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Assessment of Coronary Circulation using Bolus and Continuous Thermodilution

PhD thesis

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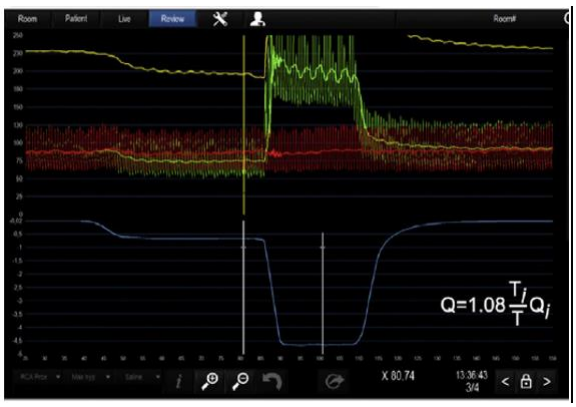

Assessment of coronary circulation using Bolus and Continuous thermodilution

PhD thesis

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"All dreams can come true if we have the courage to follow them." *– Walt Disney*

To
Srinath, Kian, Mom and Dad

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Introduction

Coronary heart disease (CHD) is the leading cause of death in developing countries [1,2]. CAD is caused by atherosclerosis of the coronary arteries, which is associated with hardening, loss of elasticity and lumen constriction. The resulting reduction in blood flow causes a mismatch between oxygen supply and oxygen demand of the myocardium [3]. The leading symptom of CHD is angina pectoris (AP). It is characterized by retrosternal pain, which can radiate into the left arm as well as the maxilla, upper abdomen or back. Stress related dyspnoea is common. Stable AP occurs mainly under stress condition and remission is achieved after a short time. In contrast, unstable AP presents with prolonged symptoms under resting conditions and can lead to myocardial infarction (MI). Different diagnostics for myocardial ischemia can be performed: non-invasive tests like stress echocardiography or stress cardiac magnetic resonance imaging perfusion (CMR), coronary computed tomography angiography (CTA) or invasive coronary angiography. Therapy is based on different approaches like lifestyle changes, medical therapy, PCI or coronary artery bypass graft (CABG). For deciding on revascularization, the current state of the art is to consider both the anatomical conditions as well as the functional hemodynamic impact of stenoses [4–7]. To understand FFR measurement, it is essential to be aware of the physiological coronary blood flow and the coronary flow reserve (CFR). Under normal conditions the myocardium extracts almost all oxygen from the blood, thus the only way to cover the increased oxygen demand under stress conditions is to increase coronary blood flow [3]. Therefore, coronary arteries dilate due to the effect of local metabolites and endothelial factors, leading to an increased coronary blood flow and maintenance of the myocardial oxygen demand [8,9]. Coronary flow reserve is defined as the ratio between maximal coronary blood flow by vasodilation to resting blood flow [8]. To avoid the impairments caused by the stenosis degree and the severity of CHD, Pijls *et al.* developed a pressure derived relative coronary flow reserve measurement, known as the FFR measurement [10,11]. With maximum hyperemia, coronary perfusion pressure and coronary blood flow can be considered proportional. This enables to estimate the severity of the stenosis by the ratio of the distal pressure to the aortic pressure.

According to fifteen-year outcome data from the DEFER (Deferral vs. Performance of Percutaneous Coronary Intervention of Functionally Nonsignificant Coronary Stenosis) study(12), delaying PCI in vessels with an FFR >0.75 is safe and associated with a low rate of clinical endpoints, while the FAME-2 (Fractional Flow Reserve versus Angiography for Multivessel Evaluation-2) study, among others, showed that patients with an abnormal FFR(i.e., lesion-specific ischemia) benefit more from revascularization than continued optimal medical therapy (13-15). Current European recommendations support FFR as a Class IA method for directing revascularization in the absence of a non-invasive diagnostic for ischemia due to the strength of the evidence supporting its use in clinical practice, particularly in patients with chronic coronary syndrome (16,17).

Patients with heart failure constitute a potential patient population in whom coronary physiology may aid in directing revascularization (HF). In fact, the justification for revascularization in patients with lower left ventricular ejection fraction (LVEF) and CAD is frequently debatable. Different imaging modalities can be used to assess each of the factors that contribute to the etiology of left ventricular systolic failure, including myocardial stunning, hibernation, the presence and degree of myocardial scar, and ischemia. Although non-invasive stress imaging only has a class IIb indication for guiding revascularization in patients with coronary artery disease and HF with lower LVEF, this de facto creates a clinical need for a decision-making test in these patients (19).

Its simplicity of interpretation contributes in part to FFR's success. One FFR measurement, which serves as a vessel-level marker and a surrogate for myocardial ischemia, influences treatment options. However, FFR as a point estimate only gives the total of the epicardial resistances caused by localized stenoses and diffuse atherosclerotic disease; it is unable to determine how each of these disease types contributes to flow impairment or forecast the functional outcome of PCI (23). Using an FFR pullback maneuvers, epicardial resistance distribution can be assessed (34). Using this method, the contribution of localized and/or diffuse CAD to the reduction in FFR along the coronary channel is revealed. Recent pressure pullback motorization experiments have made it possible to standardize the pressure-length connection. The Pressure Pullback Gradient Index (PPG index), a novel

metric that ranges between 0 and 1 and is directly correlated to the focality of epicardial disease. A extremely focal stenosis is with a PPG index of 1. On the other hand, a low PPG is linked to diffuse disease and a poor functional PCI outcome is predicted.

It is now known that microvascular dysfunction alone can cause ischemic symptoms in the absence of epicardial obstruction (21,22,35) and may contribute to persistent ischemia despite successful revascularization, even though the majority of angina patients have some degree of epicardial coronary disease (23). Due to the lack of reliable diagnostic procedures, the microcirculation has traditionally been viewed as a mysterious "black box." William Fearon developed the index of microvascular resistance (IMR) in 2003. This measurement is made after administering a short bolus of cold saline and is calculated as distal coronary pressure divided by the inverse of the hyperemic mean transit time (a correlate to absolute flow).

Index of microvascular resistance is advantageous since it is independent of hemodynamic fluctuation, is specific to the microvasculature, and may be measured concurrently with FFR without the use of additional equipment (29-31). It is still unknown whether therapeutic IMR lowering (with, for example, an intracoronary vasodilator) has any positive clinical effects. Additionally, it is unknown if therapy choices based on an IMR threshold for patients with stable CAD might improve prognosis (as has been shown to be the case with FFR). Additionally, it has been shown that the intrinsic variability of the resting mean transit time (Tmnrest) of 7–10% and the Tmnhyp of 4–8% during IMR testing. IMR, however, only serves as a surrogate for microvascular resistance and offers no data on flow or absolute resistance. In this regard, a recently developed monorail infusion catheter (RayflowTM, Hexacath, Paris, France) has opened a new window to the coronary microcirculation by enabling the measurement of absolute coronary flow (Q) and microvascular resistance (R) in the cathlab. The current approach is based on an easy fundamental idea. The rate of saline infusion (in mL/min), the temperature of the saline as it enters the coronary tree (in degrees), and the temperature of the blood after the saline and blood have mixed in the distal part of the artery are the three variables that need to be known (in degrees). The absolute Q can be calculated using the rule of three (32).

Because it has been demonstrated that saline infusion using the RayFlow catheter at room temperature reliably and uniformly generates maximal hyperemia, the computed flow is hyperemic flow (33). This method's complete operator independence, as opposed to Doppler or the index of microcirculatory resistance, is a significant advantage. The saline infusion can be continued until a true steady state is reached (usually within 10-15 seconds), and the operator keeps their hands off the patient and the catheter throughout the whole measurement procedure. The first study presenting normal absolute coronary blood flow and microvascular resistance values is presented in this thesis, along with evidence that continuous thermodilution also makes it possible to calculate resting absolute coronary flow and, consequently, coronary flow reserve.

The hemodynamic importance of coronary stenoses and the distribution of epicardial resistance are assessed in clinical practice using the hyperemic indices fractional flow reserve (FFR) and pressure pullback gradient (PPG). Guidelines also advise patients with angina and nonobstructive coronary artery disease to undergo an invasive examination of their coronary microvascular resistance. When performing a pullback maneuver to determine the pattern of coronary artery disease (e.g., focal or diffuse), the PPG is determined using FFR values along the coronary artery. The IMR approach is based on the mean transit time calculated from bolus thermodilution during pharmacologically induced hyperemia.

Intravenous (IV) adenosine has long been the preferred hyperemic drug in the catheterization lab. However, in order to achieve a dependable and sustained hyperemic response, this necessitates longer infusions, which frequently cause patient discomfort [36, 37]. papaverine is an alternate hyperemic drug suited for intracoronary injection and it produces a stable hyperemic state required for the measurements of mean transit time and IMR. (38)

In this thesis, we report the incidence, clinical and ECG characteristics of patients with papaverine-induced VAs.

Outline of the Thesis

The thesis is presented as chapters

In chapter 1 we evaluated the viability, accuracy, and reproducibility of IMR measurement using intracoronary papaverine and IV adenosine as the reference standard. We found that the use of papaverine as a hyperemic agent resulted in shorter procedure times, improved reproducibility of IMR, and was more comfortable for the patient. IMR with intracoronary papaverine was feasible and offered similar IMR results to those achieved using intravenous adenosine.

In Chapter 2 we evaluated the safety of papaverine as a hyperemic agent. Nakayama et al. demonstrated papaverine to cause ventricular arrhythmias, specifically torsade de pointes, in about 2.8% and ventricular fibrillation in 1.7%of patients. The limitations of this study was a small number pf patients included in the study. In our study we included 2152 pts in 898 days of these patients 0.9% patients developed VTAs.

Chapter 3 describes stable hyperemic state duration and vessel-specific dose-response stratified by the severity of coronary artery disease of papaverine. Several studies have verified the use of papaverine for FFR assessments. Despite having a reasonably long duration of action, a thorough analysis was lacking. We showed in our study that Papaverine administered intracoronarily causes hyperemia with a rapid onset and a steady-state, long enough for pullback maneuvers with little fluctuation. In arteries with hemodynamically significant lesions, the steady-state hyperemia lasts longer.

Chapter 4 to 7. These chapters of the thesis are a compilation of our research projects that focused into the constraints of invasive physiology-based assessment of coronary stenoses in patients with particular comorbidities, frequently linked to coronary artery disease.

Chapter 8 In this chapter, we presented studies that advance our understanding of the distribution of atherosclerosis in coronary artery disease (CAD). Pullback curves were constructed using motorized hyperemic pullbacks of a pressure wire, and a new metric of

the focality (or diffuseness) of the disease was introduced (Pullback pressure gradient index, PPG index).

Several studies have verified the use of papaverine for FFR assessments. Despite having a reasonably long duration of action, a thorough analysis of the stable hyperemic state duration and vessel-specific dose-response stratified by the severity of coronary artery disease is still unavailable.

Chapters 9-11. This section of the thesis contains a collection of research projects that use continuous thermodilution (Absolute flow and resistance) techniques to assess coronary microvascular function. Chapter 9 is a state-of-the-art review on coronary thermodilution. Chapter 11 reports normal values of thermodilution-derived absolute flow and resistance, and show the feasibility of resting coronary flow calculation by continuous thermodilution.

Chapter 1

Simplified Assessment of the Index of Microvascular Resistance.

Background

The IMR method is based on the mean transit time calculated from bolus thermodilution during pharmacologically induced hyperemia. An abnormal IMR of >25 units is a diagnostic criterion for microvascular angina. Intravenous (IV) adenosine has long been the preferred hyperemic drug in the catheterization lab.

However, in order to achieve a consistent and sustained adenosine hyperemic response, this necessitates longer infusions, which frequently cause patient discomfort.

Papaverine is an alternative to adenosine and it produces stable hyperemic platue required to measure IMR.

Using intracoronary papaverine and IV adenosine as the reference standard, we aimed to evaluate the feasibility, accuracy, and reproducibility of IMR measurement.

Methods

29 patients were included in the study. The 3 measurements of IMR and CRF are performed using ic papaverine and hyperemic agent and the next 3 measurements are performed using intravenous adenosin. The ratio between the distal coronary pressure
and aortic pressure (Pd/Pa) was recorded. Fractional flow reserve and Pd/Pa values from the first measurements of both IC papaverine and IV adenosine are presented for the current analysis.

Results

IMR measurements using IC papaverine showed excellent reproducibility (mean difference −0.34, limits of agreement −5.93 to 5.26, and ICC of 0.93 (95% CI 0.87 to 0.96) compared to adenosine. Pa was reduced by both papaverine and adenosine. When IC papaverine was used instead of IV adenosine, the time needed to perform CFR/IMR measurements was significantly shortened (3.23 (2.84, 3.78) mins vs. 5.48 (4.94, 7.09) mins; p 0.0001). Neither

papaverine nor adenosine administration resulted in any complications. None of the individuals displayed any symptoms when papaverine was being administered. 31% of patients reported experiencing shortness of breath during the IV adenosine administration, while 82% reported chest pain.

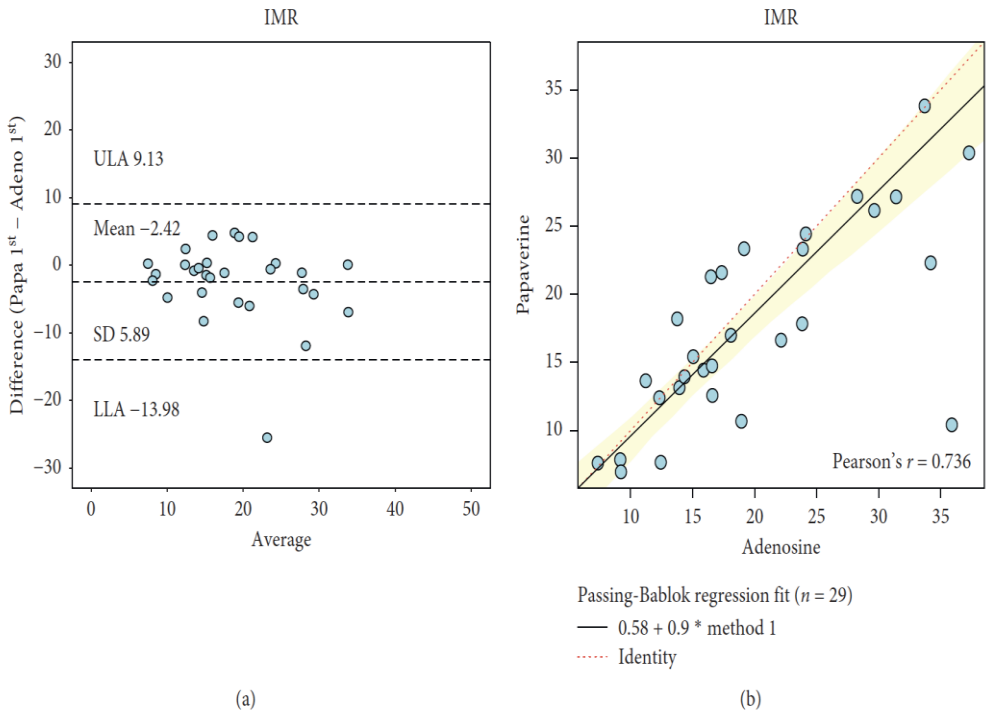


FIGURE 1: Agreement on IMR between papaverine and adenosine. (a) Bland–Altman plot of IMR measured with papaverine and adenosine. (b) Passing-Bablok regression of IMR measured with papaverine and adenosine.

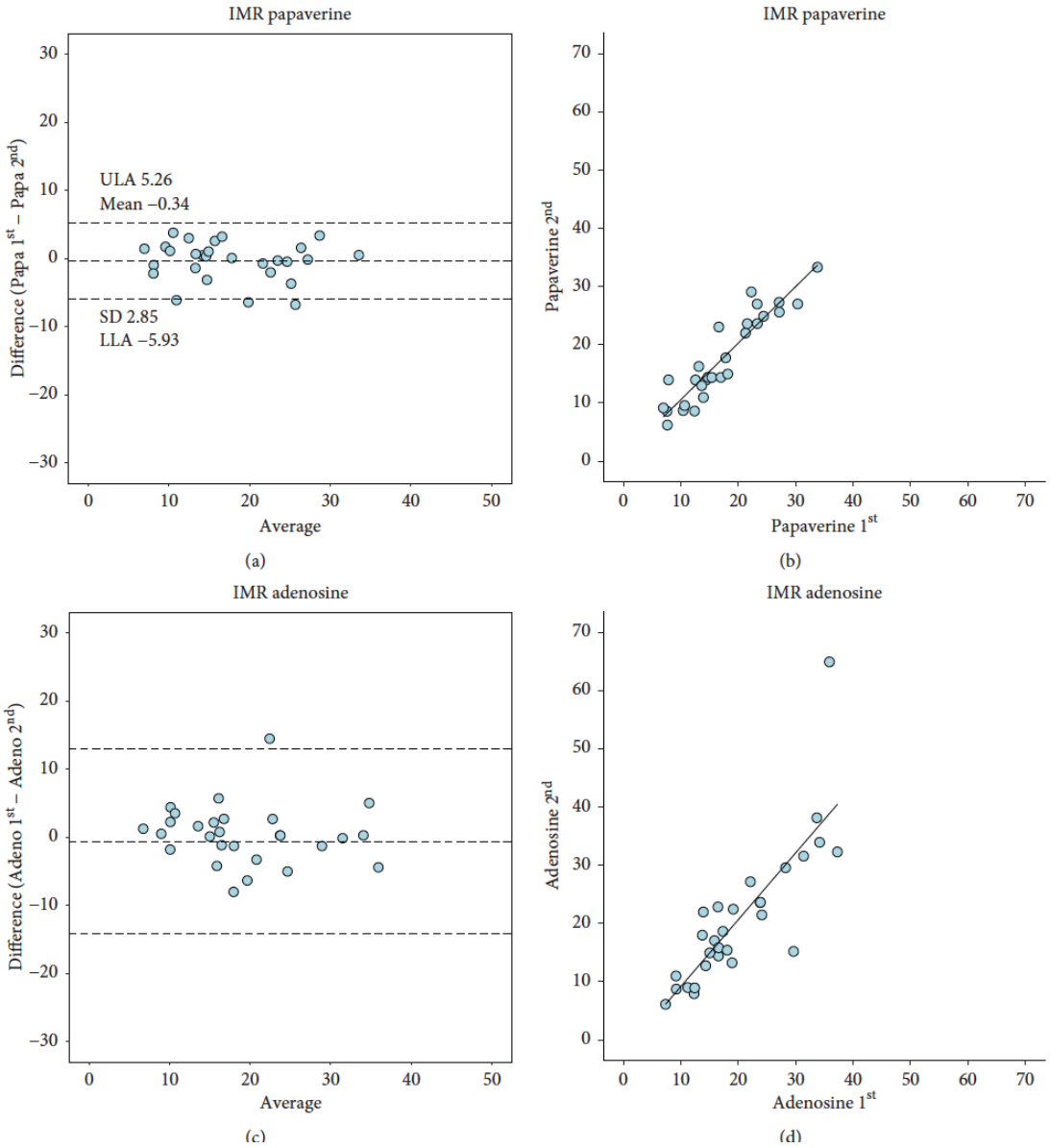


Figure 2 Reproducibility of IMR obtained with IC papaverine and IV adenosine. (a) Bland–Altman plot of IMR with repeated measures of papaverine. (b) Correlation of IMR measured with repeated measures of papaverine. (c) Bland–Altman plot of IMR measured with repeated measures of adenosine. (d) Correlation of IMR measured with repeated measures of adenosine. IMR, index of microvascular resistance; IC, intracoronary; IV, intravenous; Papa 1st, first injection of papaverine; Papa 2nd, second injection of papaverine; Adeno 1st, first injection of adenosine; Adeno 2nd, second injection of adenosine.

