# Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

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# Chapter 17

# Evaluation of Coronary Artery Disease: Implications of Invasive versus Non-Invasive Imaging

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*Submitted*

# Abstract

**Background**

Preliminary comparisons suggest a large discrepancy between an abnormal Multi-Slice Computed Tomography (MSCT) study and myocardial perfusion imaging (MPI) results. How these contradictory findings should be interpreted remains presently unclear. The purpose of the present study was to perform, in addition to MSCT and MPI, invasive imaging, not only of the coronary lumen (using quantitative coronary angiography, QCA) but also of the vessel wall (using intravascular ultrasound, IVUS).

**Methods**

A total of 62 patients underwent both MSCT and MPI followed by conventional coronary angiography and IVUS imaging (in 45 patients). QCA and IVUS measurements were performed of the severest lesion, while MSCT studies were classified as normal (no stenosis exceeding 30% luminal narrowing), or abnormal with further classification into borderline (30% to 70% luminal narrowing) or severe stenosis (≥70% luminal narrowing). Stress-rest gated MPI was performed to evaluate myocardial perfusion.

**Results**

A good agreement between modalities was observed in patients with abnormal MPI. However, a normal MPI study was in most patients associated with an abnormal MSCT study (82%) despite only minimal luminal stenosis on QCA (26.0%). Further evaluation by IVUS revealed the presence of considerable plaque burden (57.9%), yet without luminal compromise (average minimal luminal area 5.9 $mm^2$).

**Conclusion**

Observations between MPI, MSCT and QCA may appear initially contradictory as an abnormal MSCT is frequently obtained in patients with normal perfusion and conventional angiograms. In these patients, the detected atherosclerosis may be located mainly in the vessel wall, rather than extending into the coronary lumen.

# Introduction

Traditionally, the evaluation and management of patients with suspected coronary artery disease (CAD) has been based on the non-invasive detection of ischemia followed by invasive coronary angiography to confirm the presence of luminal stenosis. However, this paradigm has recently been challenged by the introduction of multi-slice computed tomography (MSCT). With this new technique, the presence of CAD is detected through direct visualization of the coronary artery stenoses rather than through their hemodynamical consequences. Preliminary comparisons between MPI and MSCT suggest a large discrepancy between imaging results and abnormal MSCT studies appear to be frequently associated with normal MPI studies [1;2]. How these diverging findings should be interpreted remains at present unclear. It is conceivable that the vast majority of patients with abnormal MSCT but normal MPI have non-obstructive CAD, located mainly in the vessel wall, rather than encroaching on the coronary artery lumen. To test this hypothesis, additional studies are needed involving invasive imaging, not only of the coronary artery lumen (using invasive coronary angiography) but also of the vessel wall (using intravascular ultrasound, IVUS).

# Methods

## Patients and study protocol

The study group consisted of 62 symptomatic patients who underwent MSCT and MPI but also invasive coronary angiography in combination with IVUS.
Exclusion criteria were contra-indications to MSCT [3], and the occurrence of unstable angina, myocardial infarction or revascularization during the study period. The study protocol was approved by the local ethics committee and informed consent was obtained in all patients.

## Multi-slice computed tomography coronary angiography

MSCT coronary angiography was performed using either an Aquilion 64 (Toshiba Medical Systems, Japan) or a Sensation 64 (Siemens, Germany). Collimation was either 64 x 0.5 mm or 64 x 0.6 mm, respectively. The tube current was 300 mA, at 120 kV. Non-ionic contrast material was administered in the antecubital vein with an amount of 80 to 110 ml for 64-slice MSCT, depending on the total scan time, and a flow rate of 5 ml/sec (Iomeron 400 ®), followed by a saline flush. Subsequently, data sets were reconstructed and transferred to a remote workstation as previously described [3].
MSCT angiographic examinations were evaluated on a vessel and patient basis by 2 experienced readers including an interventional cardiologist blinded to the SPECT data for the presence of atherosclerosis exceeding 30% luminal narrowing. Abnormal studies were further classified as borderline stenosis, showing 30% to 70% luminal narrowing, or severe stenosis, showing ≥70% luminal narrowing. In the vessel-based analysis, the left main coronary artery was considered part of the left anterior descending coronary artery.

