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Hybrid Imaging for the Detection of Obstructive Coronary Artery Disease

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ABSTRACT

Coronary artery disease (CAD) is globally one of the leading causes of morbidity and mortality. CAD develops over decades when coronary arteries obstruct, typically causing chest pain symptoms and, in the worst case, death. Nowadays, obstructive CAD can be prevented and treated with modern and potent therapies; hence, accurate diagnostic tools have become more important. The aim of this thesis was to evaluate hybrid imaging techniques, i.e., combinations of two imaging techniques, for use in the detection of obstructive CAD. We evaluated the feasibility and accuracy of combined coronary computed tomography angiography (CTA) and either positron emission tomography (PET) myocardial perfusion imaging or coronary Doppler ultrasound to detect obstructive CAD in 107 symptomatic patents with an intermediate (30–70%) pretest probability of disease. Techniques were compared with invasive coronary angiography combined with physiological evaluation by fractional flow reserve. Our results showed that hybrid PET-CTA was highly accurate for detecting obstructive CAD and more accurate than either technique alone. Furthermore, measurement of myocardial blood flow by PET during vasodilator stress only was sufficient to evaluate the hemodynamic significance of coronary stenosis. We found that assessment of the coronary flow velocity profile at rest by Doppler ultrasound provides information on the hemodynamic significance of coronary stenosis identified by coronary CTA and may aid in detecting obstructive CAD.

These results show the feasibility of hybrid imaging and demonstrate that it provides improved accuracy in detecting obstructive CAD as compared with stand-alone coronary CTA.

KEYWORDS: Coronary Artery Disease, Computed Tomography, Coronary Ultrasound, Positron Emission Tomography

Esa Joutsiniemi

Hybridikuvantaminen ahtauttavan sepelvaltimotaudin diagnostiikassa

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TIIVISTELMÄ

Sepelvaltimotauti on yksi yleisimmistä kuolemaan johtavista sairauksista maailmassa. Tauti kehittyy vuosikymmenten aikana, jolloin sepelvaltimot ahtautuvat aiheuttaen taudille tyypilliset oireet. Nykyisillä, tehokkailla hoitomuodoilla tautia voidaan ennaltaehkäistä ja hoitaa, minkä vuoksi sairauden täsmällinen diagnostiikka on muodostunut entistä tärkeämmäksi. Tämän väitöskirjan tavoite oli tutkia hybridikuvantamisen, eli kahden eri kuvantamistutkimuksen yhdistelmän diagnostista osuvuutta ahtauttavan sepelvaltimotaudin toteamisessa oireisilla potilailla, joilla taudin todennäköisyys oli keskisuuri. Tutkimme sepelvaltimoiden tietokonetomografian (TT) ja joko positroniemissiotomografia (PET) -menetelmällä mitatun sydänlihaksen verenvirtauksen tai ultraäänellä mitatun sepelvaltimovirtausprofiilin yhdistelmää 107 potilaan aineistossa. Kuvantamismenetelmiä verrattiin perinteiseen katetriangiografiaan, jota täydennettiin tarvittaessa sepelvaltimon sisäisellä painemittauksella. Tulokset osoittavat, että sepelvaltimoiden TT:n ja PET-kuvauksen yhdistelmä on tarkka menetelmä ahtauttavan sepelvaltimotaudin toteamisessa ja yhdistelmä on tarkempi kuin kumpikaan menetelmä yksin. Sydänlihaksen verenvirtauksen mittaaminen PET kameralla pelkän adenosiinirasituksen aikana ilman levossa tehtävää mittausta riittää ahtauttavan sepelvaltimotaudin toteamiseen. Lisäksi havaitsimme, että sepelvaltimon virtausprofiilin mittaaminen levossa Doppler-ultraäänellä auttaa sepelvaltimoiden TT -kuvauksessa todetun ahtauman vaikeusasteen arvioinnissa ja voi auttaa taudin diagnostiikassa.

Hybridikuvantaminen parantaa ahtauttavan sepelvaltimotaudin diagnostiikkaa verrattuna pelkkään sepelvaltimoiden TT-kuvaukseen. Hybridikuvantaminen on toteutettavissa kliinisessä diagnostiikassa.

AVAINSANAT: sepelvaltimotauti, tietokonetomografia, sepelvaltimoultraääni, positroniemissiotomografia

Table of Contents

Abbreviations

BMI	Body mass index
CAD	Coronary artery disease
CHF	Congestive heart failure
CTA	Computed tomography angiography
DM	Diabetes mellitus
FFR	Fractional flow reserve
HR	Heart rate
ICA	Invasive coronary angiography
i.v.	Intravenous
LAD	Left anterior descending artery
LCX	Left circumflex artery
LM	Left main artery
LV	Left ventricle
MI	Myocardial infarction
MBF	Myocardial blood flow
MFR	Myocardial flow reserve
NPV	Negative predictive value
PET	Positron emission tomography
PPV	Positive predictive value
PET/CT	Hybrid positron emission tomography and computed tomography
RCA	Right coronary artery
SCAD	Stable coronary artery disease
SPECT	Single-photon emission computed tomography
TTDE	Transthoracic Doppler echocardiography

List of Original Publications

This dissertation is based on the following original publications, which are referenced in the text by the corresponding Roman numerals, I-III.

I Kajander S, Joutsiniemi E, Saraste M, Pietilä M, Ukkonen H, Saraste A, Sipilä HT, Teräs M, Mäki M, Airaksinen J, Hartiala J, Knuuti J. Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease. *Circulation. 2010 Aug 10; 122(6):603–13. doi: 10.1161/CIRCULATIONAHA.109.915009. Epub 2010 Jul 26.*

II Joutsiniemi E, Saraste A, Pietilä M, Mäki M, Kajander S, Ukkonen H, Airaksinen J, Knuuti J. Absolute flow or myocardial flow reserve for the detection of significant coronary artery disease*? Eur Heart J Cardiovasc Imaging. 2014 Jun; 15(6):659–65. doi:10.1093/ehjci/jet274. Epub 2014 Jan 9.*

III Joutsiniemi E, Saraste A, Pietilä M, Ukkonen H, Kajander S, Mäki M, Koskenvuo J, Airaksinen J, Hartiala J, Saraste M, Knuuti J. Resting coronary flow velocity in the functional evaluation of coronary artery stenosis: study on sequential use of computed tomography angiography and transthoracic Doppler echocardiography. *Eur Heart J Cardiovasc Imaging. 2012 Jan; 13(1):79–85. doi: 10.1093/ejechocard/jer153. Epub 2011 Aug 30.*

1 Introduction

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in Western countries (GBD 2016 Causes of Death Collaborators). Assessment of symptoms and risk factors of cardiovascular disease are important in evaluation of the likelihood of obstructive CAD (Diamond and Forrester, 1979; Pryor *et al.*, 1983). However, accurate diagnostic tools for CAD detection are needed to efficiently target therapies of CAD. Over 70 years ago (1942), Arthur M. Master developed an exercise electrocardiography (ECG) test for medical use to recognize obstructive CAD (Wener *et al.*, 1953). Since then, the CAD diagnosis has been mainly based on clinical history, a positive exercise ECG test and an invasive coronary angiography (ICA). Non-invasive diagnostic CAD tests that are based on imaging have developed fast recently. The first rotating gamma camera was invented in 1977, which permitted detection of flow-limiting CAD by myocardial perfusion imaging with single-photon emission computed tomography (SPECT) (Hutton, 2014). The milestone of cardiac computed tomography imaging was the introduction of single-slice helical CT systems into clinical practice in 1996, when the ability to image the heart was dramatically improved. The shorter gantry rotation time led to better image quality and the use of ECG gating further improved the image quality by targeting the imaging in mid-diastolic phase when the cardiac movement is minimal (Hurlock *et al.*, 2009).

The first successful clinical coronary artery bypass grafting (CABG) was made by a team led by Robert H. Goetz in the United States on May 2, 1960, to a 38-year-old man with obstructive CAD (Goetz *et al.*, 1961). Andreas Gruentzig performed the first successful percutaneous transluminal coronary angioplasty (PTCA; at present percutaneous coronary intervention (PCI)) in Zürich on September 16, 1977. The procedure was performed to a symptomatic patient after a positive exercise test with favourable long-term follow-up results (Gruentzig, 1978; Gruentzig *et al.*, 1987; *King 3rd and Schlumpf, 1993)*. Revascularization by either PCI or CABG has proven effective in improving CAD symptoms and they also provide prognostic benefit in some patient subgroups (Montalescot *et al*, 2013).

Recent studies demonstrate that the benefits of PCI are limited to the treatment of flow-limiting stenoses (Pijls *et al.*, 2007; Tonino *et al.,* 2010; Windecker *et al.*, 2014; Mancini *et al.*, 2014). These findings have generated a need for better non-invasive

tools to assess the hemodynamic significance of stenoses detected in coronary arteries (Tonino *et al.*, 2009; Tavakol *et al.*, 2012).

Modern multidetector computer tomography equipment has emerged in the diagnostic field of cardiac imaging. It is possible to visualize coronary arteries and atherosclerotic lesions by coronary CT angiography (CTA) and reliably exclude obstructive CAD. However, CTA has only limited diagnostic value when estimating the hemodynamic significance of stenosis (Gibbons 2008). Therefore, there is a need for additional imaging techniques to discriminate between flow-limiting and non-flow-limiting stenoses. It has been pointed out since the 1980s that myocardial perfusion can be evaluated by positron emission tomography (PET) (Hack *et al.,* 1980; Bergmann *et al.*, 1984). Myocardial ischemia is visualized in perfusion imaging by reduced tracer uptake during stress, compared to the uptake at rest. When CT and PET technology improved to the current state, it became possible to combine the CT and either PET or SPECT as hybrid scanners and to perform both scans consecutively.

The usefulness of Doppler ultrasound for detection of flow-limiting coronary artery stenosis was demonstrated nearly 20 years ago (Hozumi *et al.*, 2001; Higashiue *et al.,* 2001). This method has rarely been used in clinical practice because of the need for special skills and its limited ability to visualize the right coronary artery (RCA) and the left circumflex artery (LCX) due to their anatomic course (Saraste *et al.*, 2005).

In spite of this progress there is a clinical need to develop better noninvasive diagnostic tools to diagnose CAD. Hybrid imaging combining visualization of coronary anatomy and evaluation of functional consequenses of coronary stenoses is a very promising concept in addressing this need. In our study, we have evaluated combined coronary CTA and either PET perfusion imaging or coronary ultrasound to detect hemodynamically significant CAD. In order to apply these methods in clinical decision making information on their feasibility and diagnostic performance is needed.

2 Review of Literature

2.1 Coronary artery disease

Coronary artery disease (CAD) is caused by atherosclerosis of the coronary arteries. It is usually a slowly developing process, starting in adolescence and continuing throughout one's lifetime. In the beginning, macrophages at the inner wall of the artery (intima) collect LDL-cholesterol, causing atherosclerotic plaque formation at a rate that depends on an individual's risk factor levels (Kovanen, 2016). Symptomatic CAD develops when an atherosclerotic plaque leads to a narrowing of a coronary artery (stenosis) and to reduced blood flow to the myocardium, causing an imbalance between the delivery and need for oxygen (ischemia) and nutrients. Myocardial ischemia causes the symptoms of CAD. The main symptom is discomfort or pain in the chest (angina pectoris). In some patients, ischemia can also be caused by spasm of a normal or atherosclerotic artery or dysfunction of the small arteries. Ischemia can also present as left ventricular dysfunction caused by prior myocardial necrosis, myocardial stunning or hibernation. These mechanisms may act independently or in combination. When ischemia is provoked by physical or emotional stress, the condition is called stable coronary artery disease (SCAD).

The prevalence of SCAD in population-based studies varies from 4-14%; the variation is mainly caused by age and sex. The prevalence increases with age in both sexes (Montalescot *et al.*, 2013). The most common risk factors linked to the prevalence of SCAD are age, family history, hypertension, hypercholesterolemia, diabetes, obesity, smoking and sedentary lifestyle (Piepoli *et al.*, 2016).

SCAD often appears as a chronic situation in which myocardial ischemia causes typical symptoms (as mentioned above) or heart failure. When rupture of a plaque causes coronary thrombosis and myocardial infarction (MI), the symptoms start or progress rapidly, and the situation is then called acute coronary syndrome (ACS). The term ACS is used to describe a broad spectrum of clinical conditions, from unstable angina pectoris to ST-segment elevation MI in ECG, which are all due to a continuum of myocardial ischemia. MI is defined as evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia and detection of changes in cardiac biomarker levels (e.g., cardiac troponin (cTn)); and with 1) symptoms of ischemia, 2) new ECG changes (ST-T, new LBBB, Q-waves), 3) imaging finding of new loss of myocardium or wall motion abnormality or 4) identification

of intracoronary thrombus (Thygesen *et al.*, 2012). The prognosis of CAD is highly variable, depending on risk factors, and it is very important to identify patients who benefit from aggressive preventive therapy and interventions, and, conversely, patients with a good prognosis. The reliable detection of ischemia has an important role in the evaluation of prognosis.

2.2 Diagnosis of coronary artery disease

Diagnosing SCAD is often a complex task that involves not only clinical evaluation of symptoms and risk factors but also diagnostic tests demonstrating either myocardial ischemia or coronary stenosis (Montalescot, 2013).

Clinical history is the cornerstone of the diagnosis. Risk factors alone provide a reasonable estimate on the probability of SCAD, but the nature of symptoms is more important. Discomfort of the chest can be evaluated by four characteristics: location, character, duration and relation to exertion. Myocardial ischemia usually causes discomfort in the chest, but it may be felt between epigastrium to jaw and radiate to back or arm. Typical ischemic pain is dull, often described as pressure or tightness, and it will not last over 10 minutes in the majority of cases. Chest pain caused by SCAD is typically related to exercise or emotional stress, and relieved at rest or by administration of sublingual nitrate. This classic symptom is called angina pectoris (Diamond, 1983; Fox *et al.* 2006).

