
Why Are We Interested in Myocardial Perfusion?

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Abstract

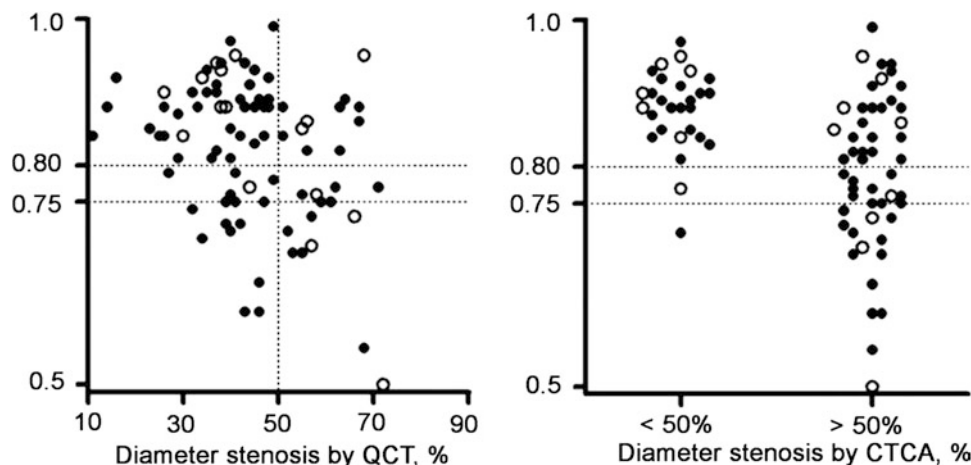
Cardiac CTA is increasingly asserting its position as an established tool for the detection and characterization of coronary plaque and stenosis, its morphological evaluation capability, however, falling short of hemodynamic assessment. This fact is of high relevance in the process of therapeutic decision making, which explains the dominance of functional imaging techniques, such as nuclear myocardial perfusion imaging, magnetic resonance imaging, or stress echocardiography. There are four major targets of functional imaging that are particularly critical to the selection of a revascularization procedure over medical treatment strategies: (1) Assessment of myocardial perfusion defects to identify treatable coronary artery disease (CAD); (2) Identification of myocardial perfusion status as an important prognostic factor for the occurrence of future cardiovascular events; (3) Assessment of myocardial viability to guide therapy; and (4) Evaluation of the hemodynamic relevance of detected coronary artery stenosis by flow measurements. This chapter reviews the current limitations of morphological assessment of coronary stenosis by cardiac CTA, describes available techniques for functional imaging, and enumerates its major targets, which have been well implemented in current management strategies for patients with suspected or known CAD.

1 Role of Imaging in the Management of Patients with Coronary Artery Disease

Contemporary imaging techniques have achieved a remarkable reliability for evaluating patients with suspected or known coronary artery disease (CAD). This is well in line with the predicted burden of CAD, which has increased substantially over the past few decades (Roger et al. 2011) and will continue to rise, requiring improved management

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Fig. 1 Scatterplots demonstrating the correlation between quantitative cardiac CTA (QCT) and fractional flow measurements (y-axis) indicating a weak correlation ($r = -0.32$, right), especially in coronary stenosis $>50\%$ (right). Coronary arteries smaller than 3.5 mm are depicted as solid circles, coronary arteries larger than 3.5 mm as open circles. From Meijboom et al. (2008)



strategies, especially enhanced diagnostic work-up strategies (Kruip et al. 2003).

The diagnostic work-up relies on several invasive and noninvasive imaging modalities. The current gold standard for the detection and evaluation of coronary stenosis is invasive angiography, a procedure which also enables direct therapeutic intervention; however, this procedure is associated with certain additional risks, such as arrhythmia, intima dissection, local bleeding, and discomfort. As result, only subjects with a high pre-test probability of CAD are referred for invasive angiography, whereas subjects with low- to intermediate pre-test probability of CAD are usually referred for non-invasive testing. Traditionally, myocardial perfusion imaging by single-photon emission computed tomography (SPECT) is the preferred noninvasive option. There is growing evidence that cardiac magnetic resonance imaging (CMR) or stress echocardiography can also serve well as gatekeepers for invasive angiography (Schuijf et al. 2005). SPECT, CMR, and echocardiography all have in common the fact that they identify ischemia by perfusion or wall motion abnormalities. Thus, traditionally, the presence and extent of myocardial ischemia have served as a reference for therapeutic decision making and referral for invasive angiography (Schuijf et al. 2007).

This paradigm has been challenged by the introduction and development of cardiac CT angiography (CTA), an imaging modality that primarily relies on the morphologic assessment of CAD. Cardiac CTA, with continuous technological development, is increasingly diffusing into clinical practice. As detailed by Dr. Nance in *Chapter 1*, current state-of-the-art protocols, though fast and comfortable for patients, involve a reasonable amount of radiation (2–3 mSv or less) and up to 100 ml of iodinated contrast agent. The true value of cardiac CTA lies in its ability to

exclude a significant stenosis with high sensitivity and high negative predictive value; on the other hand, not all subjects with a positive finding turn out to have a significant coronary stenosis on subsequent invasive coronary angiography.

