Review

Non invasive imaging of coronary arteries with 64-slice CT and 1.5T MRI: challenging invasive techniques

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Abstract. Non-invasive coronary artery imaging challenges any diagnostic modality, because of the complex and tortuous anatomy and cardiac contraction and respiration. Therefore, non-invasive coronary imaging requires high spatial and temporal resolution. Our purpose is to discuss the feasible applications in coronary imaging of Magnetic Resonance Imaging and Multi-slice Computed Tomography (MSCT). Focus will be devoted to potential indications and clinical impact of MSCT because of the fast development and the important results recently reported, in particular with the recent introduction of 64-slice equipments. MSCT of the coronary arteries is a promising imaging modality for the assessment of coronary lumen and wall. (www.actabiomedica.it)

Key words: Coronary atherosclerosis, plaque, coronary imaging, Multislice CT, 64-slice CT, Magnetic Resonance

Introduction

Invasive Conventional Coronary Angiography (CCA) is the "gold standard" method for the evaluation of vessel lumen and provides excellent results in demonstrating obstructive lesions of Coronary Artery Disease (CAD). However, CCA doesn't allow a direct visualization and evaluation of the coronary artery wall. The comparison of angiographic studies of coronary arteries before and after non-fatal myocardial infarction (MI) has shown that 49% of the pre-existing lesion before MI were <50% stenotic (1). Hence, it appears that some potentially dangerous lesions are often non-occlusive and thus difficult to diagnose by angiography. CAD may progress in different morphogenetic stages, resulting in various lesion types and clinical syndromes (2). The rupture of a thin fibrous cap atheroma may develop thrombosis and result in acute coronary syndromes. Healed lesions may still rupture or become fibro-calcific and determine lumen narrowing at the end stage (3-5).

Intravascular ultrasound (IVUS) provides a quantitative measurement of atherosclerotic plaques as well as a qualitative assessment of plaque composition. However, IVUS cannot be used for routine evaluation of plaque characteristics because of its invasiveness (6).

Our aim is to discuss Magnetic Resonance Imaging (MRI) and Multi-slice Computed Tomography (MSCT), which are currently the only non invasive diagnostic modalities for coronary atherosclerosis imaging. Focus will be devoted to potential indications and clinical impact of MSCT because of the fast development and the results recently reported.

Magnetic resonance

Technique

MR coronary images are obtained using ultra-fast spin echo, gradient echo or echo-planar imaging techniques. Data acquisition is performed with a 2D (7) or 3D (8) technique or a thick slab targeted for an individual coronary artery approach (9). It is possible to suppress or sharpen signal from specific components, such as the perivascular fat signal and myocardial signal, by modifying technical parameters. This approach has the advantage of permitting the short echo time of turbo-field-echo techniques and the short acquisition window of echo-planar-imaging techniques. Furthermore, contrast agents (i.e. ultra-small superparamagnetic iron oxide) may improve the sensitivity of in vivo MRI (10).

Results and applications

The sensitivity and specificity in identifying a significant coronary lesion ranged from 30 to 90% and 70 to 95%, respectively (11, 12). Therefore studies show a wide variation in diagnostic accuracy and only one multi-center study has been reported with an accuracy of 72% in diagnosing CAD and a feasibility of 84% in the assessment of proximal segments (13). The task of coronary angiography on MR can be very challenging and images of diagnostic quality can be obtained after thorough optimization (Figure 1).

MRI has been the first non invasive method employed in coronary plaque imaging, due to its capabilities to characterize atherosclerotic lesions and to its abitility in demonstrating carotid plaque progression/regression after lipid lowering therapy (14). The lipid components appear within the plaque hyper-intense on T1 weighted images (T1) and proton density (PD) images, and hypo-intense on T2 weighted images (T2). The fibro-cellular components appear hyper-intense on T1, T2, and PD images. Calcium deposits are hypo-intense areas on T1, T2, and PD images. Thrombotic plaques present irregularities on the lumen surface and are defined as hyper-intense on T1, T2, and PD images. However, only a few papers are reported on literature to display in-vivo detection of coronary artery plaques (15, 16).