Because chest pain is a very common symptom, clinical prediction models have been developed to estimate the probability of obstructive CAD. As early as 1979, Diamond and Forrester showed the importance of age, sex and symptoms in predicting obstructive CAD (Diamond and Forrester, 1979). In 1983 Pryor and his colleagues added risk-factors (smoking, hyperlipidemia, hypertension, diabetes and family history) to the earlier Diamond-Forrester-model and developed a better model to predict likelihood for CAD, called the Duke Clinical Score (DCS) (Pryor *et al.*, 1983). Current clinical guidelines recommend the use of pretest probability (PTP) estimates based on age, gender and type of chest pain that were updated with the prevalence of CAD in a more recent population than the original Diamond and Forrester model (Montalescot 2013, Genders 2011). This update and more recent studies indicate that the prevalence of CAD has decreased over time (Cheng 2011). Recent studies also indicate that information on coronary calcium can refine estimates of pretest probability (Genders, 2012).

If diagnosis of CAD remains uncertain after clinical evaluation, objective findings of stenosis or myocardial ischemia are needed to verify the diagnosis. Non-invasive diagnostic tests perform best when PTP is between 15-85%, i.e., from low-intermediate to high-intermediate. In current clinical practice guidelines exercise ECG or functional imaging tests detecting myocardial ischemia are recommended as the first line test in patients with a PTP of 15-85%. Coronary CTA can be considered

as an alternative to these in patients with a PTP of 15–50%. Coronary CTA has a high negative predictive value and can be used to exclude obstructive CAD. If the symptoms are non-cardiac and PTP is < 15%, other causes of chest pain than CAD, such as gastrointestinal, musculoskeletal or pulmonary causes should be considered. Conversely, if the PTP is > 85%, the CAD diagnosis can be made clinically, and further testing will not improve accuracy; however, diagnostic tests are recommended for risk stratification purposes. Proceeding directly to ICA is a reasonable option if symptoms do not respond to medical therapy or if non-invasive tests indicate a high risk of adverse cardiac events (Montalescot *et al.*, 2013). ICA may also be an option if non-invasive test are inconclusive. Taken together, non-invasive tests are recommended in patients an intermediate PTP of flow-limiting CAD. The detection of ischemia in non-invasive tests is based on ECG chances, abnormal perfusion or myocardial function during stress. Perfusion imaging techniques are described in section 2.6. Anatomic testing with CTA is also an option, especially when PTP is low-intermediate (15-50%). Depending on the PTP estimate, risk factors, symptoms, other findings, and availability, a test that performs best is individually chosen.

2.3 Electrocardiogram exercise testing

Using 12-lead ECG monitoring (exercise ECG) in patients with suspected SCAD and a moderate PTP bicycle exercise testing is a useful option because of its simplicity and availability. In addition to the diagnosis, the stress test also provides prognostic information. During the stress test, the clinician can evaluate symptoms of the patients, blood pressure response, physical state and heart rate response, which are useful information in clinical decision-making.

Acquiring the best diagnostic information from an exercise ECG means that it must be symptom- and sign-limiting and without influence of an anti-ischemic drug. The main diagnostic abnormality is a form of horizontal or down-sloping ST-segment depression in one or more ECG-leads. The ST-depression must be ≥ 0.1mV or ≥ 1mm to specify a positive test (and diagnose significant CAD), and a specificity of 85-90% and sensitivity of 45-50% were reported with these values (Froelicher *et al.*, 1998; Morise and Diamond, 1995). Exercise ECG is not diagnostic for CAD in the presence of resting ECG changes that preclude evaluation of ischemia, such as left bundle branch block (LBBB), Wolf-Parkinson-White syndrome (WPW) or ventricular paced rhythm. In addition, false positive results are more common in the presence of left ventricular hypertrophy, atrial fibrillation, electrolyte disorders, digitalis use and in patients with intraventricular conduction abnormalities other than LBBB (Pradhan *et al.*, 2012). The exercise testing is also less sensitive and specific in women for unknown reasons (Morise and Diamont, 1995; Okin and Kligfield, 1995).

2.4 Computed tomography angiography

The first clinical studies with computed tomography angiography (CTA) imaging were performed almost 40 years ago (Guthaner *et al.,* 1979). With the development of techniques and CT scanners, the CTA has gradually provided increasingly better possibilities to visualize the heart's anatomy, especially coronary arteries. The 64-row multi-detector CT has made it possible to reduce the imaging time and allow imaging of small coronary arteries with very high resolution (< 1mm). The use of a contrast medium allows direct visualization of coronary arteries, and cardiac motion can be stopped for analysis with the use of ECG gating. First clinical studies have already shown that coronary CTA can rule out the presence of CAD reliably (Nieman *et al.,* 2002), but hemodynamically significant CAD was more difficult to detect, and positive predictive value (PPV) has been only moderate (Abdulla *et al.*, 2007; Di Tanna *et al.*, 2008; Mowatt *et al.*, 2008). In 2008 Mowatt and his colleagues published a review article that included 40 studies, 28 of which provided sufficient data for inclusion in the meta-analysis, all using ≥ 50% stenosis to define CAD. In that analysis, the sensitivity of coronary CTA for detecting CAD (≥ 50% stenosis by ICA) was 99%, specificity 89%, median PPV across studies was 93% (range 64-100%) and NPV was 100% (range 86-100%). The results were 90%, 97%, 76% (44-93%) and 99% (95-100%), respectively, when analyzing segment based. Sensitivity, specificity, PPV and NPV were 95%, 83%, 64% and 99%, respectively, for detecting ≥ 50% stenosis in another prospective, multi-center study (Budoff *et al.*, 2008) in patient-based analysis. This indicates that coronary CTA is an excellent tool to exclude CAD, but it has limited accuracy for analyzing the hemodynamic relevance of stenosis, because angiographic severity is a poor predictor of hemodynamic significance (Gaemperli *et al.*, 2012). A recent meta-analysis confirmed that from non-invasive diagnostic tools, CTA performed best to detect anatomically significant CAD, but functional tests perform better in detecting functionally significant CAD (Knuuti *et al.*, 2018). After introduction of high-end, multi-detector CT scanners, the image resolution has been shown to be sufficient for evaluating even small coronary arteries (diameter < 1,5mm) (Koepfli *et al.,* 2004).

A large study of over 9000 patients proved that CTA alone provides better prognostic information than functional testing in patients who have stable chest pain with low or intermediate risk for obstructive CAD (Hoffmann *et al.*, 2017). Even with new CT scanners, the amount of false positive and false negative results increase when diagnosing patients with a body mass index over 30 kg/m². Patients with a high calcium score (over 400) and heart rate over 70 beats per minute also increase the number of artefacts and remain challenging to diagnose. (Raff *et al.*, 2005; Meijboom *et al.*, 2008, Gueret *et al.*, 2013). In a prospective, multicenter, randomized controlled trial with 4146 patients, Williams *et al.* (2016) compared standard care or standard care plus CTA to guide management of patients with coronary disease. They demonstrated that CTA can be used not only to rule out hemodynamically

significant CAD but also to guide management of patients with CAD. Furthermore, the study showed a significantly lower rate of the combined end-point of cardiovascular death or non-fatal myocardial infarction (2.3% vs. 3.9% during 5-year follow-up) in patients who had coronary CTA performed in addition to the routine testing, which consisted predominantly of exercise ECG in that study (Williams 2018).

2.5 Invasive coronary angiography

Invasive coronary angiography (ICA) has been regarded as the gold standard of CAD diagnosis. The definition of CAD is when a patient has a symptom caused by CAD with an objective finding of myocardial ischemia and/or flow-limiting coronary artery stenosis. The coronary anatomy and possible coronary stenosis can be visualized using ICA with injection of a contrast media via catheter to a coronary artery. Because of complication risks (i.e., allergic reactions from contrast media or the local anesthesia agent, contrast-induced nephropathy, cholesterol emboli, vascular injury and bleeding at the puncture site, brady- and tachyarrhythmia, MI, cerebrovascular complications, perforation of great vessels and death) (Tavakol *et al.*, 2012), ICA is usually performed after noninvasive testing in patients with suspected SCAD. ICA can be performed without noninvasive testing to verify CAD if a person has low ejection fraction (<50%) and typical angina pectoris, high event risk or other diagnostic methods are not possible (Montalescot *et al.,* 2013).

ICA is also the preferred investigation procedure in situations when a patient has high PPV for CAD and severe symptoms, an acute coronary syndrome (e.g., myocardial infarction with or without ST-elevation) or if a coronary intervention is needed. Bavry *et al.* (2006) and Elgendy and colleagues (2016) have shown that routine invasive strategy improves long-term survival and reduces the risk of ischemic events in non-ST-elevation infarction.

Even if ICA has been regarded as the gold standard, its limitations are similar to CTA's in that it provides only morphological information about the degree of stenosis. Furthermore, because of ICA's risks, a clinical need exists for accurate, noninvasive methods to diagnose hemodynamically significant CAD.

2.5.1 Invasive fractional flow reserve

Pijls and colleagues derived and published in 1993 a simple principle called fractional flow reserve (FFR), which is based on the fundamentals of fluid dynamics (Pijls *et al.*, 1993, Pijls *et al.*, 1995). It has become a useful method for aiding decision making on revascularization because of the fact that only part of the angiographic visualized 50% - 90 % stenosis are functionally flow limiting, and outcome studies show the

positive effect of FFR-guided revascularization on clinical outcomes (Pijls *et al.*, 2005; Tonino *et al.*, 2009; Tonino *et al.*, 2010; van Nunen *et al.*, 2015).

FFR is defined as the ratio of distal coronary pressure to aortic pressure during the maximal hyperemic state, and it is independent of changes in hemodynamics, microcirculation and basal flow. The normal FFR is 1, because pressure in a normal coronary artery should equal aortic pressure throughout the artery (Pijls *et al.*, 1993). The FFR ≤ 0.80 is considered to best identify a coronary stenosis with hemodynamic significance. When FFR is used together with routine angiography in decision making for coronary stenting, it reduces mortality, rate of myocardial infarction and rate of repeat revascularization compared with standard angiography-guided angioplasty (Tonino *et al.*, 2009; Pijls *et al.*, 2010; van Nunen *et al.*, 2015).

FFR measurement is an excellent tool for estimating the hemodynamic significance of stenosis and is recommended for routine use when considering coronary angioplasty, unless the stenosis is not clearly visually significant (> 90%) or non-significant (< 30%) (Tonino *et al.*, 2010). Thereby, the clinical outcome is also achieved with a lower number of stented arteries and less resource use (Tonino *et al.*, 2010; van Nunen *et al.*, 2015).

2.6 Functional tests of myocardial ischemia

Currently, there are various imaging techniques available to detect myocardial ischemia. Ischemia testing with imaging can be done with pharmacologic stress and, therefore, used for patients with diminished tolerance to physical stress. Imaging is also recommended for patients with abnormal resting electrocardiogram, or an intermediate or high probability to CAD (Cremer *et al.*, 2014). When Dehmer *et al.* (2012) analyzed the United State's National Cardiovascular Registry data from January 2010 to June 2011, they noticed that less than half of patients undergoing ICA had had a previous non-invasive diagnostic test of CAD. Over 90% of the patients tested before ICA had undergone a functional test, mostly stress myocardial perfusion imaging (81%). Ten percent had undergone a stress echocardiogram and the rest had an exercise ECG. SPECT and PET perfusion imaging were the most commonly used myocardial perfusion imaging techniques and their advantages and disadvantages are described below.

2.6.1 Single-photon emission computed tomography (SPECT)

SPECT myocardial perfusion imaging (MPI) has been widely used for almost 40 years and has proven in many publications to have both diagnostic and prognostic value (Verberne, 2015). The diagnosis of ischemia using SPECT imaging is based on imaging tracer uptake in the myocardium that reflects relative myocardial blood

flow. Myocardial ischemia is visualized by reduced tracer uptake during stress, compared to the uptake in rest. The most commonly used tracers are Technetium-99m based tracers, and they are used with a symptom-limited exercise test; a pharmacological test is an option if the patient is unable to perform the exercise test (Verberne, 2015). A pharmacological stress test uses the vasodilators adenosine or dipyridamole to produce hyperemia of the myocardium to mimic stress perfusion of the myocardium. If adenosine is contraindicated (because of asthmatic bronchospasm), either dobutamine or regadenoson is an alternative stressor. Regadenoson, the selective adenosine A2A receptor agonist, can be dosed as a single bolus and is more specific to the A2A receptor. Therefore, it causes selective coronary vasodilatation with lesser side effects (such as AV-block, angina pectoris, dyspnea, flushing and headache) (Cerqueira, 2006).

Like other imaging techniques, SPECT provides a more sensitive prediction of the presence of CAD than does an exercise ECG alone (Montalescot *et al.*, 2013; Knuuti *et al*, 2018). In 2012 Jaarsma and her colleagues performed a large meta-analysis from 114 SPECT studies that demonstrated the sensitivity of 88% and specificity of 61% in a patient-based analysis. In a vessel-based analysis sensitivity and specificity were 69% and 79%, respectively. SPECT also has disadvantages, and it is recognized that SPECT can underestimate the extent of ischemia, especially in multivessel disease. SPECT protocol also takes much more time than other MPI techniques (up to 4 hours), and attenuation artifacts and GI tracer interferences are common. (Heller *et al.*, 2009)

2.6.2 Positron emission tomography perfusion imaging

Positron emission tomography (PET) is based on short-lived positron emitting radionuclides. PET has been used for myocardial imaging for over 40 years (Hack *et al.*, 1980; Bergmann *et al.*, 1984). By the end of the 1980s, the first human studies had been published indicating that PET offers the possibility to measure quantitative myocardial blood flow (Bergmann *et al.*, 1989).