2 Limitations of Morphological Imaging by Cardiac CTA

Despite the encouraging capabilities of cardiac CTA, as with other morphologic imaging modalities, cardiac CTA is unable to determine whether or not a detected lesion is hemodynamically significant. Hemodynamic significance is what determines whether either revascularization or medical therapy will be beneficial. In fact, there is a large body of evidence indicating that there is a high discrepancy ratio between the findings on cardiac CTA and subsequent functional tests.

Hacker et al. studied 38 patients (74 % male) with both 64-slice MSCT coronary angiography and SPECT imaging (Hacker et al. 2007). While 102 of 109 (94 %) patients without coronary artery stenosis also had normal SPECT studies, only 23 of 43 (53 %) with significant coronary stenosis had impaired myocardial perfusion based on the SPECT study, indicating that despite detection of a morphological stenosis, perfusion impairment may vary. Recently, Meijboom et al. compared CTA measured degree of stenosis with measurement of fractional flow reserve (FFR) (Meijboom et al. 2008). FFR is considered to be the gold standard for functional assessment of coronary stenosis, by positioning a catheter tipped flow wire proximal and distal to the lesion. Their results indicate that there is no agreement between CTA findings and FFR measured flow ($r = -0.32$, Fig. 1) and that morphologic assessment by

CTA was not able to identify a hemodynamically relevant coronary stenosis.

Overall, these observations are not surprising but emphasize the fact that there are two different imaging approaches to CAD, each of which provides fundamentally different information:

- (1) Morphological modalities: Cardiac CTA and invasive coronary angiography, both are well established methods to visualize coronary stenosis and plaque as the anatomic correlate of CAD.
- (2) Functional modalities: nuclear myocardial perfusion imaging (i.e. SPECT), echocardiography, MRI, and invasive measurement of fractional flow reserve are equally reliable in providing information pertaining to CAD.

For the decision of whether invasive or medical treatment is indicated, evidence of functionally relevant ischemia is of critical importance. Thus, in subjects in whom a significant stenosis is detected on CT, in the absence of hemodynamic information, the potential benefits of either revascularization or medical therapy remain undetermined. In order to design evaluation algorithms that allow optimal integration of cardiac CTA, investigations comparing MSCT with other noninvasive *functional* modalities are mandatory (Schuijf and Bax 2008). This can also be observed in larger randomized trials using cardiac CTA for patients with acute chest pain. For instance, there is interesting data from the ROMICAT II study, a large randomized trial in 1,000 subjects with initially inconclusive evaluation in the emergency department (Hoffmann et al. 2012). While there was an overall benefit from using cardiac CTA in patients with acute chest pain, the benefit was primarily attributed to patients in whom the presence of a significant coronary stenosis was ruled out. In support, subjects who were found to have CAD by CTA were predominantly referred for subsequent functional testing.

From a CT perspective, this need of functional information has resulted in a new field research, which extends the CT-based technology from morphological to functional assessment.

3 Rationale for Functional Imaging

Functional imaging relies on the detection of the hemodynamic consequences of CAD—known as ischemia—rather than pathological changes in the coronary arteries. In the presence of ischemia, defined as the mismatch of oxygen demand and supply, a sequence of events is initiated, referred to as “the ischaemic cascade” (Nesto and Kowalchuk 1987). Perfusion abnormalities start as diastolic and progress toward a systolic dysfunction; only at the very end of the cascade do ECG changes and angina occur

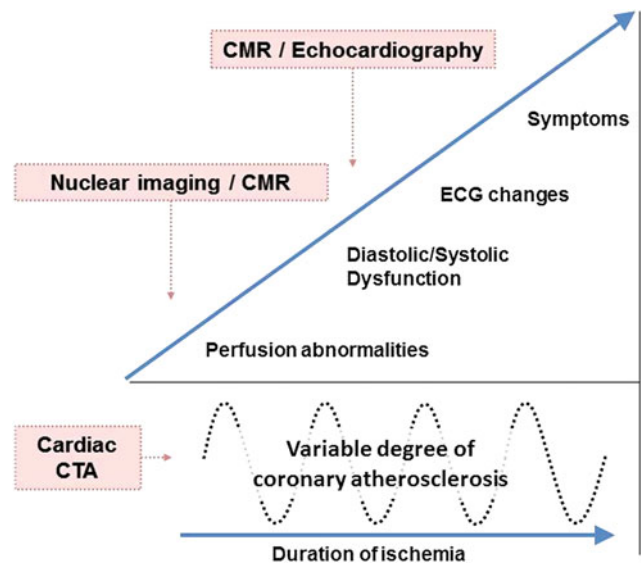


Fig. 2 The ischemic cascade represents the sequence of pathophysiological events following ischemia, with perfusion abnormalities occurring in the beginning, which can be identified by nuclear imaging techniques or CMR. The amount of the underlying degree of coronary atherosclerosis can vary and is detected and characterized by cardiac computed tomography angiography (CTA). Modified from Schuijf et al. (2005) *CMR cardiac magnetic resonance imaging*

(Fig. 2). Accordingly, the occurrence of perfusion abnormalities during stress may be more sensitive for the detection of CAD than the induction of systolic dysfunction (wall motion abnormalities) (Leong-Poi et al. 2002).