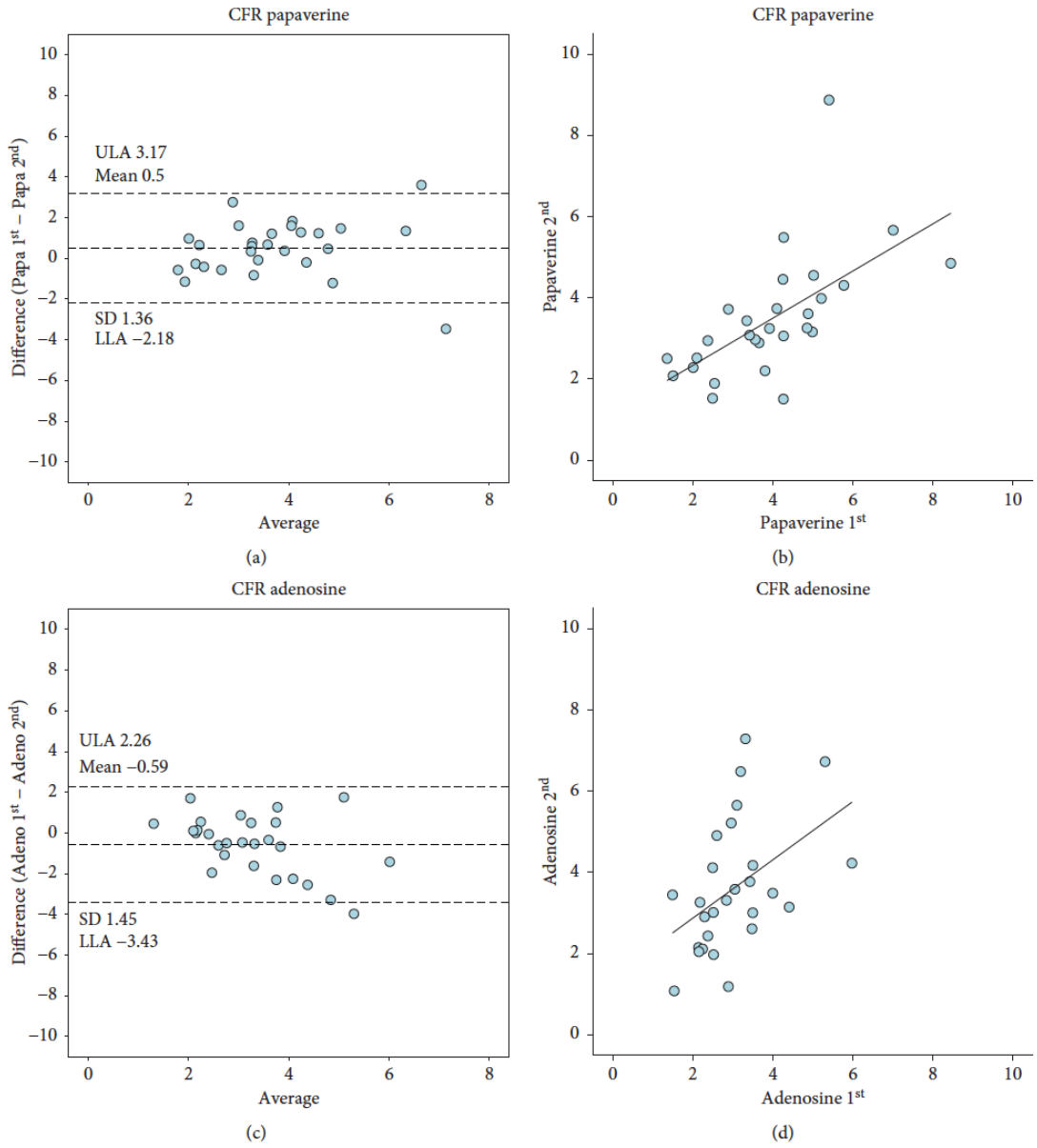


Figure 3 Reproducibility of CFR obtained with IC papaverine and IV adenosine. (a) Bland–Altman plot of CFR with repeated measures of papaverine. (b) Correlation of CFR measured with repeated measures of papaverine. (c) Bland–Altman plot of CFR measured with repeated measures of adenosine. (d) Correlation of CFR measured with repeated measures of adenosine. IMR, index of microvascular resistance; IC, intracoronary; IV, intravenous; Papa 1st, first injection of papaverine; Papa 2nd, second injection of papaverine; Adeno 1st, first injection of adenosine; Adeno 2nd, second injection of adenosine

Conclusion

It was feasible to evaluate IMR using intracoronary papaverine, and the results were comparable to those obtained using intravenous adenosine. Papaverine was used as a hyperemic drug, which shortened procedure times, increased IMR reproducibility, and improved patient comfort. The invasive evaluation of the coronary microcirculation in the catheterization laboratory is made simpler by using intracoronary papaverine for the measurement of IMR, which could result in an increase in the use of invasive microcirculation resistance measurements.

Chapter 2

Incidence of papaverine induced ventricular tachyarrhythmias

Background

Fractional flow reserve (FFR) is considered the standard for assessment of the physiological significance of coronary artery stenosis. Intracoronary papaverine (PAP) is the most potent vasodilator used for the achievement of maximal hyperaemia, however it may provoke ventricular arrythmias.

The incidence of papaverine-induced VT-VF has not yet been clarified. Some of the previous reports are only case reports, and in others, the incidence of VT/VF ranges from 2.3% to 8.8% when papaverine was administered into the coronary artery at 6–20 mg.[14–20] In one of these reports,[16] papaverine was administered for FFR study in 102 patients and polymorphic VT was induced in 3 (1.9%); QT interval prolongation and poor coronary reserve were considered risks for VT. In the literature we located 27 patients who developed VF by intracoronary papaverine administration.[12–21] Of these, 18 (66.7%) were women.

In our study we evaluated the clinical efficacy and safety of the administration of papaverine for optimal FFR measurement.

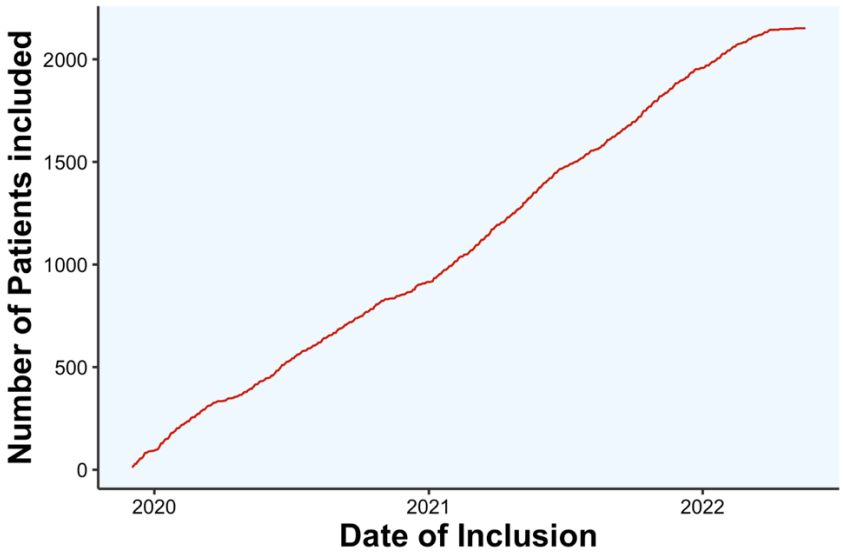
Methods

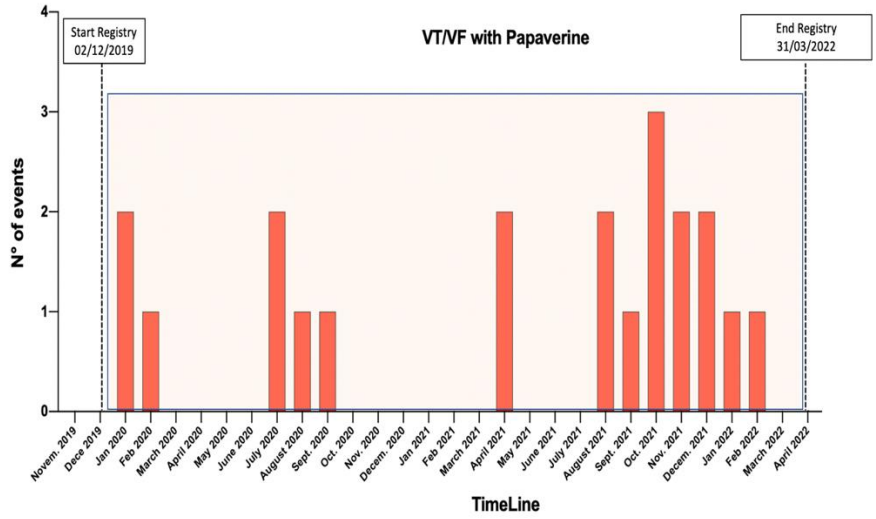
It is a single centre prospective allcomers papaverine study. Between December 2019 and March 2022, 2152pts had be included prospectively in our study. Patient undergoing coronary angiography with in indication for FFR and IMR have be included in the study. Patients with unstable angina acute coronary syndromes and acute heart failure have been excluded. Papaverine had be administered according to the standard protocol of the cathlab. Patients ECG have been recorded and all the arrythmias and symptoms post papaverine administration has be recorded in the CASTOR EDC database prospectively. The bold of the patients with arrythmia has been collected for further genetic testing.

Results

The mean age was 68.3±10.1 years, and majority were men 1502 (71%). The patient's laboratory data were normal, and the majority had hypertension (68%) and dyslipidaemia (80%). The baseline ECG was comparable in all the patients. The mean left ventricular ejection fraction was normal (57.3±7.5%). Predominantly patients presented with stable angina (90%). 21 patients (0.98%) developed VTA post papaverine administration. 14 patients (67%) are female. VT occurred in 5 pts (23%) , Ventricular fibrillation(VF) in 3 pts (14%) and Polymorphic VT (torsade de pointes TDP) in 13 pts(62%). Of those 15 pts (71%) required electric cardioversion for termination of VT. At vessel level in LM n=1(0.98%), in LAD n=13, in LCX n=4, in RCA n=3. 402 patients underwent revascularization and 1757 patients are deferred from PCI. Altogether 3pts (0.1%) vomited. 29 pts (1.4%) had chest discomfort. 9 pts (0.4%) had dyspnoe. There were no reported deaths. Majority of VTA's occurred in pts with LAD (14pts 67%) assessment.

Using adjusted logistic regression, the odds ratio (OR) of developing VTA in males compared to females is 0.12 (0.04-0.28, p<0.001). In addition, non-dyslipidemia (OR 0.38 (0.17-0.87, p=0.018), no non aspirin users (OR 0.36 (0.15-0.81, p=0.016) and lower diastolic blood pressure (OR 0.96 (0.93-0.99, p=0.015) are at an increased risk of developing papaverine induced VTA's.





Conclusion

Although rare, intracoronary administration of papaverine may induce ventricular attythmias. Female sex, non dyslipidemia, non aspirin use, lower diastolic blood pressure are associated with higher incidence of developing papaverine induced ventricular tachyarrhythmias

Part 2 of the study

Genetic analysis of the Patients with Papaverine induced VTAs

Background

FFR measurements require maximal hyperemia for the assessment of intermediate coronary artery stenosis. Papaverine is a potent vasodilator which produce stable hyperemia. However, it can cause malignant ventricular tachyarrhythmia (VTA). The purpose of this genetic substudy is to assess whether the occurrence of VTA as a result of

papaverine administration is associated with genetic variants in genes linked to cardiac arrhythmias.

Methods and Results

In our prospective, single-center, single-arm, and all-comers study that included 2,152 patients genetic testing was performed in 21 patients who exhibited papaverine induced ventricular arrythmias. In these patients full exome sequencing and related analyses of genetic variants in genes linked to cardiac arrhythmias was performed. In these we found four variants of uncertain significance (VUS) in the SCN5A gene encoding the cardiac sodium channel Na V 1.5 in three patients. In one patient the point mutation was of unknown allele frequency and the public archive of reports of the relationships among human variations and phenotypes (ClinVar) reported VUS for Brugada syndrome (BrS). Another VUS shoed a allele frequency of 0.2% ClinVar reported conflicting interpretations of pathogenicity. In the 3 rd patient two SCN5A variants with an allele frequency of 0.001% were identified and ClinVar reported VUS for BrS or VUS for various cardiac conditions. In total, the frequency of SCN5A variants were higher in the 21 patients than the probability in the normal population. Therefore, an association of SCN5A mutations and papaverine-induced VTA is reasonable. Functional studies using two-electrode voltage clamp and patch-clamp of heterologously expressed Na V 1.5 variants are currently in progress. Preliminary results show that one variant exhibits delayed recovery from inactivation after papaverine application compared with the wild-type Na V 1.5.

Conclusion

In patients who exhibited papaverine induced ventricular arrythmias the frequency of genetic SCN5A variants was higher than in the normal population. So far, four Na V 1.5 variants were identified and ClinVar queries suggest a relationship with BrS or cardiac conditions. Our preliminary data suggest that a subset of papaverine induced ventricular arrythmias is related to genetic variants of SCN5A encoding the cardiac sodium channel Na V 1.5.

Chapter 3
Duration of Hyperemia With Intracoronary Administration of Papaverine

Background

In clinical practice, two hyperemic indices—fractional flow reserve (FFR) and pressure pullback gradient (PPG)—are utilized to assess the hemodynamic significance of coronary stenoses and the distribution of epicardial resistance which require stable hyperemia for the measurements.

Several studies have verified the use of papaverine for FFR. Despite having a reasonably lengthy duration of action, a thorough examination of the stable hyperemic state duration and vessel-specific dose-response stratified by the severity of coronary artery disease is still unavailable.

Methods

46 patients (51 vessels) were included in the study. There were 8 right coronary arteries, 32 left anterior descending coronary arteries, and 11 left circumflex coronary arteries among the vessel types. Patients with intermediacoronary artery stenosis were included in the study. Hyperemia was induced with intracoronary papaverine. The time to maximal hyperemia, the minimal value of Pd/Pa after the injection of papaverine and plateau phase were computed.

Results

The plateau phase lasted 40.5 (IQR 22.2-49.8) seconds. When compared to vessels with an FFR value >0.80, the median plateau phase was substantially longer in vessels with an FFR value ≤0.80 (43.6 [IQR 36.1-60.7] seconds versus 32.6 [IQR 18.3-42.1] seconds). The time to 90% of the hyperemic onset was 12.4 (IQR 8.8-19.2) seconds in the current study utilizing standardized papaverine doses, and the duration of the hyperemic plateau was 43.6 (IQR 36.1-60.7) seconds.

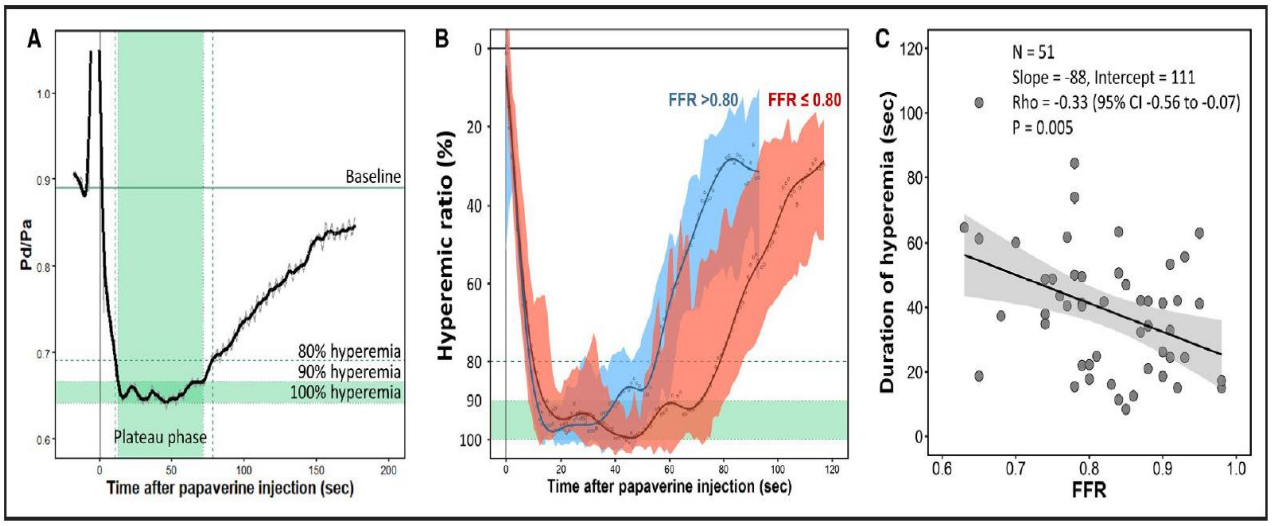


Figure. Case example of a pressure tracing after induction of hyperemia with papaverine and duration of hyperemic effect stratified by FFR.

