cm·s⁻¹ post-TAVI, $p=0.12$).

Inconsistent description of results. Neither were statistically significantly different, but one is described as decreasing and the other as “did not change”.

I again apologise for this; this section has now been removed.

P.96

FFR values significantly decreased after TAVI (0.87 ± 0.08 pre-TAVI versus 0.85 ± 0.09 post-TAVI, $p=0.0008$).

Concern 1:

In the Abstract the p value is 0.001 whilst here it is 0.0008. Both p values relate to the same result – which one is correct? Candidate suggested that Abstract should have stated <0.001 , but this calculation needs checking as there are other concerns.

Calculation of this p value used the Wilcoxon rank sum test, which is usually used for non-gaussian distributed variables – but mean and SDs were used as measures of central tendency for these data suggesting they were Gaussian. This is confusing and needs explanation.

We need to see the SD of the differences for The Wilcoxon test – did the differences follow a Gaussian distribution? More thorough justification and description of analysis is needed.

I apologise for the paradoxical nature of the presentation here, and thank the examiners for raising this and the opportunity to clarify during the Viva and again now. The data passed the test for normality, and therefore I showed the mean and SD. However, at the time I was doing the comparisons, I was anxious that with a small sample size, only severe deviations from normality would be picked up by the normality test, and I therefore used the Wilcoxon test as this is an appropriate comparator test for both normal and non-normal data. I have revised the text to explain this borderline situation.

"The Wilcoxon test was chosen as, although the data passed the tests for normality, there were concerns that due to the small sample size only severe deviations from normality would be picked up. Therefore it was felt best to use a comparison test of statistical significance that would be valid in both normal and non-normal data."

Concern 2:

What is the clinical relevance of an FFR dropping by 0.02 from 0.87 to 0.85?

It may be statistically significant but is it clinically significant? Needs more discussion

Thank you for raising this important observation which I have now acknowledged and covered in the discussion in more detail as below:

"Clinical implications

The findings of this study have potential implications for patients with severe aortic stenosis and coronary disease that are undergoing invasive haemodynamic evaluation of coronary lesions with a view to applying guideline-based thresholds to identify vessels requiring treatment. If the clinician wishes to use standard guideline thresholds for necessity of treatment of a vessel, it would be theoretically preferable to use iFR rather than FFR because the iFR measured pre-TAVI is much more consistent with its value after the aortic stenosis is removed.

The magnitude of the effect of severe aortic stenosis on FFR averaged only 0.02. This average effect could matter if the patient was close to the cutoff, and of course some patients would have a larger effect. Nevertheless, there would be many patients in whom the clinical dichotomy would not be changed."

P.96 Hyperaemic stenosis resistance (HSR) values increased after TAVI (0.34 ± 0.32 pre-TAVI versus 0.40 ± 0.32 post-TAVI, $p=0.06$).

The description of results is not correct or consistent (not statistically significant); similar problem to that above.

This section has now been removed.

Discussion

p.97 The Discussion does not discuss the results in enough critical detail - instead it describes basic physiology that is generally known.

Better to explore why these results differ from eg. other work like Pesarini et al. who found no change in FFR pre-post TAVI on a larger sample of patients. Whose results are correct? Could this simply be random variation. Scarsini found that iFR was less reliable - this needs discussion.

I am grateful for this comment that has prompted me to expand the Discussion with a new focus on critically appraising the work done by previous authors in the field, and placing this experiment into the context of the studies that have come before.

While at first Pesarini and my results appear to be in conflict, in fact there is much in their work that does not suggest any disagreement with my work:

"Pesarini et al studied FFR in 133 coronary lesions in 54 patients before and after TAVI (69). Overall they found no change in FFR values after TAVI, although positive FFR values (classified as lower than 0.80) were observed to decline further after TAVI. This was also

somewhat confirmed with the quantitative angiographic data. If the diameter stenosis was >50%, then the FFR value declined significantly after TAVI; if the diameter stenosis was <50% there was no change in FFR value after TAVI. In this study, a diameter stenosis of 30-50% was classified as an 'intermediate lesion', with a diameter stenosis being greater than 50% being classified as a severe lesion. The overall diameter stenosis in this cohort was 40%, indicating they recruited patients with a milder form of CAD than those in recruited in this current study. Furthermore, this may explain why the overall FFR values did not change; when their analysis was restricted to patients with a greater than 50% diameter stenosis, the mean FFR value dropped from 0.84 to 0.82; this is very similar to the effect observed in the present study.

Scarsini et al (71) studied iFR and FFR in 179 lesions in 85 patients with severe aortic stenosis. This was not a study of coronary flow velocity. This was also not a study of patients undergoing TAVI. The aim of the study was to test the diagnostic agreement of iFR and FFR in patients with severe AS, and compare it to patients without severe AS. The diagnostic agreement of iFR and FFR was predicated on the FFR cutoff value of 0.80 and an iFR cutoff value of 0.89. This study concluded that that correlation between FFR and iFR in patients with aortic stenosis was similar to the cohort of patients without aortic stenosis. However, the diagnostic agreement between iFR and FFR (using the defined cutoffs that are in place for patients without severe aortic stenosis) was lower in the AS patients (76.3%) when compared to the non-AS patients (86.1%). The optimal iFR cutoff for

predicting an FFR of 0.80 was an iFR of 0.83. This is likely simply a mechanism of attenuated hyperaemia meaning that FFR values are falsely elevated in the presence of severe aortic stenosis. The current experiment was able to objectively demonstrate that hyperaemic coronary flow velocity was reduced in severe aortic stenosis and improved by TAVI; it is possible that Scarsini and colleagues may have found the same thing had they been able to directly measure flow velocity. Indeed, in the Discussion of their manuscript they note that 'FFR might underestimate substantial CAD in the setting of AS because of the impaired microvascular function'; this is a suggested possible mechanism that is speculative due to the inherent limitations of performing only pressure-gradient assessments (FFR or iFR) in the absence of directly measuring flow velocity. A strength of the current study is the direct measurement of coronary blood flow velocity, and being able to observe directly and clearly that hyperaemic coronary flow velocity is indeed reduced in patients with severe aortic stenosis. Scarsini and colleagues note in this paper that 'extrapolating the same current FFR and iFR thresholds used in CAD patients to AS patients is only hypothesis generating, and its validation warrants further research'. Although the current experiment does not validate any index, it does help provide mechanistic insights into the behaviour of FFR and iFR in patients with severe aortic stenosis, namely by carefully and directly measuring the coronary flow velocity.

Scarsini and colleagues also compared iFR to FFR in a study 2018 without measuring coronary flow velocity (73). This study evaluated 145 coronary lesions in 66 patients with

severe aortic stenosis. FFR and iFR were measured before and after TAVI. The mean iFR values were identical before and after TAVI; this finding is similar to that observed in this current study. Furthermore, the iFR remained identical regardless of the angiographic severity of the coronary stenosis (in contrast to the previous work on FFR in severe aortic stenosis from the same group). Interestingly, the average FFR and iFR values pre-TAVI in this study were the same. This is also likely a function of attenuated hyperaemia. Although once again there was no direct measurement of coronary flow velocity, the FFR value being the same as the iFR likely represents the inability of adenosine to increment flow these patients. This is a finding that was objectively tested and shown in the current study, setting it apart from previous work in the field. The inability to achieve maximal hyperaemia invalidates the physical principles upon which FFR depends and therefore calls into question the validity of using this index as a *reference* standard in patients with aortic stenosis, and the use of a 0.80 cut-point. The diagnostic accuracy of iFR is reported in this study purely in terms of using an FFR of 0.80 as the gold standard, which has not been validated in patients with severe AS. The negative and positive predictive values derived in this study should therefore be interpreted cautiously. Indeed, studies using coronary flow velocity as well as pressure have highlighted the sensitivity of hyperaemic indices to aortic stenosis, albeit in patients without coronary lesions(71). Interestingly such studies suggest that hyperaemic parameters are more susceptible to change post-TAVI than resting parameters. This is consistent with Scarsini's results, demonstrating identical average iFR values pre and post-TAVI."