As coronary atherosclerosis often occurs without any hemodynamic consequences, the likelihood that a coronary stenosis may be flow limiting is related to the degree of stenosis and vice versa; severe perfusion defects are highly predictive of a critical (>90 %) coronary stenosis (Shaw and Berman 2009). Notably, a perfusion deficit may also be associated with vascular dysfunction in the setting of non-obstructive CAD, as collateral flow in a patient with obstructive CAD may result in normal flow to that region (Aarnoudse et al. 2003).

It is obvious that CAD is not necessarily a prerequisite or an immediate cause of myocardial ischemia, as there are concordant and discordant findings between functional and morphological imaging modalities. Overall, these observations explain the level of discrepancy observed in CTA studies as detailed above.

4 Established Techniques for Functional Imaging

There are three major functional imaging modalities: myocardial perfusion assessment by SPECT, wall motion abnormalities detection by echocardiography, or both of

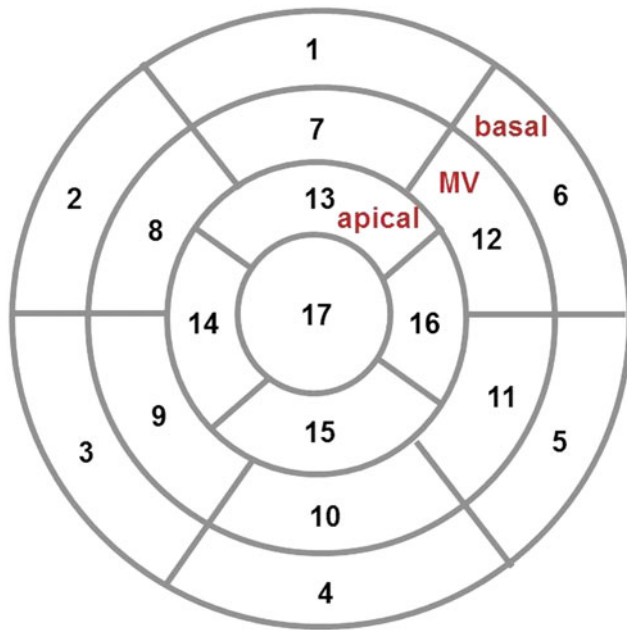


Fig. 3 Seventeen segment model developed for assessment of myocardial perfusion abnormalities, which is used to report findings for all functional imaging modalities. Modified from Cerqueira et al. (2002)

these through CMR (Marcus et al. 2011). Over time, these techniques have become complementary rather than competitive, since they provide different information. Generally, images are interpreted visually by adhering to a 17 myocardium-segment model, developed for SPECT but usually applied to all functional cardiac imaging modalities (Fig. 3) (Cerqueira et al. 2002).

It is important to note that although these functional imaging modalities primarily focus on the detection of perfusion defects as part of the ischemic cascade, usually their diagnostic accuracy is studied and reported for the detection of significant coronary stenosis. This, however, is not the appropriate comparator (as detailed above), given the discrepancy between function and morphologic information.

4.1 Nuclear Myocardial Perfusion Imaging

SPECT, using technetium-, thallium-, or tetrofosmin-based radionuclide tracers, has become the most widely used modality for the assessment of myocardial perfusion. By comparing the uptake and distribution of radionuclide by myocytes under rest and stress conditions, it allows a three-dimensional assessment of the myocardial perfusion and viability. Reversible defects (perfusion abnormalities

detected at stress but absent at rest) are indicative of ischemia; persistent defects present both in rest and stress condition represent infarcted myocardium. Examples of a reversible and persistent defect are provided in Figs. 4 and 5, respectively.

The diagnostic accuracy of SPECT in detecting morphologically significant coronary stenosis is relatively high (specificity: 87–94 % and sensitivity: 85–90 %) (Rochmis and Blackburn 1971; Mertes et al. 1993; Kapur et al. 2002; Taillefer et al. 1997; Mark et al. 2003; Merhige et al. 2007). Disadvantages of SPECT include its tracer-dependent radiation dose (9–25 mSv) and a total examination time of ~4–5 h (imaging time 10–20 min per session, with 3–4 h separation time between stress and rest acquisitions). Associated costs are moderately high (approximately \$600–\$1,000) (Merhige et al. 2007). However, there is evidence that recently improved technology, i.e. ultrafast cameras/multiple scanning detectors (D-SPECT), may reduce radiation dose, shorten study time, and improve sensitivity (Garcia et al. 2011).

4.2 Cardiac Magnetic Resonance Imaging

In contrast to SPECT, MRI is a non-ionizing radiation modality that is increasingly used for the assessment of cardiac function and myocardial perfusion (Cheong 2010). Contrast material (gadolinium chelate) has a fairly linear relationship between its concentration and signal intensity on T1-weighted sequences (Croisille et al. 2006; Donahue et al. 1997). Besides its merit in the evaluation of non-ischemic cardiomyopathies, MRI permits the differentiation between persistent defects (fixed defects, present both in rest and stress conditions, consistent with infarction) and reversible defects (present on stress acquisitions only, consistent with ischemia). Late gadolinium enhancement (pathological myocardial enhancement 10 min after contrast administration) is the hallmark of infarction; an example is provided in Fig. 6.