A, An Pd/Pa tracing after the administration of intracoronary papaverine. The dashed green lines denote the plateau phase and 80%, 90%, and 100% of maximal hyperemia. The solid green areas represent the plateau phase. **B**, The duration of hyperemic plateau stratified by FFR 0.80. Pd/Pa values in the vessel with FFR ≤0.80 and FFR >0.80 are shown by red and blue curves, respectively; the shaded red and blue areas correspond to the 95% CIs. The solid green area represents the plateau phase. **C**, Correlation between distal FFR value and duration of maximal hyperemia. The gray area corresponds to the 95% CIs. FFR indicates fractional flow reserve; Pa, aortic pressure; and Pd, diastolic pressure.

Conclusion

Intracoronary administration of papaverine produces hyperemia with a rapid onset and a steady-state duration long enough for pullback maneuvers with little fluctuation. In arteries with hemodynamically significant lesions, the steady-state hyperemia lasts longer.

Chapter 4

Fractional flow reserve in patients with reduced ejection fraction

Background

In patients with lower ejection fraction and concomitant coronary artery disease, fractional flow reserve (FFR) has never been studied (CAD). We assessed the effect of FFR on these patients' management techniques and associated outcomes.

Methods

From 2002 to 2010, all consecutive patients with left ventricular ejection fraction (LVEF) ≤ 50% who underwent coronary angiography and had at least one intermediate coronary stenosis (DS% 50-70%), were screened for inclusion in one of two groups: those whose treatment was guided by angiography (the angiography-guided group) or by FFR (the FFR-guided group).

Results

866 current patients in the Angiography-guided group were matched with 433 patients in the FFR-guided group. 617 control patients with LVEFs greater than 50% were included for outcome comparison. In comparison to the angiography-guided group, the average number of stenotic arteries per patient considerably downgraded after FFR (1.43 0.98 vs. 1.97 0.84; P 0.001). This resulted in significantly less revascularization [225 (52%) vs. 535 (62%); P 0.001] as compared to the angiography-guided group. Percutaneous coronary intervention was more frequent in the FFR-guided group [155 (36%) vs. 261 (30%) of the Angiography-guided group; P = 0.039]; whereas CABG was more frequent in the Angiography-guided group [274 (32%) vs. 70 (16%) of the FFR-guided group, P < 0.001]. The frequency of deferrals to medical therapy was higher in the FFR guided group (208 (48%) vs. 331 (38%); P<0.001] (Figure 22).

The FFR-guided group had a considerably lower all-cause death rate at 5 years of follow-up [22% vs. 31%] than the Angiography-guided group. HR (95% CI) 0.64 (0.51- 0.81); P < 0.001]. The rate of major adverse cardiovascular and cerebrovascular events (MACCEs, which are a composite of all-cause death, myocardial infarction, revascularization, and

stroke) was also considerably lower in the FFR-guided group, at 40% vs. 46% in the Angiography-guided group. HR (95% CI) 0.81 (0.67-0.97); P = 0.019]. Patients with lower LVEF experienced higher death and MACCE rates compared to the control cohort (Figure 23). When stratifying by LVEF, the therapeutic benefit of the FFR-guided strategy in all-cause death was verified in patients with LVEF 35% (n = 419) and with LVEF > 35% (n = 852) (HR [95% CI] 0.48 [0.31-0.75] and 0.74 [0.56-0.98] respectively. There was only a trend in individuals with LVEF between 36% and 50% (HR [95% CI] 0.87 [0.71-1.08]), while an FFR-guided strategy was related with improved MACCE in patients with LVEF below 35% (HR [95% CI] 0.67 [0.47-0.94]). (Figure 24).

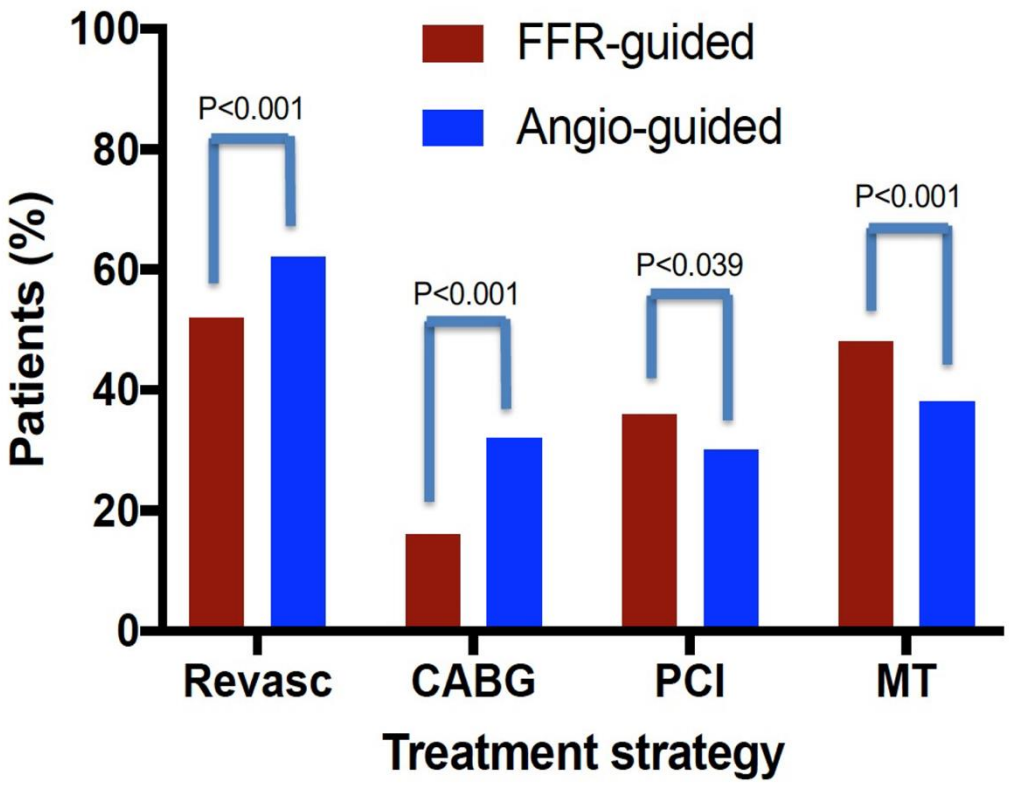


Figure 22. The difference in treatment strategies between fractional flow reserve- and Angiography-guided group. CABG, coronary artery bypass grafting; MT, medical therapy; PCI, percutaneous coronary intervention; Revasc, revascularization.

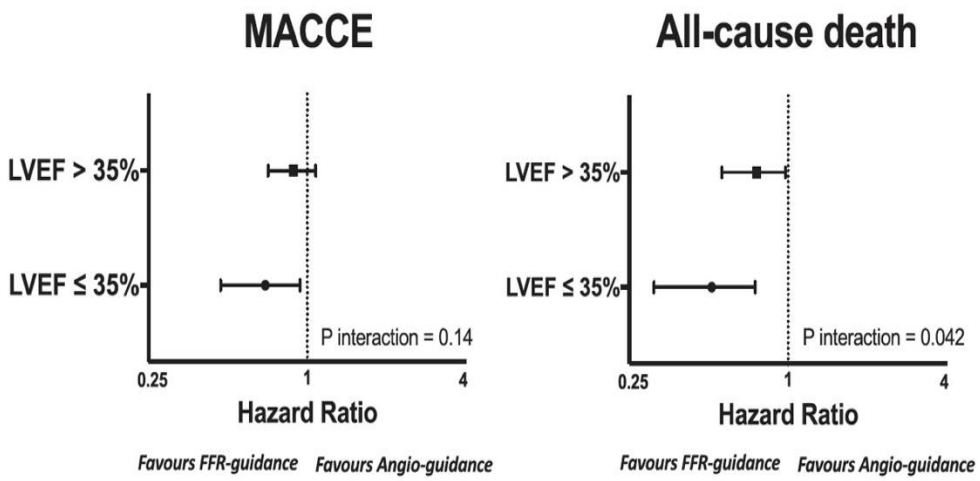


Figure 24. Impact of FFR on MACCE and all-cause death in patients with LVEF £ 35% and with LVEF 36% - 50%.

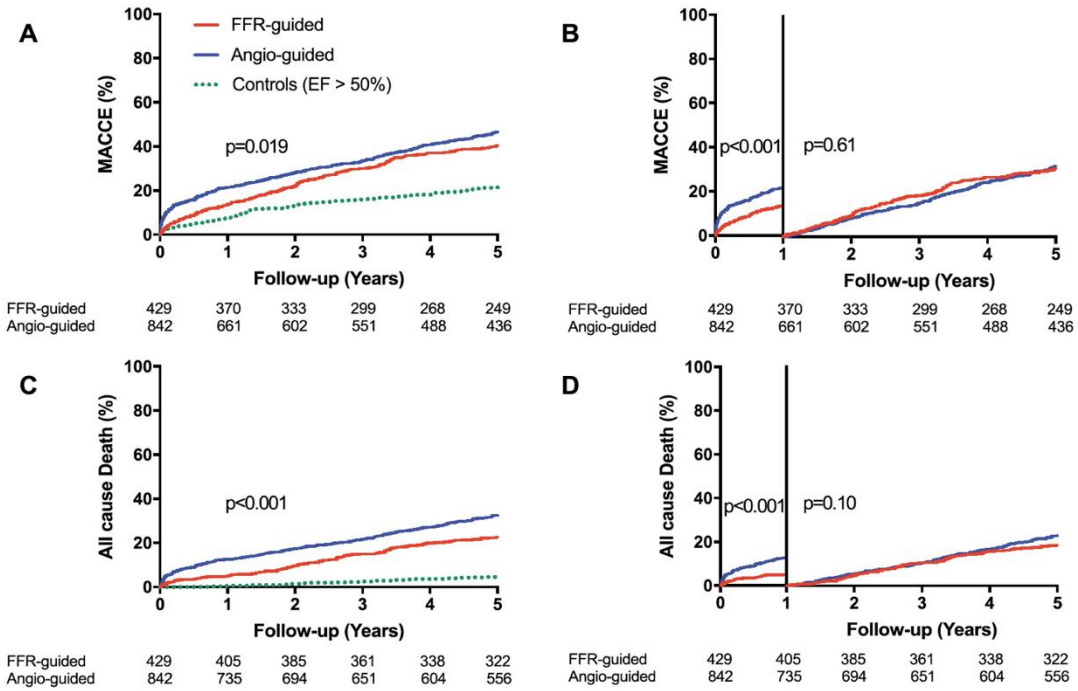


Figure 23. Cumulative incidences and landmark analysis for MACCE and all cause Death. Cumulative incidence of MACCE (A) and all-cause Death (C); landmark analysis before and after 1-year timepoint for MACCE (B) and all cause Death (D). The dotted green line represents the control cohort with preserved LVEF, for visual comparison. P values are referred to the FFR-guided and the Angiography-guided groups.

Conclusion

Compared to the Angiography-guided approach, FFR-guided revascularization was associated with reduced rates of death and MACCE at 5 years in patients with CAD and reduced LVEF. Less coronary artery bypass grafting and more patients deferral for percutaneous coronary intervention or medical treatment were also observed.

Chapter 5

Coronary Artery Bypass Grafting or Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Diabetic Patients with Multivessel Disease

Background

Contrary to percutaneous coronary revascularization (PCI), coronary artery bypass grafting (CABG) has demonstrated long-term advantages in diabetic patients with multivessel coronary disease (MVD). Although its impact in diabetic patients has never been studied, physiology-guided PCI has demonstrated to improve clinical outcomes in MVD. We compared the long-term clinical results of FFR-guided PCI to CABG in diabetic individuals with MVD.

Methods

4622 diabetic patients undergoing coronary angiography between 2010 and 2018 were assessed for inclusion. The requirement for inclusion was the existence of at least two-vessel disease, which was defined as having DS 50% and at least one intermediate stenosis (DS 30-70%) that had been treated or postponed in accordance with FFR. ST-segment elevation myocardial infarction, prior CABG, left main stenosis, and moderate or severe valvular heart disease necessitating surgical or percutaneous repair or replacement were the exclusion criteria. In order to account for baseline variations with a current cohort of patients treated with CABG, inverse probability of treatment weighting analysis was utilized. Major adverse cardiovascular and cerebrovascular events (MACCE), which are myocardial infarction, stroke, revascularization, and all-cause mortality, were the primary endpoint. Then, a multivariate unweighted cox-regression analysis was carried out utilizing the predictors as covariates. Then, using insulin therapy as a marker of diabetes severity and the predictors of 4-year mortality in the SYNTAX trial as variables, a multivariate unweighted cox-regression analysis was performed.

Results

The analysis comprised 418 patients in total. 209 of them had CABG and 209 received FFR-guided PCI. At 5 years, the FFR-guided PCI group had a greater incidence of MACCE than the CABG group (44.5% vs. 31.9%). HR [95% CI] 1.60 [1.15-2.22]; p = 0.005). The composite of all-cause mortality, MI, and stroke (28.8% vs. 27.5%) showed no difference. HR [95% CI] 1.05 [0.72-1.53]; p = 0.81). With FFR-guided PCI, repeat revascularization occurred more frequently (24.9% vs. 8.2%). HR [95% CI] 3.51 [1.93-6.40]; p < 0.001). After adjusting for age, sex, glomerular filtration rate, chronic obstructive pulmonary disease, peripheral vascular disease, left ventricular ejection fraction, Syntax score, and insulin medication, similar results were observed with multivariate cox-regression analysis.

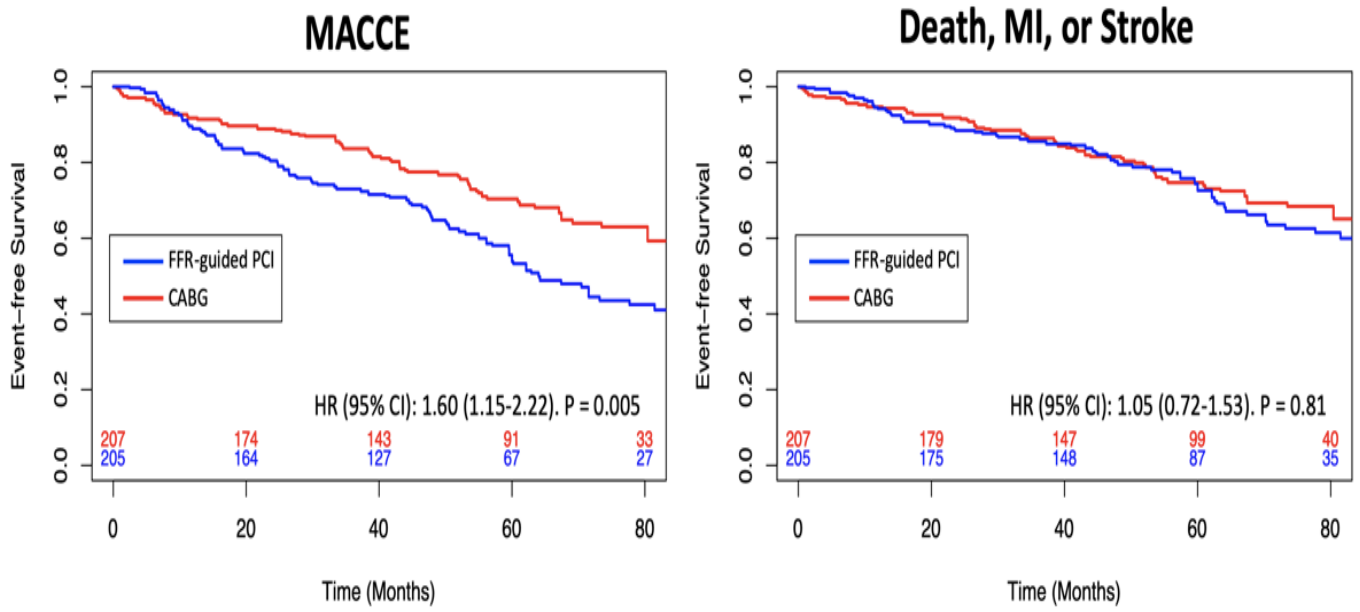
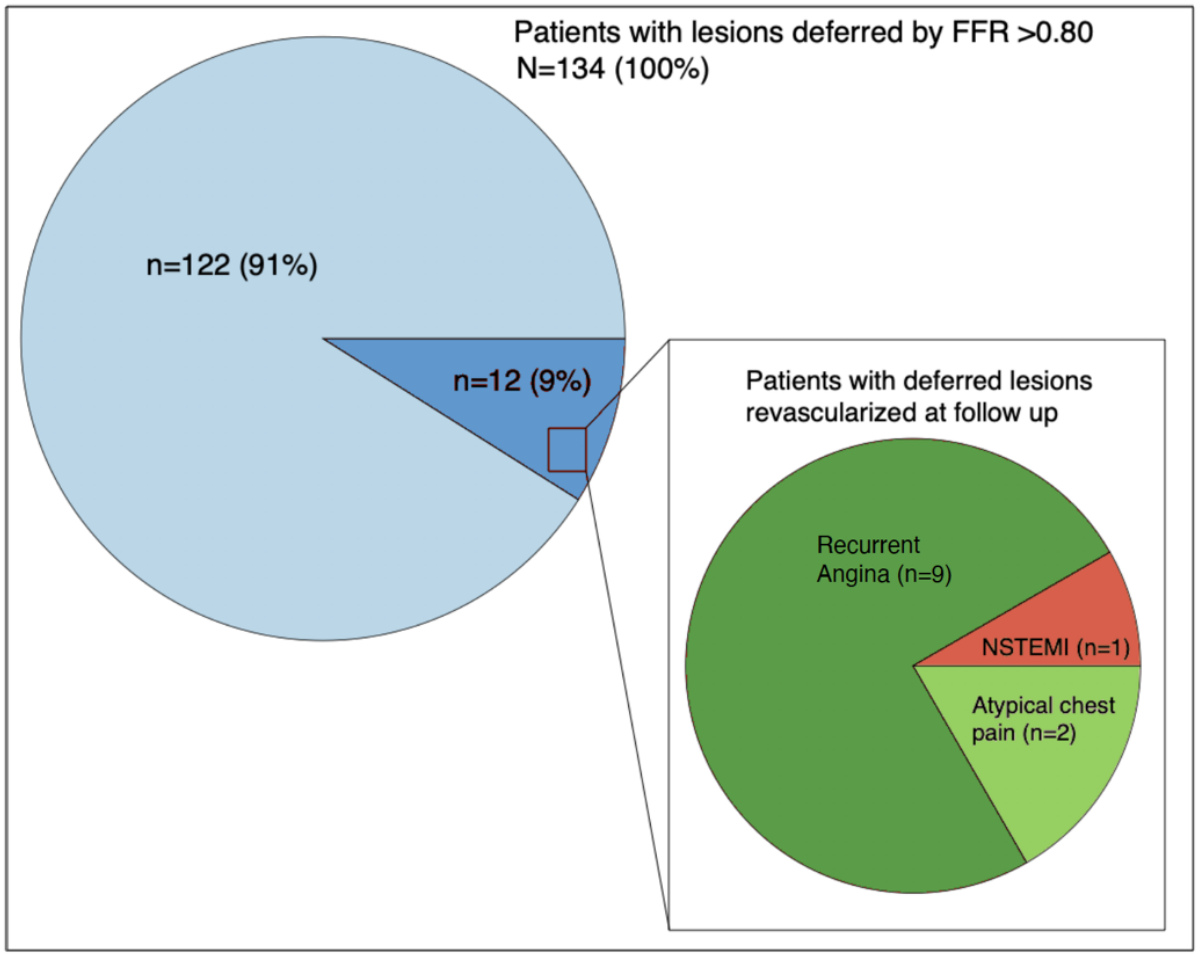


Fig: IPTW Adjusted Kaplan-Meier curves depicting event-free survival for MACCE and for the composite of all-cause death, MI, or stroke.