P.100 The blunted whole cycle hyperaemic flow pre-TAVI leads to FFR systematically under-estimating coronary stenosis severity in the presence of aortic stenosis; with an increase in hyperaemic flow post-TAVI resulting in FFR values becoming significantly lower across the same coronary stenosis

Is this a new finding? It appears that others have previously suggested that it may not be possible to achieve full hyperaemia in AS and so FFR may underestimate. Eg.

Scarsini "Therefore, FFR might underestimate substantial CAD in the setting of AS [15, 206 paper by Justin Davies] because of the impaired microvascular function [28,29]".

Candidate must refer to prior work - idea that FFR may underestimate coronary stenosis was raised 3-4 years ago.

Yes this hypothesis was raised by Sayan Sen and Justin Davies who were supervisors of mine, and we discussed it often. They included this speculation in a review article that they wrote, which was the reference pointed out here from the Scarsini paper. The Scarsini paper also provides further speculation around this hypothesis. It was interest in this hypothesis that led me to test it in this chapter.

I have now made clearer in the introduction of the chapter that this hypothesis was raised by my supervisor previously and have cited his review article.

"It has been suggested that hyperaemic coronary flow velocity is impeded by severe aortic stenosis(74), but this has never been tested in humans with severe aortic stenosis and coronary artery disease.

Previous researchers have looked purely at pressure (FFR and iFR) in patients before and after TAVI, focusing on the level of agreement between FFR and iFR. None of those researchers measured flow velocity in patients with severe aortic stenosis and coronary artery disease; and therefore they were unable to do anything more than speculate on the underlying reasons for what they found.

In this project, we focused on careful, deliberate measurements of intracoronary flow velocity before and after TAVI, which has never been done before in patients with coronary artery disease. This allows us to study the mechanistic question of whether FFR and iFR may behave differently."

P.101 There is a paucity of available data regarding coronary stenosis assessment in patients with severe aortic stenosis. The existing studies have not measured coronary flow and therefore assume it is not affected by aortic stenosis (69,71,72).

Investigators of “existing studies” may claim they had not made this assumption. How does the candidate know?

Eg. Scarsini: “In severe AS variations in the coronary blood flow occurring during the systolic and diastolic phases of the cardiac cycle [28], may explain the different behaviour of iFR observed in patients with AS in our study.”

Scarsini speculated that there *may be* severe variation in coronary blood flow in aortic stenosis, and that this *may* explain the different behaviour of iFR.

However, Scarsini could only speculate on the flow and whether it was the mechanism, because he had no measurements indicating flow.

I have now referenced this Scarsini paper and made clearer that researchers were wondering about why iFR seemed to behave differently from FFR in severe aortic stenosis, and were lacking measurements of flow velocity that could answer the question.

I have adjusted the phrasing to introduce this area as follows:

“There is a relative scarcity of available data regarding coronary stenosis assessment in patients with severe aortic stenosis. The existing studies of FFR and iFR have not measured coronary flow velocity (70,72,73).”

Clinical Implications

This refers to concern raised earlier. Is a 0.02 difference in FFR clinically significant? A re-examination of the thesis would be useful to see how often this arises and adopt a more balanced approach to interpreting this result, which is of uncertain clinical relevance and different from prior work. Equally might a change in FFR actually be a useful

Candidate: "Flow during the wave-free period of diastole is independent of the severity of the aortic valve stenosis suggesting that iFR can be used to accurately discriminate coronary stenosis severity in the setting of aortic stenosis"

Just because there was no change in iFR does not make it an accurate measure of the clinical significance of coronary stenosis. This would need a different study design including outcomes and measures of discrimination (sensitivity/specificity)?

We agree and have modified this section of the Discussion with regards to clinical implications as previously outlined.

Limitations

A main limitation is that the study offers no answer to whether FFR or iFR is the right measure. It just shows that one stays relatively constant and the other changes by a small amount.

The study design does not allow an answer to the key clinical question. How has chapter advanced knowledge?

I have significantly expanded the Limitations section to help address this point, and also provided discussion of different study designs that could follow on from those contained within this Thesis to help elucidate the clinical utility of coronary physiology for these patients:

"Limitations

This study does not on its own indicate that iFR or FFR is a better guide to the need for coronary revascularisation in patients requiring a TAVI. A cohort study might be a good study design to explore the clinical impact of various levels of iFR and FFR in such patients. A design for this could be a large cohort recruited from multiple centres, for example across the UK in which the participants have the measurements but no coronary intervention. Over a period of years, the event rates could be assessed and it could be established whether pre-TAVI iFR or FFR is a better predictor of subsequent events.

Ultimately, a randomized trial powered for clinical endpoints is the only way to determine whether intervening on lesions in a given range of iFR or FFR is beneficial or not. This

would be a major undertaking and could be pursued if the observational data described above suggests potential utility."

Conclusion

Needs major revision in the light of the above.

I have modified the Conclusion so it now reads as follows:

"The effect of TAVI on coronary flow velocity varies across the cardiac cycle. Systolic flow velocity is significantly increased after TAVI, but diastolic flow velocity is not. It also varies with the administration of adenosine, with a larger effect from the administration of adenosine seen after TAVI.

Resting flow velocity during diastole is relatively little changed by TAVI, in comparison to the changes seen in flow velocities in systole and with adenosine."

Table 3.4

If MVR is presented (not a pre-specified outcome) then the components of MVR (pressure and flow in both systole and diastole) should be presented so reader can do the calculation him/herself.

Candidate needs to consider whether presentation of these data in this Chapter is needed or whether it is just overcomplicating the message.

There is a risk of spurious associations/findings with multiple outcomes and no assessment of multiple testing has been made (most p values are on the edge of significance).

I am grateful for this suggestion, and fully agree. Therefore, resistance data has accordingly been removed from this chapter.

Chapter 4

Study design issues

Main concern with this chapter is the validity of comparing one group of patients in one study with a different group of patients in another.

This is dangerous because there are likely to be systematic difference between the study groups that could introduce important selection bias?

For example

Gp1; CAD was determined by Heart Team as not needing revascularisation

Gp 2; CAD was determined by another Heart Team as needing revascularisation

There are likely to be strong selection factors that make a doctor chose a patient for PCI beyond the coronary stenosis.

Other main concern is the meaning of the 0.74.

This is a key part of the thesis and both examiners struggled with the derivation of this value, study design and interpretation.

Thank you for pointing this out. It is now clear to me that I must not draw any conclusions from the comparisons *between* the groups since they are not in any way matched. I have rewritten this chapter to only refer to changes pre/post intervention (TAVI or PCI) and made clear in the Abstract and Discussion that no quantitative comparison is possible between the effects of TAVI and PCI. I have also removed mention of the iFR threshold of 0.74 in accordance with the examiners' comments, which on reflection I completely agree with.

The relevant clinical questions is which dominates (CAD / AS) in the AS patient and also which lesions need to be treated. It is hard to see how the 0.74 iFR came out of the modelling and how that determined if a coronary lesion was significant. Does an iFR of 0.74 mean these coronary lesions will produce ischaemia (chest pain) even if the AS is

resolved? This is relevant to patients (they will still have angina) and surgeons (these lesions need a graft).

The examiners are concerned that there is nothing we can say about 0.74 with confidence. Selection bias makes the value uninformative. Whatever value of iFR is determined, it is of unknown clinical significance in the absence knowing the screening performance of iFR on clinical outcomes (needs a completely different study design).

I fully agree, and any mention of the iFR value of 0.74 has now been removed entirely.

Study finding issues

Unclear what is new and what was previously known.

Examples

P.134 "Therefore, microvascular resistance over the wave-free period is a marker of coronary stenosis severity."