PET myocardial perfusion imaging techniques were developed during the last decade, and its clinical usefulness in CAD detection has been studied extensively (Jaarsma 2012, Knuuti 2018). Its image quality is better when compared to SPECT, its imaging protocol is shorter, and its diagnostic accuracy is higher (Bateman *et al.*, 2006; Heller *et al.*, 2009). A meta-analysis of 19 publications demonstrated that PET has high diagnostic accuracy with 92% sensitivity and 85% specificity (Nandalur *et al.*, 2008). Similar results have been achieved with PET/CT instrumentations with different tracers (Samson *et al.*, 2007). In 2012 Jaarsma *et al.* found, in a meta-analyses of 166 articles of different myocardial perfusion methods, that PET achieved the best diagnostic performance over both SPECT and cardiac magnetic resonance imaging, with a pooled sensitivity of 84% and specificity 81%.

A systematic review summarized the available literature on the prognostic value of PET perfusion imaging (Dorbala, 2013). The prognostic value of PET perfusion imaging has been demonstrated in several single-center studies and a large recent multicenter registry study of PET perfusion imaging (Dorbala, 2012). The prognostic value of PET perfusion imaging is also validated in several unique subsets of patients.

The tracers have differences in myocardial uptake, myocardial extraction fraction, half-life, positron range, production and use in clinical setting. Nowadays there are three commonly used myocardial perfusion tracers in PET imaging: ^{15}O water, ^{13}N ammonia and ^{82}Rubidium. In clinical settings the key differences between the tracers for diagnosing CAD depend on myocardial uptake and extraction fraction. In ^{15}O water the myocardial tracer does not accumulate in myocardium. Quantitative modeling is possible and interpretation is straightforward, since the uptake is linear dependent on myocardial blood flow; if the tracer uptake is 25% less from normal, the myocardial blood flow is 25% lower than normal region as illustrated in Figure 1 (Knuuti *et al*, 2009; Knuuti and Saraste, 2012; Maddahi and Packard, 2014). PET tracers do not allow imaging in combination with a treadmill exercise test because of short half life. A pharmacological stress is used, instead.

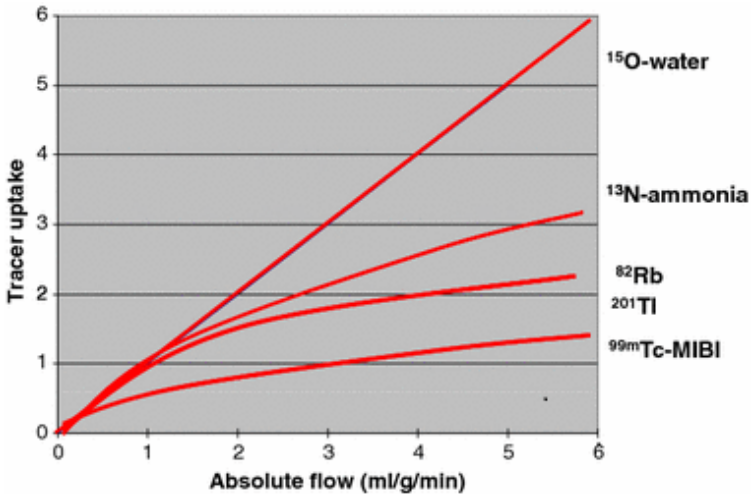

Figure 1. Graphical presentation of the relationship between absolute myocardial perfusion and tracer uptake. Reproduced with permission from J Nucl Cardiol. 2009 Jul-Aug;16(4):497–506. doi: 10.1007/s12350-009-9101-1. Epub 2009 Jun 3.

Modern PET scanners have enabled measurements of myocardial perfusion in absolute terms when evaluating patients with suspected CAD (Groves *et al.*, 2009, Knuuti and Saraste, 2012). Reduced myocardial flow reserve (MFR), defined as the ratio of maximal myocardial blood flow (MBF) at stress to basal MBF at rest, is used as a marker of the hemodynamically significant coronary artery stenosis (Uren *et al.*,

1994; DiCarli *et al.*, 1995; Murthy *et al.,* 2011). Later studies have established that MBF alone during vasodilator stress is accurate and sufficient for CAD detection in patients with no previous myocardial infarction (Hajjiri *et al.*, 2009; Danad, 2017). When measuring myocardial blood flow during adenosine induced hyperemia, studies have shown that the MBF value < 2.5 ml/g/min gives the best combination of sensitivity and specificity with diagnosing occlusive CAD (Kajander *et al.*, 2011). Recent studies by Danad *et al.* (2014) indicated that MBF value under 2.3 ml/g/min gives even better accuracy in diagnosing obstructive CAD.

Studies have also shown that quantitative MBF by PET scanner provides prognostic information on CAD and is an independent predictor of major cardiac event and cardiac mortality of patients with known or suspected CAD (Yoshinaga *et al.*, 2006; Herzog *et al.*, 2009; Murthy *et al.*, 2011; Ziadi *et al.*, 2011).

2.6.3 Stress echocardiography

Stress echocardiography remains an important tool in functional testing of myocardial ischemia (Sicari *et al.*, 2009). It is an established technique that encompasses two-dimensional echo imaging of wall motion, and also color Doppler imaging, during exercise or pharmacological stress agent infusion. Stress echocardiography provides important information on the structure of heart, global and segmental functions during rest and stress, information about valvular function, pulmonary hypertension, diastolic dysfunction, and hypertrophic myocardial diseases, and it also has prognostic value (Tweet *et al.*, 2015). While conventional exercise ECG has only moderate sensitivity and specificity, the exercise testing with echocardiography gives better diagnostic accuracy and more information about presence and location of myocardial ischemia (Gibbons *et al.*, 1997; Fox *et al.* 2006). Pooled sensitivity and specificity of stress echocardiography are reported as 81% and 86%, respectively (Mieres *et al.*, 2005; Fox *et al.*, 2006).

Physical exercise is (usually) performed via treadmill or bicycle in either supine or upright positions. Pharmacological stress agents can be used if the patient is unable to perform an exercise test. Dobutamine is the most often-used stress agent; dipyridamole or adenosine are less frequently used alternatives. Myocardial ischemia leads to abnormal wall motion during exercise detected in echocardiography. Exercise capacity/tolerance also provides important prognostic information, and it has been reported that the pharmacological stress echocardiography test has lower sensitivity and specificity compared with the use of physical exercise in single- and multivessel CAD, and there appear to be no significant differences between men and women (Mieres *et al.*, 2005). Performing stress echocardiography requires expertise and experience and is more user-dependent than other diagnostic imaging techniques of CAD; the echocardiographic image quality also varies depending on patient characteristics.

2.6.4 Coronary ultrasound

The first in vivo description of blood flow disturbance at a site of coronary stenosis by transthoracic Doppler echocardiography (TTDE) and the first transthoracic evaluation of the hemodynamic effects of a coronary artery stenosis in humans were made over 20 years ago (Kenny *et al.,* 1992). The measurements are based in Doppler phenomena arising from the change in the frequency of a sound wave due to a reflector moving towards or away from transducer. All potential ultrasound-windows are used to locate the coronary arteries in a coronary ultrasound study. The normal coronary flow velocity is lower than intracardiac blood flow velocities, and the color Doppler flow mapping scale must be adjusted between 9 cm/s to 24 cm/s to visualize the coronary blood flow in diastole (Hozumi *et al.*, 1998).

A flow-limiting coronary artery stenosis causes local acceleration and turbulence of the flow at the site of stenosis and is detectable by TTDE (Kenny *et al.*, 1992). It is possible to measure myocardial flow velocity reserve (CFVR, i.e., the ratio between rest and maximal coronary flow velocity during vasodilator-induced hyperemia) in the distal coronary artery (Hozumi *et al.*, 2001; Matsumura *et al.*, 2003). The CFVR < 2.0 implies that stenosis is hemodynamically significant and flow limiting (Kern *et al.*, 2006). Other methods include measurement of flow velocity at the site of stenosis and compare it with non-accelerated, pre-stenosis values when evaluating suspected stenosis in the coronary artery. Maximal-to-pre-stenosis ratio (M/P) over 2.0 to 2.2 has been shown as a cut-off value for over 50% stenosis, as diagnosed by quantitative coronary angiography (Holte *et al.*, 2015).

Previous studies have reported the usefulness of coronary ultrasound for stenosis detection in the LAD (Hozumi *et al.* 1998; Hozumi *et al.*, 2001; Higashiue *et al.,* 2001) and also good sensitivity (74-86%) and specificity (92-96%) (Hozumi *et al.*, 2001; Caiati *et al.*, 2009; Holte *et al.*, 2015). Both feasibility and the number of correctly diagnosed stenosis have been lower, (34-63%) and (37-40%), respectively, in the RCA and LCX (Saraste *et al.*, 2005; Holte *et al.*, 2015).

The major limitation of TTDE for routine use when imaging coronary stenosis is its poor diagnostic accuracy with RCA and LCX because of their anatomic course and variations (Saraste *et al.*, 2005). The key is to use all possible standard and non-standard windows and views to visualize RCA and LCX. Specific skills and expert knowledge of coronary anatomy and imaging is needed, which limits the usefulness of TTDE in daily clinical work. The usefulness of detecting stenosis in the LAD is commonly reported (Hozumi *et al.*, 2001; Holte *et al.*, 2015). Its other limitation is the variance in angle between coronary blood flow and Doppler beam, leading to errors in flow velocity measurements. Similarly, filling pressure, hypertrophy and regional contractility may affect the results (Holte *et al.*, 2015). Numerous reports have been published on the good feasibility and diagnostic technique for the flow limiting stenosis in LAD (Kenny *et al.*, 1992; Hozumi *et al.*, 1998, Krzanowski *et al.*, 2000; Saraste *et al.*, 2000; Saraste *et al.,* 2005). The success rate for analyzing LCX and

RCA has been limited because of anatomic obstacles (Krzanowski *et al.*, 2003; Saraste *et al.,* 2005; Vegsundvåg *et al.*, 2009). CTA combined with coronary ultrasound has also led to better PPV with finding of hemodynamically significant coronary/intracoronal plaque (Pizzuto *et al.*, 2009).

2.7 Hybrid imaging

The term hybrid imaging means the combination of information obtained with different imaging techniques into a single study (Gaemperli *et al.*, 2012). Coronary CTA gives an estimate of the degree of atherosclerotic burden and can rule out hemodynamically significant coronary artery disease, although it fails to determine the functional significance of coronary stenosis. Coronary CTA was combined with SPECT in 2007 to allow better evaluation of the spatial relationship between coronary stenosis and perfusion defects. Hybrid SPECT/CT yielded sensitivity, specificity, NPV, PPV and accuracy for the detection of any myocardial perfusion defect by patient (75%, 90%, 93%, 68% and 87%, respectively) (Gaemperli *et al.*, 2007). The major limitation of SPECT is that it only allows measurement of relative perfusion and, in that case, it is vulnerable to the balanced impairment of perfusion in 3-vessel disease, small vessel disease or in other myocardial diseases with a lack of myocardial perfusion.

PET/CT hybrid scanners allow visualization of the coronary stenosis and quantification of myocardial perfusion in absolute terms. This improves the diagnostic accuracy in cases with balanced reduction of perfusion. Studies using PET/CT hybrid imaging have shown promising results in the detection of functionally significant CAD, improving the PPV of coronary CT scanners without worsening the NPV (Namdar *et al.*, 2005). Similarly, in a recently published head-to-head comparison, quantitative PET perfusion imaging showed the best diagnostic accuracy with FFR-defined stenosis (sensitivity 87% and specificity 84%) compared with SPECT/CT, and quantification was particularly useful in patients with multivessel disease (Danad *et al.*, 2017). Reduced myocardial perfusion in PET has prognostic value and is a significant predictor of cardiac death and myocardial infarction (Ziadi *et al.*, 2011; Dorbala *et al.*, 2013, Maaniitty *et al.*, 2017).

The integration of PET and CT has made it feasible to assess coronary anatomy and perfusion in the same session and has made the diagnosis of significant CAD faster, more accurate and patient friendly. The quality of scanners has improved leading to better accuracy and PPV compared with CTA alone.

Modern hybrid PET/CT scanners offer superb diagnostic tools for evaluating symptomatic patients with suspected CAD. Single measurement of absolute MBF is a valid method to diagnose hemodynamically significant coronary artery stenosis and allows a shorter imaging protocol and lower radiation dose than measurement of MFR. The meta-analysis from 2015 showed that stress myocardial perfusion

imaging with CT/PET can accurately rule out hemodynamically significant CAD and act as a gatekeeper for PCI (Takx *et al.*, 2015).

With modern TTDE devices, it has been able to visualize the coronary artery stenosis for over 20 years (Kenny *et al.*, 1992; Saraste *et al.*, 2000). Despite better devices and better image quality, the use of TTDE for coronary flow imaging, as well as the combination of coronary ultrasound with CT, is a less common method for diagnosing significant CAD. In hybrid imaging of TTDE/CT, CTA shows the anatomic changes and stenosis of coronary arteries; when combined with TTDE of coronary arteries, it is able to assess the functional significance of each stenosis. Therefore, the hybrid imaging of TTDE/CT results in better PPV when compared with CTA alone (Pizzuto *et al.*, 2009).

Table 1. The performance of different tests for anatomically and functionally significant coronary artery disease.