In contrast to SPECT, MRI allows the visual differentiation between subendocardial and transmural infarction, a very relevant finding for guiding therapeutic intervention. Its diagnostic accuracy for the detection of morphologically significant coronary artery stenosis is high (sensitivity and specificity of 89 and 87 %, respectively) (Christiansen et al. 2010; Klem et al. 2006). There is recent data suggesting that MRI can accurately detect hemodynamically relevant CAD similar or slightly superior to SPECT (Schwitter et al. 2008).

Disadvantages of MRI include the required staff expertise, limited availability in community hospitals, relatively long

Fig. 4 Myocardial perfusion imaging (tetrofosmin) SPECT study of a 78 year old male with a reversible defect in the posterior wall consistent with ischemia (*arrowheads*). Courtesy of Dr. S. Lehner, Munich, Germany

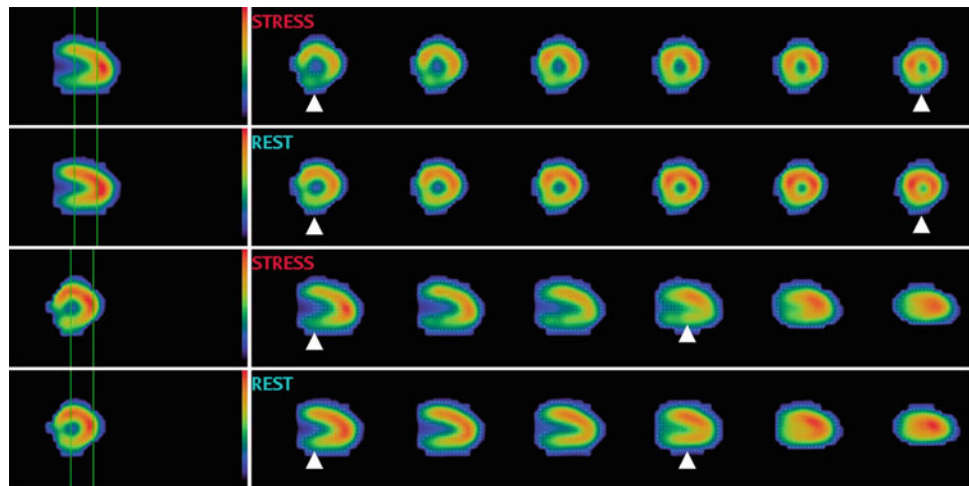
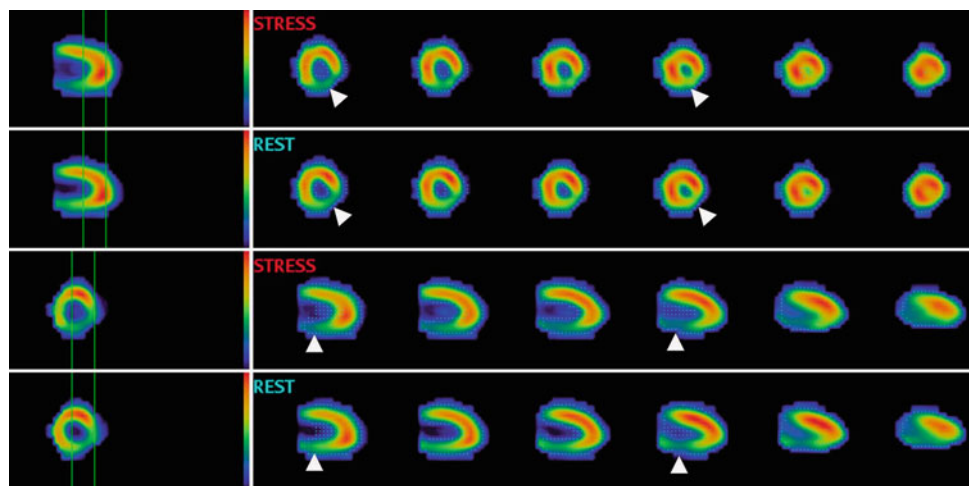


Fig. 5 Myocardial perfusion imaging (tetrofosmin) SPECT study of a 58 year old female with a persistent defect in the posterior wall consistent with infarction (*arrowheads*). Courtesy of Dr. S. Lehner, Munich, Germany



acquisition times (30–45 min), high cost, and contraindication in patients with pacemakers or implanted defibrillators.

4.3 Echocardiography

Echocardiography, the least expensive technique, is well-suited for the assessment of cardiac function, specifically global and regional dysfunction. Strain rate, which is the systolic shortening of the longitudinal and circumferential axes (negative strain) by a thickening or lengthening in the radial direction (positive strain) can be quantified by either Doppler or 2D ultrasound technique (Marwick 2006). Also, in the diastolic phase, left ventricular impairment (diastolic stunning) is a very sensitive marker of myocardial ischemia (Bonow et al. 1985; Wijns et al. 1986; Ehring and Heusch 1990). The ratio of strain changes before and after exercise has a high sensitivity of 97 % and a specificity of 93 % in detecting a significant coronary stenosis (Ishii et al. 2009; Achenbach et al. 2010), which may be improved by

administration of contrast media (microbubbles) (Hundley et al. 1998).