Almost the exact same sentence is given on p 125/6 as a previously known finding that forms part of the justification for measuring MVR in this study.

The Candidate stated that by "previously known", he meant , he had shown this as a new finding in Chapter 4. But on P.125: "Microvascular resistance over the wave-free period

has been demonstrated to reflect coronary stenosis severity(63); with low resistance suggesting a more severe stenosis and higher resistance suggesting a less severe stenosis." Indicating that this had been found in a previous study (ref 63) in 2013.

I am grateful to you for pointing this out. The sentence in the results has been deleted, as it is pointed out this has previously been demonstrated in patients without severe AS and therefore is not novel. For the sake of clarity, during the Viva, when I stated a finding was previously found by myself in Chapter 3, it was in relation to the below point regarding aortic stenosis (but this has also now been modified in accordance with the examiner comments).

P 135 "In this study I have shown that: 1) in patients with severe aortic stenosis and intermediate coronary lesions, relief of aortic stenosis acutely results in a significant increase in microvascular resistance;...."

But on page 125 justification for this work states: "It has also been shown that microvascular resistance over the wave-free period is affected by severe aortic stenosis". So is the discovery new?

As above, this was the finding pertaining to the publication that arose from Chapter 3, but the wording has now been modified for clarity and to avoid confusion.

"2) this increase is independent of the severity of any underlying coronary lesion..."

The study has only shown this when CAD is mild. The statement should not be so widely generalised. If it only applies to mild CAD, is this of any clinical relevance? Clinicians are unlikely to be concerned about mild CAD in the setting of severe symptomatic AS – they will reasonably focus on relieving the AS.

I apologise for this overly enthusiastic phrasing, which has been adjusted.

"In this study I have shown that: 1) in patients with severe aortic stenosis and intermediate coronary lesions, relief of aortic stenosis acutely results in a significant increase in microvascular resistance; and 2) this increase was consistent across the range of coronary lesions included in this study."

As previously discussed, the severity of coronary lesions included in these studies was consistent with the published literature of intermediate coronary lesions undergoing physiological assessment.

P.136 "In this study I have demonstrated that aortic stenosis also influences coronary microvascular tone and its ability to respond to stress.

Does Microvascular tone = MVR. Need to keep terminology consistent. This was known before and was the justification for the study.

I apologise for this, and have re-worded this to say 'resistance'. In the re-structuring of the thesis, I have removed resistance from Chapter 3, and therefore any confusion about whether the findings are novel or not. The reference to this was to the publication arising from Chapter 3, and the statement has now been removed from the Introduction to this chapter.

Limitations section

Needs substantial revision in the light of the Viva discussion.

I am grateful to the examiners for helping me re-work this Chapter and to avoid some of the previous pitfalls that were discussed during the Viva. I have also now expanded the Limitations section in view of this:

"Selection bias is the reason that no quantitative comparison should be made between the TAVI and PCI groups. The patients undergoing TAVI had no reason to be similar in any way to those requiring undergoing PCI, and indeed their baseline characteristics show that they are different in many respects. Even if I were to attempt to compare the FFR and iFR effects between group 1 and group 2, such a comparison would be invalid due to selection bias. For that reason, in this chapter I have focused on pre/post intervention comparisons within each group and only compared the groups qualitatively (e.g to observe that the index of resistance increases in each group)."

Typographic error p.138

It is **not common** for patients with severe aortic stenosis referred for TAVI to have coronary artery disease(4).

Thank you, this has been corrected.

Chapter 5

This an interesting experiment. Had the sample size been larger and the follow-up included clinical data, this would have gone much further to answering the clinical question behind the thesis.

Specific comments

P 157: What has age got to do with the question. Surely CAD and AS management applies to young and old?

I have removed this from the thesis now.

Why use median and IQR here, for same types of measurements – did these follow a different distribution? Why?

This was chosen due to the small sample size, and has now been clarified in the methodology section of this chapter.

P 168: Scarsini et al(72) correlated iFR to FFR values without measuring coronary flow, and showed iFR to be stable before and after the procedure. There were concerns raised regarding iFR values crossing the treatment threshold of 0.89. However, this is dependent on the distributions of values within the study sample, and on interpreting continuous values using a dichotomous cutpoint(95).

Is this a fair criticism given that the Candidate did exactly this in Chapter 4?

We have now removed the iFR threshold of 0.74 from the previous chapter.

Typographic error: Table 5.4 formatting

P 162 – intracoronary nitrate is mentioned – was it used in Ch 3 and 4 cases too?

P168 – Did LVH regress and did LVH regression correspond with microcirculatory changes?

While the number of cases was small and precludes meaningful statistical analysis, some acknowledgement of parameters such as angina resolution, mortality, exercise capability, regression of LV mass would be relevant.

I have corrected the formatting of the table. Regarding regression of LV mass, I have added the following section to the Limitations:

"Data regarding regression of LV mass was not available. In principle, one might seek a correlation between regression of LV mass and improvement in hyperaemic flow velocity. However, LV mass is vulnerable to noise in its measurement and therefore changes in LV mass over time, which are small changes within a relatively large number, are extremely vulnerable to random noise. While this does not prevent detection of correct direction and approximate magnitude of changes over time in a group, it makes it very difficult to identify a correlation with another variable reliably."

Regarding clinical outcomes, I have added the following to the Limitations and have also noted this data in the Results:

"This was a physiological study examining haemodynamic data, and was not intended to look at clinical outcomes, nor powered for this. None of the patients included in this study required coronary revascularisation for angina or acute coronary syndrome up to latest follow-up, and none of them died but in this sample size it is not possible to draw precise general conclusions from this."

P 190 Typo before

This has been corrected, thank you for noting it.

Synthesis

This needs revision.

Important to be clear which findings are novel which are confirmatory, which remain unresolved which conflict with previous results of other work and why. The measurement of doppler-derived flow is not the answer to all these issues. What discoveries materially advance our understanding of the situation seen in patients with severe aortic stenosis and coronary artery disease?

I have extensively revised the Synthesis chapter in line with the comments from the examiners during the Viva and throughout this written report, and am grateful for their guidance in improving this work. I have focused on putting these results in context with what has been previously studied in this field.

"This work within the context of prior work in the field

The majority of the previous published work in the field of coronary physiology in patients with severe aortic stenosis has come from the Verona group. Pesarini et al studied FFR in 133 coronary lesions in 54 patients before and after TAVI (69). This particular study did not include iFR, and did not include any measure of coronary flow velocity. Overall they

found no change in FFR values after TAVI, but a more nuanced reading of the data permits a more refined interpretation. Lesions with functionally significant FFR values (classified as lower than 0.80) were observed to decline after TAVI. This was also seen with quantitative angiographic data. If the diameter stenosis was $>50\%$, then the FFR value declined significantly after TAVI; if the diameter stenosis was $<50\%$ there was no change in FFR value after TAVI. The overall diameter stenosis in this cohort was 40%, indicating they recruited patients with a milder form of CAD than those recruited in the series of experiments that comprise this thesis. The average diameter stenosis in the experiments contained within this thesis was approximately 55%. This is consistent with the severity of stenosis examined in clinical trials of coronary physiology in patients without severe aortic stenosis (average diameter stenosis 60% in FAME; average diameter stenosis 48% in the deferral and performance groups in DEFER, and 57% in the reference group of FFR <0.75 in DEFER). Furthermore, this may help explain why the overall FFR values did not change in Pesarini's study; in fact, when their analysis was restricted to patients with a greater than 50% diameter stenosis, the mean FFR value dropped from 0.84 to 0.82. This is an effect very similar to that observed in the first experiment that formed chapter 3 of this thesis.