## Myocardial perfusion imaging

In all patients, stress-rest MPI (using either technetium-99m tetrofosmin or technetium-99m sestamibi) was performed with symptom-limited bicycle exercise or pharmacological (dipyridamole, adenosine or dobutamine) stress [4]. Data were acquired with either a dual-head SPECT camera (Vertex Epic ADAC Pegasus) or a triple-head SPECT camera (GCA 9300/HG, Toshiba Corp., Tokyo, Japan) followed by reconstruction into long- and short-axis projections perpendicular to the heart-axis; data were presented in polar map format (normalized to 100%), and a 17-segment model was used in which myocardial segments were allocated to the territories of the different coronary arteries as previously described [5;6]. Perfusion defects were identified on the stress images (segmental tracer activity less than 75% of maximum) and divided into ischemia (reversible defects, with ≥10% increase in tracer uptake on the resting images) or scar tissue (irreversible defects)[2]. Accordingly, examinations were classified as being either normal or abnormal, the latter being further divided in those demonstrating reversible defects and those demonstrating irreversible defects. The gated images were used to assess regional wall motion to improve differentiation between perfusion abnormalities and attenuation artifacts [7]. The left ventricular ejection fraction was derived from the gated SPECT data using previously validated and automated software (quantitative gated SPECT [QGS]; Cedars-Sinai Medical Center, Los Angeles, CA); gating was only performed at rest.

## Conventional coronary angiography

Conventional coronary angiography was performed according to standard clinical protocols. Quantitative coronary angiography (QCA) was performed using QCA-CMS 6.0 (Medis, Leiden, the Netherlands). For each coronary artery, the most severe stenosis was identified. The tip of the catheter was used for calibration and after automated vessel contour detection with manual correction if needed, percentage diameter stenosis was calculated.

## Intravascular ultrasound

IVUS imaging was performed with 2.9Fr 20-MHz catheters (Eagle Eye, Volcano, Brussels, Belgium). After intracoronary administration of nitrates, the IVUS catheter was advanced to the distal portion of coronary artery under fluoroscopic guidance. Using automated pullback device, the transducer was withdrawn at a continuous speed of 0.5 mm/s up to the coronary ostium. Cine runs before and during contrast injection were performed to confirm the position of the IVUS transducer before IVUS evaluation was started. All data were stored digitally and were analysed off-line with the use of QCU-CMS 4.0 (Medis, Leiden, The Netherlands). After motion correction had been applied, coronary arteries were divided into segments according to the modified American Heart Association classification [8] using coronary ostia and side branches as landmarks. In each coronary segment, the frame with the most severe cross-sectional area of narrowing was selected for analysis. In addition, proximal and distal reference sites that had the largest lumen area by IVUS in the proximal and distal portion of the vessel segment in the 10 mm adjacent (but before any side-branch) to the lesion site were selected. Subsequently, lumen and external elastic membrane (EEM) contours were manually traced to determine lumen area and EEM area at the lesion site and proximal and distal reference site. EEM area was defined as the area that was circumscribed by the border between the hypoechoic media zone and the surrounding echocardiographically bright adventitia. Plaque plus media area was calculated as the difference between the EEM and the lumen area. Based on these parameters, minimal lumen area (MLA), plaque area, plaque burden, lumen area stenosis, lumen diameter stenosis and corrected lumen area stenosis were calculated per coronary segment as previously described [9;10].

In addition, vascular remodelling was determined in 2 ways, as previously described [11;12]. First, the impact of excess plaque accumulation (at the lesion compared with the reference section) on lumen compromise was calculated using the following formula: (reference lumen area- MLA)/ (plaque area at the lesion – plaque area at the reference section) [11]. Accordingly, with increasing index values, the impact of plaque accumulation on lumen compromise will be more severe. In contrast, an index of 0 will be obtained if all the additional plaque accumulation is accommodated for by arterial remodelling, resulting in no decrease in lumen area. Secondly, the number of lesions with positive remodelling was determined by calculating the remodelling index (RI) by dividing the lesion EEM area by the average of the proximal and distal reference EEM area. Subsequently, positive remodelling was defined as a RI ≥ 1.0, whereas RI < 1.0 was classified as negative remodelling [12].

## Statistical analysis

Data were analysed on a per-patient and per-vessel basis and for the corresponding calculations, the coronary artery and coronary segment showing the most severe stenosis on either QCA or IVUS were used respectively. Continuous variables were described by mean ± SD. Comparisons between patient groups were performed using the independent samples T test for continuous variables and the $\chi^2$ test with Yates' correction was used for comparison of categorical variables. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS (SPSS Institute, Chicago, Illinois, USA).