155 stenoses in 134 patients in the FFR-guided PCI group were deferred to medical therapy due to an FFR value > 0.80. At a follow-up of 46 (29-53) months, revascularization was performed for 13 lesions (8%) in 12 patients (9%) Recurrent angina was the cause of revascularization in 9 patients, NSTEMI in 1, and atypical chest pain in 2

patients who were referred for coronary angiography and revascularized despite no evidence of lesion progression on angiography (Figure below).



Revascularization events in lesions deferred to medical therapy on the basis of FFR >0.80 at the index procedure.

Conclusions

When compared to FFR-guided PCI, CABG was associated with a reduced rate of MACCE in diabetic patients with MVD. This difference was mostly due to a higher rate of repeat revascularization. Between CABG and FFR-guided PCI, there was no change in the composite of all-cause death, MI, or stroke at the 5-year follow-up.

Chapter 6

Heart failure with preserved ejection fraction or non-cardiac dyspnea in paroxysmal atrial fibrillation: The role of left atrial strain

Background

It can be difficult to diagnose heart failure with preserved ejection fraction (HFpEF) in people who have dyspnea and paroxysmal atrial fibrillation (AF). Left ventricular filling pressures and left atrial phasic function can be accurately estimated using left atrial strain (LAS) determined from speckle tracking. Nevertheless data on the clinical effectiveness of LAS in patients with AF and dyspnea are lacking. We assess relationship between LAS and probability of HFpEF in patients with dyspnea and paroxysmal AF.

Methods

The study included 205 consecutive patients (average age, 62 years old, 58% males) who had speckle tracking echocardiography and natriuretic peptide (NT-proBNP) measurement while in sinus rhythm and had limited dyspnea (NYHA II), paroxysmal AF, and intact LVEF (50%). Patients with cardiomyopathy and evident ischemic heart or valve disease were excluded. H2FPEF and HFA-PEFF scores, which integrate clinical features, echocardiographic data, and natriuretic peptides, were used to determine the probability of HFpEF.

Results

A total of 61 (30%), 115 (56%) and 29 (14%) patients had high, intermediate, and low probabilities of having HFpEF, respectively. In comparison to patients in low-to-intermediate probability groups, patients with high probability of HFpEF were substantially older, had higher body mass index, NT-proBNP, E/e', pulmonary artery pressure, and greater LA volume index (all p 0.05). There were found to be two different LA phasic function patterns. First off, reservoir LAS shown a strong unfavorable correlation with rising HFpEF likelihood. Second, in patients with high HFpEF probability,

contractile LAS showed an initial drop followed by a compensatory increase in the moderate probability category. LV overall longitudinal strain, however, was comparable between groups (NS). Reservoir LAS was found to be the best independent predictor of HFpEF determined by using both scores in multivariable regression analysis. Reservoir LAS shown sensitivity of 86% and specificity of 70% to identify high probability of HFpEF with an appropriate cut off value of 24%. The accuracy of any parameter alone was not improved by combining LAS with NT-proBNP.

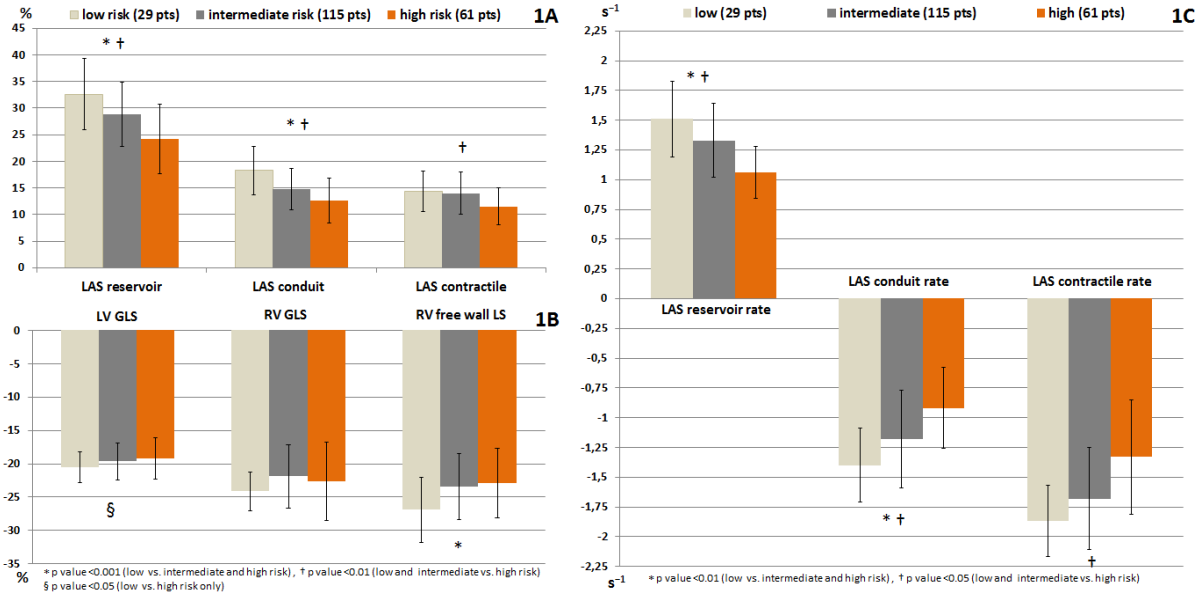


Figure 1: Change in value of LA phasic strain (LAS) and strain rate in three groups of patients based on HFA-PEFF risk scores.

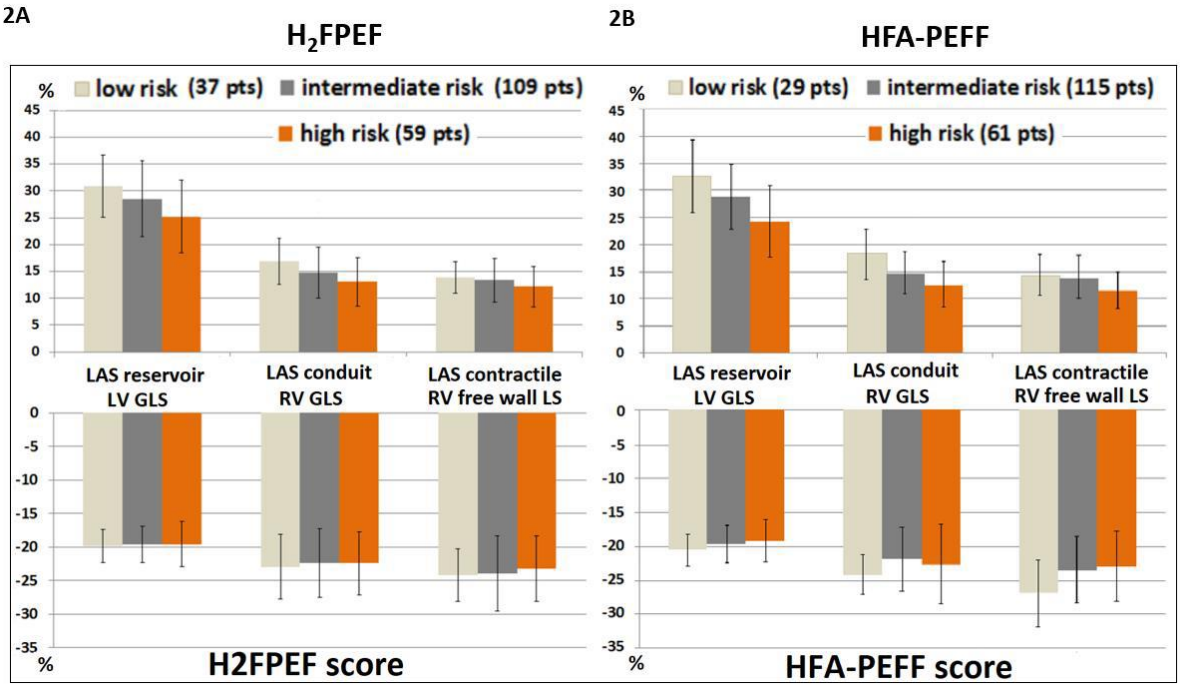


Figure 2. RV, LV and LA phasic strain in patients with low, intermediate and high probablity of HFpEF defined by the H2FPEF (2A) and the HFA-PEFF (2B) scores.

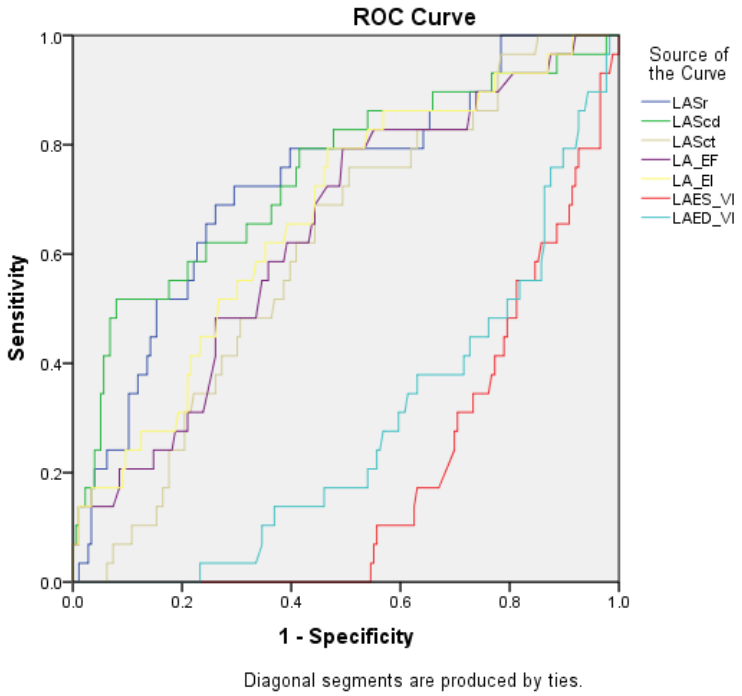


Figure 3: Receiver operating characteristics curves of left atrial (LA) volume and strain derived; LAED_VI; LA end-diastolic volume index; LAES_VI, LA end-systolic volume index; LA_EI, LA expansion index; LA_EF, LA emptying fraction; LASr, LA reservoir

strain; LAScd, LA conduit strain and LASct, LA contractile strain to predict the high risk of developing HF

Conclusion

Using both scores in a multivariable regression analysis, reservoir LAS was discovered to be the best independent predictor of HFpEF. Reservoir LAS demonstrated a suitable cut off value of 24% with a sensitivity of 86% and specificity of 70% to diagnose high risk of HFpEF. The combination of LAS with NT-proBNP did not increase the accuracy of any parameter when used alone.

Chapter 7

Vessel Fractional Flow Reserve and Graft Vasculopathy in Heart Transplant Recipients

Introduction

Cardiac transplant-related arteriopathy remains a leading cause of morbidity and mortality in heart transplant recipients with one in 3 patients developing cardiac allograft vasculopathy (CAV) in the first 5 years after heart transplantation. In contrast to the focal, proximal epicardial lesions in atherosclerosis, CAV affects both epicardial and intramural vessels and is characterized by progressive intimal proliferation in its early stage and by luminal narrowing and microvascular dysfunction in its later stage. Its etiology is likely complex and is thought to involve an interplay between immunologic (human leukocyte antigen and other mismatches), infectious (cytomegalovirus and others), and classical atherosclerotic risk factors (lipid status, diabetes, and others). Nowadays, a grading system based on coronary angiography is recommended by the international society of
heart and lung transplantation (ISHLT) to evaluate the severity and extent of CAV [4]. However, coronary angiography lacks the resolution to diagnose early as well as diffuse stages of CAV, a limitation that has partly been overcome by more recent imaging techniques, such as intravascular ultrasound (IVUS). On his turn, however, IVUS findings are unable to assess the functional significance of vascular disease. In this regard, fractional flow reserve (FFR), an index to identify epicardial disease responsible for myocardial ischemia might be helpful. In heart transplant patients, an abnormal epicardial physiology on the basis of an FFR <0.90 predicts worse clinical outcome, defined by the cumulative survival free of death or retransplantation. While FFR can be measured during routine coronary angiography using a pressure sensor guidewire to calculate
the ratio between coronary pressure distal to a coronary artery stenosis and aortic pressure under conditions of hyperemia, FFR can also be computed from the 3-dimensional reconstruction of the coronary artery obtained from invasive coronary

angiography using computational fluid dynamics calculations or by a mathematical approach. Angiography-based FFR (vFFR) estimates have been shown to perform well against invasive FFR and have a high diagnostic performance against dichotomous FFR categorization. Angiography-based FFR (vFFR) estimates have been shown to perform well against invasive FFR and have a high
diagnostic performance against dichotomous FFR categorization. However, data on the use of vFFR in heart transplant recipients are lacking. (Therefore, the aim of the present study was to evaluate CAV by comparing the standard ISHLT grading system with functional vFFR measurements.

Methods

In HTx patients referred for annual check-up, undergoing surveillance COR, the extent of CAD was graded according to the criteria proposed by the international society of heart and lung transplantation (ISHLT). In addition, three-dimensional coronary geometries were constructed from COR to calculate pressure losses using vFFR.
Angiography-Derived FFR. (e angiography-derived FFR was performed using vessel FFR software (vFFR, CAAS 8.2 Software, Pie Medical Imaging, Maastricht, the Netherlands). For the calculation of vFFR, 2 projections of at least 30 degrees of difference in angulation/rotation are used to create a 3D reconstruction of the coronary artery. Temporal
alignment of the cardiac cycle was performed automatically by electrocardiogram (ECG) triggering. Contour detection was automatic, and manual correction was allowed and recorded. (e pressure drop was calculated by applying physical loss of blood behavior with patient-specific aortic pressure. vFFR was calculated as the ratio of distal coronary pressure to aortic pressure. vFFR values were obtained for each major native coronary vessel. (e most distal value was used for the analysis, and vFFR values ≤0.80 were considered as significant disease. In cases of the serial vFFR analysis, angiographies acquired
in projections with 30 degrees of the previous angiographies were utilized. vFFR values were visually matched using anatomical landmarks. For the patient-level analysis, the lowest vFFR value of the 3 major epicardial vessels was selected. Significant functional

progression was defined as change in vFFR higher than two standard deviation of the interobserver reproducibility [9]. All the analyses were performed by an independent core laboratory.

Results

In 65 HTx patients with a mean age of 53.7 ±10.1 years, 8.5 years (IQR 1.90, 15.2) years after HTx, a total number of 173 vessels (59 LAD, 61 LCX, and 53 RCA) were analyzed. (e mean vFFR was 0.84±0.15 and median was 0.88 (IQR 0.79, 0.94). A vFFR≤ 0.80 was present in 24 patients (48 vessels). HTx patients with a history of ischemic cardiomyopathy (ICMP) had numerically lower vFFR as compared to those with non-ICMP (0.70±0.22 vs. 0.79 ±0.13,
p ⁄0.06). (e use of vFFR reclassified 31.9% of patients compared to the anatomical ISHLT criteria. Despite a CAV score of 0, a pathological vFFR≤ 0.80 was detected in 8 patients (34.8%).

Table 3: Functional characteristics according to the CAV grade.

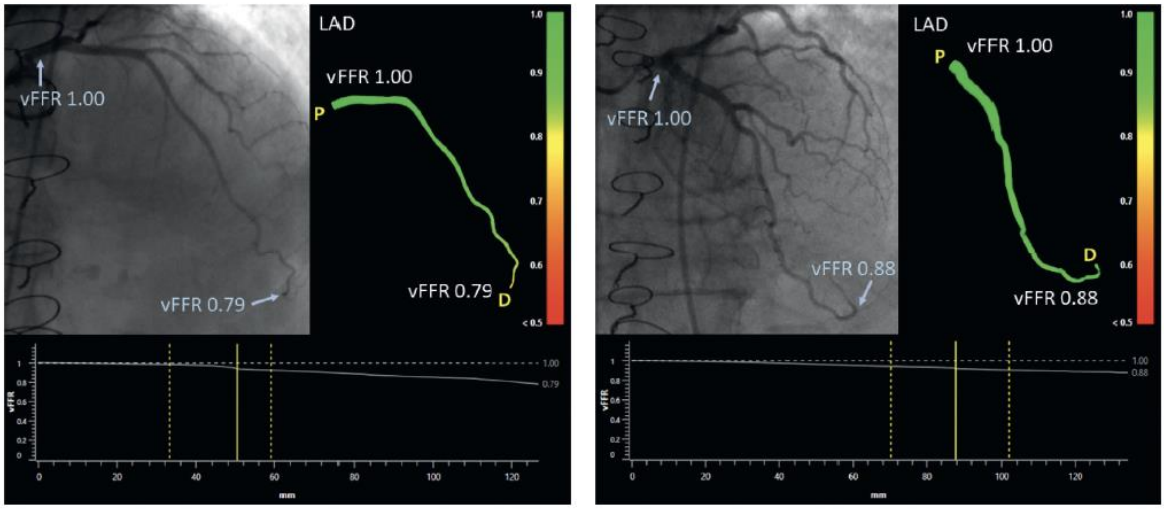
	CAV 0 ($n = 23$)	CAV 1 ($n = 12$)	CAV 2 ($n = 4$)	CAV 3 ($n = 8$)	p value
vFFR, median (IQR)	0.84 (0.80, 0.88)	0.76 (0.70, 0.89)	0.72 (0.53, 0.80)	0.54 (0.47, 0.78)	0.009
Lesion length (mm), median (IQR)	26.0 (14.7, 45.5)	22.2 (17.8, 30.0)	31.2 (29.0, 70.7)	36.2 (18.8, 48.4)	0.51
MLD (mm), median (IQR)	1.53 (1.26, 1.72)	1.65 (0.89, 1.73)	0.92 (0.88, 1.62)	0.80 (0.59, 1.38)	0.08
Diameter stenosis (%), median (IQR)	31.0 (25.0, 42.0)	36.0 (31.0, 43.0)	57.0 (56.5, 60.5)	64.0 (59.5, 72.5)	<0.001
Reference diameter (mm), median (IQR)	2.29 (2.03, 2.70)	2.51 (1.54, 2.79)	2.33 (2.23, 3.79)	2.88 (1.67, 3.51)	0.85

CAV, cardiac allograft vasculopathy; vFFR, vessel fractional flow reserve derived from angiography; IQR, interquartile range; and MLD, minimal lumen diameter.