Scarsini et al (71) from the same group then studied iFR and FFR in 179 lesions in 85 patients with severe aortic stenosis. This study also did not include any assessment of coronary flow velocity, highlighting a key difference of the work that has formed the basis of this thesis. It is important to note that this was not a study of patients undergoing TAVI,

which involved physiological assessments before and after valve intervention. The aim of the study was to test the diagnostic agreement of iFR and FFR in patients with severe AS, and compare it to the diagnostic accuracy of a control group without severe AS. The diagnostic agreement of iFR and FFR was predicated on the FFR cutoff value of 0.80 and an iFR cutoff value of 0.89. This study concluded that that correlation between FFR and iFR in patients with aortic stenosis was similar to the cohort of patients without aortic stenosis. However, the diagnostic agreement between iFR and FFR (using the defined cutoffs that are in place for patients without severe aortic stenosis) was lower in the AS patients (76.3%) when compared to the non-AS patients (86.1%). The optimal iFR cutoff for predicting an FFR of 0.80 was an iFR of 0.83. This is likely simply a mechanism of attenuated hyperaemic flow velocity meaning that FFR values are falsely elevated in the presence of severe aortic stenosis. This hypothesis could not be tested in Scarsini's study as there was no measurement of flow velocity.

The experiments that comprise this thesis are able to show that hyperaemic coronary flow velocity was reduced in severe aortic stenosis and improved by TAVI. This mechanism is hinted at in the Discussion of their manuscript: 'FFR might underestimate substantial CAD in the setting of AS because of the impaired microvascular function'; this is a suggested possible mechanism that is speculative due to the inherent limitations of performing only pressure-gradient assessments (FFR or iFR) in the absence of directly measuring flow velocity.

A strength of the current series of studies within this thesis is the direct measurement of coronary blood flow velocity, and being able to observe directly and clearly that hyperaemic coronary flow velocity is indeed reduced in patients with severe aortic stenosis. Scarsini and colleagues note in this paper that 'extrapolating the same current FFR and iFR thresholds used in CAD patients to AS patients is only hypothesis generating, and its validation warrants further research'. Their findings are not at all in conflict with the results of the studies within this thesis, but they are an artefact of using an FFR cutpoint of 0.8 as a gold-standard ischaemic reference to which another index is compared.

Wiegernick and colleagues performed an assessment of invasive coronary flow velocity in patients with severe aortic stenosis before and after TAVI in 2015 (71). It is important to note that this study included only patients with unobstructed coronary arteries, which is a key difference from the work contained within this thesis. Furthermore, all analyses were restricted to the left coronary artery. This study included a control group without severe aortic stenosis: the main aim of this study was to evaluate the effects of severe aortic stenosis on coronary haemodynamics as compared with a cohort of patients without AS. This study did show that hyperaemic flow velocity was lower in patients with severe AS when compared to controls, as was CFR. These findings helped inform the design of the series of experiments within this thesis, where we sought to evaluate coronary flow

velocity in patients with severe aortic stenosis and coronary artery disease, before and after TAVI.

Scarsini and colleagues subsequently compared iFR to FFR in a study 2018 (73). This study evaluated 145 coronary lesions in 66 patients with severe aortic stenosis. FFR and iFR were measured before and after TAVI. This was a study of pressure-gradients without assessments of flow velocity.

The mean iFR values were identical before and after TAVI; this finding is similar to that observed in the experiments that comprise this thesis. The mean iFR value was also very similar to the mean FFR value before TAVI in this study. This is again similar to the results of the experiments within this thesis.

Therefore Scarsini's results do not appear to be in conflict to my own. A key difference and advance that this thesis represents, is the measurement of flow velocity to permit mechanistic insights that explain the behaviour of iFR and FFR in severe aortic stenosis. For example, the similar pre-TAVI iFR and FFR values in Scarsini's study are likely to be a function of impaired hyperaemic flow velocity in severe aortic stenosis leading to higher FFR values. However, this hypothesis could not be tested in Scarsini's study. This is a finding, however, that was objectively tested and shown in this thesis, setting it apart from previous work in the field. The inability to achieve maximal hyperaemia challenges the

physical principles upon which FFR depends and therefore calls into question the validity of using this index as a *reference* standard in patients with aortic stenosis, and particularly the use of a 0.80 cut-point. The diagnostic accuracy of iFR is reported in this study purely in terms of using an FFR of 0.80 as the gold standard, which was validated in patients without severe AS. The negative and positive predictive values derived in this study should therefore be interpreted cautiously. There was also a reported 15% categorisation change by iFR after TAVI. This finding is an artefact of the distribution of iFR values close to the cutpoint, in contrast to the FFR values. The majority of patients in this study had iFR values that group around the iFR cutpoint of 0.89. Any biological variation will therefore lead to treatment reclassification when the inherent variability causes the iFR value to cross the cutpoint. In contrast, the majority of patients had FFR values significantly further away from the FFR cutpoint (due to the attenuated hyperaemia detailed previously). Therefore, the biological variation and numerical changes in FFR will lead to less reclassification. The classification change, or lack of change, is therefore a function of: 1) using a continuous variable such as FFR or iFR dichotomously; 2) stenosis distribution and 3) attenuated hyperemia.

In fact, this categorisation variability around the treatment threshold has previously been defined in FFR. When measured 10 minutes apart in the same patient FFR itself has a categorisation change in 15%, increasing to 50% when FFR values are close to the treatment threshold(75)."

I have also introduced the core questions this thesis answered, which are all novel findings:

"This thesis has investigated coronary haemodynamics in patients with severe aortic stenosis and coronary artery disease, performing the first systematic assessment of invasively measured coronary flow velocity before and after transcatheter aortic valve implantation (TAVI) in patients with coexistent CAD. The novel aspects of this thesis pertain to the invasive measurement of coronary flow velocity, which permits a better mechanistic understanding of how commonly used indices of coronary stenosis severity (FFR and iFR) behave in severe aortic stenosis.

This thesis has answered the following 3 key questions:

Question 1. In patients with severe AS and CAD, what is the effect of the presence of severe AS on coronary flow velocity, and consequently on FFR and iFR?

Question 2. Does aortic stenosis affect microvascular physiology?

Question 3. Is the effect of aortic stenosis on coronary physiology only short-term, i.e once the aortic stenosis is removed, there is no further change, or is there a longer-lasting effect?"

Examiner's Preliminary Report Form

To be prepared prior to the oral examination and brought to the examination

Name of PGR:	Yousef Ahmad	Degree	PhD

1. Compliance with Imperial College Regulations on PhD

5.1.1 The thesis shall:

(a) consist of the candidate's own account of their investigations, the greater proportion of which shall have been undertaken during the period of registration under supervision for the degree;

Yes

The part played by the candidate in any work done jointly with the supervisor(s) and/or fellow research workers must be clearly stated by the candidate and certified by the supervisor.

To be determined

It is unclear how much of this work is the candidate's own work. Much of the work is multicentre so some must have been done by others unless he was present in every centre. The candidate attributes everything to himself with frequent use of terms like "I have found, I have discovered...." repeated throughout the thesis. This may be true but it is unusual for work like this not to involve a team, especially as the paper cited at the start of chapters 3.4 and 5 have more than one author. Needs clarification

I have now included the following section in the Methods to clarify this aspect, which I was also grateful to be able to clarify during the Viva examination:

"Overall data collection and synthesis

As described earlier, the majority of patients were recruited from The Hammersmith Hospital, Imperial College Healthcare NHS Trust. There were two principle challenges to data collection:

- 1) Occurrence of intraprocedural complications that precluded completion of the research protocol after valve implantation
- 2) Obtaining high-fidelity Doppler flow traces

In the earlier phases of recruitment, procedural complications occurred relatively more commonly owing to larger sheath sizes and being comparatively earlier on in the learning curve of the procedure. For the purposes of the protocol, paired data before and after valve implantation were essential. Therefore, if a procedural complication occurred that precluded further physiological assessment (i.e. haemorrhage, conversion to open surgery) then the data could not be used for analysis.

