Coronary atherosclerosis assessment by CCTA: detailed plaque features and atherosclerotic burden scores

Coronary CT angiography (CCTA) is now widely recognized as a useful tool to noninvasively rule out significant coronary stenosis, and is increasingly used as a gatekeeper for invasive coronary angiography, which is becoming more and more reserved for patients at high probability of coronary artery disease in need of a revascularization procedure (1). Although still not in the clinical arena, one of the most appealing features of CCTA is the ability to look beyond the luminal stenosis and provide a detailed evaluation of the coronary wall depicting several features like plaque composition (calcified, noncalcified or mixed), plaque burden, remodeling index and degree of attenuation measured in Hounsfield units (HU), and several of these features have been associated with the future development of events (2–8) (Figure 1). In fact, the potential prognostic value of these detailed plaque features provided by CCTA has opened a new field of research in coronary artery disease, which in the last 2–3 decades has been struggling in the search of the vulnerable plaque (10,11). In addition, when looking for the same disease using a different imaging modality, it seems wise to follow the steps of previous research and therefore the excitement in this field has to be balanced by the difficulties that other imaging modalities, some of which of very high spatial resolution, have faced in the search of these vulnerable plaques. Some landmark studies that used invasive intracoronary imaging have prospectively linked several plaque features to the development of...
future coronary events, although with a modest positive predictive value (12-14). Studies with CCTA have also demonstrated the prognostic value of some of these detailed plaque features like positive remodeling, the presence of low attenuation plaques and the presence of a napkin ring sign. Since several coronary plaques are frequently found in the coronary tree even in low to intermediate CAD probability patients undergoing CCTA to rule out coronary stenosis (15,16), and since detailed plaque evaluation is time consuming, requires very good image quality and can be associated with low interobserver variability, another possible approach is to provide the total coronary atherosclerotic burden as a score, and some have been developed and validated as prognostic tools (17-19), providing imagers and researcher with additional tools and a change of focus from just the vulnerable plaque to the vulnerable coronary tree (20).

**The search of functional information with CT angiography**

Recently, CTA has been increasingly looked as a possible provider of functional information, moving from the traditional view of a purely anatomical exam. The rational for this is two-sided: on one hand, current clinical decision making on the need for myocardial revascularization is based on the presence of ischemia, since it has been extensively documented that there is no expected benefit of intervention for coronary stenosis that are not functionally significant (21,22). On the other hand, although several diagnostic tools are already available, some of them have limited diagnostic performance (like exercise ECG), several patient related potential limitations (like stress Echocardiography and cardiac magnetic resonance imaging), depend on a significant amount of radiation exposure (like single photon emission computed...
tomography) and have availability issues apart from some selected centers (like cardiac MRI) (23). In what concerns CTA, the impressive reductions in radiation exposure of last generation scanners (24-26), coupled with their increasingly availability makes CTA a very attractive 2 in 1 modality to evaluate both the presence and the impact of CAD. Therefore, cardiac CT is becoming more and more a modality that is able not only to rule out CAD with a very high accuracy but also to provide functional information, moving beyond the usual classification of obstructive vs. nonobstructive to a more functional-based interpretation of signipara-doxicallyficant vs. nonsignificant CAD, a feature that is more in line with current clinical decision algorithm (9).

In line with this rational, the following research lines have been explored like myocardial perfusion imaging, fractional flow reserve computed from CTA (FFR$\text{CT}$), transluminal attenuation gradients and corrected coronary opacification indexes, which have been recently reviewed elsewhere (9), and some of them are revisited in the same issue of this journal.

One additional line of research aimed at extracting functional significance out of CTA datasets, the more recent and least explored of these, is the link between certain atherosclerotic plaque characteristics and the functional impact of coronary lesions, which will be developed further in the following chapter.

Atherosclerotic plaque characteristics and functional information: beyond stenosis severity