Anatomically significant CAD				
Test	**Sensitivity (%), (95% CI)**	**Specificity (%), (95% CI)**	**+LR (95% CI)**	**−LR (95% CI)**
Stress ECG	58 (46–69)	62 (54–69)	1.53 (1.21–1.94)	0.68 (0.49–0.93)
Stress echo	85 (80–89)	82 (72–89)	4.67 (2.95–7.41)	0.18 (0.13–0.25)
CCTA	97 (93–99)	78 (67–86)	4.44 (2.64–7.45)	0.04 (0.01–0.09)
SPECT	87 (83–90)	70 (63–76)	2.88 (2.33–3.56)	0.19 (0.15–0.24)
PET	90 (78–96)	85 (78–90)	5.87 (3.40–10.15)	0.12 (0.05–0.29)
Stress CMR	90 (83–94)	80 (69–88)	4.54 (2.37–8.72)	0.13 (0.07–0.24)
Functionally significant CAD				
Test	**Sensitivity (%), (95% CI)**	**Specificity (%), (95% CI)**	**+LR (95% CI)**	**−LR (95% CI)**
ICA	68 (60–75)	73 (55–86)	2.49 (1.47–4.21)	0.44 (0.36–0.54)
CCTA	93 (89–96)	53 (37–68)	1.97 (1.28–3.03)	0.13 (0.06–0.25)
SPECT	73 (62–82)	83 (71–90)	4.21 (2.62–6.76)	0.33 (0.24–0.46)
PET	89 (82–93)	85 (81–88)	6.04 (4.29–8.51)	0.13 (0.08–0.22)
Stress CMR	89 (85–92)	87 (83–91)	7.10 (5.07–9.95)	0.13 (0.09–0.18)

(+LR = positive likelihood ratio, -LR = negative likelihood ratio, CI = confidence interval, CCTA = coronary computed tomography angiography, CMR = cardiac magnetic resonance) Referenced from *Eur Heart J. 2018 Sep 14;39(35):3322-30. doi: 10.1093/eurheartj/ehy267*

3 Aims of the Study

The purpose of the study was to investigate hybrid imaging methods in the diagnosis of stable CAD in symptomatic patients with intermediate (30-70%) pretest likelihood of CAD.

The detailed aims were as follows:

1. To study the feasibility of hybrid PET/CT in the detection of obstructive CAD (Study I)
2. To compare the accuracy of quantified myocardial flow reserve and absolute stress myocardial blood flow alone in the diagnosis of obstructive CAD (Study II)
3. To study the feasibility and accuracy of sequential CTA and TTDE in the detection of hemodynamically significant CAD (Study III)

4 Materials and Methods

4.1 Study design

The study comprises three substudies (I–III) that were performed during 2007 – 2013. The aim of these studies was to investigate the accuracy and feasibility of hybrid imaging methods in patients with an intermediate pretest likelihood of CAD.

Study I studied the feasibility and accuracy of hybrid PET/CT imaging to detect CAD in a symptomatic patient population. Study II compared absolute stress perfusion alone to perfusion reserve for detecting hemodynamically significant CAD. Study III evaluated the feasibility of sequential use of CTA and TTDE for a combined anatomic and functional evaluation of coronary stenosis; the combination of CTA/TTDE was compared with CTA alone.

4.2 Subjects

4.2.1 Study I

The study population comprised 107 subjects with an intermediate pretest likelihood of CAD based on age, sex, symptoms and their exercise test results (Table 2). The exclusion criteria were atrial fibrillation, heart failure, severe renal dysfunction, unstable asthma, iodine allergy, second or third degree AV-block, unstable angina pectoris or pregnancy. Patients with a clinical history of myocardial infarction or angiographically proven CAD were ineligible. All patients went PET-CTA using a 64-slice scanner with quantitative PET (^{15}O-water) and CT angiography. In Study I, the PET/CT results were compared with invasive angiography and FFR measurement when appropriate.

Table 2. Patient characteristics (Study I, n=107)

Gender (M/F)	64/43
Mean age (Y)	63.6 ± 7.0 (range, 49–80)
Weight (kg)	77.9 ± 17.8 (range, 50–113)
BMI	26.6 ± 3.9 (range, 18.4–39.1)
Risk factors for CAD	#positive
Family history	48 (45%)
Diabetes	15 (14%)
Hypertension	44 (41%)
Hypercholesterolemia	54 (50%)
Smoking or ex-smoking	28 (26%)
Exercise test	90 (84%)
Medication	
Statins	54 (50%)
Beta blockers	64 (60%)
Aspirin	78 (73%)
Long acting nitrates	10 (9%)

(Reproduced with permission from *Circulation. 2010 Aug 10;122(6):603–13. doi: 10.1161/CIRCULATIONAHA.109.915009. Epub 2010 Jul 26*)

4.2.2 Study II

In Study II, the study population was the same as in Studies I and III, but the complete PET images of three patients were unavailable and the patients were excluded. Thus, the final study population comprised 104 patients, whose characteristics are shown in Table 3.

Table 3. Characteristics of study patients (Study II, n=104)

Gender (male/female)	64/40
Age (years)	64 (50–80)
Weight (kg)	78 (50–116)
Body mass index	26.6 (18.0–39.1)
Risk factors:	
Family history of CAD	42 (40.4%)
Diabetes	13 (13.0%)
Impaired glucose tolerance	9 (8.7%)
Hypertension	39 (37.5%)
Hypercholesterolemia	53 (51.0%)
Current or previous smoker	24 (23.1%)
Medication:	
Statin	49 (48.5%)
Beta blocker	56 (53.8%)
Aspirin	70 (67.3%)
Long acting nitrate	7 (6.7%)

(Reproduced with permission from *Eur Heart J Cardiovasc Imaging. 2014 Jun;15(6):659–65. doi: 10.1093/ehjci/jet274. Epub 2014 Jan 9.*)

4.2.3 Study III

As part of a study I, we prospectively enrolled 107 patients with chest pain and 30–70% pretest likelihood of CAD based on age, symptoms, sex, and the exercise test result. Exclusion criteria were the same as in Study I. Six patients were excluded from the study because of failure to perform TTDE prior to invasive coronary angiography. Table 4 summarizes the characteristics of the final study population comprising 101 patients.

Table 4. Characteristics of study III patients. *Reproduced with permission from* Eur Heart J Cardiovasc Imaging. 2012 Jan; 13(1):79–85. doi: 10.1093/ejechocard/jer153. Epub 2011 Aug 30*).*

Gender (male/female)	60/41
Age (years)	64 (50–80)
Weight (kg)	78 (50–116)
Body mass index	26.6 (18.0–39.1)
Risk factors:	
Family history of CAD	43 (42.6%)
Diabetes	14 (13.9%)
Impaired glucose tolerance	9 (8.9%)
Hypertension	40 (39.6%)
Hypercholesterolemia	56 (55.5%)
Current or previous smoker	26 (25.7%)
Medication:	
Statin	49 (48.5%)
Beta blocker	58 (57.4%)
Aspirin	72 (71.3%)
Long acting nitrate	8 (7.9%)

4.3 Methods

4.3.1 Imaging protocols

4.3.1.1 CT imaging

Figure 2 demonstrates the imaging protocol in all studies (I-III). All patients were scanned with a 64-row PET/CT scanner (GE Discovery VCT, General Electric Medical Systems, WI, USA). If not contraindicated, 0-30 mg intravenous metoprolol was administered before the scan to reach the target heart rate (HR) of <60/min. 800 μg of sublingual nitrate was given prior to the scan. An iodinated contrast infusion (60-80 ml of 400 mg I/ml iomeprolol at 4-4.5 ml/s) was followed by a saline flush. The collimation was 64x0.625 mm, gantry rotation time 350 ms, tube current 600-750 mAs and voltage 100-120 kV, depending on patient size. Prospectively gated acquisition was applied whenever possible (86/107 patients) to reduce the radiation

dose. ECG-based tube current modulation was utilized to decrease the dose when the retrospectively gated mode was used (21 patients).

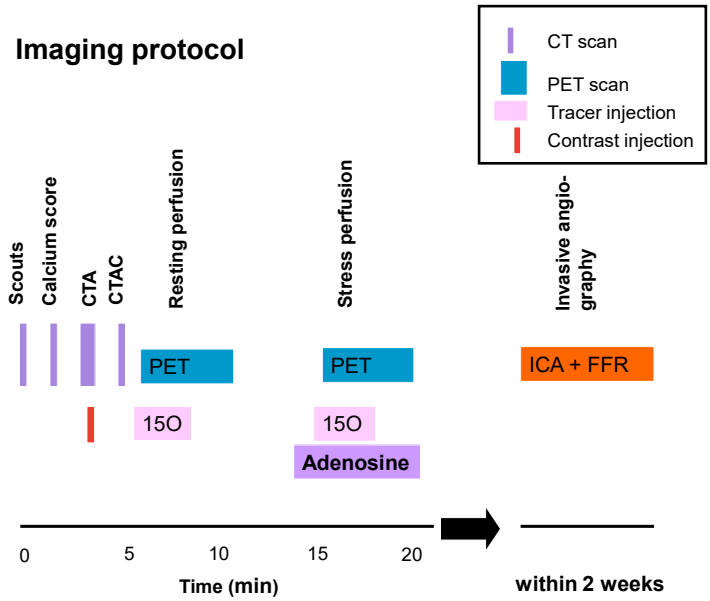

Figure 2. The combined PET/CT imaging protocol used in study I and II. (CTAC = CT-based attenuation correction) (Reproduced with permission from *Circulation.2010Aug10;122(6):603–13. doi: 10.1161/CIRCULATIONAHA.109.915009. Epub 2010 Jul 26).*

4.3.1.2 PET imaging

In Studies I and II, the rest-stress perfusion cardiac PET was performed immediately after CT angiography with a 64-row PET/CT scanner. Dynamic PET scans at rest and during pharmacologic stress were performed. ^{15}O-labeled water (900-1100 MBq) was injected (Radiowater Generator, Hidex Oy, Turku, Finland) as an intravenous bolus over 15s at an infusion rate of 10 ml/min. A dynamic acquisition of 4 min 40 s was performed (14x5 s, 3x10 s, 3x20 s and 4x30 s). A stress scan was performed during adenosine-induced hyperaemia after a 10 min decay of the ^{15}O radioactivity. Adenosine was started two minutes before the scan start and infused to the end of the scan at 140µg/kg body weight/min. Alignment of PET images and CT images used for attenuation correction was instantly adjusted and confirmed visually for all rest and stress studies after imaging. Images were reconstructed using 2D OSEM algorithm.

4.3.1.3 TTDE imaging

Study III evaluated coronary artery segments with >20% stenosis in CTA using TTDE by cardiologists who were blinded to the severity of stenosis in CTA in a separate imaging session using Acuson Sequoia C512 ultrasound unit (Siemens Acuson, Mountain View, CA, USA) equipped with a standard 3.5-MHz transducer (3V2c). The expected anatomic course of the coronary artery segments of interest was studied using color Doppler mapping and all possible standard and non-standard windows and views as previously described. The velocity scale of color Doppler was actively changed, but it was initially set to 0.24 m/s. The color box size was reduced to maintain the high frame rate. The left main coronary artery (LM) and proximal LAD were studied from the left parasternal short- and long-axis views focusing on the area adjacent to the sinus Valsalva (Figure 2). The origin of the first septal branch of the LAD marking the border between the proximal and the middle segments of the LAD could be visualized in most patients. The left parasternal windows, at varying levels using modified short- and long-axis views focusing on the anterior interventricular groove (LAD) or atrioventricular groove (LCX) were used to visualizethe middle and the distal LAD as well as the proximal LCX. The more distal parts of the LCX were studied using the apical long-axis view, focusing on the lateral mitral ring, and the four-chamber view, focusing on the inferior mitral ring. The ostium and the proximal RCA were seen from the left parasternal short-axis view in the area of the right sinus Valsalva. The part of the RCA passing the anterior surface of the tricuspid ring until the inferior margin of the right ventricle was considered as the proximal RCA, and the proximal and the middle RCA were searched from the right parasternal short- and long-axis views when the patients were lying on their right side, focusing on the anterior and medial tricuspid rings. The subcostal short-axis view, focusing on the medial tricuspid ring on the inferior surface of the heart, was also used. The distal RCA was visualized from the subcostal four- and two-chamber views, focusing on the posterior tricuspid ring. The right posterior descending branch of the RCA was visualized using a modified, apical two-dimensional view.

Possible coronary stenosis was identified in the segments of interest as localized color aliasing, indicating accelerated and turbulent flow, as described earlier and illustrated in Figure 3. Accelerated and turbulent flow at the site of stenosis causes a strong signal that facilitates its identification, whereas normal coronary flow is slow and laminar and causes only a weak Doppler signal. To assess severity of coronary stenosis by TTDE, we measured maximal flow velocity by pulsed-wave Doppler at the site of aliasing and prestenotic flow velocity in the nearest proximal, non-aliased point of the vessel to calculate the M/P ratio (Figure 3). Blood flow velocity was measured at the beginning of diastole, using a pulsed-wave Doppler with 2 MHz frequency in an average sample volume of 5 mm. Successive cardiac cycles were analyzed to find average flow velocity. The angle between flow and Doppler beam

was kept as small as possible and used angle correction. In some coronary segments, because of the artery's horizontal course, the angle between ultrasound beam and flow remained >60°. In these segments, stenotic flow velocity was approximated by the appearance of aliasing upon rescaling of the color Doppler Nyqvist limit. A predefined cut-off value was used for the M/P ratio (2.2) for comparison of CTA alone vs. CTA and TTDE (Hozumi *et al.*, 2000), in addition to testing the optimal cut-off value of the M/P ratio to detect significant stenosis in our patients.

Flow in the septal branches of the LAD were also evaluated from left parasternal short-axis views using color Doppler to detect total LAD and RCA occlusions, as described previously (Saraste *et al.*, 2005; Otsuka *et al.*, 2005; Watanabe *et al.*, 2001). Chronic occlusion results in heightened collateral flow through septal branches that causes flow acceleration and makes long, continuous segments of flow signals visible by TTDE. In patients with non-detectable flow in either the LAD or the RCA, reversed heightened flow from right to left in the septal branches of the LAD were considered as a marker of total occlusion in the LAD, whereas heightened Doppler signals in the normal direction were considered as a sign of total occlusion in the RCA.