Table 4: Agreement between the vFFR value and CAV score.

	vFFR > 0.80	vFFR ≤ 0.80	Total
CAV 0	15	8	23 (48.9)
CAV 1	6	6	12 (25.5)
CAV 2	1	3	4 (8.5)
CAV 3	0	8	8 (17.1)
Total	22 (46.8)	25 (53.2)	47

Values are n or n (%). vFFR, vessel fractional flow reserve derived from angiography; CAV, cardiac allograft vasculopathy.



(a) (b)

Figure 2: (a) Normal coronary angiogram with functionally significant CAV according to the vFFR analysis. The LAD shows no stenosis on angiography; however, the vFFR shows diffuse pressure losses, and the distal vFFR value is 0.79. (b) Normal angiogram without functionally significant CAV according to the vFFR analysis. The LAD shows no stenosis on angiography, and the vFFR shows small pressure losses resulting in a distal FFR value of 0.88. CAV, cardiac allograft vasculopathy; LAD, left anterior descending coronary artery; and vFFR, vessel fractional flow reserve.

Conclusion

The impairment in epicardial conductance assessed by vFFR in a subgroup of patients without CAV according to standard ISHLT criteria suggests the presence of a diffuse vasculopathy undetectable by conventional angiography. Therefore, we speculate that vFFR may be useful in risk stratification after HTx.

Chapter 8

Measurement of Hyperemic Pullback Pressure Gradients to Characterize Patterns of Coronary Atherosclerosis

Background

Diffuse atherosclerosis is frequently seen in segments with normal angiograms in affected patients with stable coronary artery disease (CAD). The distribution of epicardial resistance along the vessel can be evaluated using coronary physiology. This study's goal was to identify the pathophysiological patterns of CAD by invasive pressure pullbacks during contin hyperemia.Patients undergoing clinically indicated coronary angiography due to stable angina participated in this prospective, multicenter study. A pressure-wire pullback device was set at a speed of 1mm/s. Based on fractional flow reserve (FFR) pullback curve and coronary angiography, the CAD patterns were classified as either focused, diffuse, or both. The hyperemic pullback pressure gradients were used to characterize the epicardial resistance distribution. The PPG index, a continuous metric based on the magnitude of pressure drop over 20 mm and on the extent of functional disease, was computed to determine the pattern of CAD. Low PPG index indicates diffuse CAD.

The purpose of the present study was to characterize the pathophysiological patterns of CAD utilizing motorized coronary pressure pullbacks during continuous hyperemia and provide a quantitative assessment of the spatial distribution of the epicardial resistance in patients with stable CAD.

Methods

A pressure-wire pullback device with a speed of 1 mm/s was used in this prospective, multicenter study of patients undergoing clinically indicated coronary angiography due to stable angina. In summary, the pressure wire sensor was visually positioned in distal coronary segments with diameters greater than 2mm. To determine the pullback start

point, the pressure wire position was recorded using contrast injection. Invasive coronary pressures were measured using the RadiAnalyzer Xpress (St. Jude Medical, Minneapolis, Minnesota) and the QUANTIEN Integrated FFR System (Abbott Vascular, Abbott Park, Illinois). Following intracoronary nitrate administration, a 140 mg/kg/min continuous intravenous adenosine infusion was administered via a peripheral or central vein to achieve steady-state hyperemia for at least 2 minutes. A pullback device (Volcano R 100, San Francisco). A pullback device (Volcano R 100, San Diego, California), adapted to grip the coronary pressure wire (PressureWire X, St. Jude Medical), was set at a speed of 1 mm/s to pull back the pressure wire sensor up to the tip of the guiding catheter during continuous pressure recording. The maximum pullback length per vessel was 130 mm. If there was FFR drift (>0.03), the FFR pullback was repeated. An FFR value was extracted from the pressure tracing every 10 mm. FFR was defined as the ratio of between distal and proximal coronary pressures. FFR pullback curves were created and analysed by an independent core laboratory.

Based on coronary angiography and on the fractional flow reserve (FFR) pullback curve, the patterns of CAD were adjudicated as focal, diffuse, or a combination of both. The distribution of epicardial resistance was characterized using the hyperemic pullback pressure gradients (PPGs). The PPG index, a continuous metric based on the magnitude of pressure drop over 20 mm and on the extent of functional disease was computed to determine the pattern of CAD. Specifically, PPG index is defined as:

$$\frac{\left\{\frac{MaxPPG_{20mm}}{\Delta \mathrm{FFR}_{vessel}} + \left(1 - \frac{\text{Length with functional disease (mm)}}{\text{Total vessel length (mm)}}\right)\right\}}{2}$$

Maximal PPG was defined as the maximum pressure gradients over 20 mm, and delta FFR vessel as the

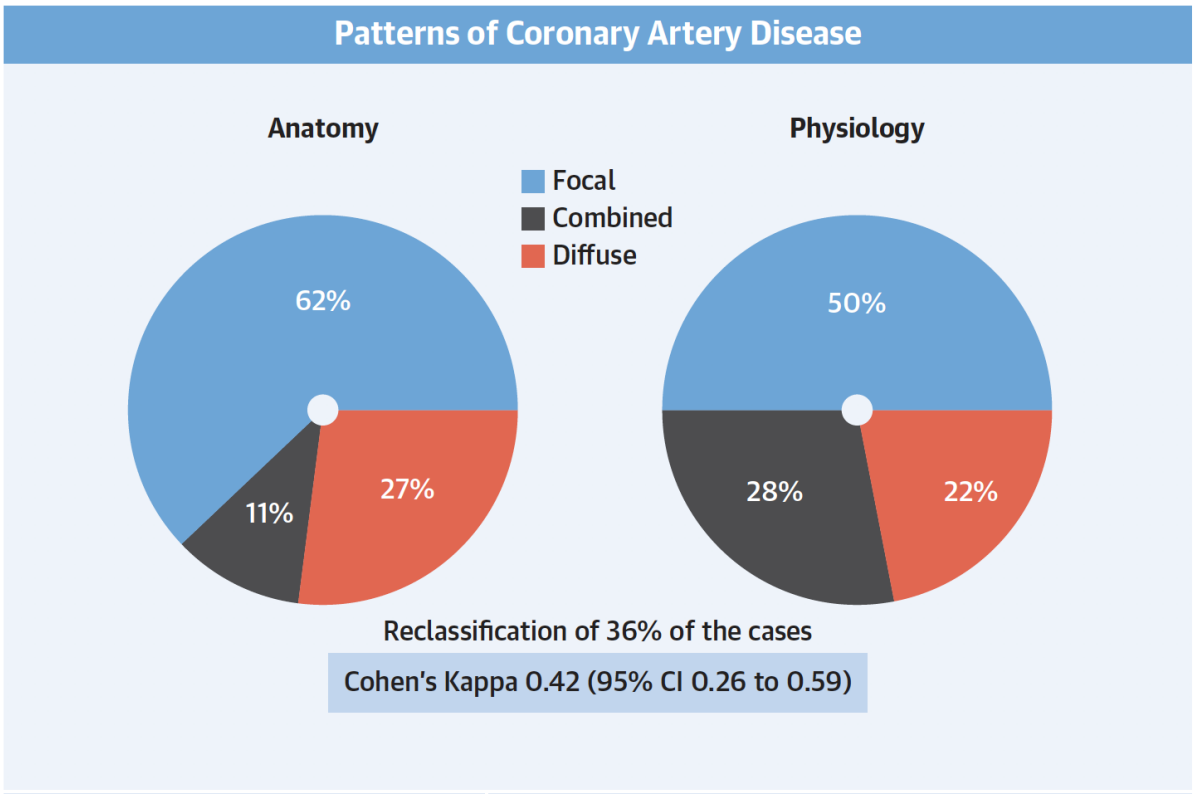
difference between FFR values obtained at the ostium of the vessel and at the most distal anatomical location.

The length of functional disease and the total vessel length were derived from the

motorized pullback pressure tracing. The length of functional CAD was defined as the length, in millimetres, with FFR drop ≥ 0.0015/mm. This cut-off was selected based on the analysis of curve variations in segments without functional disease. This was defined as FFR pullback curves with slope equal to zero. Subsequently, the 95th percentile of FFR curve variation was selected as the cut-off to minimize the effect of minor artifacts on this parameter. The combination of these 2 ratios was used to calculate the PPG index, a metric that characterizes the pattern of CAD based on coronary physiology. The PPG index is a continuous metric: values approaching 1.0 represent focal hemodynamically focal CAD, whereas values close to 0 diffuse CAD.

Results

A total of 158 vessels (117 patients) were included. Overall, 984.813 FFR values were used to generate 100 FFR pullback curves. Using coronary physiology, 36% of the vessel disease patterns were reclassified compared to angiography. The median of maximal PPG over 20 mm was 0.083 (interquartile range: 0.063 to 0.118) FFR units, and the mean extent of functional disease was 39.3 Å} 21.3 mm. The mean PPG index was 0.58 Å} 0.18 and differentiated pathophysiological focal and diffuse disease ($p < 0.001$).
Pathophysiological patterns of CAD can be characterized by motorized hyperemic PPGs. The
evaluation of the FFR pullback curve reclassified one-third of the vessels' disease patterns compared with conventional angiography. The PPG index is a novel metric that quantifies the distribution of epicardial resistance and discriminates focal from diffuse CAD.



		Anatomy		
		Diffuse	Combined	Focal
Physiology	Diffuse	10	0	9
	Combined	10	7	7
	Focal	3	2	37

Figure 1. Reclassification Between Anatomical and Physiological Assessment on the Pattern of CAD. The left pie chart presents the classification of the pattern and CAD based on coronary angiography (n = 85 vessels). The right pie chart shows declassification of the CAD patterns by visual assessment of the motorized FFR pullback curve. CAD = coronary artery disease; CI = confidence interval; FFR = fractional flow reserve.

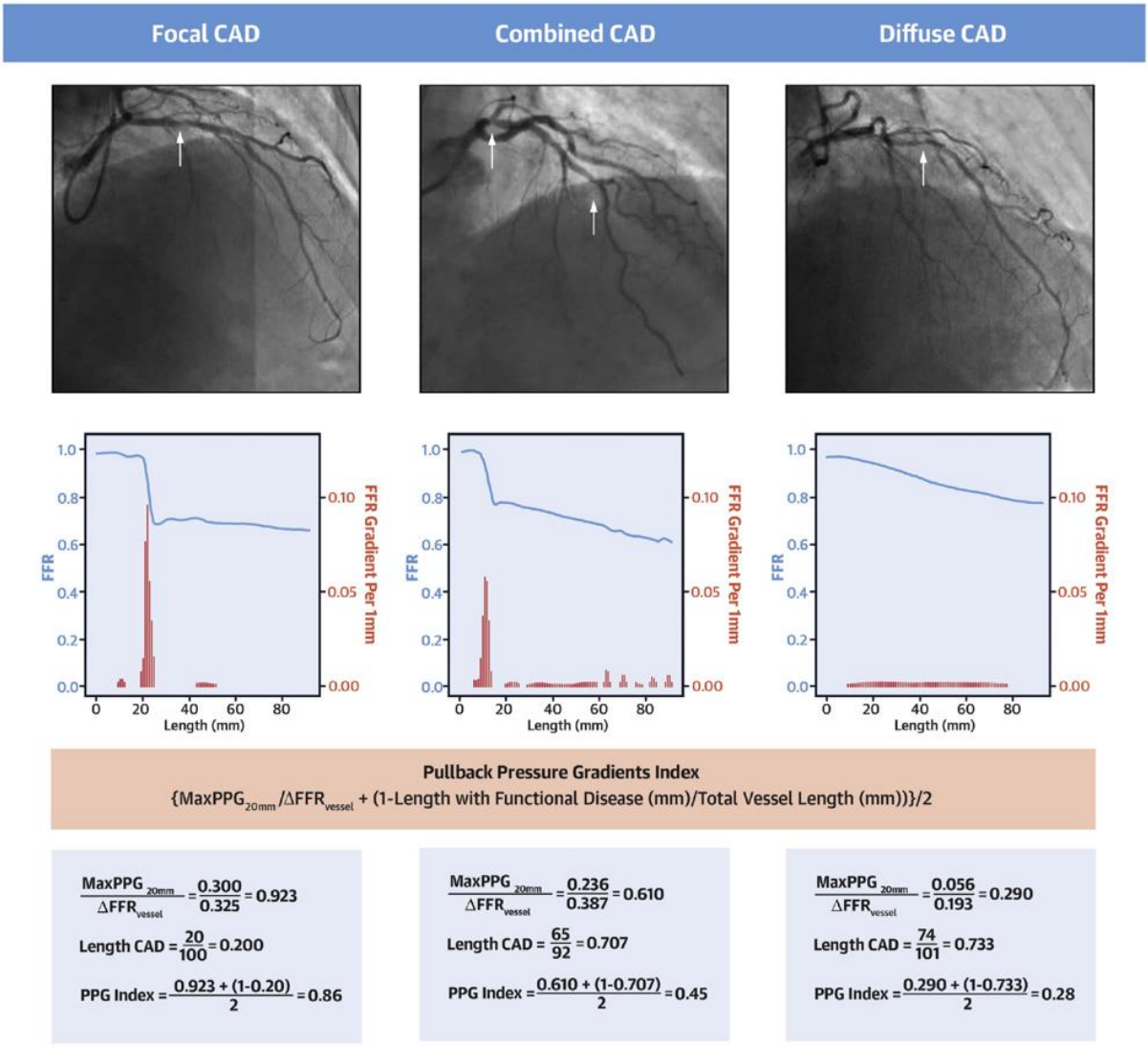
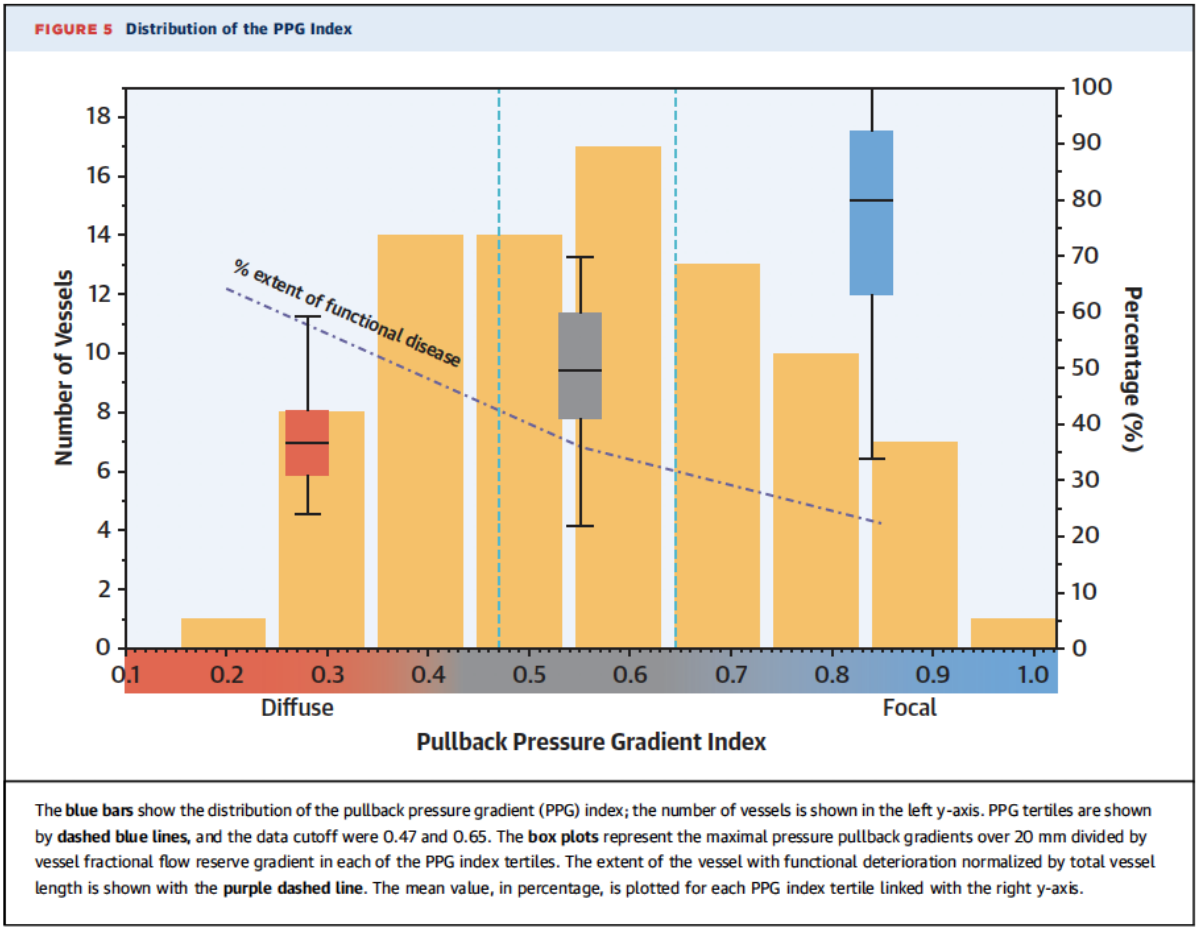


Figure 2. Pathophysiological Coronary Artery Disease Patterns and PPG Index. Three case examples depicting the pathophysiological patterns of CAD. (Top) Conventional coronary angiography; (middle) the FFR pullback curves; and histograms depicting the magnitude and extension of FFR drop; and (bottom) details of the PPG calculation. The red bars indicate FFR drops $0.0015. On the top left panel, the angiography shows a severe lesion in the mid LAD (white arrow) with a distal FFR of 0.68. This lesion produced an FFR drop responsible for 86% of the distal FFR with a maximum pullback pressure gradient over 20 mm of 0.30 FFR units. Only 20% of the vessel showed functional disease. The PPG index was 0.86, indicating physiological focal CAD. The top middle panel shows a severe lesion at the proximal LAD and a moderate lesion at mid LAD (white arrows). The maximum pullback pressure gradient over 20 mm was 0.236 FFR units, with 70.7% of the vessel length showing FFR deterioration, and the PPG index was 0.45. In the top right panel, an anatomical lesion at the mid LAD (white arrow) was observed with distal FFR of 0.78. The maximum pullback pressure gradient over 20 mm was 0.056, while 73.3% of the vessel length showed physiological disease. The PPG index was 0.28, indicating physiological diffuse CAD. CAD = coronary artery disease; FFR = fractional flow reserve; LAD = left anterior descending artery; PPG = pullback pressure gradient.