The concept that there is a modest correlation between the degree of anatomical stenosis and functional significance is not new and has been pointed out in several studies using ICA and the gold standard invasive FFR (21,27) and also with CCTA and noninvasive FFR (FFR$\text{CT}$) (28,29). Also important is the fact that these mismatches can also be observed on their counterparts, meaning that not only some of the apparently significant lesions (>50% and even >70% stenosis) are not causing ischemia (27), but also that nonobstructive (<50% stenosis) lesions can paradoxically be associated with ischemia, both on invasive (ICA/FFR) (30) and noninvasive (CCTA/FFR$\text{CT}$) (31) coronary evaluation. In a study including 1,000 patients evaluated by invasive coronary angiography and FFR, 16% of those with nonobstructive (<50% stenosis) were reversed mismatches, having a significant (<0.80) FFR (30). Although the limitations in quantifying stenosis severity using ICA have to be acknowledged, this study reinforces the concept that nonobstructive lesions can be associated with ischemia. Interestingly in this study was the fact that these reverse mismatches were more often found in the left main and independently associated with a left anterior descending artery location and the presence of a larger plaque burden and plaque rupture, features that link atherosclerotic plaque features to functional significance of coronary lesions. Recently this relation was also depicted using CCTA. In a study that included 252 stable patients undergoing both CCTA and ICA with FFR, Park et al. were able to document an association between certain CCTA atherosclerotic plaque characteristics (APCs) and the presence of ischemia by invasive FFR (31). In their study, lesion length, positive remodelling (index $\geq$1.1), and the presence of low attenuation plaque (<30 HU) were independent predictors of ischemia by invasive FFR. Besides the expected finding that a significant percentage of CCTA obstructive (>50% stenosis) lesions were not functionally significant by FFR, the most but striking result was the fact that even among nonobstructive CAD lesions, 17% were associatathero-scleroticed with ischemia, a result that was in line with the previously discussed studies that documented the visual functional mismatches between FFR and invasive coronary angiography. In another small study, including 58 patients with intermediate stenosis on CCTA undergoing ICA with FFR, the extent of coronary atherosclerotic burden quantified as aggregate plaque volume (APV), has been found to be incremental to several luminal narrowing measurements (diameter stenosis, minimum luminal diameter, area stenosis and minimum lumen area) to predict functional significance (FFR <0.80) (32). Taken together these studies underline the fact that some nonobstructive lesions but with high CTA risk features can be associated with the presence of ischemia. The reason for this might be related to the fact that these lesions with high plaque burden can be associated with endothelial dysfunction, since it has been demonstrated in small studies using virtual histology (IVUS-VH) that plaques with larger necrotic core are more prevalent in patients with endothelial dysfunction (33). The pathophysiological mechanism linking plaque features and ischemia deserves further evaluation but in any case the prognostic impact of coronary plaque burden is not a new concept. In a large study including 4,137 patients pooled from 6 IVUS studies, Nicholls et al. were able to demonstrate that percent atheroma volume (PAV) was an

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independent predictor of events (34). Also interesting in
that study was the fact that not only PAV but also disease
burden progression was associated with outcomes, a
result that is in line with the recent study of Motoyama
et al. relating coronary events to plaque progression
documented on patients undergoing serial scans (6).
Similar observations have been made using oesouptical
coherece tomography and simultaneous functional
assessment of the lesions. Yonetsu et al. showed a direct
association of a larger lipidic arc and lipid length with
micrcirculatory disturbances (35). Usui et al. reported
that physiological severe stenosis were twice as prevalent
in thin cap fibroatheroma lesions. These reports suggest
that these high risk lesions may affect the microcirculation
downstream (36). Taqueti et al. recently presented data
comparing CAD lesions in women and men assessed
by angiography and coronary flow reserve (CFR) in
which women had lower plaque burden. The adjusted
cardiovascular events were higher in the women's group,
two times higher when compared to men's, despite the
lower CFR values in women's group (37).

Recently a new terminology was proposed regarding
those mismatches between anatomy and function: The
NIPSS (no ischemia in the presence of significant stenosis)
and the PINSS (presence of ischemia with no significant
steno-sis), recognizing this interesting subset of patients
in which certain plaque features might be responsible
for the apparent contradiction between anatomy and
physiology (38). In fact, lesions in this last subgroup can
be considered “false negative” of CCTA and might explain
the worse than expected prognosis of patients that don’t
have obstructive lesions but have high disease burden, as
it has been recently demonstrated with the use of CCTA
coronary atherosclerotic burden scores (17-19) that take in
consideration all lesions independent of stenosis severity.
As the knowledge of coronary disease pathophysiology
advances, the traditional anatomic-based dichotomic
concept of obstructive vs. nonobstructive is becoming more
and more outdated and becoming replaced by a concept of
high vs. low risk plaque features/burden, more in line
with the recent evidence provided by both invasive and
noninvasive atherosclerosis imaging. Further, the field of
functional assessment will be revisited in light of the recent
reports. In the FUTURE trial (American Heart Association
2016), Rioufol et al., showed an increase in mortality from
any cause in FFR guided management group of patients
when compared to the optimal medical treatment alone,
interrupting prematurely the study (39).