Limitations and outlook

MR coronary imaging is a task harder than carotid plaque visualization. A number of unsolved pro-

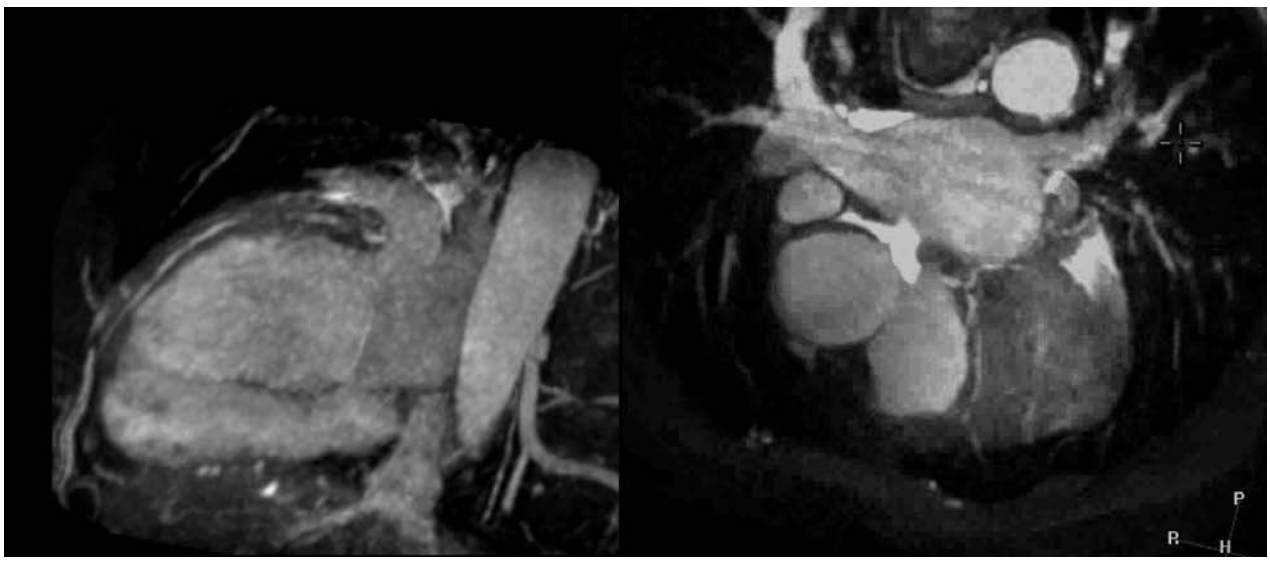


Figure 1. Magnetic Resonance Coronary Angiography at 1.5T. The long axis view (Left panel) reveals a consecutive stenosis of the distal left main (arrowhead) and of the prox-mid left anterior descending (arrow). The spider view (Right panel) shows the same finding with origin of left circumflex (arrow).

blems limit MRI reliability. MRI coronary angiography applications are still hampered by the long acquisition time and by the fact that some segments cannot be evaluated, due to cardiac and respiratory motion artifacts, the complex anatomy, and the relatively small size of the coronary arteries. Furthermore coronary plaques, in contrast with carotid arteries, are not always lipid-rich and often not obstructive. The slice thickness (from 3 to 5 mm) causes partial volume effect with overestimation of the vessel wall. Tailored phased-array coils should be used to improve spatial resolution. New developments of MRI may be achieved by gathering images from high magnetic fields or employing specific tissue-binding gadolinium-labeled peptide (17-19). Intra-vascular catheter coils have been recently introduced in order to improve the signal-to-noise ratio and to obtain a spatial resolution of 250-300 μm (20). The latter solution requires an invasive approach which is beyond clinical application at the moment.

Multi-slice computed tomography

Technique

Non-invasive coronary imaging requires high spatial and temporal resolution, and a fast anatomical coverage to scan within one breath-hold. The introduction of the Electron Beam CT allowed the examination of a moving structure, such as the coronary artery, but its spatial resolution allowed the exploration of only the proximal portion of the coronary arteries. The main application of this technique was the quantification of coronary artery calcium.