Its main limitations include a very high observer dependency associated with a high interobserver variability.

5 Relevance of Functional Imaging for Patient Management

The clinical value of functional imaging for patients with suspected or known CAD is complex but can be simplified and categorized into a number of scenarios in which obtained functional information have shown to be beneficial for patient management.

5.1 Identification of Treatable Ischemia

Most data demonstrate that perfusion imaging is able to effectively identify subjects for subsequent angiography,

Fig. 6 Cardiac magnetic resonance imaging study (1.5 T) of a 61 year old male with an adenosine-stress induced perfusion defect in the inferior and infero-septal wall (arrowheads)



with SPECT currently being the most frequently used test in the United States (Min and Berman 2009). Early studies indicate that myocardial perfusion is significantly impaired in the presence of a $\geq 70\%$ coronary stenosis (Gould and Lipscomb 1974). SPECT has the ability to identify disease in individual coronary arteries, since perfusion abnormalities correlate closely with coronary artery perfusion territories (Elhendy et al. 2000).

The largest body of evidence of the value of perfusion imaging stems from a cohort of 10,000 subjects without prior CAD, who underwent stress SPECT prior to intervention or medical therapy (Hachamovitch et al. 2003). Despite a non-randomized, retrospective approach, the results indicate that after 2 years of follow-up, subjects with moderate to severe perfusion defects who underwent revascularization had a significantly improved mortality as compared to subjects with no or mild perfusion defects who were revascularized. The value of the assessment of myocardial perfusion imaging has recently been confirmed by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, the largest randomized trial of patients with chronic CAD (Boden et al. 2007). In the main study, in 2,287 patients, a strategy of optimal medical therapy plus revascularization was not

associated with an improved outcome compared with optimal medical therapy alone. The nuclear substudy subsequently published by Shaw et al. confirmed the importance of the quantitative noninvasive assessment of perfusion on serial stress SPECT imaging in a subset of 314 patients (Shaw et al. 2008). Patients having significant improvement in ischemia, which was achieved more often in the interventional group, had fewer subsequent cardiovascular events (Fig. 7).

Similarly, stress CMR can be used to accurately detect significant coronary stenosis as shown in a recent meta-analysis pooling results of 1,516 patients with an intermediate likelihood of disease (prevalence 57.4%) (Nandalur et al. 2007). The results by Nandalur et al. indicate a relatively high sensitivity and specificity of 0.91 and 81%, respectively.

5.2 Relevance of Myocardial Viability

Assessment of myocardial viability is critical for the management of patients with ischemic cardiomyopathy, as only viable myocardium will benefit from revascularization. From an array of imaging modalities, including PET and contrast echocardiography, CMR and SPECT are the predominant