# Results

## Patient characteristics

Characteristics of the study population are summarized in Table 1. Briefly, 62 patients were included, of which 41 (66%) were male with an average age of 62 ± 11 years. CAD was known in 5 (8%) patients, and suspected in the remaining 57 (92%) patients. Previous coronary artery bypass grafting was previously performed in one patient. A total of 2 vascular territories were excluded from the analysis, since these territories were supplied by coronary artery bypass grafts. In all patients MPI, MSCT and conventional coronary angiography (with QCA) were performed. In 45 patients, additional vascular imaging with IVUS was performed in a total of 94 coronary arteries.

**Table 1.** Clinical characteristics of the study population (n=62).

| | n (%) |
|---|---|
| **Gender (M/F)** | 41/21 |
| **Age (years)** | 62 ± 11 |
| **Risk factors for CAD** | |
| Diabetes Mellitus18 | (32%) |
| Hypertension41 | (72%) |
| Hypercholesterolemia | 31 (54%) |
| Positive family history | 22 (39%) |
| Current smoking | 22 (39%) |
| Obese (BMI ≥ 30 kg/m$^2$) | 12 (25%) |
| **Agatston calcium score (range)** | 374 ± 764 (0,4828) |
| **LVEF on gated SPECT** | 58% ± 14% |
| **Nr of significantly stenosed vessels on angiography** | |
| 0 | 31 (50%) |
| 1 | 12 (19%) |
| 2 | 11 (18%) |
| 3 | 8 (13%) |

*Abbreviations: BMI: body mass index, CAD: coronary artery disease, IVUS: intravascular ultrasound, LVEF: left ventricular ejection fraction, SPECT: single photon emission computed tomography.*

## MPI versus MSCT and invasive angiography

### *Patient basis*

The results of the analysis on a patient basis (n=62) are presented in Table 2 and Figure 1. Abnormal perfusion on SPECT was noted in 23 (37%) patients. This abnormal perfusion was associated an abnormal MSCT in all patients, with borderline stenosis in 9 (39%) patients and at least 1 severe lesion in 14 (61%). Considering the most severe stenosis per patient on conventional angiography, QCA showed an average percentage stenosis of 78.3% ± 16.5%.

The remaining 39 (63%) patients had normal perfusion on SPECT. In these patients, MSCT was abnormal in 32 (82%) patients with all patients classified as having borderline stenosis. However, average percentage stenosis of the most severe lesion was only 26.0% ± 16.8% on QCA (P<0.001 versus patients with abnormal SPECT).

**Table 2.** Angiographic characteristics (MSCT and QCA) for patients with respectively abnormal and normal perfusion.

| | MPI abnormal (n=23) | MPI normal (n=39) | P -value |
|---|---|---|---|
| **MSCT** | | | |
| Normal | 0 | 7 (18%) | |
| Abnormal | 23 (100%) | 32 (82%) | P=NS |
| Borderline stenosis | 9 (39%) | 32 (100%) | |
| Severe stenosis | 14 (61%) | 0 (0%) | P<0.01 |
| **QCA** | 78.3% ± 16.5% | 26.0% ± 16.8% | P<0.01 |