The fast development of CT scanner technology gave way to equipments with more than a single row of detectors and equipped of faster gantry rotation speed. The resulting improvement in temporal and spatial resolution has placed CT in the field of cardiac clinical applications (21). A new generation of MSCT scanners has recently been introduced which provides the simultaneous acquisition of 64-slices and a fast gantry rotation speed (330 msec) with a "half scan" reconstruction algorithm (temporal resolution of 165 msec).

A bolus of 80-100 ml contrast material with high iodine concentration (350-400 mg of Iodine per mL) is injected through the brachial vein with a flow rate of 4-5 ml/second. A test bolus or a bolus-tracking technique may be used to synchronize the arrival of the contrast in the coronary arteries with the beginning of the scan. The image data is acquired during one breath hold varying in duration from approximately 18-25 seconds (16-slice CT) to less than 12 seconds (64-slice CT).

The electrocardiographic (ECG) track is acquired during the scan and afterwards the image reconstruction is performed with retrospective gating. After acquisition of the CT data the operator may set the reconstruction window at any point within the cardiac cycle by selecting the motionless dataset throughout the entire R-R interval (usually during mid-to-end diastole or end-systolic phase) (22).

The reconstructed contiguous axial slices (0.6/0.75 mm effective thickness) are stacked in a volume to generate a 3D dataset from which any plane can be created. Currently, MPR (Multi Planar Reformatting), cMPR (curved Multi Planar Reformatting), MIP (Maximum Intensity Projection), and VRT (Volume Rendering Technique) are the tools employed to obtain a diagnostic three-dimensional view of the coronary artery tree. Calcium score and left ventricular systolic function can also be evaluated in every patient with dedicated software.

Results and applications

The literature on 4-slice CT and 16-slice CT shows a progressive improvement of the results in the detection of significant coronary stenosis. Motion artifacts, low spatial resolution and long acquisition time limited 4-slice CT generation (23, 24). With 16-slice CT scanners the increased temporal and spatial resolution determined an increased diagnostic accuracy. The number of excluded segments was reduced and diagnostic accuracy improved. The sensitivity ranged between 72% and 95%, while the specificity ranged between 86% and 98% (21, 25-30). Early studies with 64-sliceCT confirmed high diagnostic accuracy and negative predictive value (Table 1) (31-33).

MSCT Coronary Angiography may be used to exclude the presence of significant stenosis in patients

Table 1. Diagnostic performance of CT coronary angiography as compared to conventional coronary angiography in detecting significant (≥50 lumen diameter reduction) coronary stenoses.

Study	Slice	Pop. (n)	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Nieman et al. Circulation '02	12	58	95	86	80	97
Ropers et al. Circulation '03	12	77	92	93	79	97
Mollet et al. JACC '04	16	128	92	95	79	98
Mollet et al. JACC '05	16	51	95	98	87	99
Leschka et al. Eur Heart J '05	64	67	94	97	87	99
Raff et al. JACC '05	64	70	86	95	66	98
Mollet et al. Circulation '05	64	52	99	95	76	99

Abbreviations: Number of patients enrolled (Pop.); Sensitivity (Sens.), Specificity (Spec.), Positive (PPV) and Negative predictive value (NPV)

with low pre-test probability because of the high negative predictive value. In these settings, the proper use of MSCT would be after an inconclusive or borderline stress test or in patients with atypical chest pain. MSCT has a negative predictive value of 100% in patients with stable angina (27). MSCT can detect chronic total occlusion adding important information as compared to invasive CCA, such as the morphology of the occlusion trajectory (34). Given the high sensitivity and negative predictive value of the technique, CT could represent an alternative to CCA in patients with dilated cardiomiopathy of unknown origin and prior to cardiac valve surgery or transplant and major non-coronary cardiac surgery.

Few studies evaluated the diagnostic accuracy of 4 and 16-slice CT for the study of CABG reporting high sensitivity and specificity (35, 36).

MSCT is also useful to assess the stent patency and to evaluate the in-stent restenosis of the proximal coronary arteries. 16 slices CT permits to reach a sensitivity of 78% and a specificity of 100% in the assessment of stent patency and a sensitivity of 75% and a specificity of 96% on the intimae hyperplasia (37).

MSCT may clearly demonstrate coronary anomalies, which may cause unexpected sudden death in the younger population, such as the "interarterial" course of a coronary artery between the aorta and pulmonary artery (38).