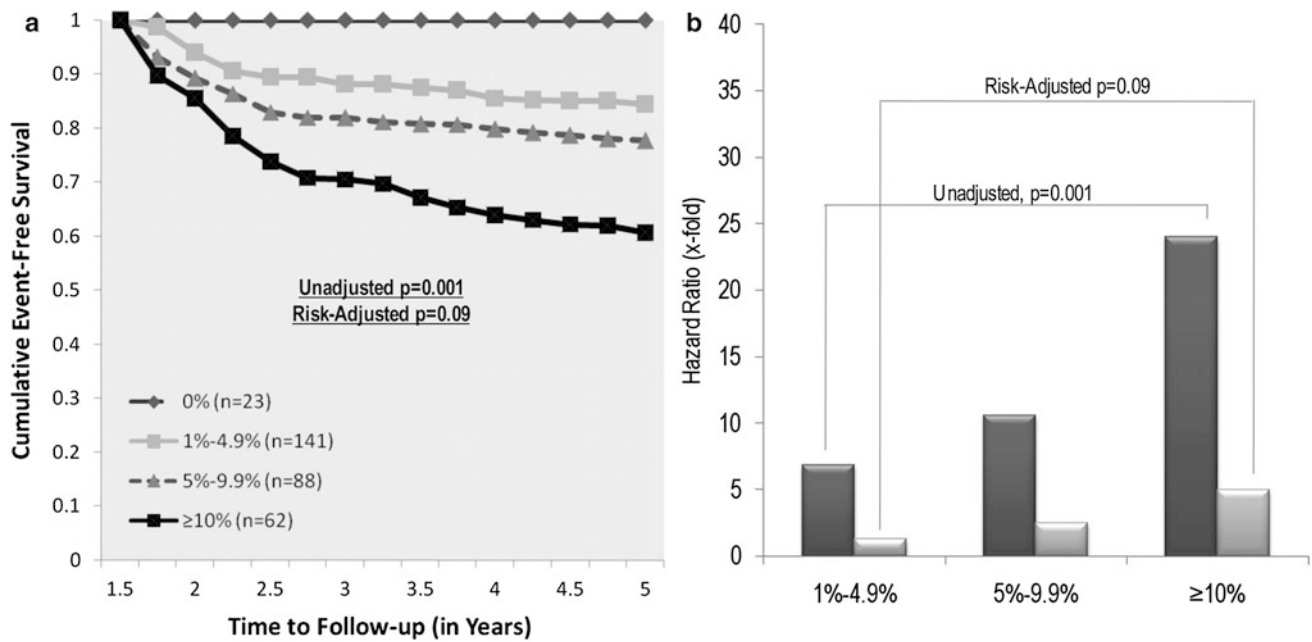


Fig. 7 Kaplan-Meier-survival curves **a** and hazard ratios associated with residual perfusion defects after treatment **b** in the COURAGE trial. From Shaw et al. (2008)

methods used for the assessment of myocardial viability, based on perfusion and scan quantification (Schinkel et al. 2007). On CMR, late gadolinium enhancement represents non-viable myocardium or fibrosis (rarely myocarditis), whereas non-enhancing areas represent viable tissue. In SPECT, fixed and reversible defects (between rest and stress acquisitions) differentiate viable from non-viable myocardium, respectively.

If assessed early after MI, there is evidence that the extension of non-viable, infarcted area may predict recovery of left ventricular function. In a small initial study of 40 patients, Choi et al. demonstrated that the extent of dysfunctional myocardium that was not infarcted or had necrosis comprising less than 25 % of the wall thickness, as determined by CMR, was the best predictor of global improvement in the left ventricular function (Choi et al. 2001).

The transmural extension of non-viable, infarcted myocardium predicts the recovery of left ventricular function after revascularization (Kim et al. 2000). Selvanayagam et al. studied 50 patients with known coronary artery disease and left ventricular dysfunction prior to surgical revascularization (CABG) using CMR (Selvanayagam et al. 2004). Following revascularization, subjects were assessed for improvement of left ventricular function. They found that the likelihood of recovery from left ventricular dysfunction decreased with increase of the transmural extent of late gadolinium enhancement (LGE) on CMR. Specifically, they found that 78 % of myocardial segments without necrosis improved, whereas only 17 % of segments with LGE greater than 75 % transmural improved at follow-up (Fig. 8).

While improvement of left ventricular function may be a less relevant outcome, there is also evidence from Allman et al. who demonstrated in a meta-analysis of 24 prognostic studies, including 3,088 patients, that the amount of viable myocardium has strong prognostic implications (Allman et al. 2002). Their results show a low annual death rate in patients who had viable myocardium and were revascularized, whereas the death rate in patients with viable myocardium who were treated medically was substantially higher (3.2 vs. 16 % annual death rate, respectively).

5.3 Risk Stratification and Prognosis

Assessment of patient's prognosis plays a central role in the primary and secondary prevention setting and many imaging modalities have been used for risk stratification.

There is strong evidence supporting the prognostic value of SPECT MPI and its ability to risk-stratify patients with suspected or documented CAD in a variety of clinical settings. Primarily, in patients with stable coronary artery disease, the number of ischemic myocardial segments has been shown to be a strong predictor for cardiac events (Brown et al. 1983; Ladenheim et al. 1986). Hachamovitch et al. studied 5,183 consecutive patients who underwent stress/rest SPECT and were followed up for the occurrence of cardiac death or myocardial infarction over a mean period of almost 2 years (Hachamovitch et al. 1998). The presence of mildly abnormal, moderately abnormal, or severely abnormal perfusion defects was associated with an

Fig. 8 Relationship between transmural extent of LGE on CMR before surgery and likelihood of increased regional function after surgery in all dysfunctional segments (*left*) and in all segments with severe hypokinesia, akinesia, or dyskinesia. From Selvanayagam et al. (2004)