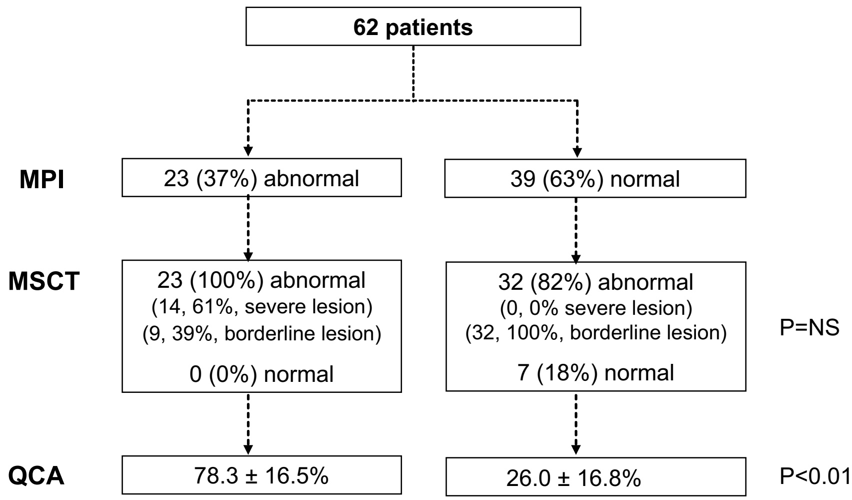


**Figure 1.** Flow chart describing the MSCT and QCA findings in 62 patients with respectively abnormal and normal MPI results. Note the discrepancy between the imaging modalities in patients with normal MPI. In the majority of these patients MSCT was abnormal, despite normal perfusion and only minimal luminal narrowing on QCA. *Abbreviations: MPI: myocardial perfusion imaging, MSCT: multi-slice computed tomography, QCA: quantitative coronary angiography.*

### *Vessel basis*

On a vessel basis, abnormal myocardial perfusion was noted in 34 (17%) of 184 vascular territories with ischemia in 29 and fixed perfusion defects in 3 vascular territories (Table 3). In all of the corresponding coronary arteries, MSCT was abnormal as well. At least 1 severe lesion was observed in 16 (47%) coronary arteries, while lesions were classified as borderline in 18 (53%) vessels. Average percentage stenosis on QCA was 70.6% ± 24.5%.

In 150 (82%) vascular territories with normal perfusion on SPECT, atherosclerosis was detected on MSCT in 109 (73%) of the corresponding coronary arteries, of which the majority (105, 96%) were classified as showing borderline stenosis. A total of 41 (27%) coronary arteries were normal on MSCT. According to QCA, average percentage stenosis in coronary arteries associated with normal perfusion was 22.1% ± 18.7% (P<0.001 as compared to abnormal SPECT).

**Table 3.** Angiographic characteristics (MSCT and QCA) for vascular territories with respectively abnormal and normal perfusion.

| | MPI abnormal (n=34) | MPI normal (n=150) | P –value |
|---|---|---|---|
| **MSCT** | | | |
| Normal | 0 | 41 (27%) | |
| Abnormal | 34 (100%) | 109 (73%) | P=NS |
| Borderline stenosis | 18 (53%) | 105 (96%) | |
| Severe stenosis | 16 (47%) | 4 (4%) | P<0.01 |
| **QCA** | 70.6% ± 24.5% | 22.1% ± 18.7% | P<0.01 |

## Correlation of MPI with MSCT, invasive angiography and IVUS (Figure 2)

In 45 of 62 (73%) of patients, additional vascular imaging with IVUS was performed in a total of 94 coronary arteries. In the remaining 17 patients, IVUS imaging was not possible due to the presence of left main stenosis, severe stenosis or occlusion (n=10) and technical problems or time constraints during conventional coronary angiography (n=7).

### *Patient basis*

In total, MPI was abnormal in 14 of 45 (31%) of patients in whom IVUS imaging was obtained. In all patients, MSCT was abnormal as well with severe stenosis in 3 (21%). Average percentage of luminal narrowing as determined by QCA was relatively low in these patients (58.6 ± 24.3%), possibly due to the exclusion of patients with severe stenosis in whom IVUS imaging could not be performed. Nonetheless, average MLA was 3.5 ± 1.3 $mm^2$ with an average plaque area and plaque burden of respectively 9.9 ±5.2 $mm^2$ and 71.7% ± 10.6%, confirming the presence of potentially flow-limiting stenoses. At these lesions, the impact of plaque accumulation on lumen compromise was on average 1.7 ± 2.3. Moreover, 12 (86%) lesions were associated with constrictive remodelling.

Normal perfusion was observed in the remaining 31 (69%) of the 45 patients that underwent additional IVUS imaging. In these patients, MSCT revealed atherosclerosis in 27 (87%), all classified as having borderline stenosis.