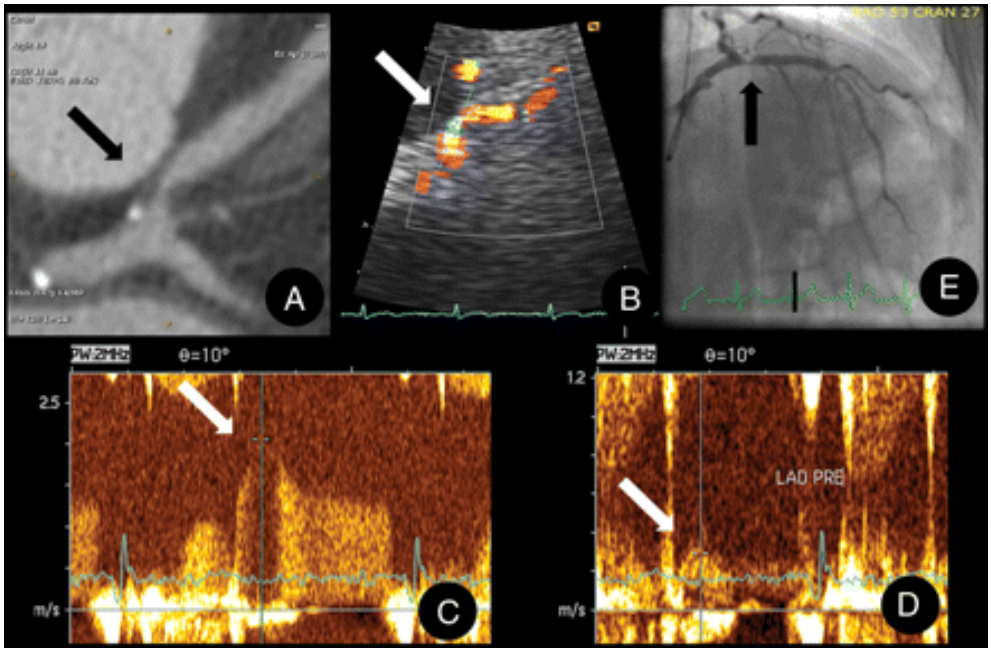

Figure 3. Analysis of coronary stenosis by sequential computed tomography angiography and transthoracic Doppler echocardiography.

(A) Computed tomography angiography image of >50% stenosis in the proximal left anterior descending (LAD; arrow). Transthoracic Doppler echocardiography

demonstrates accelerated coronary flow at the site of stenosis seen as local aliasing (arrow) in a modified parasternal short-axis color Doppler image when Nyqvist limit is set to 0.2 m/s (B). Pulsed-wave Doppler recording at the site of aliasing demonstrates maximal diastolic flow velocity of 2.4 m/s (arrow in C), whereas prestenotic flow velocity is 0.24 m/s (arrow in D) resulting in the M/P ratio of 10. Invasive coronary angiography demonstrated significant stenosis causing luminal narrowing of 73% (arrow in E). (Reproduced with permission from *Eur Heart J Cardiovasc Imaging. 2012 Jan;13(1):79-85. doi: 10.1093/ejechocard/jer153. Epub 2011 Aug 30*).

4.3.1.4 Invasive angiography and FFR

All coronary angiographies were performed on the Siemens Axiom Artis coronary angiography system (Siemens, Munich, Germany). FFR measurement was performed on stenosis > 30%, when feasible, using ComboMap® pressure/flow instrument and a 0.014-inch BrightWire® pressure guidewires (Volcano Corp., Rancho Cordova, CA, USA). Hemodynamically significant stenosis was detected based on FFR value <0.8 in 14/23 of these vessels. FFR was calculated as the ratio between mean distal pressure and mean aortic pressure; the pressure was measured distally to the lesion during maximal hyperemia induced by 18 μg intracoronary boluses of adenosine with simultaneous measurement of aortic pressure through the coronary catheter.

4.3.2 Data analysis

4.3.2.1 CT analysis

An experienced cardiologist and radiologist analyzed the vessels separately and then in concord on an ADW 4.4 Workstation (General Electric, Milwaukee, WI., USA) blinded to other results and clinical data, using a standard 17 vessel segment system adapted from the original AHA model.

4.3.2.2 PET analysis

Studies I and II quantitatively analyzed the PET images using validated Carimas™ software; an experienced observer analyzed the images blinded to other results and clinical data as studied earlier (Nesterov *et al.*, 2009). The definition of regions of interest (ROI) in the myocardium and blood pool inside the left ventricular cavity was performed automatically but was usually accompanied by visual confirmation and appropriate manual adjustment. Volume view and reorientation were done manually, but modelling and reporting of results were automatic. The

reproducibility of the analysis has been reported by Nesterov *et al.* (2009). Average MBF values were measured for regions of the RCA, LAD and LCX, using individual known coronary anatomy both at rest and during stress. The 312 region was altogether analyzed. Average MFR was calculated in each region as the ratio of stress-to-rest MBF. The absolute increase was calculated as the absolute difference between stress and rest MBF. Optimal threshold values of MFR, absolute increase of MBF and absolute stress MBF for detecting significant coronary stenosis were defined by ROC analysis. We also tested 2.0 as the predefined cut-off value of MFR (Uren *et al.*, 1994) and 2.4ml/g/min as the predefined cut-off value of absolute stress MBF (Nesterov *et al.*, 2009). Stenosis in the LM coronary artery was considered to affect perfusion in both the LAD and LCX areas.

4.3.2.3 TTDE analysis

Coefficient of variation for repeated measurements of the M/P ratio by the same or two independent observers in 10 stenoses varying from 30 to 95% (2, 6 and 2 in the RCA, LAD, LCX, respectively) in four patients were 5 and 6%, respectively.

4.3.2.4 ICA analysis

Quantitative analysis of coronary angiograms (QCA) was performed using software with an automated edge detection system (Quantcore, Siemens, Munich, Germany) by an experienced cardiologist blinded to the results of PET, CTA and FFR.

Significant stenosis was defined as luminal diameter narrowing >50% by QCA. Regardless of the degree of narrowing, stenosis with FFR ≥0.8 was classified as non-significant when FFR was available.

4.3.3 Statistical methods

4.3.3.1 Study I

Sensitivity, specificity, PPV, NPV, and accuracy were calculated for each imaging method (CT, PET and PET/CT). An ROC analysis curve was used to reconfirm the best cutoff points of MBF stress in the current population. The McNemar test was performed to compare the accuracy of CT, PET, and PET/CT against the gold standard (i.e., ICA with FFR). A value of $P<0.05$ was considered statistically significant. Statistical tests were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC).

4.3.3.2 Study II

Accuracy, sensitivity, specificity, PPV and NPV were calculated for each imaging method (CT, PET, and PET/CT). A ROC analysis curve was used to reconfirm the best cut-off points of MBF stress, MFR, and the absolute increase of MBF at stress in the current population. Area under the curve (AUC) values were compared using the Chi-square test. McNemar's test was performed to compare the accuracy of stress MBF, increase of MBF and MFR cut-offs <2.0 and <2.5 against the gold standard (i.e., ICA with FFR). The effect of beta-blocker therapy was tested using Fisher's exact test. The analyses were performed both per main vessel and per patient (correctly classified as either with or without significant coronary artery stenosis). A P-value of <0.05 was considered statistically significant. The statistical tests were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC).

4.3.3.3 Study III

Continuous variables are expressed as the mean ± SD and compared between two groups by independent sample t-test. Receiver operating characteristic (ROC) analysis was used to find the optimal cut-off point of the M/P ratio. Sensitivity, specificity, PPV, NPV, and accuracy were calculated for CTA alone and in combination with focused TTDE (in all lesions that were evaluated by TTDE, stenosis was classified according to TTDE findings) on patient and segment levels. McNemar's test was performed to compare accuracy, sensitivity, and specificity of the strategy of CTA alone and in combination with focused TTDE. A P-value of <0.05 was considered as statistically significant.

5 Results

5.1 Cardiac positron emission tomography/ computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease (Study I)

5.1.1 Patent characteristics

For the study we enrolled 107 patients without previous myocardial infarction with 30-70% pretest likelihood of CAD.

All patients underwent coronary CTA. Myocardial PET perfusion was successfully made to 104 patients with PET/CT hybrid scanner, and ICA was made within two weeks. The FFR measurements were performed in > 30% stenoses when feasible. When coronary artery was either totally occluded or stenosis was > 90% and FFR was not performed, the clinical information of ICA and quantitative analysis of coronary angiogram (QCA) was considered positive and vessel graded accordingly.

Forty-four patients of 107 (41%) had ≥ 50% stenosis in their coronary arteries in ICA, and after FFR, stenosis was graded significant in 40 patients. In 18 patients out of 40, the stenosis was either total occlusion or > 90% stenosis, such that FFR was not performed. Four other patients had intermediate stenosis in which FFR could not be performed due to logistic or technical reasons. Patients without FFR and stenosis ≥ 50% by QCA were considered as having a significant stenosis. By the combination of ICA, QCA and FFR, 80 of 428 arteries were significantly stenosed.

5.1.2 CT Angiography

CTA alone had a PPV of 81%, an NPV of 97%, and an accuracy of 90% per patient. In per vessel analyses PPV, NPV and accuracy were 76%, 94%, and 91%, respectively. In most false cases, CT overestimated the degree of stenosis. There were only two patients in whom CAD was missed, but in 10 patients, at least one significantly stenosed coronary artery was not detected. These lesions were evenly distributed into different coronary branches.

5.1.3 PET Perfusion Imaging

Perfusion at rest was normal in all patients. The stress perfusion in patient-based analysis had a PPV, an NPV, and an accuracy of 86%, 97%, and 92%, respectively. The corresponding values in per vessel analysis were 78%, 98%, and 92%. Potentially false-negative PET perfusion results occurred in two patients. They had ≥50% stenosis detected at ICA, but FFR could not be performed. Six patients had false-positive PET perfusion; five of them had diffusely reduced myocardial perfusion but no epicardial CAD. A regional perfusion defect was incorrectly diagnosed in one patient. In per vessel analysis, four other patients exhibited at least one perfusion abnormality in a region without significant epicardial CAD.

5.1.4 Hybrid Imaging

Most patients with false-positive CT angiography had normal PET perfusion, which corrects the diagnoses. Four out of five patients with false-positive PET findings had diffusely abnormal perfusion, but no epicardial CAD in CT; these cases were correctly identified in hybrid imaging. In one case, there was diffusely reduced perfusion, but one stenosed vessel. Table 5 shows the characteristics of the five patients with suspected microvascular disease (i.e., those with diffusely reduced perfusion without accompanying epicardial CAD). Furthermore, CTA vessel analysis helped to assign the perfusion zones of the LCX and the RCA, because the dominant vessel is easily distinguished. In combined analysis, only one false-negative and no false-positives were diagnosed. PPV, NPV, and accuracy were 100%, 97%, and 98%, respectively.

Table 5. Patients with diffuse perfusion abnormalities but non-stenotic epicardial coronary arteries

Patient	gender	smoker	Body Mass Index	Diabetes	Family history of CAD	PET stress MBF (ml/g/min)	Agatston score
P006	male	no	21.8	no	no	**1.7–2.1**	117
P010	male	yes	33.1	no	yes	**1.2–2.3**	6
P077	male	no	19.4	no	yes	**1.4–1.8**	16
P079	female	no	19.1	no	yes	**1.6–2.0**	0
P090	male	yes	25.7	no	yes	**1.7–1.8**	0

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PPV, NPV, and accuracy of per vessel analysis were 96%, 99%, and 98%, respectively. In three vessels with intermediate (30% to 70%) stenosis in CTA, hybrid imaging was abnormal but invasive tests identified non-significant lesions. Hybrid imaging suggested non-significant lesions in five other vessels, but ICA showed ≥ 50%

stenosis. All of these vessels, however, were classified according to ICA alone because of a lack of FFR. Table 6 summarizes the discrepant findings between hybrid imaging and the gold standard.

Hybrid imaging was more accurate per patient than CTA ($P = 0.0039$) or PET alone ($P = 0.014$) and was better in the per vessel analysis ($P < 0.0001$ and $P < 0.0001$, correspondingly). Figures 4 and 5 present ROC tables that are in agreement with earlier cutoff values (Nesterov *et al.*, 2009). An MBF value of 2.5 ml/g/min gives the best combination of sensitivity and specificity when analyzed both with and without CTA information. The estimated probability of CAD based on ROC analysis (Figures 6 and 7) demonstrated that practically all regions with MBF < 2.0 ml/g/min were abnormal.

Table 6. Discrepant findings between combined CTA and PET against gold standard

Patient	Vessel	CTA stenosis	PET stress MBF (ml/g/min)	Invasive stenosis (QCA)	Suspected explanation for discrepancy
P020	LAD	50–69%	3.1 (normal)	55 %	Mid LAD intermediate stenosis, no successful FFR
	RCA	50–69%	2.1 (abnormal)	39 %	Two stenoses distally in RCA, no FFR.
P031	RCA	50–69%	2.0 (abnormal)	40 %	Severe calcifications in CTA and reduced flow, in ICA intermediate stenosis in mid RCA, no FFR
P033	LAD	>70%	3.0 (normal)	50–60%	Proximal and mid LAD intermediate stenoses, no successful FFR
P034	RCA	30–49%	0.8 (abnormal)	30–49%	Long but mild wall irregularities in distal RCA, no successful FFR
P070	LAD	50–69%	3.1 (normal)	50 %	Mid LAD intermediate stenosis, FFR was not successful
P084	RCA	50–69%	1.9 (abnormal)	39 %	Distal RCA intermediate stenosis, no FFR

(Reproduced with permission from *Circulation. 2010 Aug 10;122(6):603–13. doi: 10.1161/CIRCULATIONAHA.109.915009. Epub 2010 Jul 26)*.