In total, 12 experiments were abandoned with incomplete data due to intraprocedural complications. In order to help mitigate against this loss of data, international collaborators were invited to participate. After appropriate training on the use of the Combowire and the protocol, data was collected from three other centres: Skane University Hospital, Lund, Sweden; Amsterdam Medical Center, Amsterdam, The Netherlands; and Aarhus University Hospital, Aarhus, Denmark. All data collected from international collaborators was sent to Imperial for all aspects of analysis, which were

performed by myself with oversight from my primary supervisor. All traces underwent quality control to ensure only the highest fidelity data was used for analysis; 25% of traces sent from other centres were ultimately discarded and not utilised in analysis. A total of 3 patients from Sweden, 6 from Denmark and 8 from The Netherlands were included for analysis; a total of 38 from London were included. I was present for each case performed in London and ensured the protocol was completed accurately, and that high-quality haemodynamic data was obtained. This would often necessitate repeating the protocol several times to ensure high-quality data was obtained for each condition (resting pre-TAVI data, hyperaemic pre-TAVI data, resting post-TAVI data, hyperaemic post-TAVI data).

The process of taking an invasive haemodynamic study performed in the cardiac catheterisation laboratory to yielding pressure and flow data suitable for analysis and presentation in scientific manuscripts was all performed at Imperial by myself with oversight from my primary supervisor. This process took approximately 20 hours for each individual case, taking into account the multiple steps involved, and that each case needed separate analysis for each separate condition (resting pre-TAVI data, hyperaemic pre-TAVI data, resting post-TAVI data, hyperaemic post-TAVI data)."

2. (b) and form a distinct contribution to the knowledge of the subject and afford evidence of originality by the discovery of new facts and/or by the exercise of independent critical power;

To be determined

This is unclear. The candidate claims that this is the first systematic assessment of coronary physiology pre and post TAVI, when it is not. Italian studies (eg. Scarsini et al) on more patients preceded the candidates work and came to different conclusions. There is therefore incomplete attribution, priority and a failure to fully recognise previous work.

This has been a major focus of the revision process, and I have now discussed the findings of Scarsini et al extensively within this Thesis and helped to put my results in the context of what has been previously studied and published within the field. There is now a new section in the Synthesis dedicated to this area.

"This work within the context of prior work in the field

The majority of the previous published work in the field of coronary physiology in patients with severe aortic stenosis has come from the Verona group. Pesarini et al studied FFR in 133 coronary lesions in 54 patients before and after TAVI (69). This particular study did

not include iFR, and did not include any measure of coronary flow velocity. Overall they found no change in FFR values after TAVI, but a more nuanced reading of the data permits a more refined interpretation. Lesions with functionally significant FFR values (classified as lower than 0.80) were observed to decline after TAVI. This was also seen with quantitative angiographic data. If the diameter stenosis was >50%, then the FFR value declined significantly after TAVI; if the diameter stenosis was <50% there was no change in FFR value after TAVI. The overall diameter stenosis in this cohort was 40%, indicating they recruited patients with a milder form of CAD than those recruited in the series of experiments that comprise this thesis. The average diameter stenosis in the experiments contained within this thesis was approximately 55%. This is consistent with the severity of stenosis examined in clinical trials of coronary physiology in patients without severe aortic stenosis (average diameter stenosis 60% in FAME; average diameter stenosis 48% in the deferral and performance groups in DEFER, and 57% in the reference group of FFR <0.75 in DEFER). Furthermore, this may help explain why the overall FFR values did not change in Pesarini's study; in fact, when their analysis was restricted to patients with a greater than 50% diameter stenosis, the mean FFR value dropped from 0.84 to 0.82. This is an effect very similar to that observed in the first experiment that formed chapter 3 of this thesis.

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of this thesis. It is important to note that this was not a study of patients undergoing TAVI, which involved physiological assessments before and after valve intervention. The aim of the study was to test the diagnostic agreement of iFR and FFR in patients with severe AS, and compare it to the diagnostic accuracy of a control group without severe AS. The diagnostic agreement of iFR and FFR was predicated on the FFR cutoff value of 0.80 and an iFR cutoff value of 0.89. This study concluded that that correlation between FFR and iFR in patients with aortic stenosis was similar to the cohort of patients without aortic stenosis. However, the diagnostic agreement between iFR and FFR (using the defined cutoffs that are in place for patients without severe aortic stenosis) was lower in the AS patients (76.3%) when compared to the non-AS patients (86.1%). The optimal iFR cutoff for predicting an FFR of 0.80 was an iFR of 0.83. This is likely simply a mechanism of attenuated hyperaemic flow velocity meaning that FFR values are falsely elevated in the presence of severe aortic stenosis. This hypothesis could not be tested in Scarsini's study as there was no measurement of flow velocity.

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pressure-gradient assessments (FFR or iFR) in the absence of directly measuring flow velocity.

A strength of the current series of studies within this thesis is the direct measurement of coronary blood flow velocity, and being able to observe directly and clearly that hyperaemic coronary flow velocity is indeed reduced in patients with severe aortic stenosis. Scarsini and colleagues note in this paper that 'extrapolating the same current FFR and iFR thresholds used in CAD patients to AS patients is only hypothesis generating, and its validation warrants further research'. Their findings are not at all in conflict with the results of the studies within this thesis, but they are an artefact of using an FFR cutpoint of 0.8 as a gold-standard ischaemic reference to which another index is compared.

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series of experiments within this thesis, where we sought to evaluate coronary flow velocity in patients with severe aortic stenosis and coronary artery disease, before and after TAVI.

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The mean iFR values were identical before and after TAVI; this finding is similar to that observed in the experiments that comprise this thesis. The mean iFR value was also very similar to the mean FFR value before TAVI in this study. This is again similar to the results of the experiments within this thesis.

Therefore Scarsini's results do not appear to be in conflict to my own. A key difference and advance that this thesis represents, is the measurement of flow velocity to permit mechanistic insights that explain the behaviour of iFR and FFR in severe aortic stenosis. For example, the similar pre-TAVI iFR and FFR values in Scarsini's study are likely to be a function of impaired hyperaemic flow velocity in severe aortic stenosis leading to higher FFR values. However, this hypothesis could not be tested in Scarsini's study. This is a finding, however, that was objectively tested and shown in this thesis, setting it apart from

previous work in the field. The inability to achieve maximal hyperaemia challenges the physical principles upon which FFR depends and therefore calls into question the validity of using this index as a *reference* standard in patients with aortic stenosis, and particularly the use of a 0.80 cut-point. The diagnostic accuracy of iFR is reported in this study purely in terms of using an FFR of 0.80 as the gold standard, which was validated in patients without severe AS. The negative and positive predictive values derived in this study should therefore be interpreted cautiously. There was also a reported 15% categorisation change by iFR after TAVI. This finding is an artefact of the distribution of iFR values close to the cutpoint, in contrast to the FFR values. The majority of patients in this study had iFR values that group around the iFR cutpoint of 0.89. Any biological variation will therefore lead to treatment reclassification when the inherent variability causes the iFR value to cross the cutpoint. In contrast, the majority of patients had FFR values significantly further away from the FFR cutpoint (due to the attenuated hyperaemia detailed previously). Therefore, the biological variation and numerical changes in FFR will lead to less reclassification. The classification change, or lack of change, is therefore a function of: 1) using a continuous variable such as FFR or iFR dichotomously; 2) stenosis distribution and 3) attenuated hyperemia.

In fact, this categorisation variability around the treatment threshold has previously been defined in FFR. When measured 10 minutes apart in the same patient FFR itself has a

categorisation change in 15%, increasing to 50% when FFR values are close to the treatment threshold(75)."

(c) and be an integrated whole and present a coherent argument;

To be determined

An argument is made that iFR may be more suitable than FFR in the assessment of Coronary artery disease in patients with aortic stenosis undergoing TAVI procedures. This may be true but it is not a position that supported by sufficient evidence. In particular no study design has been used, with clinically relevant outcomes (eg, subsequent clinical events due to coronary artery disease (MI, death, unplanned PCI for example) that would be able to determine which measurement if ether is worthwhile. These are significant methodological problems.