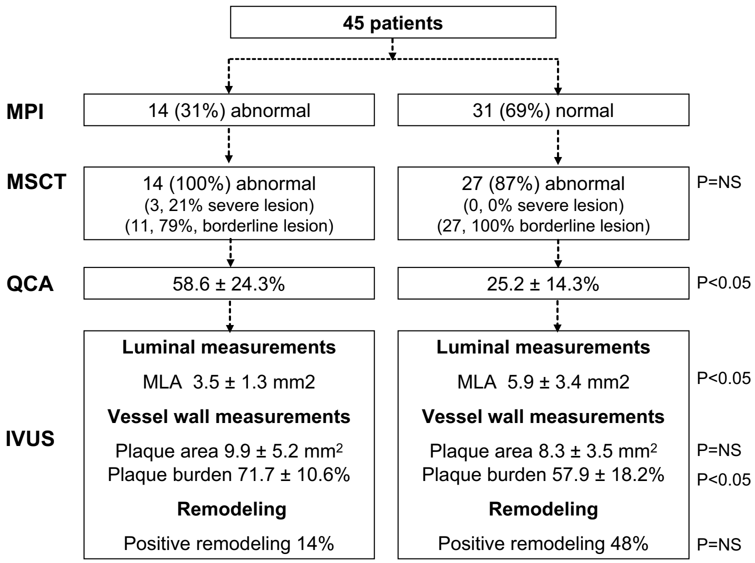


**Figure 2.** Flowchart describing the observations in 45 patients in whom additional IVUS imaging was performed. In almost all patients with normal MPI, the presence of atherosclerosis was observed on MSCT with negligible luminal narrowing identified on QCA. IVUS imaging confirmed the presence of substantial atherosclerosis (plaque burden 57.9%), yet without luminal compromise (MLA 5.9 mm2).
*Abbreviations: IVUS: intravascular ultrasound, MLA: minimal lumen area, MPI: myocardial perfusion imaging, MSCT: multi-slice computed tomography, QCA: quantitative coronary angiography.*

Considering only the most severe percentage stenosis per patient, an average of only 25.2% ± 14.3% luminal narrowing was observed on QCA, indicating minimal stenosis on angiography. In line with these observations, preservation of the lumen was observed on IVUS with an average MLA of 5.9 ± 3.4 $mm^2$, significantly higher as compared to patients with abnormal MPI (P<0.01). Nonetheless, considerable atherosclerosis was identified on IVUS with an average plaque area of 8.3 ± 3.5 $mm^2$, not significantly different as compared to patients with perfusion abnormalities (P=0.29). Also substantial plaque burden was observed, with an average of 57.9% ± 18.2% (P<0.05 as compared to abnormal MPI). The impact of plaque accumulation on lumen compromise was considerably less as compared to patients with abnormal MPI ( -0.21 ± 5.8 versus 1.7 ± 2.3, P=0.24). In line with this observation, positive remodeling was identified in approximately half (15, 48%) of patients with normal MPI, as compared to 14% in patients with abnormal MPI (P=0.03). Details are specified in Table 4.
In Figure 3, an example of a patient with discrepant MPI and MSCT observations is provided.

***Vessel basis***

In total, 14 (15%) of 94 coronary arteries were associated with abnormal perfusion in the corresponding vascular territory during MPI. In all coronary arteries with abnormal perfusion, atherosclerosis was identified on MSCT, with severe stenosis on MSCT in 3 (21%) coronary arteries and an average degree of stenosis of 57.1% ± 26.1% on QCA. In the remaining 80 (85%) coronary arteries without perfusion abnormalities, atherosclerosis was absent on MSCT in 15 (19%). The average degree of stenosis on QCA was 21.4% ± 13.8%. Further details of the IVUS measurements on a vessel basis are provided in Table 5.
Finally, as shown in Figure 4, significant differences in IVUS measurements were observed when comparing patients with and without atherosclerosis on MSCT.

**Table 4.** IVUS characteristics of the most severe lesion in patients with respectively abnormal and normal perfusion on MPI.