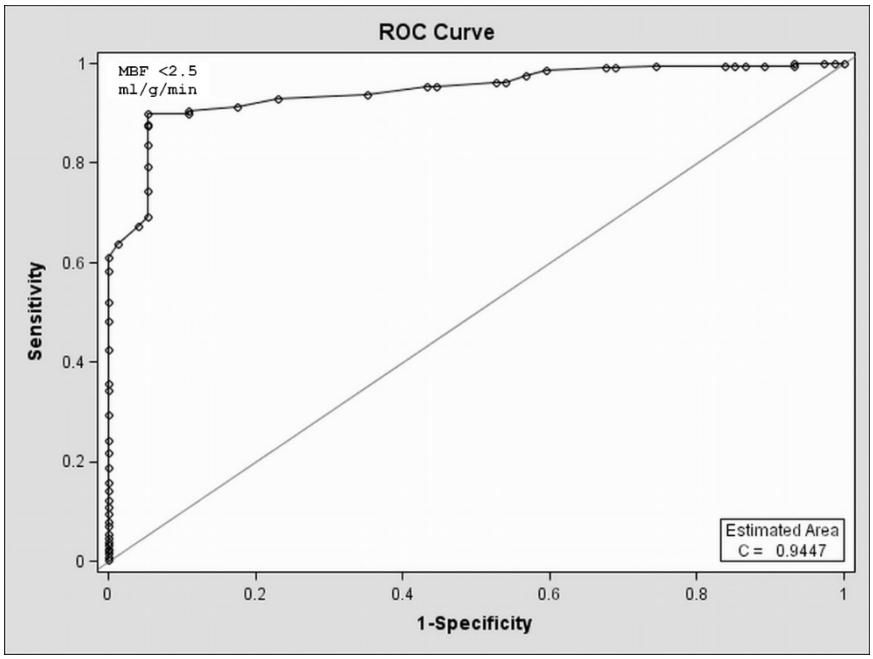

Figure 4. ROC curve of vessel-based PET perfusion against gold standard (ICA + FFR) with cut-off values (without CTA information).

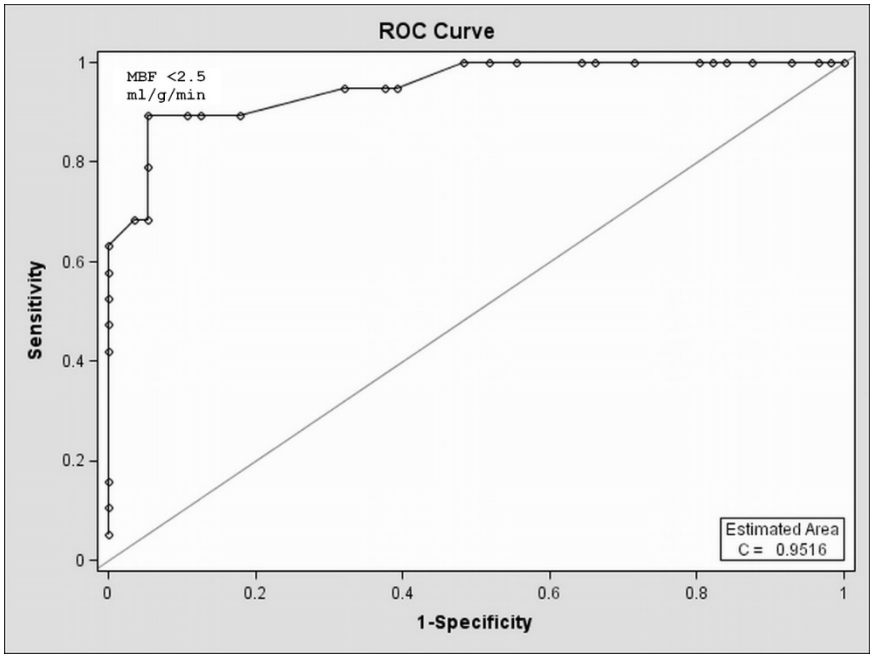

Figure 5. ROC curve of PET perfusion against gold standard with cut-off values (with CTA information). (Reproduced with permission from *Circulation*. 2010 Aug 10;122(6):603–13. doi: 10.1161/CIRCULATIONAHA.109.915009. Epub 2010 Jul 26).

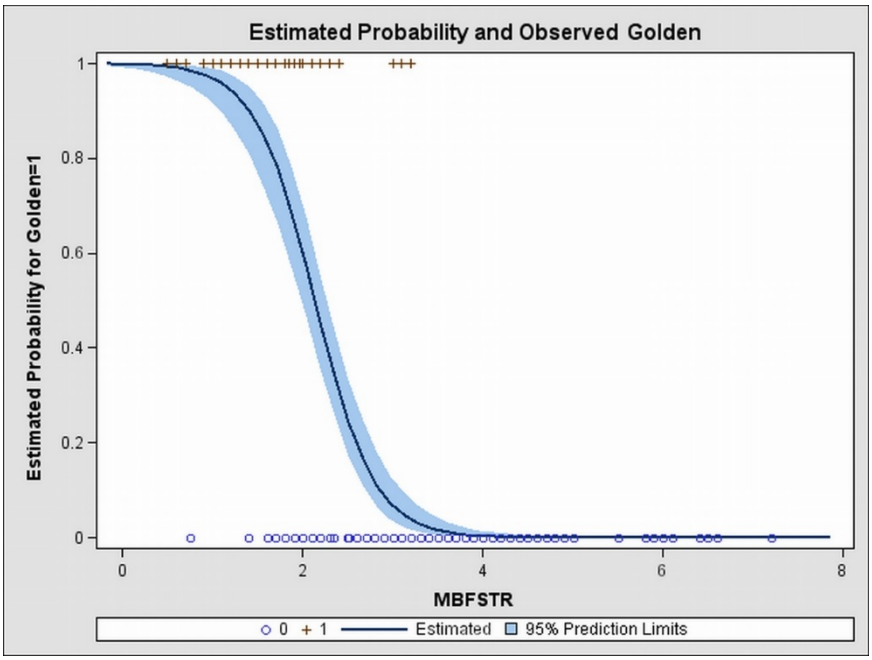

Figure 6. Estimated probability of significant CAD against stress MBF.

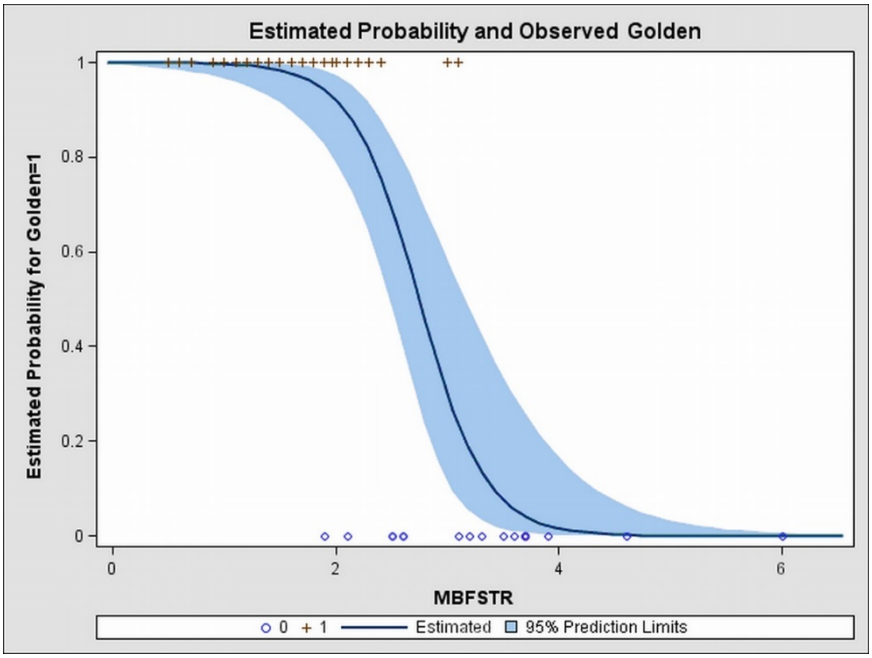

Figure 7. Estimated probability of significant CAD against stress MBF (with significant stenosis in CTA). (Reproduced with permission from *Circulation*. 2010 Aug 10;122(6):603–13. doi: 10.1161/CIRCULATIONAHA.109.915009. Epub 2010 Jul 26).

5.2 Comparing of absolute flow vs myocardial flow reserve in significant CAD (Study II)

Study II analyzed the original PET perfusion data by comparing myocardial quantitative blood flow (MBF) during adenosine stress to myocardial flow reserve (MFR). Also the absolute increase of MBF from rest to stress was measured and compared with MFR. The effect of beta-blocker therapy was also considered in its own analysis.

5.2.1 Threshold values of absolute MBF and MFR for detection of stenosis

In the analysis the average rest MBF was comparable in the myocardial regions subtended by significantly stenosed coronary arteries and non-stenosed arteries (0.96 ± 0.27 vs. 1.0 ± 0.25 mL/g/min, P = 0.04), but absolute MBF during adenosine stress was significantly lower in the regions subtended by significantly stenosed coronary arteries (1.77 ± 0.59 vs. 3.53 ± 1.0 mL/g/min, P < 0.0001). The absolute increase of MBF was significantly lower in the stenosed regions than in non-stenosed regions (0.81 ± 0.59 vs. 2.49 ± 0.95 mL/g/min, P < 0.0001). Thus, average MFR was lower in the presence of hemodynamically significant stenosis than in the absence of stenosis (1.94 ± 0.79 vs. 3.5 ± 1.0, P < 0.001). Figure 8 shows example polar maps of absolute MBF at rest and stress in a patient with significant coronary stenosis.

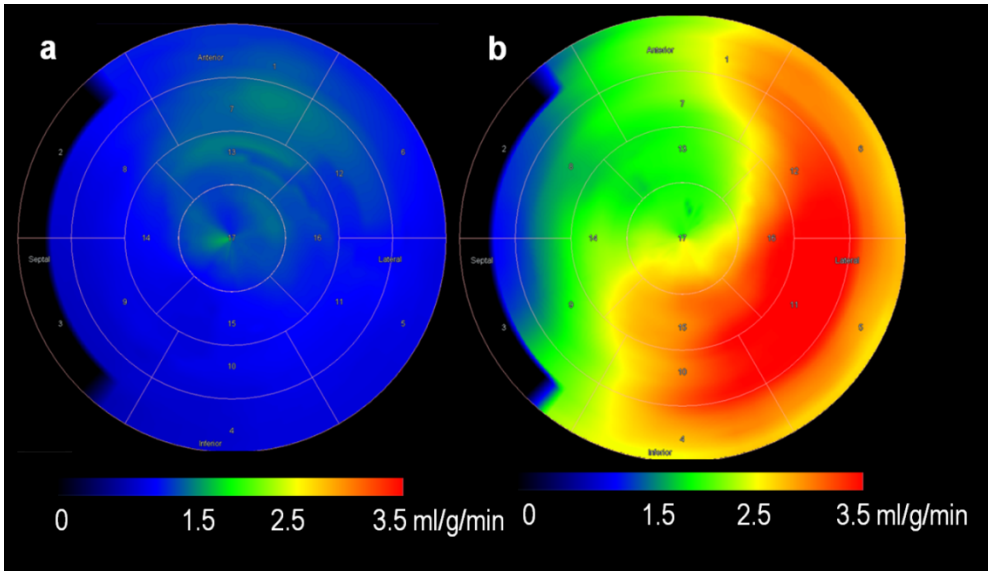

Figure 8. Examples of polar maps of MBF as assessed by ^{15}O-water PET and analysed using the CARIMAS™ -software at rest (a) and during adenosine stress (b). Reproduced with permission from *Eur Heart J Cardiovasc Imaging*. 2014 Jun; 15(6):659–65.doi: 10.1093/ehjci/jet274. Epub 2014 Jan 9.

Figure 9 shows the ROC curves of MFR, rest MBF alone, stress MBF alone, and an increase of MBF from rest to stress for detection of significant coronary stenosis. The optimal cut-off value for detecting significant coronary stenosis was: absolute stress (AUC: 0.95) MBF was 2.4 mL/g/min, absolute increase of MBF from rest to stress was 1.5 mL/g/min (AUC: 0.95) and MFR 2.5 (AUC: 0.90).

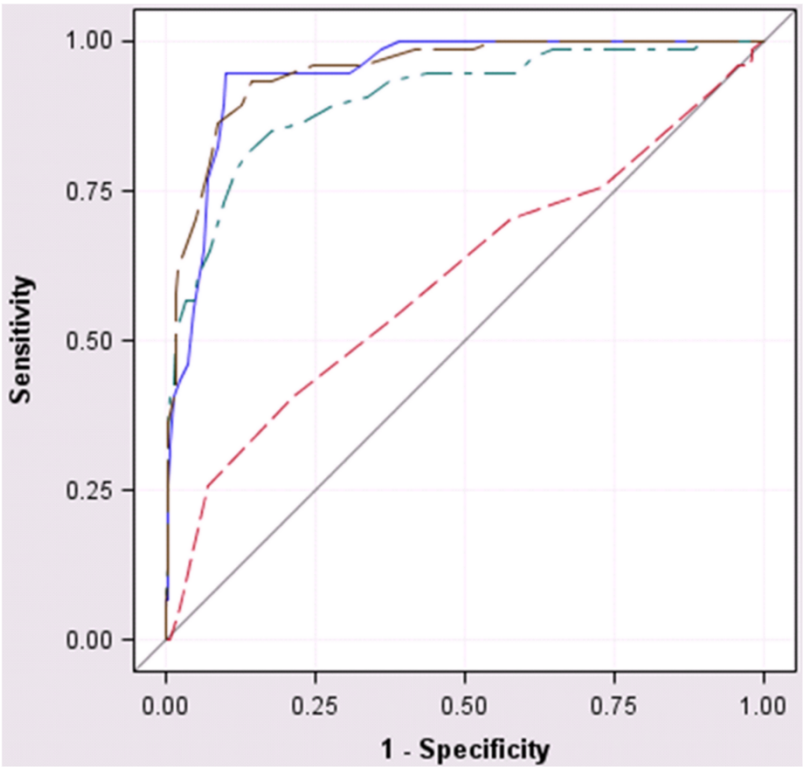

Figure 9. The ROC curves comparing diagnostic accuracy of MFR (green, dotted line), stress MBF alone (blue, continuous line), absolute increase of MBF from rest to stress (brown, cut line), and rest MBF alone (red, cut line) for detection significant coronary stenosis. Reproduced with permission from *Eur Heart J Cardiovasc Imaging*. 2014 Jun;15(6):659–65. doi: 10.1093/ehjci/jet274. Epub 2014 Jan 9.