4. (d) and give a critical assessment of the relevant literature, describe the method of research and its findings, include discussion on those findings and indicate in what respects they appear to the candidate to advance the study of the subject; and, in so doing, demonstrate a deep and synoptic understanding of the field of study, (the candidate being able to place the thesis in a wider context), objectivity and the capacity for judgment in complex situations and autonomous work in that field;

No:

1. Lack of critical assessment of prior data on FFR and iFR in stable CAD. For example, in using an FFR cut-off of 0.8 (mentioned as standard), what is the detection rate (sensitivity) for identifying future MI/cardiac death and what is the false positive rate. Given that FFR is a continuous variable, what is the screening performance (DR for a given FPR) of 0.8 or other cut-offs. The candidate cites two trials and a class 1A guideline recommendation to support the use of this practice but this is insufficient for a PhD.

I agree that it is shocking that these indices have become dichotomous indicators of therapy with no assessment of sensitivity and specificity and its proponents recommend it forcefully and with absolute certainty (shown below) and they have been adopted uncritically in the guidelines. These two trials are the sole basis of the class I indication and we have grants rejected now because it is considered unethical to test further something that already has class I guidelines.

Coronary pressure never lies.

Koolen JJ¹, Pijls NH.

 Author information

Abstract

Fractional Flow Reserve (FFR), calculated by coronary pressure measurement, is the invasive gold standard to assess the hemodynamic significance of a coronary stenosis. FFR reliably indicates whether a stenosis is responsible for inducible ischemia and if percutaneous coronary intervention is appropriate. False positive or negative FFR is rare. Occasionally, however, a clinical or angiographic condition is encountered in which in first instance the FFR measurement contradicts the intuitive feeling of the interventionalist. Further examination in such cases, however, often reveals a clear physiologic explanation and in this manner FFR "lifts the veil". Two such patients are presented in this case report and the reasons for apparent or actual false positive or negative FFR are discussed.

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With regards to other study designs, I have now discussed how a prospective cohort study may be useful to glean information regarding events occurring at different levels of iFR or FFR, and how the results from such a study could inform the design of a randomised trial.

"A cohort study might be a good future design to explore the clinical impact of various levels of iFR and FFR in such patients. A design for this could be a large cohort recruited from multiple centres, for example across the UK in which the participants have the measurements but no coronary intervention. Over a period of years, the event rates could be assessed and it could be established whether pre-TAVI iFR or FFR is a better predictor of subsequent events.

Ultimately, a randomized trial powered for clinical endpoints is the only way to determine whether intervening on lesions in a given range of iFR or FFR is beneficial or not. This would be a major undertaking and could be pursued if the observational data described above suggests potential utility."

2. CABG often accompanies Surgical AVR, and some advocate a visual stenosis of 50% or more to justify grafting the vessel – what is the evidence that this is the right thing to do – are there RCTS? Prior understanding of this practice and the role of coronary physiology seems highly relevant to this thesis but there is a lack of evidence appraisal.

I agree this is an important point worthy of further discussion. The Synthesis chapter has now been updated with a critical appraisal of the available evidence.

A parallel situation? Surgical treatment

TAVI is a new procedure, and the literature and evidence base is inherently limited by this.

There are potential lessons that can be learned from the surgical literature which is by definition much more extensive and historical.

The first factor to consider is that different patient profile of one with isolated severe AS versus one with severe AS and CAD. A 2013 study(27) of almost 4000 patients demonstrated that those with AS and CAD were older, more symptomatic and had poorer ventricular function. It is this group that is likely most analogous to the TAVI population, where patients are more likely to be older and more likely to have coexistent CAD. Patients undergoing AVR and CABG worse 10-year prognosis than those with isolated AS undergoing AVR + CABG (10-year survival 43% versus 59%). This pattern of increased risk of AVR and CABG versus AVR alone was also seen in a large German registry of 13,860 patients(109). In-hospital mortality was 2.1% after isolated AVR but 4.5% after AVR and CABG combined. These results, however, are likely a reflection of the higher-risk patient group who required combined surgery, rather than purely a hazard of the procedure itself. Put more simply, the patients having isolated AVR did not have CAD and therefore were inherently lower risk. Performing additional CABG in addition to AVR does, however, increase the surgical time and time spent on bypass, and therefore the attendant complexity and risk of the operation.

A more nuanced understanding can be gained from other historical surgical studies. Data published in 1987 compared outcomes for patients undergoing surgical AVR who were stratified into four groups: those without CAD, those with CAD who did not undergo CABG, those with CAD who did undergo CABG, and those who did not undergo

angiography. Focusing on the patients who had CAD, 30-day mortality was 10.3% in patients who did not undergo CABG versus 6.3% in those who did (and 4.5% in those without CAD). This pattern continued out to 10-years: those who did not undergo CABG had a 10-year survival of 36%, compared to 49% for those who did undergo CABG (and 63% for those who did not have CAD). Another historical study conducted from 1975 to 1986 showed a similar pattern(28): both early and late survival were worst in patients with CAD not undergoing CABG, compared to either patients with no CAD or those who underwent CABG. One study stratified by CAD severity angiographically(29), where one group had lesions >60% bypassed and another had lesions of 40-60% bypassed. Bypassing the milder lesions did not appear beneficial, whereas complete revascularisation of the more severe lesions was associated with reduced late coronary events and better long-term survival. Finally, another historical cohort study(110) demonstrated that late cardiac deaths in patients who had undergone AVR were more common in patients with CAD, and those with CAD which was not bypassed were more likely to have sudden cardiac death.

The surgical data has no randomized data comparing concomitant revascularization with CABG versus no revascularization for patients with severe AS undergoing AVR. In the absence of randomised data proving superiority of concomitant CABG, there are still conclusions that can be drawn from the surgical experience. First, that the presence of CAD is an adverse prognostic factor for patients with severe AS undergoing AVR. Second,

that the combined operation of AVR and CABG is more complex than isolated AVR, and that these patients have poorer outcomes than those who did not undergo CABG (likely through a combination of not having CAD, and having simpler and shorter operations). Finally, observational data suggests that patients with CAD have better outcomes when undergoing CABG than those with unbypassed CAD - although this last statement is the least secure due to the confounded nature of the observational data.

It seems attractive, therefore, to limit performing combined CABG and AVR to situations where it is truly necessary. The benefits of a simpler operation must be balanced against the risks of ischaemia which may impede the patient getting off of cardiopulmonary bypass and their initial progress in-hospital. The decision of whether to bypass CAD is currently performed on angiographic basis, with non-invasive ischemia tests actively discouraged by guidelines in the presence of severe valvular heart disease(8). Current guideline recommendations are class I for concomitant CABG for stenoses greater than 70%, although the low level of evidence (C) reflects the limitations of this data described above. For patients with 50-70% stenoses, the recommendation is IIa. It may be that physiologically-guided revascularization can help provide this 'balance' of limiting revascularisation to haemodynamically significant lesions while avoiding the potential pitfalls of leaving residual ischaemia that might lead to haemodynamic instability that hampers the patient's recovery.

3. Are there RCTS ongoing and planned comparing revascularisation with no revascularisation in patients with AS undergoing TAVI? This would seem likely but there is little/no mention of these.

I apologise for not discussing this in more detail, which I have now rectified in the Synthesis section:

"The field of TAVI has the opportunity to generate higher-quality data than that which currently supports surgical practice. There are a number of ongoing randomised trials which will may to answer the unanswered questions regarding the optimal management of PCI in TAVI patients. The ACTIVATION trial(111) aims to enrol 310 patients who are planned for TAVI, and have significant CAD. Significant CAD is defined as $\geq 70\%$ stenosis in a major epicardial coronary or $\geq 50\%$ in a vein graft or protected left main stem. The primary endpoint is a composite of mortality and rehospitalisation at 12 months. This trial has a non-inferiortity design: the overall aim, therefore, could be said to be proving that is safe to treat coexistent CAD medically in patients undergoing TAVI.