| | Abnormal perfusion (n=14) | Normal perfusion (n=32) | P-value |
|---|---|---|---|
| **Reference section** | | | |
| EEM area ($mm^2$) | 15.0 ± 6.1 | 15.6 ± 4.0 | 0.21 |
| Lumen area ($mm^2$) | 8.9 ± 3.6 | 10.2 ±3.2 | 0.24 |
| **Lesion section** | | | |
| EEM area ($mm^2$) | 13.4 ± 5.8 | 14.2 ± 4.4 | 0.62 |
| MLA ($mm^2$) | 3.5 ± 1.3 | 5.9 ± 3.4 | <0.01 |
| Plaque area ($mm^2$) | 9.9 ± 5.2 | 8.3 ±3.5 | 0.29 |
| Lesion plaque burden (%) | 71.7 ± 10.6 | 57.9 ± 18.2 | <0.01 |
| Lumen area stenosis (%) | 60.4 ± 17.6 | 42.6 ± 22.9 | 0.01 |
| Lumen diameter stenosis (%) | 39.0 ± 16.3 | 25.8 ± 15.5 | 0.01 |
| Corrected lumen area stenosis (%) | 74.8 ± 10.3 | 60.9 ±20.9 | <0.01 |
| **Remodeling** | | | |
| Impact plaque on lumen index | 1.7 ± 2.3 | -0.2 ± 5.8 | 0.24 |
| Positive remodeling (n, %) | 2 (14%) | 15 (48%) | 0.03 |

*Abbreviations: EEM: external elastic membrane, MLA: minimal lumen area.*

# Discussion

The main observations of the present study can be summarized as follows.

Comparison of MSCT to SPECT showed that abnormal perfusion was in all cases associated with an abnormal MSCT. In these patients, significant CAD was also observed during invasive imaging, as reflected by an average percentage stenosis of 78% on conventional angiography as well as an average MLA of less than 4.0 $mm^2$ on IVUS.

However, in many patients with normal perfusion on SPECT, discrepant findings were obtained. Frequently, MSCT showed extensive atherosclerosis, whereas only minor stenosis (average 26.0%) was observed on conventional coronary angiography/QCA. Nonetheless, IVUS revealed considerable plaque burden (57.9%). Importantly, the observed atherosclerosis involved the arterial wall rather than leading to luminal compromise, as reflected by a preserved MLA of 5.9 $mm^2$ on average.

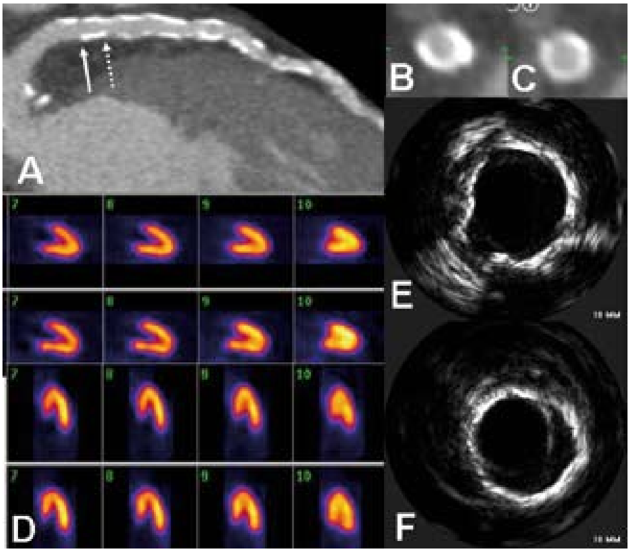


**Figure 3.** A 60-year old male presented to the outpatient clinic with dyspnea and an elevated risk profile for coronary artery disease, including hypertension, hypercholesterolemia and smoking. Contrast enhanced MSCT coronary angiography revealed considerable atherosclerosis in the left anterior descending coronary artery (Panel A). Panels B and C are cross-sectional images of the areas indicated by the arrows in Panel A. In contrast, myocardial perfusion imaging (Panel D), which was performed during exercise stress (first and third panel) and rest (second and fourth panel), showed normal perfusion. However, also during intravascular ultrasound imaging (Panels E and F), considerable plaque burden was demonstrated, yet with preservation the coronary lumen.

## Hemodynamically relevant stenoses

Abnormal perfusion on SPECT was in all cases associated with an abnormal MSCT. In line with these observations, lesions that were flow-limiting as determined by MPI were also associated with significant focal luminal narrowing on invasive imaging. On QCA, an average percentage diameter stenosis of 78% was obtained. Also, in the subset of patients undergoing IVUS imaging, an average

MLA of 3.5 $mm^2$ was identified, in line with previous investigations. Nishioka and colleagues compared IVUS measurements in 70 coronary lesions to gated SPECT [9] and observed an average MLA of 3.3 $mm^2$ in lesions with a positive SPECT study. Similar findings have been obtained in other studies employing fractional flow reserve [12;13] indicating a clear convergence of findings between the different imaging modalities in the presence of hemodynamically relevant stenoses.