Conclusion

Motorized hyperemic PPGs can identify CAD pathophysiological patterns. When compared to traditional angiography, the FFR pullback curve reclassified one-third of the arteries' disease patterns. The PPG index is a novel metric that quantifies the distribution of epicardial resistance and discriminates focal from diffuse CAD.

Chapter 9

Basics of Coronary Thermodilution

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Introduction:

In patients with chest pain, coronary microvascular dysfunction (CMD) is highly prevalent. CMD causes or exacerbates ischemia in patients with or without obstructive coronary artery disease and is linked to poor clinical outcomes. CMD affects especially, although not only, women and deserves a targeted treatment. To understand the mechanisms regulating coronary blood flow, it is convenient to consider the coronary arterial circulation as a 2-compartment model. The epicardial compartment consists of conductance arteries with cross-sectional diameter >400 mm. They are visible on angiography and are often the site of obstructive atherosclerosis. Fractional flow reserve (FFR) is the metric of choice to quantify the functional significance of stenotic lesions in the epicardial arteries (9). The microcirculation includes vessels with cross-sectional diameter <400 mm. Small arteries and arterioles are resistive arteries and regulate myocardial blood flow supply. Capillaries form an interconnecting network, are made of 1 or 2 layers of endothelial cells surrounded by a basal membrane, and are in direct contact with the myofilament and their contractile apparatus, which they feed. The capillary bed is not considered a direct contributor to the resistance of the microvasculature. Although the microvasculature represents the major part of the volume of the coronary circulation, it remains poorly understood for at least 3 reasons: 1) it cannot be directly visualized; 2) there is no satisfactory animal model; and 3) microvascular resistance, its quintessential metric, has not until recently been quantified in absolute terms. In this review, we summarize the basic principles of indicatordilution techniques and focus on intracoronary thermodilution techniques that allow the assessment of microvascular resistance.

The general indicator-dilution theory

Virtually all approaches to measure cardiac output apply the principles of the indicator-dilution theory. An "indicator," in the sense used here, is a traceable substance or a physical property (e.g., temperature, concentration, pH) that makes it possible to quantify the flow of the fluid in which the indicator under study is diluted. Depending on the way the indicator is added to the fluid, there are 2 general methods for performing indicator dilution–based measurements. Either the indicator can be injected as a bolus or it can be infused continuously. In the remainder of this review, we focus on "cold" as the indicator. Saline at room temperature (i.e., colder than body temperature) can be injected as a bolus ("bolus thermodilution") or can be infused continuously at a fixed rate ("continuous thermodilution").

Thermodilution by bolus injection

When briskly injecting a bolus of saline, at a temperature lower than that of blood, through the guiding catheter, a V-shaped time-based temperature change can be recorded in the distal part of the artery. When the exact volume of the indicator is not known, Q (in ml/s) can be approximated by dividing the vascular volume (V; in ml) by the mean transit time of the indicator (Tmn; in s):

$$Q = V/Tmn$$

Vascular volume (V) is not known. However, assuming V to be constant during consecutive measurements and under hyperemic conditions, Tmn is an index of flow inversely proportional to flow:

$$Q \approx 1/Tmn$$

Therefore, coronary bolus thermodilution does not allow quantification of flow in milliliters per minute. As an index of flow, Tmn has been used to evaluate coronary flow reserve (CFR) and to calculate the index of microcirculatory resistance (IMR).

CFR represents the extent to which myocardial or coronary flow can increase above its baseline value. Accordingly, bolus thermodilution–derived CFR has been described as the ratio between resting and hyperemic Tmn:

CFRthermo = Qhyper/Qrest = Tmn,rest/Tmn,hyper

IMR has been introduced by Fearon as the first index to specifically address the microcirculation. By analogy with Ohm's law for electric resistance, the absolute minimal resistance (R) across the microvascular bed equals the ratio of the pressure gradient across a given vascular territory (DP; in mm Hg) divided by the hyperemic blood flow across this territory (Q; in ml/min):

$$R = \frac{\Delta P}{Q} \quad or \quad R = \text{)\_\_\_\_\_*/)0P}$$

where Pd is the pressure at the distal segment of a coronary artery and Pv is the coronary venous pressure. Assuming that Pv is negligible compared with Pd, and given Q z1/Tmn, equation 6 can be rearranged as follows:

$$R \approx \frac{Pd}{\frac{1}{Tmn}} \quad and \quad thus = Pd \cdot Tmn$$

An example of coronary bolus thermodilution measurement is reported in figure 55

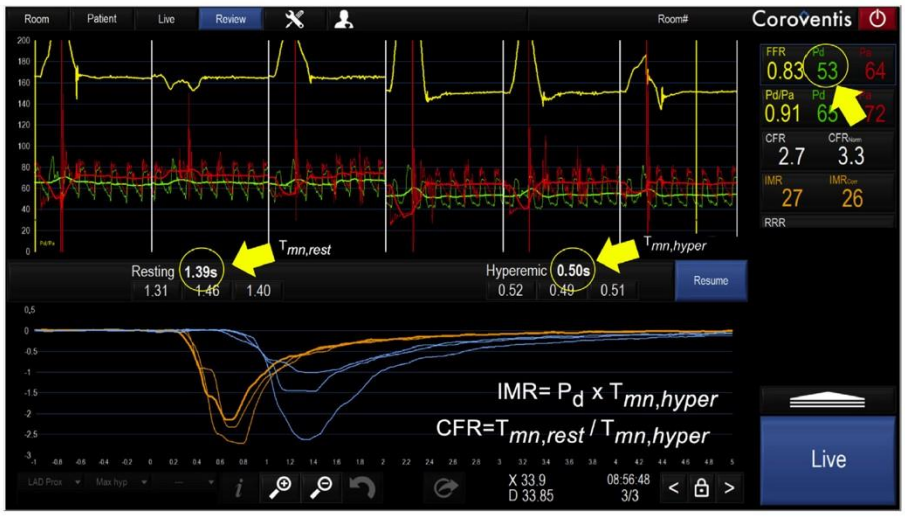

Figure 55. Illustration of simultaneous recordings of aortic pressure (Pa; red tracing), distal coronary pressure (Pd; green tracing), their ratio (Pd/Pa; yellow tracing), and intracoronary temperature after consecutive injections of 3 boluses at rest (blue tracings) and 3 boluses during steady-state hyperemia (orange tracings). Hyperemia can be induced by intravenous adenosine or intracoronary papaverine. These recordings allow simultaneous measurement of fractional flow reserve (FFR), coronary flow reserve (CFR), and the index of microvascular resistance (IMR). The yellow arrows point to the average values of resting and hyperemic mean transient time (Tmn) as well as to the average distal coronary pressure (Pd) during hyperemia. These values are needed to derive CFR and IMR.

Thermodilution by continuous infusion

The basic principle of continuous thermodilution is relatively simple. Assuming that heat exchanges with the arterial wall are negligible and that the indicator, in this case the "cold" of saline, is homogeneously mixed in the volume of blood to be measured and can therefore be considered a constant fraction of this volume, a simple rule of 3 makes it possible to derive the absolute flow (in ml/min) as follows:

$$Q = 1.08 \times Qi \times \frac{Tb - Ti}{Tb - T}$$

where Q is the volumetric coronary blood flow (in ml/min), Qi is the infusion rate of saline at room temperature (typically a fixed rate between 8 and 25 ml/min, set up on the infusion pump), T is the temperature (in °C) of the blood mixed with the indicator as measured in the distal part of the coronary artery, Tb is the temperature (in °C) of blood, Ti is the temperature (in °C) of the saline when it enters the coronary artery; and the constant 1.08 accounts for the densities and specific heat of blood and saline. When Tb is set to zero, and Ti and T represent the deviation of the respective temperatures from Tb, the equation can be further simplified:

$$Q = 1.08 \times Qi \times Ti$$

$$T$$

Absolute resistances (R) are calculated, by analogy to Ohm's law, as the ratio of pressure and flow (expressed in dyn s cm^{-5}, mPa s m^{-3}, or mmHg/l/ min [Wood units]). The latter units are traditionally used in human cardiovascular physiology.

An example of coronary thermodilution by continuous infusion is reported in figure 56

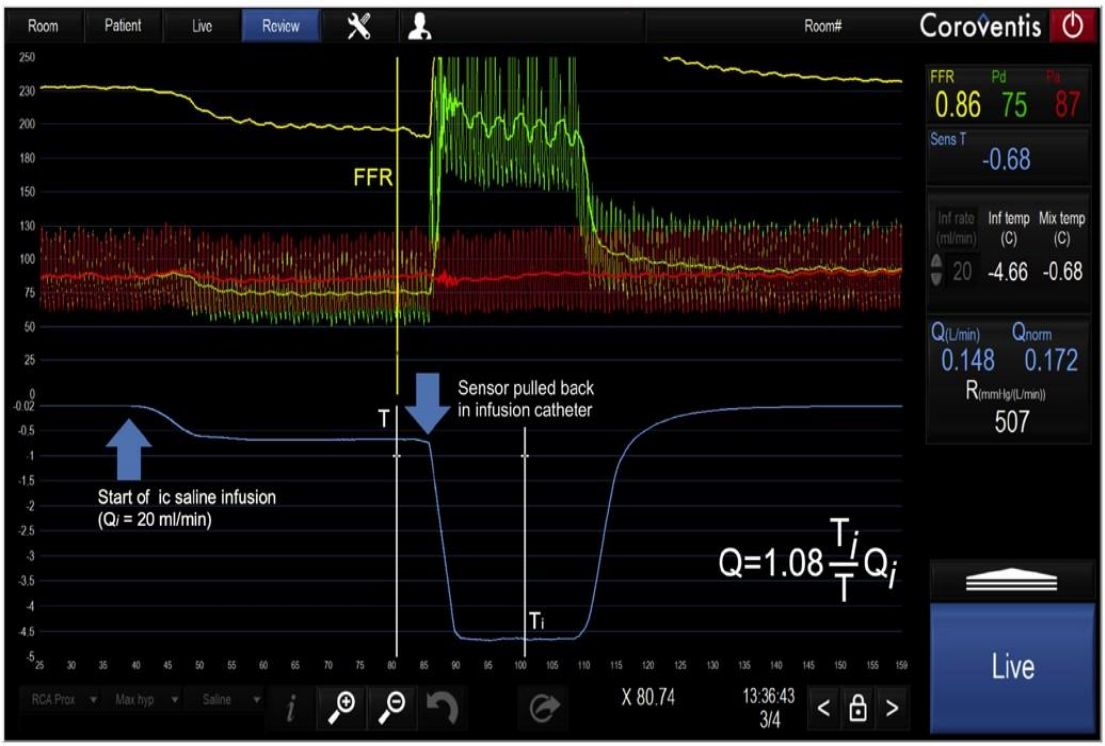

Figure 56. Example of simultaneous recording of aortic pressure (red tracing), distal coronary pressure (green tracing), and coronary temperature (blue tracing) during continuous thermodilution to measure absolute coronary flow (Q) and absolute microvascular resistance ®. The saline infusion flow rate (Qi) in this example is 20 ml/min. These recordings make it possible to simultaneously measure fractional flow reserve (FFR), absolute hyperemic coronary blood flow (Q; in ml/min), and hyperemic microvascular resistance (R; in mm Hg/l/min or Wood Units). The blue arrows indicate the start of the saline infusion and the pull back of the pressure/temperature sensor to be placed in the tip of the infusion catheter. T = mixed temperature (in °C); Ti = infusion temperature (in °C).

Practical considerations

To obtain continuous thermodilution–based absolute Q and R, the following equipment is needed:

- A pressure/temperature wire (PressureWire, Abbott Vascular, Santa Clara, California) advanced into the distal part of the artery. The sensor is to be placed in the distal part of the artery as during PCI or FFR measurements.
- A dedicated monorail infusion catheter with 4 side holes (RayFlow, Hexacath, Paris, France) to enable instantaneous and complete mixing of saline and blood in the proximal part of the artery.
- Saline at room temperature.
- A regular contrast injector or infusion pump to infuse saline at a steady flow rate ranging from 8 to 20 ml/min during several minutes.
- Dedicated software (CoroFlow, Cardiovascular System, Coroventis Research, Uppsala, Sweden) to display all measurements in real time.

Hyperemic flow was initially measured during concomitant intravenous infusion of adenosine. Subsequently, it was observed that the infusion of saline in a proximal epicardial artery by itself induced a maximal steady-state microvascular dilatation in the territory supplied by the artery under study. This was the case only when saline was infused through a specially designed catheter with 4 side holes at flow rates >15 ml/min. The accuracy of these hyperemic absolute flow measurements has recently been confirmed against [15O]H_2O positron emission tomography and has been extensively validated

in animals. Resting flow measurements were recently proposed and validated against simultaneous intracoronary pressure and Doppler measurements. Infusion rates between 8 and 10 ml/min were seen to allow proper delta temperature detection without significant changes in Pd/Pa or averaged peak velocity and with an optimal signal-to-noise ratio during infusion in comparison with baseline. Obtaining these measurements is safe, accurate, operator independent, and highly reproducible.

Conclusions

Intracoronary bolus thermodilution and continuous thermodilution have the potential to assess the function of the coronary microcirculation. IMR as derived from bolus thermodilution has been shown to carry prognostic value after myocardial infarction and in patients with chronic coronary syndromes. Continuous coronary thermodilution enables, for the first time, highly accurate measurement of absolute coronary Q and absolute Rm at rest and during hyperemia. The clinical correlates of these measurements still need to be established. Yet these developments pave the way for more specific and quantitative approaches to studying the microcirculatory compartment and, subsequently, to applying novel therapies targeting the dysfunctional coronary microcirculation.

Chapter 10

Thermodilution-derived volumetric resting coronary blood flow measurement in humans

Background

Quantification of microvascular function requires the measurement of flow and resistance at rest and during hyperemia. Continuous intracoronary thermodilution accurately measures coronary flow during hyperemia. We aimed to study whether continuous coronary thermodilution using lower infusion rates also enables volumetric coronary blood flow measurements (in mL/min) at rest.

Methods

In 59 patients (88 arteries), the ratio of distal to proximal coronary pressure (Pd/Pa), as well as absolute blood flow (in mL/min) by continuous thermodilution, were recorded using a pressure/temperature guide wire. Saline was infused at rates of 10 and 20 mL/min. In 27 arteries, Doppler average peak velocity (APV) was measured simultaneously. Pd/Pa, APV, thermodilutionderived coronary flow reserve (CFRthermo) and coronary flow velocity reserve (CFVR) were assessed. In 10 arteries, simultaneous recordings were obtained at saline infusion rates of 6, 8, 10 and 20 mL/min.

Results

Compared to baseline, saline infusion at 10 mL/min did not change Pd/Pa (0.95±0.05 versus 0.94±0.05, p=0.49) nor APV (22±8 versus 23±8 cm/s, p=0.60); conversely, an infusion rate of 20 mL/min induced a decrease in Pd/Pa and an increase in APV (Figures 52 and 53).

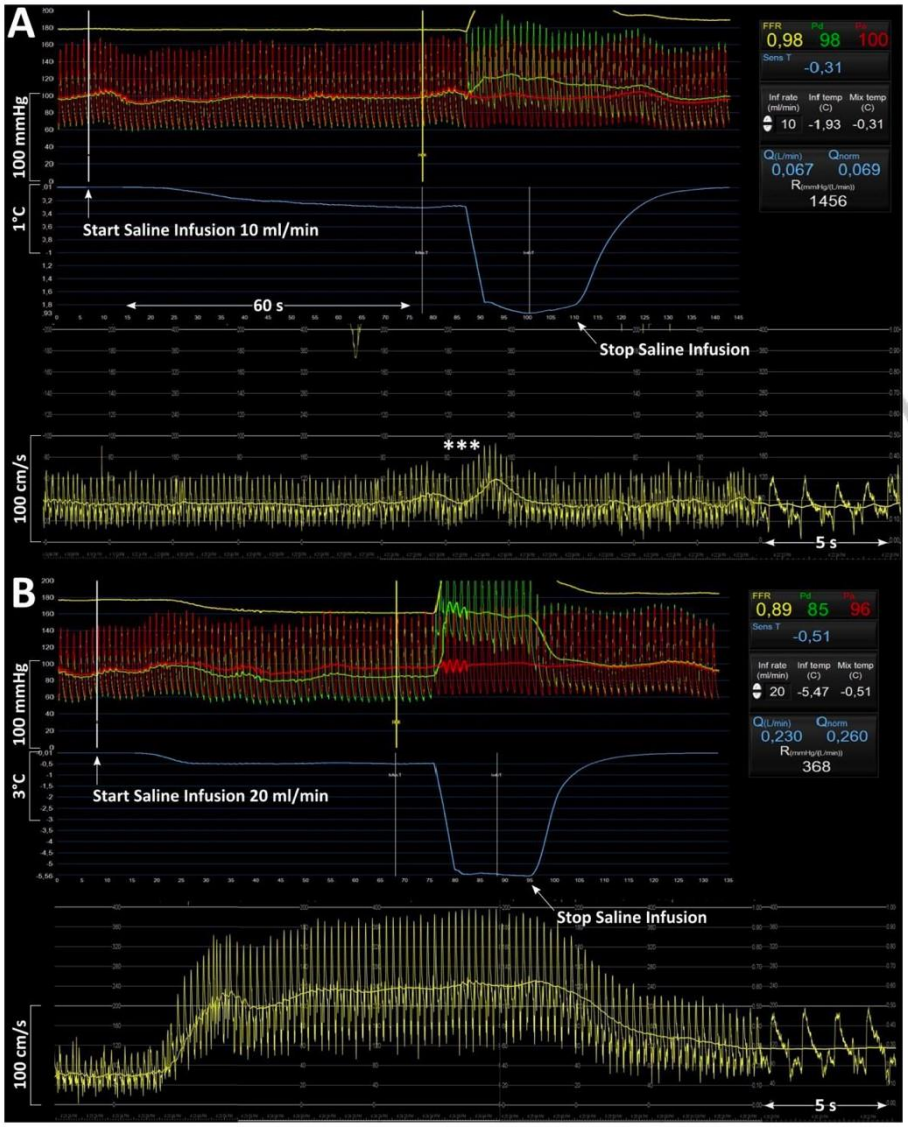

Figure 52. Example of simultaneous tracings of phasic and mean central aortic pressure, distal coronary pressure, average peak velocity and thermodilution during the infusion of 10 mL/min (Panel A) and of 20 mL/min (Panel B) in the LAD of a 77-year-old male patients with mild wall irregularities. Panel A: after the start and during the next 70 s of the infusion of saline at 10 mL/min through the RayFlowTM catheter located in the proximal LAD, no changes in distal coronary pressure, in Pd / Pa, or in APV were observed (reflecting a resting state). The slight oscillations in flow velocities (***) are caused by the pull-back of the pressure/temperature pressure wire. Panel B: in contrast, after the start and during the next 70 s of the infusion of saline at 20 mL/min through the RayFlowTM catheter located in the proximal LAD, a decrease in Pd, a decrease in Pd/Pa, and an increase in APV were observed. After cessation of the intracoronary saline infusion, these indices returned to their baseline level. On the right-hand side, the CoroflowTM software displays instantaneously all relevant parameters, including infusion rate, flow and resistance.