5.2.2 Comparison of diagnostic accuracy

In ROC curve analysis (Figure 9), absolute stress MBF alone performed better than MFR in the detection of significant coronary stenosis (area under the ROC curve 0.95 vs. 0.90, P = 0.02). The performance of absolute stress MBF and increase of MBF (area under the ROC curve 0.95) was comparable (P = 0.52).

Table 7 shows the diagnostic accuracies for detecting significant stenosis in the whole patient group (vessel- and patient-based) with MFR, absolute stress MBF alone, and absolute increase of MBF from rest to stress. Sensitivity of absolute

increase of MBF from rest to stress by adenosine was better than that of MFR with 2.5 cut-off (P = 0.003), while specificity remained comparable (P = 0.08). Similarly, stress MBF alone resulted in better sensitivity (P = 0.035) than MFR with cut-off 2.5 without compromising specificity (P = 0.27). The stress MBF alone had better accuracy than MFR with cut-off 2.5 (P = 0.04), whereas absolute increase of MBF and MFR had comparable accuracy.

Table 7 shows that on patient-based analysis, diagnostic accuracies, sensitivities and specificities of MFR, stress MBF alone, and absolute increase of MBF from rest to stress, were comparable. The number of patients with all regions correctly classified by stress MBF alone was 88 (accuracy 84%) and MFR 75 (accuracy 74%).

Table 7. Diagnostic accuracy of myocardial flow reserve (stress MFR <2.5), absolute stress myocardial blood flow (MBF) and absolute increase of (increase MBF) for the detection of significant stenosis in the whole patient group. *Reproduced with permission from* Eur Heart J Cardiovasc Imaging. 2014 Jun;15(6):659–65. doi: 10.1093/ehjci/jet274. Epub 2014 Jan 9.

	Vessel-based analysis (n=312)				
	accuracy	sensitivity	specificity	PPV	NPV
MFR	86	80	87	66	93
Stress MBF	90*	89*	90	73	96
Increase MBF	88	92	87	69	97
	Patient-based analysis (n=104)				
	accuracy	sensitivity	specificity	PPV	NPV
MFR	88	87	88	80	92
Stress MBF	91	95	89	84	97
Increase MBF	89	95	86	80	97

PPV=positive predicive value, NPV=negative predictive value, *:p<0.05 vs. MFR

We compared diagnostic accuracies of MFR with the cut-off value of 2.5 or 2.0. On vessel-based analysis, the accuracy, sensitivity, specificity, PPV, NPV, and of MFR with cut-off value of 2.0 were 87, 57, 95, 84, and 88% (for both sensitivity and specificity P < 0.0001 vs. 2.5 cut-off), respectively. The corresponding values on patient-based analysis were 85, 66, 95, 89 (P = 0.005 vs. 2.5 cut-off), and 83% (P = 0.03 vs. 2.5 cut-off). Table 6 shows the results with MFR cut-off value of 2.5.

5.2.3 Effect of beta-blocker therapy

Because of i.v. beta-blocker usage before CT angiography and the PET scans, diagnostic accuracy of MFR and absolute stress MBF were studied separately in patients who received (n = 79) or did not receive (n = 25) i.v. beta-blocker therapy prior to perfusion imaging. In the regions that were subtended by non-stenosed coronary arteries, rest MBF was comparable in patients who received or did not receive beta-blocker prior to imaging (1.0 ± 0.2 vs. 1.0 ± 0.3 mL/min/g, P = 0.60). MFR was not different (3.5 ± 1.0 vs. 3.1 ± 0.9 mL/min/g, P = 0.10), though stress

MBF was slightly higher in patients who received beta-blocker (3.5 ± 1.0 vs. 3.0 ± 0.9 mL/min/g, P = 0.04).

Table 8 shows that the diagnostic accuracy of MFR, absolute stress flow, and absolute increase of MBF during adenosine stress were comparable in patients who received or did not receive beta-blocker therapy.

Table 8. Diagnostic accuracy of myocardial flow reserve (stress MFR), absolute stress myocardial blood flow (MBF) and absolute increase of (increase MBF) for the detection of significant stenosis in patients who received or did not receive intravenous beta-blocker prior to imaging (vessel-based analysis). *Reproduced with permission from* Eur Heart J Cardiovasc Imaging. 2014 Jun;15(6):659–65. doi: 10.1093/ehjci/jet274. Epub 2014 Jan 9.

	beta-blocker (n=237)				
	accuracy	sensitivity	specificity	PPV	NPV
MFR	87	83	88	63	95
Stress MBF	91	96	90	69	99
Increase MBF	88	91	87	64	98
	no beta-blocker (n=75)				
	accuracy	sensitivity	specificity	PPV	NPV
MFR	80	78	81	70	87
Stress MBF	91	93	90	83	96
Increase MBF	88	93	85	78	95

PPV=positive predicive value, NPV=negative predictive value.

5.3 Resting coronary flow velocity in the functional evaluation of coronary artery stenosis (Study III)

5.3.1 Patients

Study III measured the ratio of maximal diastolic flow velocity to prestenotic flow velocity (M/P ratio) in the coronary segments with stenosis in CTA in patient population described 4.2.3.

5.3.2 Invasive coronary angiography (ICA)

There were no cardiac events between CTA and ICA. In invasive coronary angiography, 34 (34%) patients out of 101 had stenosis ≥ 50% in their coronary arteries. Hemodynamically significant lesions after invasive angiography and FFR were detected in 33 patients. In 14 of them, the lesions were either total occlusions or extremely tight (> 90%) stenosis in which FFR was not possible. Four other patients had 30 – 70% stenosis in which FFR could not be performed due to scheduling or technical reasons. In patients with no FFR performed, > 50% stenosis by QCA was considered positive and the vessel graded accordingly. Altogether, there were 66 significant coronary artery stenoses; 39 in the LAD, 12 in the LCX, and 14 in the RCA. Only one patient had significant LM disease. Among these stenoses were

six total occlusions (three in the mid LAD and three in the mid RCA). There were two subsequent stenoses in 10 vessels (8 LAD, 1 LCX, and 1 RCA). Fifteen patients had single-vessel disease, 10 had two-vessel disease, and eight had multivessel disease.

5.3.3 Feasibility of TTDE

Figure 3, (page 30) shows the assessment of a coronary stenosis with the use of TTDE together with corresponding CTA and invasive coronary angiography. Based on CTA, 285 lesions causing luminal narrowing of > 20% in 670 segments in 76 patients were evaluated with TTDE. There were 224 lesions (83% of the evaluated segments without total occlusion) in which the M/P ratios were quantified using the pulsed-wave Doppler recordings of flow velocity profiles. In 52 segments, either TTDE indicated the total occlusion or the M/P ratio was approximated based on color Doppler signal due to inability to align ultrasound beam with the flow. There were eight segments in the RCA and one in the LAD in which the area of interest could not be visualized by TTDE (3% of segments).

The average M/P ratio was higher in coronary segments with hemodynamically significant than non-significant stenosis (3.59 ± 1.82 vs. 1.28 ± 0.60 m/s, $P < 0.001$, Figure 10). The optimal cut-off value of the M/P ratio based on ROC curve analysis for discriminating non-significant and significant stenosis was 2.2 (AUC = 0.92 ± 0.02, sensitivity 82%, specificity 94%, n = 224 stenosis, $P < 0.001$, Figure 11).

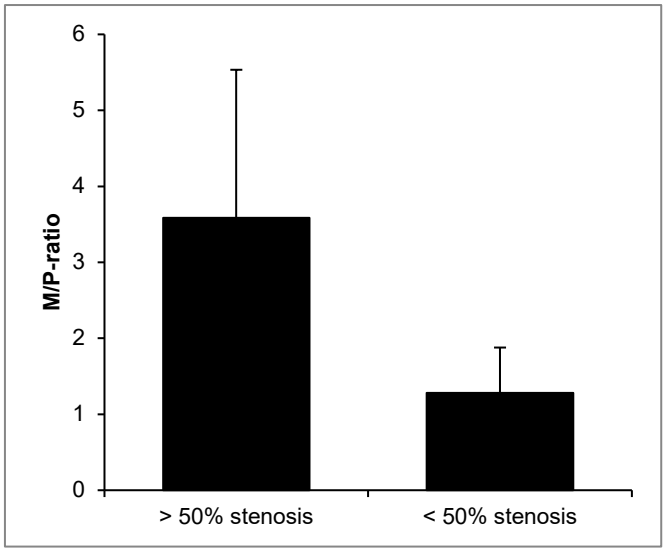

Figure 10. Validation of the M/P-ratio in 224 coronary lesions evaluated by TTDE; the average M/P-ratio was significantly higher in significant (n=53) than non-significant (n=169) stenosis. Modified from *Eur Heart J Cardiovasc Imaging*. 2012 Jan; 13(1):79–85. doi: 10.1093/ejechocard/jer153. Epub 2011 Aug 30).

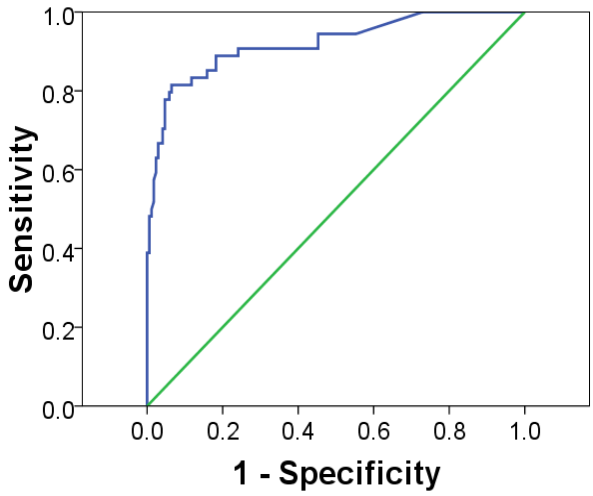

Figure 11. Based on the receiver operating characteristic curve analysis, the optimal cut-off value for the detection of significant stenosis was 2.2 (AUC 0.92) providing good diagnostic accuracy (P < 0.001). Reproduced with permission from *Eur Heart J Cardiovasc Imaging. 2012 Jan; 13(1):79–85. doi: 10.1093/ejechocard/jer153. Epub 2011 Aug 30*).

Based on the evaluation of flow in the septal branches of LAD, TTDE correctly diagnosed two total occlusions in both the RCA and the LAD. One total occlusion in both vessels was missed.

5.3.4 Sequential computed tomography angiography and transthoracic Doppler echocardiography vs. computed tomography angiography alone

Coronary CTA alone showed high diagnostic accuracy for detecting significant stenosis or total occlusion on both a patient level (accuracy 90%, sensitivity 91%, specificity 89%, PPV 82%, and NPV 95%, n = 101) and a segment level (accuracy 93%, sensitivity 71%, specificity 95%, PPV 61%, and NPV 97%, n = 670) as Figures 12A and 12B shows. False findings were those with the detected stenosis overestimated by CTA resulting in a reduction in PPV.

Subsequent CTA and TTDE provided higher PPV (78%) and better diagnostic accuracy on a segment level than CTA alone (accuracy 96%, p = 0.006) without impairment of NPV (97%; Table 9, Figure 12A). The false negative results (8 in the LAD, 3 in the LCX, and 3 in RCA) included two total occlusions, two subtotal (> 95%) stenosis, seven stenoses that were 65 – 90%, and seven stenoses that were 50 – 65% by QCA. The specificity of subsequent CTA and TTDE for significant stenosis was better (98%, *P = 0.004), whereas sensitivity was comparable (77%, P = 0.39) with CTA alone.

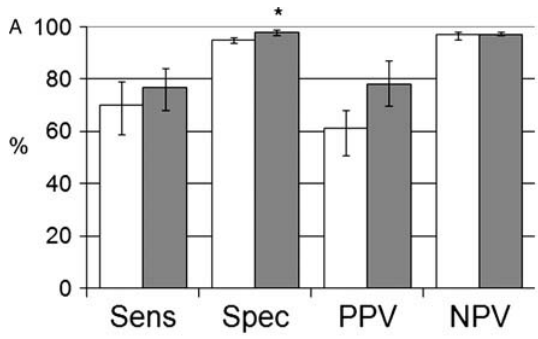

Figure 12A. Diagnostic performance of CTA alone (white bars) and in combination with TTDE (grey bars) (segment level). Reproduced with permission from *Eur Heart J Cardiovasc Imaging. 2012 Jan; 13(1):79–85. doi: 10.1093/ejechocard/jer153. Epub 2011 Aug 30*).

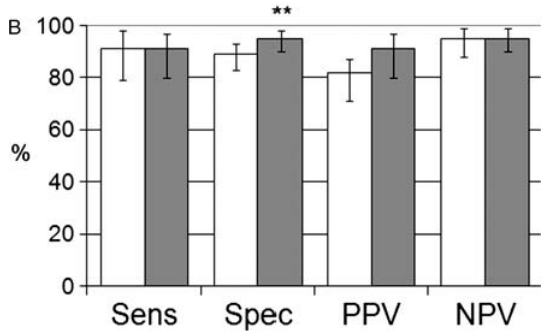

Figure 12B. Diagnostic performance of CTA alone (white bars) and in combination with TTDE (grey bars) (patient level). Reproduced with permission from *Eur Heart J Cardiovasc Imaging. 2012 Jan; 13(1):79–85. doi: 10.1093/ejechocard/jer153. Epub 2011 Aug 30*).