A pre-clinical application of coronary CTA is plaque imaging which might become a relevant diagnostic tool for risk stratification (39-41). It has been reported that coronary CTA has the potential to detect coronary plaques, quantify their volumes and eventually characterize their composition, based on the x-ray attenuating property of each structure (measured in Hounsfield Units, HU). Schroeder et al analyzed the configuration of 34 plaque lesions and found a correct differentiation of soft, intermediate, and calcified plaques by MSCT, using IVUS as the gold standard (39). Leber et al showed that lesion echogenicity correlates well with MSCT attenuation measurements in coronary plaques. MSCT correctly classified 78% of sections containing hypo-echoic plaque areas (soft plaques), 78% of sections containing hyper-echoic plaque areas (fibrous plaques), and 95% of sections containing calcified plaque tissue (40). However, a sub-classification between lipid and fibrous plaques appears difficult, since a substantial overlap of density between hypo-echoic (lipid-rich) and hyper-echoic (fibrous) plaques was observed in the same study. Moreover, a sensitivity of only 53% in detecting non calcified plaque is reported. The visualization of non-calcified lesions is hampered by plaque size and vessel size, with an improving accuracy by restricting the analysis to proximal segments (42). Furthermore, Leber et al. demonstrated that there is a substantial difference in coronary plaque composition between patients with acute myocardial infarction and stable angina pectoris. Non-calcified plaques are more frequent in the first group. Therefore, the severity of coronary atherosclerosis in patients with infarction is underestimated if only calcified plaques are considered (43). In an ex-vivo free motion model, Becker et al correlated the atherosclerotic lesions in coronary specimens detected by 4-MSCT with the histo-pathological findings. A statistically significant difference

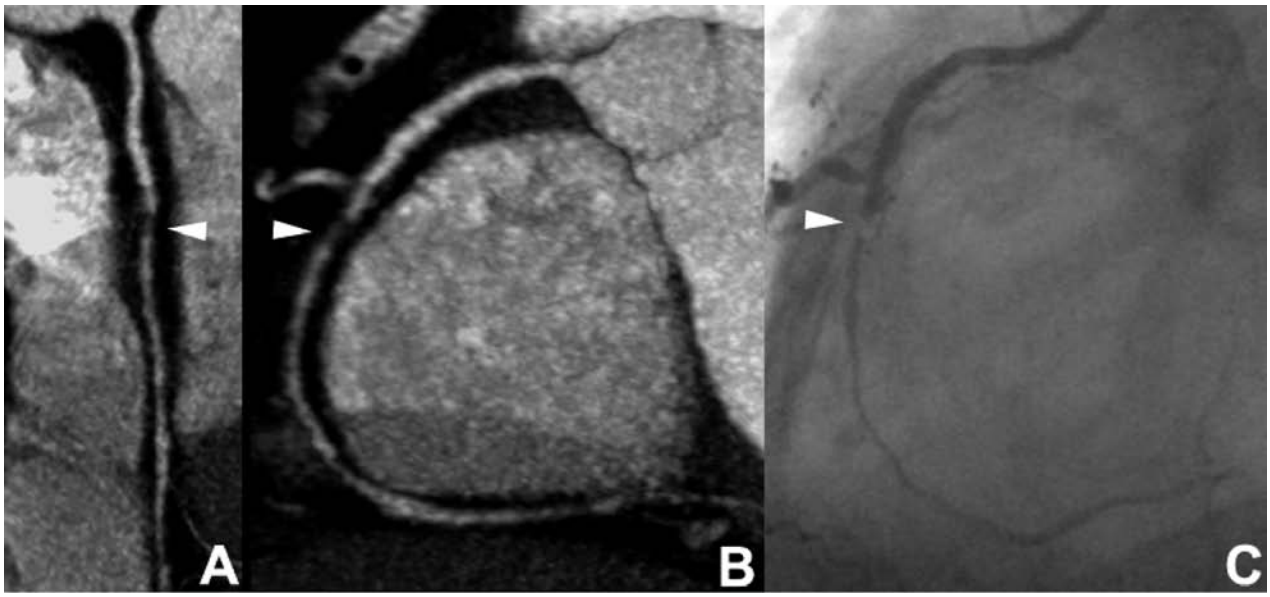


Figure 2. The 64-slice CT reveals a significant occlusion (arrowhead) of the right coronary artery in a patient with acute coronary syndrome (A, B). The lesion (arrowhead) was confirmed by CCA (C).

between lipid rich (47±9 HU) and fibrous calcified plaques (104±28 HU) has been reported (44).