**Table 5.** IVUS characteristics in coronary arteries with respectively abnormal and normal perfusion in the corresponding vascular territory.

| | Abnormal perfusion (n=14) | Normal perfusion (n=80) | P-value |
|---|---|---|---|
| **Reference section** | | | |
| EEM area ($mm^2$) | 15.9 ± 6.1 | 15.1 ± 5.2 | 0.62 |
| Lumen area ($mm^2$) | 9.0 ± 3.9 | 9.9 ± 3.7 | 0.39 |
| **Lesion section** | | | |
| EEM area ($mm^2$) | 14.3 ± 5.8 | 14.2 ± 5.2 | 0.93 |
| MLA ($mm^2$) | 3.6 ± 1.6 | 6.7 ± 3.7 | <0.01 |
| Plaque area ($mm^2$) | 10.7 ± 5.0 | 7.5 ± 3.7 | <0.01 |
| Lesion plaque burden (%) | 73.2 ± 9.3 | 51.9 ± 17.3 | <0.01 |
| Lumen area stenosis (%) | 59.1 ± 20.1 | 33.3 ± 21.2 | <0.01 |
| Lumen diameter stenosis (%) | 38.3 ± 17.6 | 19.5 ± 13.7 | <0.01 |
| Corrected lumen area stenosis (%) | 75.6 ± 10.2 | 54.5 ± 19.0 | <0.01 |
| **Remodeling** | | | |
| Impact plaque on lumen index | 1.5 ± 2.3 | 0.34 ± 5.7 | 0.20 |
| Positive remodeling | 4 (29%) | 34 (43%) | 0.36 |

*Abbreviations: EEM: external elastic membrane, MLA: minimal lumen area.*

## Atherosclerosis in the presence of normal perfusion

In 39 patients, a normal MPI study was obtained. In these patients, only mild luminal narrowing (26.0%) was observed during conventional coronary angiography. Contradictory findings were obtained with MSCT, since only 7 (18%) patients were classified as having normal coronary arteries. Similarly, on a vessel basis only 41 of 150 (27%) of coronary arteries were normal on MSCT. In line with the observations of conventional coronary angiography/QCA, average lumen diameter stenosis on IVUS was only 25.8% and 19.5% on a patient and vessel basis respectively. However, considerable plaque burden was detected with an average of 58% in patients with abnormal MSCT. Importantly, this observed atherosclerosis involved the arterial wall rather than leading to luminal compromise, as reflected by an average MLA of 5.9 $mm^2$.

A discrepancy in imaging findings has been described previously in studies comparing MPI to coronary calcium scoring. In a large cohort of 1195 patients without history of CAD, extensive atherosclerosis as reflected by a calcium score >400 was observed in 31% of patients with normal MPI studies [14]. Moreover, the presence of substantial disease has been described in angiographically normal segments previously; Mintz et al showed in a large consecutive series of patients that atherosclerosis is commonly present in angiographic reference segments and only 6.8% of studied segments were classified as entirely normal by both QCA and IVUS imaging [15].

Accordingly, the noted discrepancies in fact reflect that the techniques provide information on different aspects of CAD. Conventional coronary angiography and MPI detect anatomically significant and hemodynamically relevant stenoses respectively. In contrast, the techniques remain limited in depicting the distribution and extent of diffuse, non-obstructive atherosclerosis, a process which primarily involves the arterial wall.