On a patient level, consecutive CTA and TTDE had accuracy of 93% (P = 0.07 vs. CTA alone), sensitivity of 91% (P = 1.0 vs. CTA alone), specificity of 95% (P** = 0.21 vs. CTA alone), PPV of 91%, and NPV of 95% (Figure 12B).

Seventy-five stenoses were classified as > 50% by CTA alone. In these segments, accuracy, sensitivity, specificity, PPV, and NPV of TTDE were 79, 80, 77, 84, and 72%, respectively. The nine false negative results (6 in the LAD, 1 in the LCX, and 2 in the RCA) included two total occlusions, two subtotal stenosis (> 95%), and two intermediate stenoses between 50 and 65% by QCA. Thirty-eight stenoses were measured as 50 – 70% by CTA alone. In these segments, accuracy, sensitivity, specificity, PPV, and NPV of TTDE were 82, 86, 75, 83, and 80%, respectively. TTDE correctly identified 15 of 20 stenoses in the vessels with two consecutive stenoses.

Table 9. Diagnostic performance of sequential CCTA and TTDE for the detection of significant stenosis. *Reproduced with permission from* Eur Heart J Cardiovasc Imaging. *2012 Jan; 13(1):79–85. doi: 10.1093/ejechocard/jer153. Epub 2011 Aug 30).*

	stenosis (n)	sensitivity (%)	specificity (%)	PPV (%)	NPV (%)
All*	66/670	77	98	78	97
LAD	39/218	82	96	82	96
LCX	12/151	67	99	89	97
RCA	14/214	79	98	69	98

*=LM+LAD+LCX+RCA (there was only one diseased LM)

6 Discussion

6.1 Studies I, II and III

Study I compared hybrid PET/CT imaging with individual imaging modalities in the detection of flow-limiting CAD. It demonstrated superiority of PET/CT hybrid imaging and had several unique features. 1) The first study to take full advantage of CT angiography and PET perfusion was performed with a hybrid imaging device, including quantitative perfusion analysis. 2) The study was performed in symptomatic patients with intermediate pretest likelihood of CAD as part of a routine clinical diagnostic work-up. 3) The patients underwent ICA blinded to the non-invasive test results to avoid referral bias. 4) The CTA and CT/PET results were compared to the combination of ICA and FFR, providing anatomic and functional results of circulation and perfusion of heart for comparisons.

Study I shows that hybrid PET/CT is an excellent non-invasive, diagnostic method to rule out and diagnose hemodynamically significant CAD and to assess its severity. The imaging protocol is also short with a low radiation dose. The CTA alone had very good NPV (97% per patient and 94% per vessel) but only modest PPV compared with ICA, and with CTA it was very difficult to accurately evaluate the severity of stenosis. Even with a certain degree of stenosis, it is very difficult to estimate its functional significance to the myocardial perfusion, a common handicap in all anatomic imaging. Because normal PET perfusion rules out hemodynamically significant CAD (NPV 97% per patient and 98% per vessel), we can use PET perfusion imaging by itself to exclude occluding CAD. Reduced perfusion can also be a sign of microvascular disease, not only epicardial coronary artery disease. These changes can also increase the risk of cardiac events and death (Herzog *et al.*, 2009) but are difficult to diagnose with common anatomic imaging methods. The PPV result of 86% (per patient in PET) suggests that small-vessel disease was also contributing to the findings.

Myocardial flow reserve (MFR), i.e., ratio of stress and rest flow, has been commonly used to detect hemodynamically significant CAD with many imaging modalities, but we used absolute quantification of perfusion in PET in this study. Although absolute quantification has been validated in many studies with other tracers (Muzik *et al.*, 1998; Yoshinaga *et al.*, 2003; Parkash *et al.*, 2004), it has rarely been used in clinical studies. Our study used ^{15}O-water, which has not commonly

used because it requires an on-site cyclotron. The advantage of ^{15}O-water is the linear uptake depending on the perfusion flow. Our ROC curve shows that the cut-off between normal and pathological MBF is < 2.5 ml/g/min, and practically all regions with MBF < 2.0 ml/g/min were abnormal. MBF values between 2.0 – 2.5 ml/g/min are considered mildly abnormal and clinical decisions are made by cardiologist depending on patient symptoms and other findings. Absolute quantification allows accurate detection of each myocardial region individually without relative changes in perfusion distribution, leading to better PPV and also more reliable diagnosis of CAD in multivessel and small-vessel diseases (Kajander *et al.*, 2011; Ziadi *et al.*, 2012; Fiechter *et al.*, 2012; Naya *et al.*, 2014).

Performing CTA and PET perfusion imaging separately makes it possible to take advantages of both of these techniques. We avoid PET imaging when CTA is normal in everyday clinical use, but in this novel study, we needed to get information about the plaques that are not flow-limiting. It is valuable to diagnose CAD changes even if myocardial perfusion is not impaired. This will help us to advise our patient about correct preventive actions (i.e. start preventive medications or advice lifestyle modification) (Newby *et al.*, 2015; Fordyce *et al.*, 2016). The hybrid PET/CT perfusion imaging successfully combines both anatomical and functional imaging techniques. When CTA detects the degree and location of stenosis in a coronary artery and in that way separates microvascular from epicardial disease, the PET perfusion shows whether the findings are flow-limiting or not. In this study, the accuracy of the PET/CT hybrid imaging was superior. Also, the recent meta-analysis of hybrid cardiac imaging demonstrated improved diagnostic specificity of obstructive CAD when compared with stand-alone coronary CTA, without lowering sensitivity (Rizvi *et al.*, 2018).

Study II continued our research on the clinical value of absolute quantification of MBF with the same patient population as Study I's. Because quantitative analysis has been shown to improve diagnostic accuracy and provide prognostic information (Muzik *et al.*, 1998, Haijjiri *et al.*, 2009) when compared with traditional myocardial flow reserve measurements, we wanted to study if stress MBF alone could be accurate and sufficient to detect CAD in patients without previous myocardial infarction. By measuring the MBF alone, we simplify and shorten the imaging protocols and reduce the radiation dose to the patient. The hypothesis that quantification of MBF during stress alone is reliable for diagnosing the CAD had not been prospectively validated in the clinical setting before this study.

Study II is a prospective study to show that absolute stress MBF alone is sufficient to diagnose CAD in a relatively large number of patients. This study provides the first data showing that the stress MBF actually performs better than MFR in CAD detection. There are several factors that can explain the superiority of MBF over MFR. First, the reduced MFR may be caused by changes in resting flow, not necessarily changes in stress flow. Hypertension, hypertrophic cardiomyopathy and

dilated cardiomyopathy are examples of states that can increase cardiac workload at rest and may cause distortion to the measurements and diagnosis (Neglia *et al.*, 2002; Cecchi *et al.*, 2003). Second, the quantification of MBF involves dynamic and complex data acquisition and processing and, therefore, a single measurement is less affected by statistical noise. It is important, however, to realize that neither stress MBF nor MFR can differentiate whether reduced maximal flow is caused by microvascular dysfunction or epicardial coronary stenosis. This is not a problem when using a hybrid PET/CT scanner like we used in Study I, whereas in MBF analysis the reduced perfusion is diagnosed even when in relative MFR analysis these patients are classified as normal.

The optimal threshold value of stress MBF for detecting >50% flow-limiting coronary stenosis was 2.4 ml/g/min in this study, which was in line with previous PET studies with ^{15}O-water. In MFR analysis the value < 2.0 is usually considered abnormal, but in our study the optimal threshold for detection of significant coronary stenosis was 2.5 instead of 2.0, leading to a better specificity without reducing sensitivity. Figure 9 (page 40) presents the ROC curve analysis comparing the diagnostic accuracy of MFR, stress MBF alone, absolute increase of MBF from rest to stress, and rest MBF alone for hemodynamically significant coronary artery stenosis.

As Study I reported, the imaging protocol included coronary CT angiography in the same imaging session as the PET perfusion study. Therefore, beta-blocking therapy was used in most of the patients (79 out of 104) to reduce heart rate < 60 bpm before imaging. We separately analyzed MBF for patients with and without beta-blocking therapy and found no difference in diagnostic accuracy between these two groups. It has been also previously demonstrated that beta blockers do not affect invasive measurements of FFR (Ozdemir *et al.*, 2007).

Study III demonstrated that the combination of CTA and TTDE is a potential method for anatomical and functional evaluation of CAD. Previous studies have demonstrated good sensitivity (64 – 86%) and specificity (92 – 96%) for diagnosing flow-limiting LAD stenosis in CAD but only limited feasibility when analyzing RCA (17 – 62%) or LCX (37 – 38%) (Krzanowski *et al.*, 2000; Saraste *et al.*, 2005; Caiati *et al.,* 2009). This study was the first demonstration of a combined use of CTA and TTDE that can improve the success rate, since CTA allows focused analysis of TTDE. Relative increase in resting flow velocity by TTDE can discriminate flow-limiting stenosis from non-significant coronary lesions, defined by invasive coronary angiography and FFR.

When measuring the coronary flow with TTDE, the turbulent and accelerated flow in-site of stenosis causes a strong color signal that is easy to notice when you know the expected location of coronary stenosis. The fact that CTA provided the exact location of stenosis is likely to contribute to the high success rate of measurements in Study III. However, coronary TTDE gives only limited information

about anatomical structures, and examination requires specific training and expertise on coronary anatomy.

The study measured the ratio of maximal diastolic flow velocity to prestenotic flow (M/P-ratio), and the site of stenosis was located with CTA. Our findings confirm the prior observations that M/P-ratio is an accurate indicator of the severity of coronary stenosis. The study gives important additional information to previous studies on this subject, because our study validated the M/P-ratio for the first time with invasive FFR measurements. When analyzing the results, we found that the M/P-ratio of 2.2 was the best cut-off value to confirm the significant flow-limiting coronary artery stenosis. That is in line with the findings of previous studies in diagnosing > 50% stenosis of LAD (Hozumi *et al.*, 2000; Caiati *et al.*, 2009). It is important to measure prestenotic and maximal flow velocity close to each other to avoid the additive effects of consecutive lesions on the M/P-ratio.

Numerous single- and multicenter studies have shown the strength of CTA for excluding significant coronary stenosis, and the NPV is high, making CTA an excellent tool for investigating patients with low to intermediate pretest likelihood of flow-limiting CAD. However, CTA has only limited capacity to diagnose the severity of stenosis, and the PPV is relatively low. Typically, CTA tends to overestimate the stenosis, especially in the presence of densely calcified coronary plaques. Our study provides the first demonstration that evaluation with TTDE at the site of stenosis located by CTA can improve the diagnostic accuracy and PPV when compared with CTA alone. When treating symptomatic patients in a real-life setting, it is strongly recommended to get an objective finding of ischemia prior to revascularization. TTDE is a widely available bedside technique with no radiation exposure and provides an excellent tool for demonstration of flow-limiting stenosis before deciding on the management of CAD. In this blinded study protocol, we used the 17-segment model and predefined criteria for each coronary segment to match TTDE and CTA evaluation of stenosis. In real life, this could be facilitated by inspection of stenosis from CTA images by cardiologists, followed by echocardiography to further evaluate any suspected flow-limiting stenosis.

6.2 Limitation of the studies

The limitations of Studies I and II are that FFR could not be measured for all stenoses. This was due to the anatomy of some vessels and lesions as well as logistics in a busy invasive laboratory. The agreement between hybrid imaging and combined ICA and FFR was very good, but FFR also has limitations. Our goal was to evaluate all stenoses with borderline significance with FFR, which was possible in most patients. Another limitation is the relatively small patient population. Furthermore, more than half of the patients did not have obstructive CAD. The latter can also be regarded as

strength, because negative findings are important when investigating real-life patient populations with atypical symptoms and intermediate pretest likelihood of CAD.

Study III was part of Study I with the same patient population. Again, all lesions were not evaluated with FFR. Because of that, further studies are needed in the future to compare the M/P-ratio with invasive hemodynamic measurements. Our study population included only one significant LM stenosis and six total occlusions, and more research is needed to clarify the results in these circumstances. Similarly, the number of lesions in RCA and LCX was relatively small compared with LAD, and segments with diameter < 1.5 mm were excluded. The value of sequential CTA and TTDE in these settings needs further clarification.

6.3 Clinical implementation

The use of coronary CTA has increased in patients with suspected CAD. Recent studies have provided evidence that this approach results in good clinical outcomes (Newby *et al*, 2015; Hoffmann *et al*, 2017). Current clinical practice guidelines recommend functional tests to risk stratify and identify patients with ischemia prior to ICA, if CTA remains inconclusive (Montalescot *et al*, 2013; Moss *et al*, 2017). Most of modern PET/SPECT scanners are hybrid devices, which makes anatomic and functional testing in the same session feasible in practice. Combination of coronary ultrasound and CTA remains mainly for reseach purposes due to the need for spesific training and skills to visualize coronary flow. In addition to other hybrid imaging methods, myocardial CT perfusion imaging and FFR-CT are new promising methods to evaluate CAD in the future (Seitun *et al*, 2018; Sevag Packard *et al*, 2017).

7 Conclusions

The following conclusions may be drawn from the studies presented in this thesis.

I Cardiac hybrid PET/CT imaging provides accurate, noninvasive detection of CAD in a symptomatic population with intermediate pretest likelihood of CAD.

II Absolute quantification of MBF is an excellent diagnostic tool for evaluating symptomatic patients with intermediate likelihood of CAD. Absolute stress perfusion alone is superior to perfusion reserve when diagnosing hemodynamically significant coronary artery stenosis; it allows a shorter imaging protocol with a lower radiation dose than perfusion reserve.

III A combination of coronary CTA and TTDE is feasible for combined anatomic and functional evaluation of coronary stenosis. Compared with coronary CTA alone, addition of TTDE improved the accuracy of diagnosing CAD.

These results show the feasibility of hybrid imaging and demonstrate that it provides improved accuracy in detecting obstructive CAD as compared with stand-alone coronary CTA.

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