The NOTION 3 trial (NCT03058627) aims to enroll 452 patients and compare FFR-guided complete revascularisation to medical therapy in patients undergoing TAVI with coexistent CAD. The conventional 0.8 FFR cutpoint will be used. The primary endpoint is a composite of all-cause mortality, MI, and urgent revascularisation at 1-year. Finally, the FAITAVI trial (NCT03360591) aims to enrol 320 patients, and will again utilise FFR and the 0.8 cutpoint. The control group will, however, not be medical therapy but be angiographic guided PCI, with stenting of all stenoses with diameter stenoses >50% by visual estimation. The primary endpoint will be a composite of all-cause death, MI, stroke, major bleeding and target-vessel revascularisation at 12-months."

5. (e) and be written in English and the literary presentation shall be satisfactory,

Yes, Thesis is well presented with some typos and some repetition that could be corrected.

Word count not given

This is now provided on the Title Page.

6. (f) and not exceed 100,000 words;

Yes

7. (g) and include a full bibliography and references;

Yes

8. (h) and demonstrate research skills relevant to the thesis being presented;

No

Concerns over the proper study design to assess whether FFR or iFR or any other metric is worthwhile in determining the appropriate management of coronary artery disease in patients undergoing TAVI for AS.

I have clarified my thesis to make clear that I am only testing which variable can be used with greater confidence before TAVI to give an answer that can be used clinically in place of the post-TAVI value, which is never available at the time the decision has to be made. I have clarified that this Thesis was not intended to directly lead to changes in management of patients, and also discussed possible future study designs.

Concerns over reaching unjustified conclusions.

I have softened the wording where appropriate in line with guidance from the examiners' comments.

Concerns over use of multiple correlated outcomes and lack of adjustment for multiple testing in chapters 3 and 4.

These analyses have now been streamlined in line with the comments from the examiners during the Viva and in this report.

Concern of statistical analyses -eg. Chapter 3, p values for main outcome given as $p=0.001$ and $p=0.0008$ (not sure which if either are correct).

This has now been corrected.

Failure to consider selection bias in Chapter 4 when comparing two separate sets of patients in separate studies and using one as the control for the other.

This has now been considered in much more detail, and has helped to inform a change in the analysis and overall focus for this chapter.

Concern that the clinical question (what to do with CAD in patients with AS undergoing TAVI?) has not been answered at all – no study design used that could have answered this.

9. (i) and be of a standard to merit publication in whole or in part or in a revised form (for example, as a monograph or as a number of articles in learned journals).

A number of papers have been published in peer reviewed journals

2. Significance of the work within the context of research in this area

There is a valid question over how to manage CAD in the setting of Severe AS treated by TAVI. Expectations in the Introduction are set that this will be addressed, but, none of the experiments help answer this question

The study designs do not permit an answer to this question. One would need cohort studies (measurements in all without CAD treatment and follow-up) and an RCT if there was a basis for an observational cut-off that was usefully discriminatory.

In fact, the thesis included 3 different studies/experiments:

1. Within-person comparison of Flow, FFR and iFR (and other derived measures) immediately before and after TAVI (n=28, with 30 lesions). Result: FFR slightly lower after TAVI (0.87 changing to 0.85), IFR the same. It is unclear what this result means. Much is made of 0.02 change in FFR but the change, is not clinically significant and would not alter management of these or any similar patients.

2. Comparison of TAVI changes with PCI changes in two separate studies. Uncertain clinical relevance of outcomes, selection bias a clear problem when comparing outcomes from different studies
3. Within-person comparison of FFR and iFR coronary artery values immediately before and after TAVI and then again 6 months later (n=13). Result, FFR lower after TAVI and even lower 6 months later. iFR stable. This is an interesting study but it included only 13 patients.

Limitations

Study 1: The main limitation in study 1 is that study offers no answer to whether FFR or iFR is the better measure of CAD ischaemia in setting of AS. It shows that one stays relatively constant and the other changes by a tiny amount (not a clinically meaningful amount in the context of the studied patients). There are errors in the statistical analyses (discrepant p values on main result). It is hard to see any clinical implications of these results and there appear no significant advance in knowledge. To the extent that flow was measured directly (stated as a first in man) it was shown to track the pressure -derived measure of

flow (FFR) - so even though it may be the first albeit small study to show this, the main conclusion seems to be that we don't need doppler assessment of flow. To be discussed.

I would argue that study 1 shows that **if** FFR and iFR are equally valid outside the setting of AS, then if a clinician needs to measure one and act on it without AS present, it makes more sense to use iFR than FFR, because iFR is shown in study 1 to be less distorted than FFR, by the presence of severe aortic stenosis.

I have clarified that FFR is not a pressure-derived measure of flow. The 'F' for 'flow' in FFR is a misnomer.

This study does not make a conclusion on the need for Doppler assessment of flow, because the Doppler assessment was performed purely to answer the scientific question as to the mechanism of any difference of behaviour of iFR and FFR. Doppler assessment of flow was not necessary before these studies nor is necessary after the study, in clinical practice, because in clinical practice mechanisms are not being studied.

Study 2: The main limitation of study 2, is the within study selection bias. The patients in the TAVi group were deemed to have non-significant CAD that did not need revascularisation. The opposite is true in the PCI group. The clinical relevance of an iFR of 0.74 is uncertain.

Yes, I fully accept this very wise point and I have completely rewritten this chapter to emphasise on the pre-post within group comparisons, and to remove any quantitative comparisons between groups.

Study 3: Main limitation is size (acknowledged) but also a lack of LV mass data to support explanation of continuous decline in FFR over time. No clinical data on subsequent angina/MI to correlate with FFR levels below the “usual” threshold for PCI (although would be limited even if observed due to sample size). No idea whether a stable iFR over this time simply reflects the possibility that it is a useless measurement.

The novel finding in this chapter is the drop in FFR between pre and immediately post TAVI, and further drop at 6 months; along with smaller effects in iFR. My reasoning is that since the presence of severe aortic stenosis is what makes FFR and iFR values not interpretable in the guidelines, the measurement that varies less when aortic stenosis is removed is closer to being usable than the one that varies more. The Reviewer is completely correct that any arbitrary, almost constant variable (such as the patient’s year of birth) would be relatively stable with time, and therefore simple stability with time is not on its own a reason to recommend one variable over another. However, FFR and iFR are correlated and have been shown in randomised controlled trials to be equally efficacious as pointers to the need for intervention (DEFINE-FLAIR and iFR-SWEDEHEART). They both have equal standing in guideline recommendations. My thesis on its own cannot cast light on whether the guidelines are correct in issuing these recommendations, and it was never

intended to test this question. The only question it addresses (on the assumption that the guideline recommendations are correct) is how they may be extrapolated with the least risk of error to patients being evaluated for possible TAVI.

Had the thesis focused on this experiment (3), with many more patients and clinical outcomes to prospectively determine who had events over time then this would have resolved most of the methodological concerns and could have contributed substantially to answering the key question.

Summary

It is unclear how any of these results help us know how to manage CAD in patients with severe AS undergoing TAVI. Does a stable iFR confer better outcomes? Maybe the fact that it is "stable"- does not change is a disadvantage and impairs predictive value- its just not possible to determine from any of the experiments conducted

These results are not intended to change management.

I have clarified that the intention of my thesis is not to change management but rather explore an area which guidelines have been unable to speculate on because of the lack of even exploratory mechanistic data. I tackled three new questions.

Question 1. In patients with severe AS and CAD, what is the effect of the presence of severe AS on coronary flow velocity, and consequently on FFR and iFR?

Question 2. Does aortic stenosis affect microvascular physiology?