Abbreviations: APV = Average peak velocity; LAD = left anterior descending coronary artery; Pd= distal coronary pressure; Pa aortic pressure

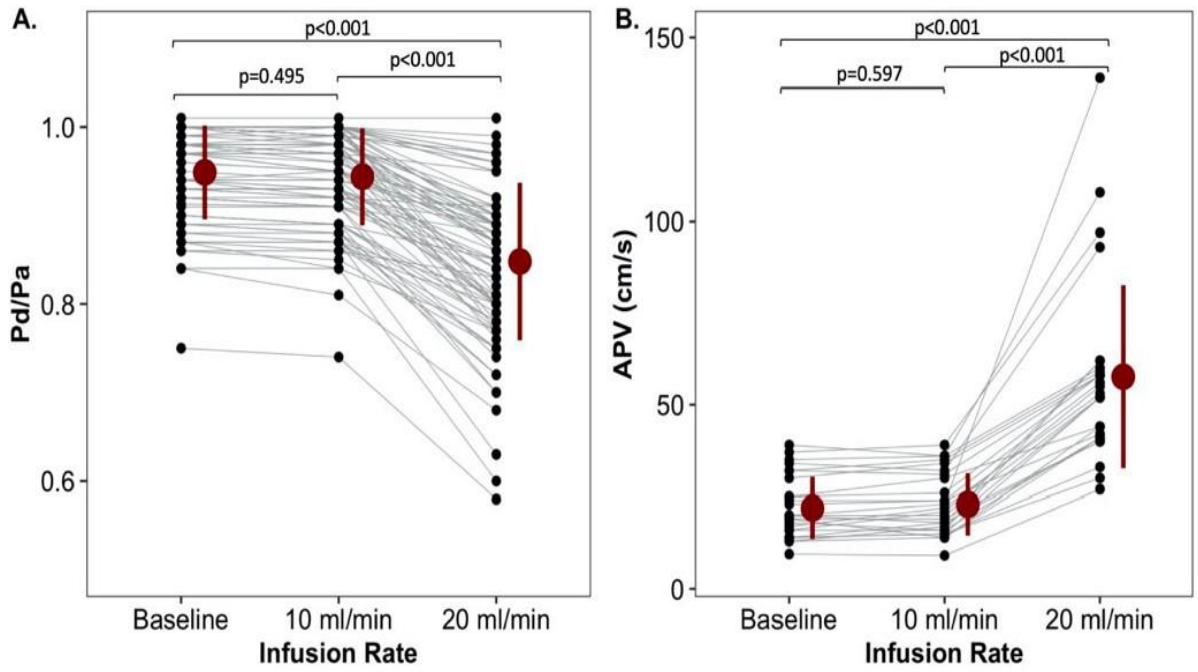

Figure 53. Individual values, mean and SD of Pd/Pa (Panel A) and APV (Panel B) observed at baseline and during saline infusion at 10 and 20 mL/min.

Abbreviations: APV = Average peak velocity; Pd= distal coronary pressure; Pa aortic pressure

Stable thermodilution tracings were obtained during saline infusion at 8 and 10 mL/min, but not at 6 mL/min. Mean values of CFRthermo and CFVR were similar (2.78±0.91 versus 2.76±1.06, p=0.935) and their individual values correlated closely (r=0.89, 95%CI 0.78 - 0.95, p<0.001) (Figure 54).

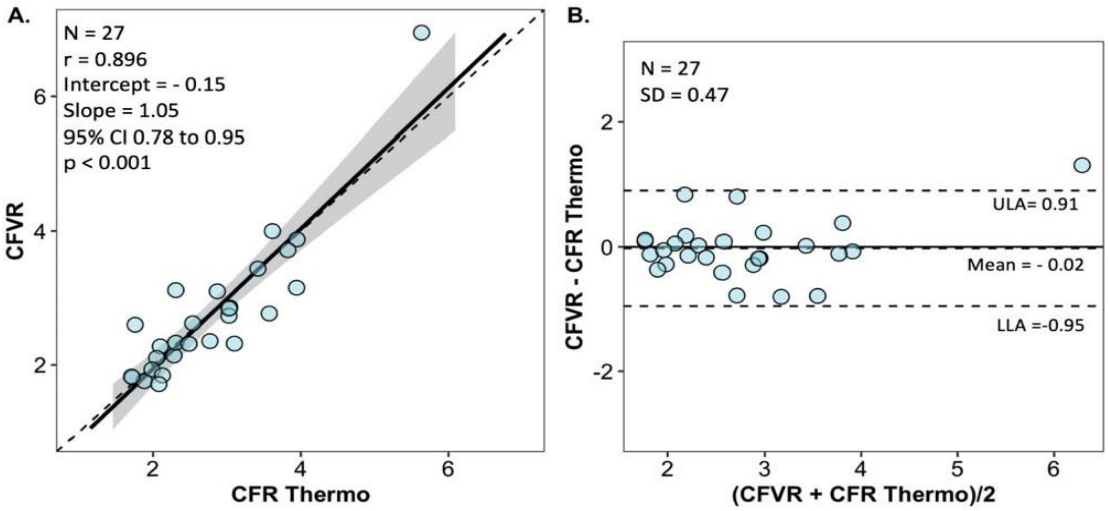

Figure 54. Correlation (Panel A) and agreement (Panel B) between thermodilution-derived coronary flow reserve (CFRthermo) and coronary flow velocity reserve (CFVR).

Conclusions

In addition to hyperemic flow, continuous thermodilution can quantify absolute resting coronary blood flow; therefore it can be used to calculate coronary flow reserve and microvascular resistance reserve.

Chapter 11

Normal values of thermodilution-derived absolute coronary blood flow and microvascular resistance in humans

Background

Absolute hyperaemic coronary blood flow (Q, in mL/min) and resistance (R, in Wood units [WU]) can be measured invasively by continuous thermodilution. The aim of this study was to assess normal reference values of Q and R.

Methods

In 177 arteries (69 patients: 25 controls, i.e., without identifiable coronary atherosclerosis; 44 patients with mild, non-obstructive atherosclerosis), thermodilution-derived hyperaemic Q and total, epicardial, and microvascular absolute resistances (Rtot, Repi, and Rmicro) were measured: A 6 Fr arterial sheath was introduced into the radial or femoral artery, 100 U of heparin/kg of body weight was administered intravenously and intracoronary nitroglycerine (0.2 mg) was administered. A pressure/temperature sensor-tipped guidewire (PressureWire™ X; Abbott Vascular, Santa Clara, CA, USA) was zeroed, passed through the guiding catheter and, after proper equalisation with central aortic pressure, advanced into the distal part of the coronary artery. First, the FFR value was measured. Then, a dedicated monorail infusion catheter (RayFlow®; Hexacath, Paris, France) was connected to an infusion pump (Medrad Stellant; Medrad Inc, Warrendale, PA, USA), and flushed with saline at room temperature. The RayFlow catheter was advanced over the guidewire into the proximal segment of the artery to be measured. All coronary pressure and temperature tracings are wirelessly transmitted and analysed by a dedicated console equipped with a software (CoroFlow™; Coroventis, Uppsala, Sweden) that automatically calculates coronary blood flow (Q) and microvascular resistance (Rmicro). A visual representation of the involved formulas is depicted in figure 49

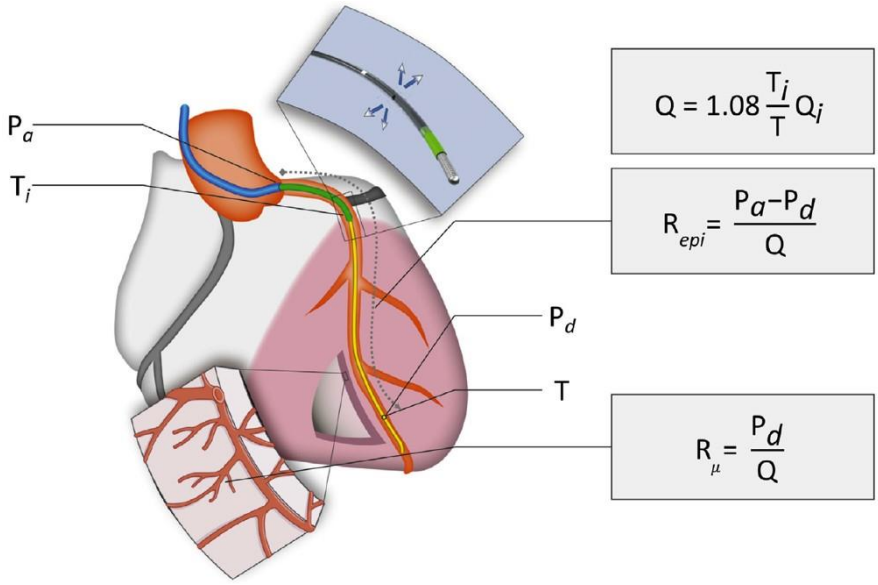

Figure 49. Continuous thermodilution makes it possible to calculate absolute coronary blood flow (Q; in ml/min) and the total resistance of the coronary vessel under examination (Rtot, in Wood Units) as well as its components, namely, epicardial resistance (Repi) and microcirculatory resistance (Rm). Pa =mean aortic pressure recorded by the guiding catheter (in mm Hg); Pd = mean distal coronary pressure recorded by the pressure wire (in mm Hg); Q = volumetric coronary blood flow (in ml/min); Qi = fixed infusion rate of saline at room temperature; T = temperature of the blood mixed with the indicator (in °C); Ti = temperature of the saline (in °C).

In 20 controls and 29 patients, measurements were obtained in all three major coronary arteries, thus allowing calculations of Q and R for the whole heart. In 15 controls (41 vessels) and 25 patients (71 vessels), vessel-specific myocardial mass was derived from coronary computed tomography angiography by an independent core lab (HeartFlow Inc, Redwood City, CA, USA) blinded to the results of the invasive measurements.

Results. Whole heart hyperaemic Q tended to be higher in controls compared to patients (668±185 vs 582±138 mL/min, p=0.068). In the left anterior descending coronary artery (LAD), hyperaemic Q was significantly higher (293±102 mL/min versus 228±71 mL/min, p=0.004) in controls than in patients (Figure 50). This was driven mainly by a difference in Repi (43±23 vs 83±41 WU, p=0.048), without significant differences in Rmicro (Figure 51). After adjustment for vessel-specific myocardial mass, hyperaemic Q was similar in the

three vascular territories (5.9±1.9, 4.9±1.7, and 5.3±2.1 mL/min/g, p=0.44, in the LAD, left circumflex and right coronary artery, respectively).

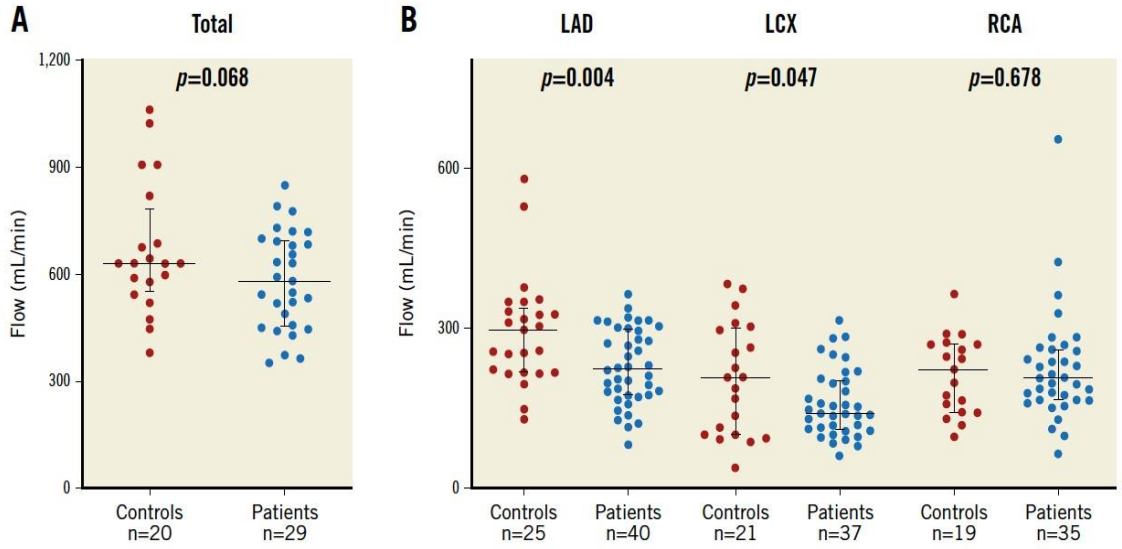

Figure 50. Absolute coronary artery blood flow. A) Individual values of whole heart coronary blood flow in normals and in patients with mild, non-obstructive atherosclerosis, i.e., sum of the flow in the LAD, the LCX and the RCA. B) Individual values of flow as stratified by coronary artery in normals and in patients with mild atherosclerosis.

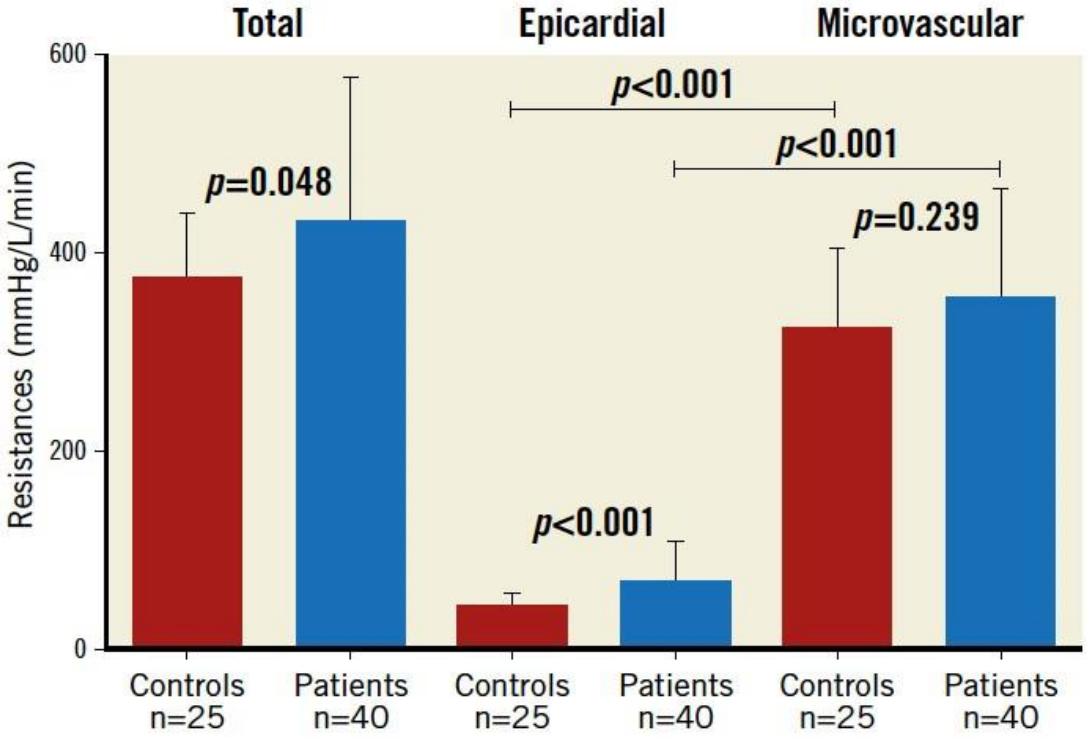

Figure 51. Total, epicardial, and microvascular resistances for the LAD in normals (red bars) and in patients with mild, non-obstructive atherosclerosis (blue bars) (mean±SD).

Conclusions

The present report provides reference values of absolute coronary hyperaemic Q and R. Q was homogeneously distributed in the three major myocardial territories but the large ranges of observed hyperaemic values of flow and of microvascular resistance preclude their clinical use for inter-patient comparison.

Discussion

Part 1

Validating papaverine as hyperemic agent for IMR measurements.

The main findings of this study can be summarized as follows:

1. IMR with IC papaverine is feasible
2. IMR using IC papaverine provides similar results to the ones obtained using IV adenosine
3. IMR measurement using IC papaverine showed higher reproducibility compared to IMR obtained using IV adenosine
4. IC papaverine shortened the time required to assess IMR compared to IV adenosine, although drug preparation is not accounted in this time frame.