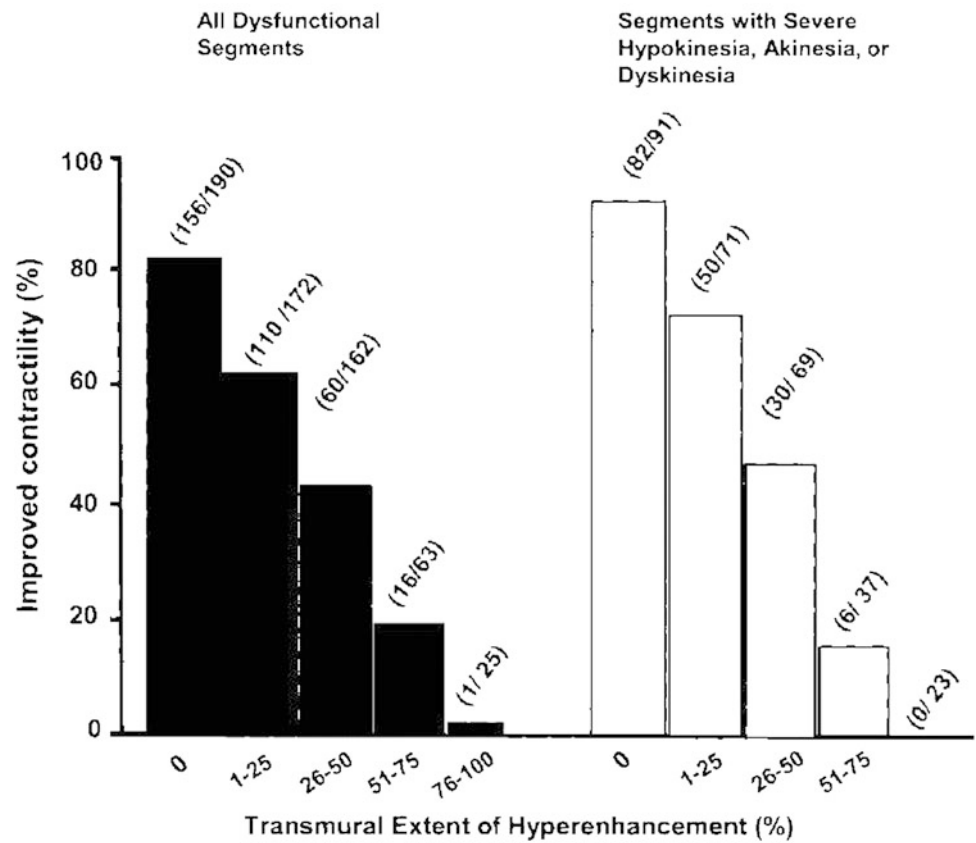
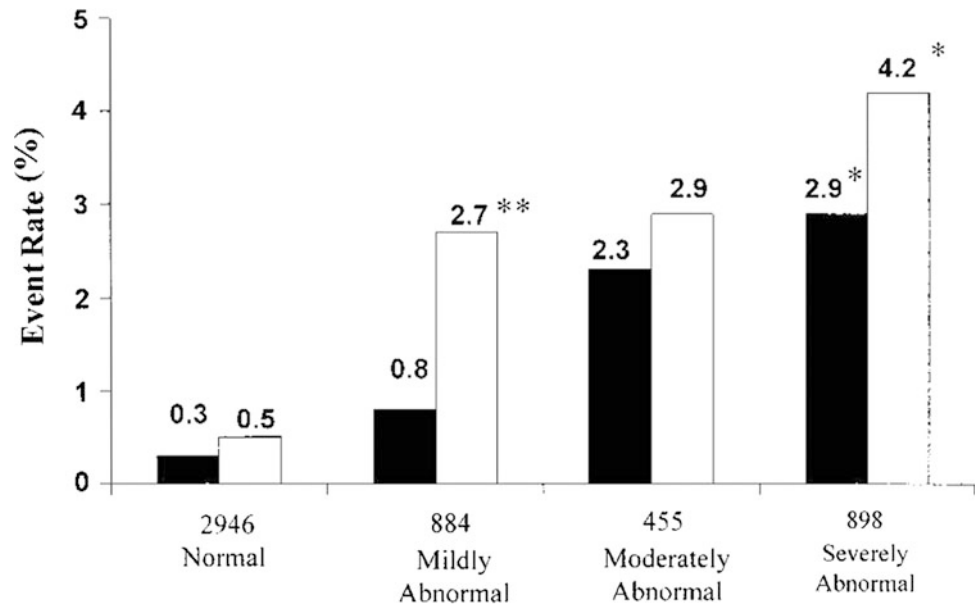


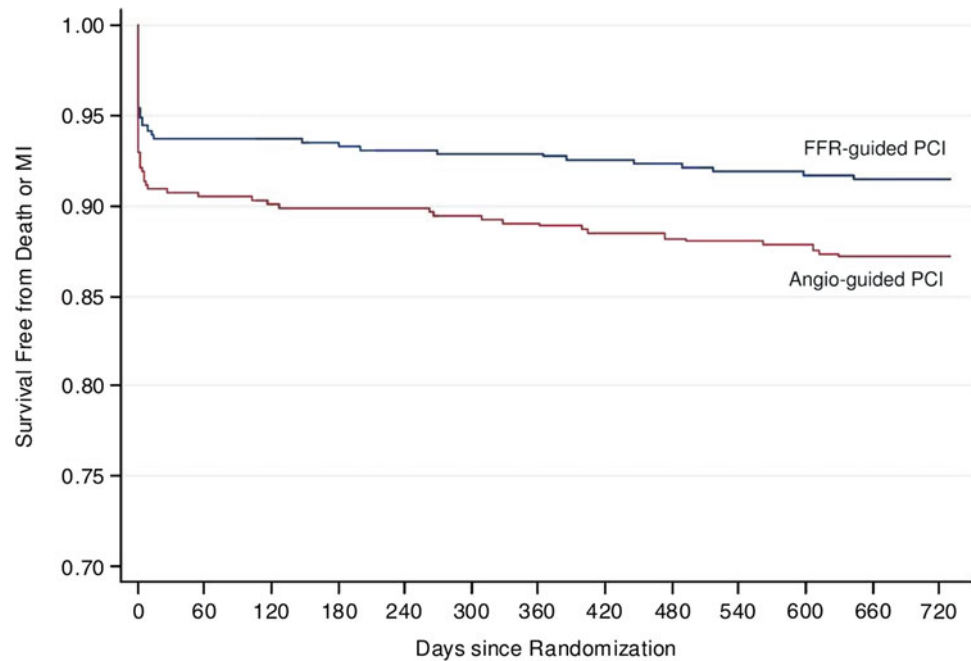
Fig. 9 Annualized event rates associated with findings on SPECT myocardial perfusion imaging. From Hachamovitch et al. (1998)