Question 3. Is the effect of aortic stenosis on coronary physiology only short-term, i.e once the aortic stenosis is removed, there is no further change, or is there a longer-lasting effect?

The number of participants is smaller than previous work (albeit without direct flow measurements) and the previous data is neither properly examined up front nor in the light of his own results. The possibility that his results appear to differ from prior work (Scarsini's results) needs to be explored and discussed.

I am grateful for these comments and the opportunity to discuss this issue in detail within the Synthesis chapter.

"This work within the context of prior work in the field

The majority of the previous published work in the field of coronary physiology in patients with severe aortic stenosis has come from the Verona group. Pesarini et al studied FFR in 133 coronary lesions in 54 patients before and after TAVI (69). This particular study did not include iFR, and did not include any measure of coronary flow velocity. Overall they found no change in FFR values after TAVI, but a more nuanced reading of the data permits a more refined interpretation. Lesions with functionally significant FFR values (classified as lower than 0.80) were observed to decline after TAVI. This was also seen with quantitative angiographic data. If the diameter stenosis was $>50\%$, then the FFR value declined significantly after TAVI; if the diameter stenosis was $<50\%$ there was no change in FFR value after TAVI. The overall diameter stenosis in this cohort was 40%, indicating they recruited patients with a milder form of CAD than those recruited in the series of experiments that comprise this thesis. The average diameter stenosis in the experiments contained within this thesis was approximately 55%. This is consistent with the severity of stenosis examined in clinical trials of coronary physiology in patients without severe aortic stenosis (average diameter stenosis 60% in FAME; average diameter stenosis 48% in the deferral and performance groups in DEFER, and 57% in the reference group of FFR <0.75 in DEFER). Furthermore, this may help explain why the overall FFR values did not change in Pesarini's study; in fact, when their analysis was restricted to patients with a greater than 50% diameter stenosis, the mean FFR value dropped from 0.84 to 0.82. This is an effect very similar to that observed in the first experiment that formed chapter 3 of this thesis.

Scarsini et al (71) from the same group then studied iFR and FFR in 179 lesions in 85 patients with severe aortic stenosis. This study also did not include any assessment of coronary flow velocity, highlighting a key difference of the work that has formed the basis of this thesis. It is important to note that this was not a study of patients undergoing TAVI, which involved physiological assessments before and after valve intervention. The aim of the study was to test the diagnostic agreement of iFR and FFR in patients with severe AS, and compare it to the diagnostic accuracy of a control group without severe AS. The diagnostic agreement of iFR and FFR was predicated on the FFR cutoff value of 0.80 and an iFR cutoff value of 0.89. This study concluded that that correlation between FFR and iFR in patients with aortic stenosis was similar to the cohort of patients without aortic stenosis. However, the diagnostic agreement between iFR and FFR (using the defined cutoffs that are in place for patients without severe aortic stenosis) was lower in the AS patients (76.3%) when compared to the non-AS patients (86.1%). The optimal iFR cutoff for predicting an FFR of 0.80 was an iFR of 0.83. This is likely simply a mechanism of attenuated hyperaemic flow velocity meaning that FFR values are falsely elevated in the presence of severe aortic stenosis. This hypothesis could not be tested in Scarsini's study as there was no measurement of flow velocity.

The experiments that comprise this thesis are able to show that hyperaemic coronary flow velocity was reduced in severe aortic stenosis and improved by TAVI. This mechanism is

hinted at in the Discussion of their manuscript: 'FFR might underestimate substantial CAD in the setting of AS because of the impaired microvascular function'; this is a suggested possible mechanism that is speculative due to the inherent limitations of performing only pressure-gradient assessments (FFR or iFR) in the absence of directly measuring flow velocity.

A strength of the current series of studies within this thesis is the direct measurement of coronary blood flow velocity, and being able to observe directly and clearly that hyperaemic coronary flow velocity is indeed reduced in patients with severe aortic stenosis. Scarsini and colleagues note in this paper that 'extrapolating the same current FFR and iFR thresholds used in CAD patients to AS patients is only hypothesis generating, and its validation warrants further research'. Their findings are not at all in conflict with the results of the studies within this thesis, but they are an artefact of using an FFR cutpoint of 0.8 as a gold-standard ischaemic reference to which another index is compared.

Wiegernick and colleagues performed an assessment of invasive coronary flow velocity in patients with severe aortic stenosis before and after TAVI in 2015 (71). It is important to note that this study included only patients with unobstructed coronary arteries, which is a key difference from the work contained within this thesis. Furthermore, all analyses were restricted to the left coronary artery. This study included a control group without severe aortic stenosis: the main aim of this study was to evaluate the effects of severe aortic

stenosis on coronary haemodynamics as compared with a cohort of patients without AS. This study did show that hyperaemic flow velocity was lower in patients with severe AS when compared to controls, as was CFR. These findings helped inform the design of the series of experiments within this thesis, where we sought to evaluate coronary flow velocity in patients with severe aortic stenosis and coronary artery disease, before and after TAVI.

Scarsini and colleagues subsequently compared iFR to FFR in a study 2018 (73). This study evaluated 145 coronary lesions in 66 patients with severe aortic stenosis. FFR and iFR were measured before and after TAVI. This was a study of pressure-gradients without assessments of flow velocity.

The mean iFR values were identical before and after TAVI; this finding is similar to that observed in the experiments that comprise this thesis. The mean iFR value was also very similar to the mean FFR value before TAVI in this study. This is again similar to the results of the experiments within this thesis.

Therefore Scarsini's results do not appear to be in conflict to my own. A key difference and advance that this thesis represents, is the measurement of flow velocity to permit mechanistic insights that explain the behaviour of iFR and FFR in severe aortic stenosis. For example, the similar pre-TAVI iFR and FFR values in Scarsini's study are likely to be a

function of impaired hyperaemic flow velocity in severe aortic stenosis leading to higher FFR values. However, this hypothesis could not be tested in Scarsini's study. This is a finding, however, that was objectively tested and shown in this thesis, setting it apart from previous work in the field. The inability to achieve maximal hyperaemia challenges the physical principles upon which FFR depends and therefore calls into question the validity of using this index as a *reference* standard in patients with aortic stenosis, and particularly the use of a 0.80 cut-point. The diagnostic accuracy of iFR is reported in this study purely in terms of using an FFR of 0.80 as the gold standard, which was validated in patients without severe AS. The negative and positive predictive values derived in this study should therefore be interpreted cautiously. There was also a reported 15% categorisation change by iFR after TAVI. This finding is an artefact of the distribution of iFR values close to the cutpoint, in contrast to the FFR values. The majority of patients in this study had iFR values that group around the iFR cutpoint of 0.89. Any biological variation will therefore lead to treatment reclassification when the inherent variability causes the iFR value to cross the cutpoint. In contrast, the majority of patients had FFR values significantly further away from the FFR cutpoint (due to the attenuated hyperaemia detailed previously). Therefore, the biological variation and numerical changes in FFR will lead to less reclassification. The classification change, or lack of change, is therefore a function of: 1) using a continuous variable such as FFR or iFR dichotomously; 2) stenosis distribution and 3) attenuated hyperemia.

In fact, this categorisation variability around the treatment threshold has previously been defined in FFR. When measured 10 minutes apart in the same patient FFR itself has a categorisation change in 15%, increasing to 50% when FFR values are close to the treatment threshold(75)."

The addition of doppler flow appears new but is of minor interest and adds little more than confirming that pressure-derived flow is reasonably accurate. Candidate is not suggesting that doppler flow replace pressure-derived flow.

I apologise for any confusion and have now clarified within the thesis to avoid the possibility of misunderstanding; and have made it clear that there is no such thing as 'pressure-derived flow', or any way of deriving flow from pressure. Flow and pressure are different.

As noted by the examiners, I am not suggesting that Doppler flow replace pressure measurements in clinical practice. The additional measurement of Doppler flow was conducted for experimental reasons, to establish mechanisms.