Approximately half of the patients undergoing coronary angiography, even with a positive noninvasive test, do not exhibit obstructive epicardial coronary artery disease [39]. In these patients, a potential pathophysiological mechanism for myocardial ischemia is CMD. Moreover, identifying CMD as the cause of the patient complaints triggers medical and risk factors management, which has been associated with improvement in angina and quality of life [40]. Nonetheless, a systematic evaluation of the coronary microcirculation in clinical practice is seldom performed. 'e main limiting factors have been attributed to the necessity of dedicated devices such as pressure/temperature or Doppler wires and the need to induce hyperemia. In the catheterization laboratory, the administration of IV adenosine is time-consuming, costly, and is associated with patient discomfort [41]. 'e present study validated a simplified approach using an intracoronary hyperemic agent with immediate onset and providing sufficient time for the measurement of IMR. Furthermore, papaverine does not evoke symptoms, and the cost is substantially lower compared to adenosine [38].

The reproducibility of measurement is of utmost importance for its clinical applicability. IMR has been shown to have high intra and interobserver reproducibility. Payne et al. have reported a mean difference between IMR measurements of 0.01 (mean standard error 1.59 (95% CI −3.52 to 3.54)) between observers [19]. In the present study, we observed a mean difference −0.63 (limits of agreements −14.2 to 12.95) between duplicated measurements of IMR using IV adenosine. 'e reproducibility between repeated measurements using adenosine may be related to its heterogeneous and the unstable effect in the coronary circulation
and aortic pressure [42,43]. Changes in the hyperemic state during the IMR measurement can affect the result affecting its reproducibility. Papaverine, in contrast, provides
minimal variation during maximal hyperemia. In this cohort, the mean difference between repeated IMR measurements using IC papaverine was −0.34 (limits of agreements −5.93 to 5.26).

CFR/IMR measurement obtained using intracoronary papaverine was able to reduce in more than 2 minutes the time required to acquire the measurement. The intracoronary route of administration simplified the logistics in the CathLab, avoiding the need to start a peripheral infusion with adenosine. The simplified approach interchanging the hyperemic agent can increase the adoption of microcirculation assessment in clinical practice.

Papaverine has been described as the ideal hyperemic agent [44]. Nonetheless, in approximately 1.4% of the cases, it has been shown to trigger ventricular arrhythmias,
namely, torsade de pointes. Okabe et al. have identified multivessel disease as a predictor of torsade de pointes during papaverine administration [45]. In the present study, we used papaverine in patients with no obstructive coronary artery disease and observed no after the return to resting conditions was achieved, we cannot exclude that residual hyperemia was present, thus potentially affecting the subsequent measurement. Fourth, the interchangeability of hyperemic agents proposed in this study is based on comparable results
with the traditional technique. We did not evaluate the relationship with patient-related outcomes.

Part 2

Duration of papaverine hyperiemia

Our analysis expands our knowledge by ascertaining that vessels with hemodynamically significant lesions, based on a contemporary criterion (ie, FFR ≤0.80), have similar time to hyperemic onset and longer stable-state hyperemic duration compared with vessels with nonsignificant lesions. These findings portray clinical implications given the increased use of the FFR pullbacks to evaluate the functional pattern of coronary artery disease using PPG and refine percutaneous coronary intervention indication and strategy. Recently, PPG was described as potentially influencing percutaneous coronary intervention outcomes. In clinical practice, vessels with an FFR ≤0.80 will be considered for PPG measurement. Based on the results of the present study, papaverine provides sufficient time to perform a pullback maneuver for at least 30 seconds under maximal hyperemic conditions. Therefore, the current study provides the foundations for the recommendation of a pullback technique using intracoronary papaverine administration. Intracoronary administration of papaverine provides rapid onset hyperemia with a duration of steady-state sufficient for pullback maneuvers with minimal variability. The duration of steady-state hyperemia is longer in vessels with hemodynamically significant lesions.

Part 3

Invasive physiology evaluation of coronary disease in patients with comorbidities

Pressure wire-based fractional flow reserve (FFR) has become the standard of reference for decision making regarding coronary revascularization. Deriving FFR from routine angiograms could facilitate the uptake of FFR-based clinical decisions. However in patients clinical outcomes in reduced ejection fraction have never been studied.

In our thesis in patients with reduced ejection fraction and at least 1 intermediate coronary stenosis (DS 50-70%) treated based on angiography or according to FFR, we evaluated treatment strategies and clinical outcomes (19). Less patients were revascularized in the FFR-guided group due to a considerable downgrade in the number of diseased arteries, and the chosen method of revascularization was more often PCI in the FFR-group and

CABG in the angiography-guided group. At 5 years of follow-up, all-cause death and major adverse cardiovascular and cerebrovascular events were considerably lower in the FFR-guided group as compared to the Angiography-guided group.

Atherosclerosis often demonstrates characteristics that make accurate diagnosis difficult in persons with diabetes mellitus. Diabetics have a high prevalence of diffuse atherosclerosis, with a tendency for negative vessel remodelling, which might lead to an underestimate of the degree of coronary stenosis on angiography.
However, due to accelerated atherosclerosis, the reliability of fractional flow reserve (FFR)-based PCI deferral in diabetic patients has recently been put into question (46,47). There are little available data on the safety and long-term outcome of FFR guidance for PCI in diabetic patients. Therefore, we compared long-term clinical outcomes of diabetic patients with multivessel coronary disease treated with FFR-guided PCI or CABG.
At follow-up, we discovered an increase of revascularizations among PCI patients. At 5 years, there was no change in the safety endpoints of death, myocardial infarction, or stroke. Furthermore, only 9% of lesions deferred because of a negative FFR value were revascularized at the follow-up (48). The integration of coronary physiology and intracoronary imaging will be critical in identifying unstable plaques that may require revascularization despite a negative FFR value.

Part 4

Characterizing the physiological patterns of epicardial coronary disease

Pressure reductions along a coronary artery can occur abruptly or gradually, but angiography alone cannot reliably identify the focality or diffuseness of atherosclerosis. Pullback curves were constructed using motorized hyperemic pullbacks of a pressure wire, and a novel metric of disease focality (or diffuseness) was developed (Pullback pressure gradient index, PPG index). Along with the qualitative interpretation of pullback curves, the PPG index can identify focal stenosis, which is the condition that benefits the most with PCI (20,49). Notably, diffuse functional disease can occur in patients with angiographically visible stenosis. At the time, it is uncertain what to do with these patients in terms of treatment strategy, which opens up a whole new area of research.

Part 5

Coronary microcirculation

The study of coronary microcirculation has gotten a lot of attention from academics and interventionalists in recent years, because microvascular dysfunction can induce ischemia symptoms in the presence or absence of epicardial coronary disease.

The development of novel metrics, derived using bolus or continuous thermodilution, has enabled the quantification of coronary flow and resistence, and hence the estimation of microvascular function. In our thesis, we present a state-of-the-art review that describes all theoretical and procedural elements of thermodilution-based indexes in depth. The fundamental concepts of indicator-dilution theory and their application to coronary thermodilution procedures.

Intracoronary bolus thermodilution and continuous thermodilution have the ability to evaluate the function of the coronary microcirculation. IMR generated by bolus thermodilution has been demonstrated to have prognostic value after myocardial infarction and in individuals with chronic coronary syndromes. Finally, we described studies in which we adopted an unique continuous thermodilution method to evaluate normal values of absolute coronary hyperaemic flow and resistance (50). Unfortunately, the large ranges of observed hyperaemic values of flow and of microvascular resistance preclude their clinical use for inter-patient comparison. However, measuring these parameters in the same patient at different time points (for example, before and after PCI, before and after TAVI) would undoubtedly give more information on the mechanism of microcirculatory dysfunction. Continuous thermodilution can be utilized to compute coronary flow reserve and microvascular resistance reserve.

Conclusion

Coronary physiology and imaging play an important role in achieving an ideal PCI result. FFR is a gold standard for assessing hemodynamically significant epicardial coronary artery stenosis and microvasculature can be assessed using IMR (bolus thermodilution) and direct flow and resistance (continuous thermodilution).

Coronary hyperaemia is required for FFR and IMR measurements. Adenosine is a preferred hyperemic agent in the cathlab, however to achieve a consistent and sustained adenosine hyperemic response, this necessitates longer infusions, which frequently cause patient discomfort. Papaverine is an alternative to adenosine and it produces stable hyperemic platue required to measure IMR, PPG and FFR. Papaverine can be used as a hyperemic drug, which shortened procedure times, and improved patient comfort.

The invasive evaluation of the coronary microcirculation in the catheterization laboratory can be made simpler by using intracoronary papaverine for the measurement of IMR, which could result in an increase in the use of invasive microcirculation resistance measurements. This will help in improving clinical outcomes of patients suffering from angina.

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Curriculum Vitae

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EDUCATION AND TRAINING

1/11/2019–Present **Cardiopath Phd**

International Cardovascular Pathophysiology and Therapeutics (CardioPaTh) PhD Programme
Federico II University of Naples (Italy) – Cardiovascular Center Aalst (Belgium)

3/2018– Present **Fellowship in advanced interventional cardiology** OLV cardiovascular research center, Aalst (Belgien)

4/2017–5/2018 **Adintional qualification interventional cardiology**
Hegau Bodensee Klinikum, Singen (Deutschland)

6/2016–3/2018 **Specialist for Internal medicine and Cardiology**
Hegau Bodensee Klinikum, Singen (Deutschland)

1/2016–3/2016 **Resident Doctor - Internal medicine and Cardiology**
Rotkreuz klinikum - Wertheim

17/8/2013–28/9/2013 **Hospitation / Dept of Cardiology and Interventional Cardiology**
Prime Hospital, Hyderbad (Indien)

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1/6/2011–31/8/2016 **Resident Doctor - Internal medicine and Cardiology**
Medizinische Universität Sofia und Tokuda Hospital Sofia, Sofia (Bulgarien)

2/2005–2/2011 **Medical Doctor**
Medizinische Universität, Pleven (Bulgarien)

1990–2004 **High school**
St Johns , Gannavaram (Indien)

PERSONAL SKILLS

MOTHERTOUNG (n) Telugu

Languages(n)	VERSTEHEN		SPRECHEN		SCHREIBEN
	Hören	Lesen	An Gesprächen teilnehmen	Zusammenhängendes Sprechen	
Englisch	C2	C2	C2	C2	C2
Deutsch	C1	C1	C1	C1	B2
Niederländisch	B1	B1	B1	B1	B1
Bulgarisch	C1	C1	C1	C1	C1
Hindi	C1	C1	C1	C1	C1

Niveaus: A1 und A2: Elementar - B1 und B2: Selbstständig - C1 und C2: Kompetent
Gemeinsamer Europäischer Referenzrahmen für Sprachen

Kommunikative Fähigkeiten

Sehr gute Kommunikationsfähigkeiten. Umgehen mit komplizierten Patienten.
Einsatzfreude und Integrationsfähigkeit ins Team. Toleranz.
Ich adaptiere mich im internationalen Umfeld, dank meiner Erfahrung, im Ausland erworben.

Additional qualifications

Technical skills and competencies
Advanced training in interventionelle kardiologie

- PCI – bifurcations/ LM/Rotablations
- Functional assessment – FFR , PPGindex, IMR, Abolute Flow and resistance - Interventions in Heart failure patients – link rechts catheterization
- PFO closure
- TAVI (basic)
- Mitraclip (basic)
- Imaging – OCT / IVUS/Coronary CT/ FFR CT
- Angiography derived FFR – Angio FFR, V FFR
- Clinical trial organization - Live course organization

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Goal

Vorstellungen für die weitere Karriere-Entwicklung: Weiterbildung im Bereich der Interventionelle Kardiologie und structural interventions, langfristige Festanstellung

Digital competencies

Ausgezeichnete EDV-Kenntnisse – Microsoft Windows, Microsoft Office (Word, Excel, PowerPoint, SPSS, u.a.) und alle Internet basierte Anwedungen, Grundlagen von Photoshop.

Other competencies

Mitarbeit bei der Entwicklung von:
Pullback pressure gradient index (PPG index)
AngioFFR software
VFFR software
Direct measurement of flow and resistance in coronary arteries
FFR-CT – HeartFlow – P3 study

Führerschein

B

ZUSÄTZLICHE INFORMATIONEN

Konferenzen 2018-2019 AHA Philadelphia – 2019 –presenter

ESC congress 2019 – Paris – presenter

Euro PCR 2019 - Paris – presenter

Euro PCR 2020 - Think-tank committee and organization

Coronary complications course 2019- Lausanne

Bifircation course 2018 – Massy , France

CTO course 2018 – Darmstadt

OCT course 2017/ 2020 – Aalst , Belgium - Faculty
Rotablation course 2017/2020 – Aalst , Belgium - Faculty

Physiology course – 2018 – OLV und Catharina hospitals - Faculty

Memberships

European society of Cardiology, Belgian society of Cardiology, EAPCI, ESC Young cardiologists of tomorrow, ACCA. DGK

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Publications https://pubmed.ncbi.nlm.nih.gov/?term=kodeboina

Aachen, 25/11/2022

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Ort, Datum

M.Kodeboina

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Unterschrift

List of all publications

- Clinical Outcomes Following Coronary Bifurcation PCI Techniques: A Systematic Review and Network Meta-Analysis Comprising 5,711 Patients.
  Di Gioia G, Sonck J, Ferenc M, Chen SL, Colaiori I, Gallinoro E, Mizukami T, Kodeboina M, Nagumo S, Franco D, Bartunek J, Vanderheyden M, Wyffels E, De Bruyne B, Lassen JF, Bennett J, Vassilev D, Serruys PW, Stankovic G, Louvard Y, Barbato E, Collet C
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- Basics of Coronary Thermodilution.
  Candreva A, Gallinoro E, van 't Veer M, Sonck J, Collet C, Di Gioia G, Kodeboina M, Mizukami T, Nagumo S, Keulards D, Fournier S, Pijls NHJ, De Bruyne B.JACC Cardiovasc Interv. 2021 Mar 22;14(6):595-605. doi: 10.1016/j.jcin.2020.12.037.PMID: 33736767

- Duration of Hyperemia With Intracoronary Administration of Papaverine.
  Mizukami T, Sonck J, Gallinoro E, Kodeboina M, Canvedra A, Nagumo S, Bartunek J, Wyffels E, Vanderheyden M, Shinke T, De Bruyne B, Collet C.
  J Am Heart Assoc. 2021 Feb 2;10(3):e018562. doi: 10.1161/JAHA.120.018562. Epub 2021 Jan 17.PMID: 33459027

- Simplified Assessment of the Index of Microvascular Resistance.
  Kodeboina M, Nagumo S, Munhoz D, Sonck J, Mileva N, Gallinoro E, Candreva A, Mizukami T, Van Durme F, Heyse A, Wyffels E, Vanderheyden M, Barbato E, Bartunek J, De Bruyne B, Collet C.
  J Interv Cardiol. 2021 Jun 2;2021:9971874. doi: 10.1155/2021/9971874. eCollection 2021.PMID: 34149324

- Thermodilution-derived volumetric resting coronary blood flow measurement in humans.
  Gallinoro E, Candreva A, Colaiori I, Kodeboina M, Fournier S, Nelis O, Di Gioia G, Sonck J, van 't Veer M, Pijls NHJ, Collet C, De Bruyne B.
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- Fractional flow reserve in patients with reduced ejection fraction.
  Di Gioia G, De Bruyne B, Pellicano M, Bartunek J, Colaiori I, Fiordelisi A, Canciello G, Xaplanteris P, Fournier S, Katbeh A, Franco D, Kodeboina M, Morisco C, Van Praet F, Casselman F, Degrieck I, Stockman B, Vanderheyden M, Barbato E.
  Eur Heart J. 2020 May 1;41(17):1665-1672. doi: 10.1093/eurheartj/ehz571.PMID: 31419282

- Normal values of thermodilution-derived absolute coronary blood flow and microvascular resistance in humans.
  Fournier S, Keulards DCJ, van 't Veer M, Colaiori I, Di Gioia G, Zimmermann FM, Mizukami T, Nagumo S, Kodeboina M, El Farissi M, Zelis JM, Sonck J, Collet C, Pijls NHJ, De Bruyne B.
  EuroIntervention. 2021 Jul 20;17(4):e309-e316. doi: 10.4244/EIJ-D-20-00684.PMID: 33016881

- Vessel Fractional Flow Reserve and Graft Vasculopathy in Heart Transplant Recipients.
  Nagumo S, Gallinoro E, Candreva A, Mizukami T, Monizzi G, Kodeboina M, Verstreken S, Dierckx R, Heggermont W, Bartunek J, Goethals M, Buytaert D, De Bruyne B, Sonck J, Collet C, Vanderheyden M.
  J Interv Cardiol. 2020 Jul 12;2020:9835151. doi: 10.1155/2020/9835151. eCollection 2020.PMID: 32733172

- Heart failure with preserved ejection fraction or non-cardiac dyspnea in paroxysmal atrial fibrillation: The role of left atrial strain.
  Katbeh A, De Potter T, Geelen P, Di Gioia G, Kodeboina M, Balogh Z, Albano M, Vanderheyden M, Bartunek J, Barbato E, Van Camp G, Penicka M.Int J Cardiol. 2021 Jan 15;323:161-167. doi: 10.1016/j.ijcard.2020.08.093. Epub 2020 Sep 1.PMID: 32882295

- Measurement of Hyperemic Pullback Pressure Gradients to Characterize Patterns of Coronary Atherosclerosis.
  Collet C, Sonck J, Vandeloo B, Mizukami T, Roosens B, Lochy S, Argacha JF, Schoors D, Colaiori I, Di Gioia G, Kodeboina M, Suzuki H, Van 't Veer M, Bartunek J, Barbato E, Cosyns B, De Bruyne B.J Am Coll Cardiol. 2019 Oct 8;74(14):1772-1784. doi: 10.1016/j.jacc.2019.07.072.PMID: 31582137

- Coronary Artery Bypass Grafting or Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Diabetic Patients With Multivessel Disease.
  Di Gioia G, Soto Flores N, Franco D, Colaiori I, Sonck J, Gigante C, Kodeboina M, Bartunek J, Vanderheyden M, Van Praet F, Casselman F, Degriek I, Stockman B, Barbato E, Collet C, De Bruyne B.Circ Cardiovasc Interv. 2020 Oct;13(10):e009157. doi: 10.1161/CIRCINTERVENTIONS.120.009157. Epub 2020 Oct 12.PMID: 33040579

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I would like to thank all the nurses, technicians and secretaries in Aalst for their friendship and for the wonderful experience.

During my time at OLV I inherited a wealth of knowledge which is far more valuable than anything.

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