Intravascular coronary imaging and its relation
with functional lesion assessments

The 3-dimensional and dynamic nature of the coronary
vasculature cannot be fully appreciated by planar
angiography. Frequently, defining the proper angiographic
angulation that provides a straight, nonforeshortened
view of the target coronary segment without overlapping
of other vessels may be a challenge in the catheter
laboratory. In addition, determination of disease severity
by angiography is hampered by the diffuse nature of
atherosclerosis and its most common eccentric growth in
the vessel wall. Hence, lesions can appear more stenotic
in one orthogonal view than in the other, making clinical
decisions difficult. The so-called intermediate lesion
is the more prevalent phenotype in the coronary tree.
The American Heart Association/American College of
Cardiology/Society for angiography and Interventions
(AHA/ACC/SCAI) guidelines define an intermediate
coronary lesion as a plaque producing a 50–70%
angiographic stenosis (40). These plaques represent a
heterogeneous group of coronary lesions, which may or
may not be hemodynamically flow limiting. Intravascular
imaging, particularly IVUS, was granted a class IIb
indication (level of evidence B) for the “IVUS may be
reasonable for the assessment of non–left main coronary
arteries with angiographically intermediate coronary
stenoses” and a class IIA indication (level of evidence B)
for the “IVUS is reasonable for the assessment of
angiographically indeterminant left main coronary artery
disease” in the American Guidelines. In the European
guidelines is also a class IIA indication (level of evidence B)
for the “IVUS to assess severity and optimize treatment
of unprotected left main lesions”. For other intermediate
lesions IVUS is not endorsed by the European Guidelines
in the absence of prospective randomised evidence (41).

IVUS minimum luminal cross-sectional area (MLA) has
proved to be a good morphometric surrogate of coronary
physiology. IVUS MLA showed a direct correlation with
coronary flow reserve determined by Doppler flow-wire
(r=0.831, P<0.001) (42). FIRST trial, demonstrated, in a
cohort of 350 patients with intermediate lesions and FFR
≤0.8, a MLA <3.07 mm² (64.0% sensitivity, 64.9% specificity
and area under curve of 0.65) and a FFR correlation
with plaque burden size (r=-0.220, P<0.001) (43). Han
et al. reported similar results after assessing 881
lesions with a MLA <3.0 mm² (and MLA<2.75 mm²
for Asians) (44). In 2014, a meta-analysis pooled
15 studies enrolling a total of 3,428 patients (3,775 lesions), showing a mean MLA of 2.59 mm² with 73% sensitivity, 66% of specificity and AUC =0.778 (45). The optical coherence tomography (OCT) was also used to evaluate lesions with FFR ≤0.75 and demonstrated a correlation with MLA <1.91 mm², minimum lumen diameter (MLD) <1.35 mm, plaque burden >70% (46). Thus, accessing only FFR ≤0.8 lesions, Gonzalo et al., compared OCT and IVUS measurements presenting an IVUS MLA of 2.36 mm² and 1.95 mm² for OCT, with a relative difference of 32.3±26% and absolute difference of 0.65±0.62 mm² (limits of agreement of −0.57 to 1.87 mm²) (47). The MLD value for IVUS was 1.59 mm², 1.34 mm² for OCT with a relative difference of 19.5±16%, absolute difference of 0.27±0.23 mm² (limits of agreement of −0.20 to 0.72 mm²) and area of stenosis of 61% for IVUS and 70% for OCT (46). When assessed using virtual histology (IVUS-VH) inter-mediate lesions showed a prone to have less necrotic core (14.2±8% vs. 19.2±10.2%, P=0.08) and greater plaque burden (54.6±0.7% vs. 51.7±0.7% P=0.1) (Table S1) (48). In 73 patients studied pre-intervention, an MLA of ≥ 4.0 mm² had a diagnostic accuracy of 89% in predicting a coronary flow reserve >2.0. Likewise, IVUS has been correlated with noninvasive single-photon emission computed tomography (SPECT) (49). A 4 mm² MLA by IVUS had 88% sensitivity and 90% specificity to discriminate the SPECT (+) group from the SPECT (−) group. The relatively simple cut-off of 4.0 mm² MLA can be used as a criterion in the clinical decision making process. This cut-off value has also been identified using fractional flow reserve (FFR) as the gold standard in the assessment of lesion severity (50). The association of MLA and ischaemia has been revisited more recently using an existing IVUS imaging database: 170 coronary lesions (150 patients) which were imaged with IVUS and underwent stress myocardial single-photon emission computed tomography (SPECT) were analysed. By receiver operator characteristic curve analysis, the best cut-off value of MLA was ≤2.1 mm² (38.6% positive predictive value, and a 91.3% negative predictive value versus lesions with a positive SPECT) area under the curve: 0.690, 95% CI: 0.615 to 0.759, P<0.01 (51).