The introduction of MSCT could be useful in the emergency workup of non-cardiac thoracic pain, such as aortic dissection, pericarditis or mediastinum disease. The possibility to scan the entire thorax visualizing the thoracic aorta, the pulmonary arteries and the coronary arteries could provide a new approach to the triage of acute chest pain (45). If CT scanners with cardiac state-of-the-art capabilities are installed in emergency department, the early diagnosis of acute coronary syndromes (Figure 2) with still negative enzymes and non-diagnostic ECG alterations may be also possible (46).

Limitations and outlook

Patients with significant respiratory failure, major allergy to iodine containing contrast material and renal failure are not eligible for the scan or may be treated accordingly. Persistent arrhythmia (i.e. atrial fibrillation) precludes MSCT coronary imaging. A heart rate > 70 bpm results in poor image quality and therefore it is recommended to lower the heart rate with administration of β-blockers prior to the scan (i.e. 100 mg metoprolol 1 hour before the scan) (47). Patients candidated for MSCT need to be able to hold their breath for up to 12 sec with the 64-slice CT (31).

The high radiation exposure associated with CT scanning is still a matter of great concern. The effective doses of 4-slice CT coronary angiography is reported to be 6.7 to 10.9 mSv for males and 8.1 to 13.0 mSv for females (48). The radiation dose is higher with the use of 16 and 64-slice CT scanners (30, 32).

Highly attenuating materials, such as surgical clips or metallic mash of coronary stents, cause "blooming" artifacts and may preclude a reliable assessment. It has been reported that a high coronary calcium score can impair the diagnostic accuracy and therefore patients should be excluded from MSCT based on their Agatston score. However, it has been shown that the difference in the diagnostic accuracy of MSCT between low calcium score and high calcium score patients is not significant in detecting any stenosis ≥50%, with no change in the negative predictive value (49).

MSCT coronary angiography is a technique that requires considerable training and still remains operator-dependent. Highly qualified teams can perform this type of diagnostic procedure with good clinical outcomes. The introduction of software that is able to

provide a reproducible quantification of the degree of coronary stenosis may improve this issue, even though much of the operator dependency has to do with the recognition and optimization of scan and reconstruction parameters. Automated vessel lumen and wall analysis might also overcome current limitations in coronary plaque characterization and quantification.

The use of the new generation of CT scanner such as the 64-sliceCT and the dual-source CT will provide better results, mainly due to improved spatial and temporal resolution (effective temporal resolution = 83 ms), and reduction of motion artifact.

Discussion

Given the progressive nature of coronary atherosclerosis, an ideal imaging technique should be able not only to detect lumen stenosis but also to characterize coronary wall. CCA has been the gold standard technique in visualizing the coronary artery lumen and in detecting stenosis for forty years. However, CCA cannot allow characterizing of not lumen narrowing plaques. IVUS is currently considered supplemental to CCA, rather than a comprehensive alternative. It allows an assessment of vessels that are difficult to image by angiography, including diffusely diseased segments, ostial or bifurcation stenoses, eccentric plaques, and angiographically foreshortened vessels, and it is employed as a guidance of provisional stenting. Furthermore, IVUS allows an accurate measurement of vessel borders, lumen area, plaque size, calcification and vascular remodeling area as well as a qualitative assessment of plaque composition. However, IVUS cannot be used for routine evaluation of plaque characteristics because of its invasiveness and related increased risk, additional time and cost. Other catheter based techniques such as elastography, Optical Coherence Tomography (OCT), angioscopy, Raman spectroscopy and thermography aim to locally visualize and identify plaques accordingly to their chemical or physical properties. Nuclear medicine (SPECT or PET) explores the functional aspects of atherosclerosis, even if the intrinsic lack of spatial resolution makes this tool less feasible than other techniques in visualizing atherosclerotic plaques. Theoretically, MRI is a versatile non-invasive tool for detecting coronary plaques and stenoses due to the absence of x-ray exposure. Currently 1.5 T MRI images are affected by a poor effective resolution. In addition, MRI techniques are still hampered by relatively long acquisition time, poor reproducibility, and the large percentage of non-assessable segments. Apart from the complex OCT, which is still being tested, the thickness of thin fibrous cap (the main feature of the vulnerable plaque) is below the spatial resolution of all available techniques (Table 2) (50). MSCT could be able to achieve both