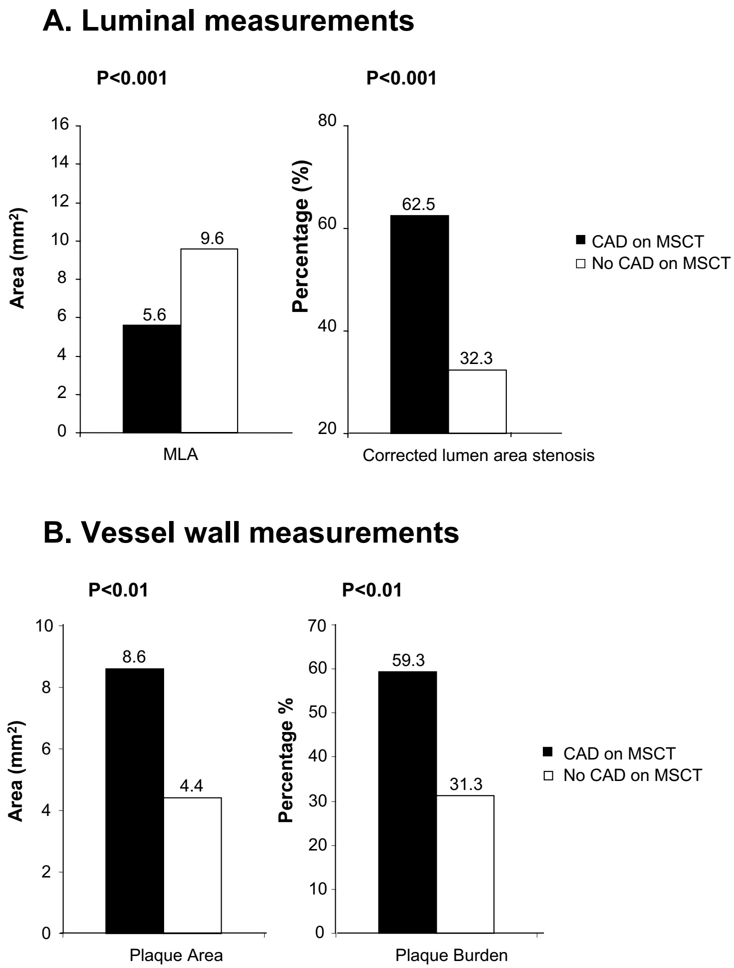


**Figure 4**. Differences in IVUS measurements between coronary arteries with CAD and without CAD as determined on MSCT.
Panel A: MLA (mm2) and corrected lumen area stenosis (%). Panel B: plaque area (mm2) and plaque burden (%).
All measurements were significantly different between coronary arteries with and without CAD identified on MSCT.
*Abbreviations: CAD: coronary artery disease, IVUS: intravascular ultrasound, MLA: minimal lumen area, MSCT: multi-slice computed tomography.*

## Clinical implications

Traditionally, non-invasive detection of CAD is based on demonstration of ischemia [16]. However, with the introduction of new non-invasive imaging techniques such as MSCT, clinicians started to appreciate better the different stages of CAD, ranging from early coronary atherosclerosis to obstructive stenoses. Indeed in the current study, we identified patients with perfusion defects on MPI, indicating hemodynamically obstructive stenoses, representing advanced CAD; these patients revealed significant stenoses on invasive angiography with QCA, and IVUS further strengthened these findings by demonstration of obstructive CAD.

On the other end of the spectrum, patients with (pre-clinical) atherosclerosis were identified. These patients presented with normal perfusion on MPI, with (nearly) normal invasive angiography/QCA. Many of these patients however had extensive atherosclerosis on MSCT; this was further supported by the IVUS findings indicating absence of obstructive stenoses, but confirming extensive atherosclerosis, mainly located in the vessel wall.

The main clinical implication of the current study is thus that integrated use of the non-invasive imaging techniques (MPI and MSCT) may permit optimal characterization of atherosclerotic lesions and differentiate early atherosclerosis without hemodynamic consequences from atherosclerotic lesions that result in ischemia. Whether this advanced characterization of atherosclerotic lesions will result in superior prognostification of patients, remains to de determined.

## Study limitations

In the present study, MSCT examinations were visually assessed, as no validated quantification algorithms are currently available for MSCT. Also, IVUS imaging was not performed in all vessels in every patient. In addition, MSCT has several disadvantages in general including the high radiation burden and the need for a low and stable heart rate during data acquisition.

## Conclusion

The current findings demonstrate a good agreement between non-invasive imaging techniques (MPI, MSCT) and invasive techniques (angiography, QCA and IVUS) in patients with advanced CAD. These patients exhibited abnormal perfusion on MPI, atherosclerosis on MSCT, and obstructive stenoses on angiography/QCA and IVUS.

In patients with early atherosclerosis, discrepant findings were noted. Perfusion on MPI was normal, but MSCT demonstrated atherosclerosis. Although invasive angiography/QCA did not reveal significant coronary lesions, IVUS demonstrated considerable atherosclerosis, which was however mainly located in the vessel wall and associated with positive remodeling, rather than resulting in luminal obstruction.

The current observations further support the integrated use of MPI and MSCT to better characterize atherosclerotic lesions.

Accordingly, the current findings underline the complementary nature of MSCT and MPI.

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