annualized event rate of 2.7, 2.9, or 4.2 %, respectively (see Fig. 9). There is more recent data from another large-scale study of 2,225 women, who were followed for almost 4 years (Cerci et al. 2011). Similar to the earlier results, the presence of any perfusion abnormality was associated with a significantly higher event rate of 14 %.

Conversely to the risk associated with perfusion abnormalities, there is even stronger evidence that normal myocardial perfusion presents a very low risk for cardiovascular events, approximately 1 % the annual cardiac event rate (Berman et al. 2006). In the study by Hachamovitch et al., subjects with a normal MPI study had an annualized event

Fig. 10 Kaplan-Meier survival curves demonstrating differences between the FFR-guided and the standard angiography-guided strategy for the occurrence of death and myocardial infarction. From Pijls et al. (2010)



rate for cardiac death and myocardial infarction of less than 0.5 and 0.3 %, respectively (Hachamovitch et al. 1998). A more recent meta-analysis by Shaw et al., pooling 19 studies with more than 39,000 patients with a mean follow-up of 2.3 years, demonstrated an event rate of 0.6 % in association with a negative SPECT perfusion study (Shaw and Iskandrian 2004). In a number of subgroups, such as patients scheduled for non-cardiac surgery, the presence of reversible ischemia has been found to be a significant predictor of perioperative cardiac events (Leppo 1995).

Similar to SPECT, CMR-detected myocardial perfusion defects are predictive of events; however, CMR is the younger of the two technologies and there is less prognostic data available at the time of this writing. In 420 patients with known or suspected CAD, Bodi et al. found that the presence of a perfusion defect on CMR was associated with a 17 % event rate (Bodi et al. 2007). In contrast, subjects without any perfusion deficit on CMR had a significantly lower event rate (5 %). In subjects with acute chest pain ($n = 135$), none of the subjects with a normal CMR experienced a cardiac event during a 1 year follow-up (Ingkanisorn et al. 2006).

Therefore, there is strong evidence that the identification of myocardial perfusion deficits and more importantly the absence of any defects have overwhelming prognostic value.

5.4 Hemodynamic Relevance of Coronary Artery Stenosis by FFR

Catheter-based invasive flow measurement for FFR has established itself as a complement to invasive angiography.

FFR can be performed once a morphological coronary stenosis has been detected and may provide important functional information regarding the indication for an interventional procedure.

In a landmark trial, the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME), 1,005 subjects scheduled for stent revascularization were randomized to either a standard or interventional approach, dependent on whether the FFR measurement indicated ischemia (Tonino et al. 2009; Pijls et al. 2010). The 1-year event rate for major adverse cardiovascular events was 18.3 % in the angiography group and 13.2 % in the FFR group, while the recurrence of angina was similar between the two groups; this demonstrates the clear benefit of using an FFR-guided policy (Tonino et al. 2009). Also, as shown in Fig. 10, after a 2-year follow-up, there was a significant difference in rate of mortality or myocardial infarction, with a rate of 8.4 % for the FFR-based strategy versus 12.9 % in the angiography alone group ($p = 0.02$) (Pijls et al. 2010).

6 Conclusions and Consequences for Cardiac CTA

It is well recognized that functional information with regard to ischemia or flow impairment are key features determining the indication for revascularization procedures in patients with CAD. The large body of evidence accumulated over the last few years demonstrates without doubt that the benefit associated with stent placement or CABG is directly related to information provided by functional

imaging modalities, such as SPECT, CMR, stress echocardiography, or FFR measurement, provided the expected outcome improvement outweighs the risk associated with an intervention. This appears to only be the case if the degree of ischemia is sufficiently high enough to be measurable by functional imaging modalities.

The established paradigm has been challenged by the rapid development and advancement of cardiac CTA, which is increasingly reaching clinical practice. However, the value of cardiac CTA rests in the morphological assessment of coronary artery disease and per se does not provide any functional information. Although there is an overlap of morphological changes and their functional relevance, i.e., with high degree lesions being more likely to cause perfusion defects, clinicians should be aware of the discordance between a morphological attest and a functional test.

There has been an increasing effort to extend the ability of cardiac CTA toward a functional imaging procedure, which would provide a highly attractive combined imaging modality. Substantial advances have been made in the field of CT perfusion and viability imaging through different techniques and approaches, and there is no doubt that cardiac CTA can be used to assess left and right ventricular function as well. This new development and field of research is critical as the wide applicability for various patient populations will depend on the ability to combine functional and morphologic information in a single relevant examination. Only such a noninvasive test may enable us to accommodate the predicted rise in the prevalence of CAD over the coming decades.

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