There have been previous comparative studies showing good to excellent correlation between CCTA and IVUS geometrical parameters (52). This has led to the use of CCTA to prospectively evaluate changes in IVUS-like parameters such as MLA (53).

It is worth noting that this value does not apply to small vessels (54) or to large segments such as the left main (LM) or venous bypass grafts.

**Conclusions**

In this fast moving field of advanced coronary imaging, CTA has moved from just a “rule-out CAD” modality and has been explored in several different lines of research, due to its unique ability to non-invasively depict several atherosclerotic plaque features and quantify the extent of plaque burden in the coronary tree. One of the most interesting research lines is exploring the relation between these plaque features and coronary burden of disease, not only with adverse outcomes but also recently with the development of ischemia, which might help to understand the pathophysiological link between anatomy and function in ischemic heart disease and a better identification of patients at risk of future coronary events.

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None.

**Footnote**

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**References**


27. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in


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<td>Takagi et al. (55)</td>
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<td>Prospective 50% of Intermediate lesions (30–70%) Stable patients</td>
<td>42 patients 51 lesions</td>
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<td>43 patients 53 lesions</td>
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<td>84 patients 92 lesions</td>
<td>FFR vs. IVUS</td>
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<td>Kang et al. (58)</td>
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<td>Prospective Intermediate lesions (30–75%) Single center Stable patients</td>
<td>201 patients 236 lesions</td>
<td>FFR vs. IVUS</td>
<td>≤0.80</td>
<td>&lt;3.2 mm²</td>
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<td>252 patients 267 lesions</td>
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<td>Retrospective, de novo lesions (30–90%) Stable patients</td>
<td>692 patients 784 lesions</td>
<td>FFR vs. IVUS</td>
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<td>2.4 mm²</td>
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<td>Prospective Intermediate lesions (40–70%) Single center Stable patients</td>
<td>185 patients 205 lesions</td>
<td>FFR vs. IVUS</td>
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<td>FFR vs. IVUS</td>
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<td>3.03 mm²</td>
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<td>Waksman et al. (43)</td>
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<td>Prospective Intermediate lesions (40–80%) Multi-center Stable patients</td>
<td>350 patients 367 lesions</td>
<td>FFR vs. IVUS</td>
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<td>&lt;3.07 mm²</td>
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<td>Chen et al. (61)</td>
<td>2013</td>
<td>Prospective, de novo lesions ≥40% Stable patients</td>
<td>323 patients 323 lesions</td>
<td>FFR vs. IVUS</td>
<td>≤0.80</td>
<td>2.97 mm²</td>
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<td>141 patients 165 lesions</td>
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<td>3.15 mm²</td>
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<td>822 patients 881 lesions</td>
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<td>≤0.80</td>
<td>3.00 mm² (Westen) 2.75 mm² (Asians)</td>
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<td>Niakanuma et al. (63)</td>
<td>2014</td>
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<td>109 patients 132 lesions</td>
<td>FFR vs. IVUS</td>
<td>≤0.80</td>
<td>2.70 mm²</td>
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<tr>
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<td>2014</td>
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<td>206 patients 206 lesions</td>
<td>FFR vs. IVUS</td>
<td>≤0.80</td>
<td>3.2 mm²/2.5 mm²</td>
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<td>Doh et al. (65)</td>
<td>2014</td>
<td>Prospective, Intermediate lesions (30–70%) Multi-center Stable patients</td>
<td>151 patients 181 lesions</td>
<td>FFR vs. IVUS</td>
<td>≤0.80</td>
<td>2.82 mm²</td>
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<td>Intermediate lesions, stable patients</td>
<td>59 patients 62 lesions</td>
<td>FFR vs. OCT</td>
<td>≤0.75</td>
<td>&lt;1.91 mm²</td>
<td>&lt;1.35 mm</td>
<td>&gt;70.0%</td>
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<td>IVUS/OCT</td>
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<td>56 patients 61 lesions</td>
<td>FFR vs. OCT and IVUS</td>
<td>≤0.80</td>
<td>IVUS: 2.36 mm² OCT: 1.95 mm² Relative difference: 32.3±26% Absolute difference: 0.65±0.62 mm² (limits of agreement of -0.57 to 1.87 mm²)</td>
<td>IVUS: 1.59 mm² OCT: 1.34 mm² Relative difference: 19.5±16% Absolute difference: 0.27±0.23 mm² (limits of agreement of -0.20 to 0.72 mm²)</td>
<td>IVUS: 61%</td>
<td>OCT: 70%</td>
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