Table 2. Spatial resolution of coronary atherosclerosis imaging techniques

Techniques	Principle	Spatial Resolution (μm)
Catheter-based		
IVUS	Ultrasound reflection	100-200 axial 200-250 lateral
Intravascular MRI	H + resonance	250-300[1]
Non invasive		
SPECT	γ emission	10000
PET	positron emission	4000
1.5 T MRI	H + resonance	400[2]
3 T MRI	H + sonance	110[3]
9 T MRI	H + resonance	97[4]
16-MSCT	X-rays attenuation	300x300x600
64-MSCT	X-rays attenuation	300x300x400

Legends: SPECT: Single photon emission tomography; PET: Positron emission tomography; [1] image resolution obtained in rabbit in-vivo models and in human ex-vivo coronary arteries; [2] In-vivo in plane resolution; [3] Ex-vivo in plane resolutions; [4] In plane resolution obtained in mice

purposes providing an overall view (i.e. stenoses and plaques) of coronary atherosclerosis (Figure 3 and 4), even if the spatial resolution is still insufficient in visualizing plaques prone to rupture.

MSCT coronary angiography might become the initial tool for risk stratification in patients with known or suspected CAD and may represent the *"gatekeeper"* to other existing modalities when positive findings oc-

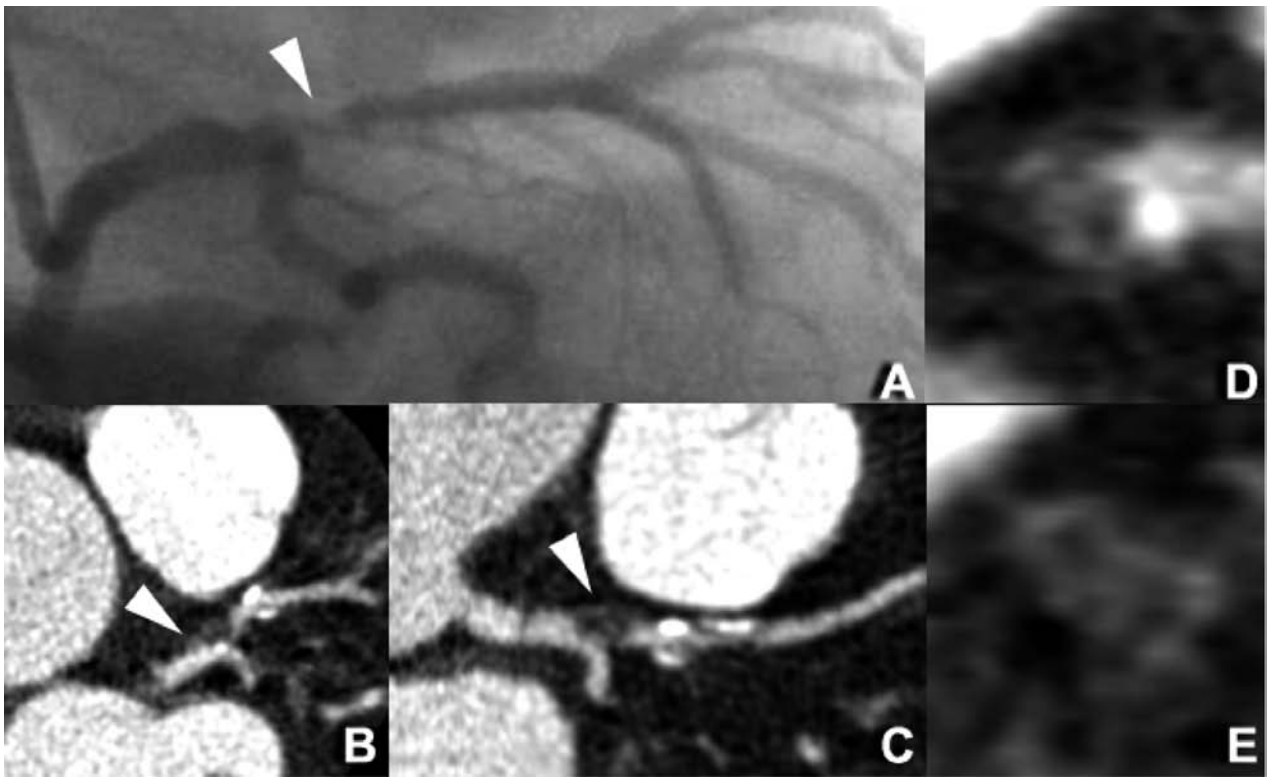


Figure 3. The CCA displays a stenosis (arrowhead) in the proximal LAD (A). The 64-slice CT reveals a large mainly non calcified plaque (arrowhead) by MPR (B) and cMPR (C) images. The cross sections depict the plaque at the bifurcation (D) and in the proximal LAD (E).

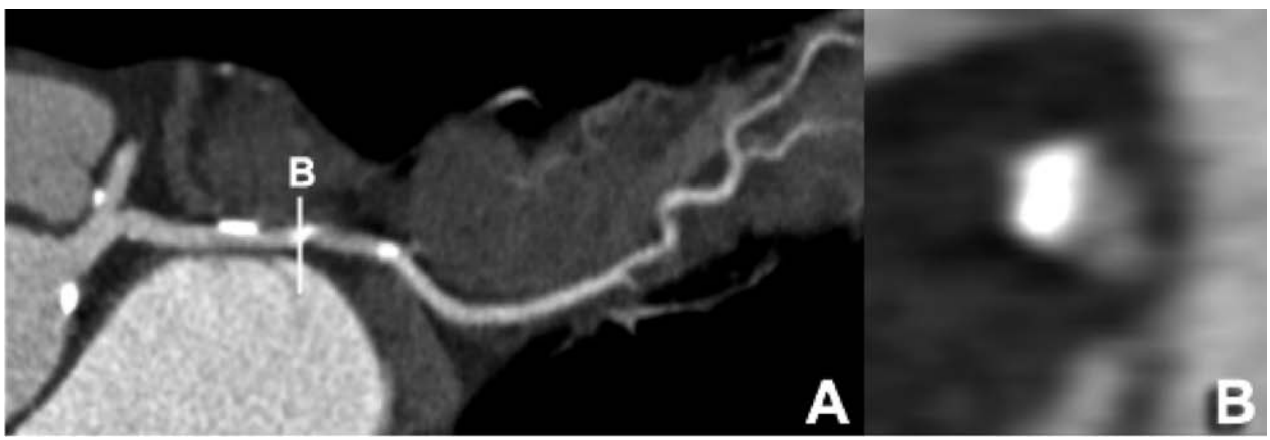
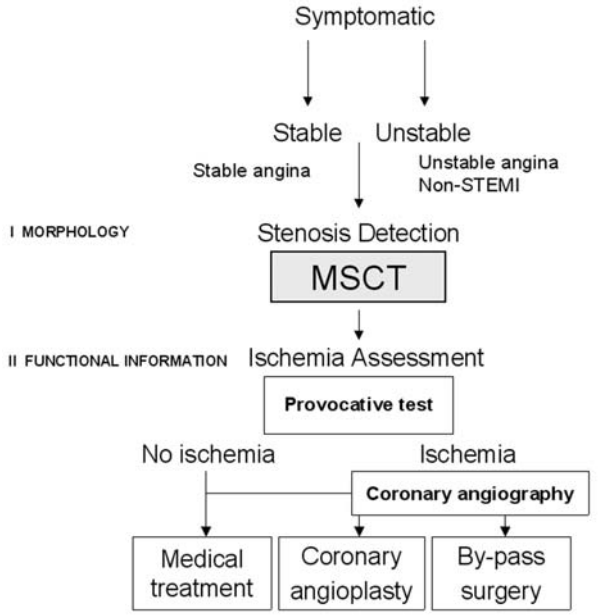


Figure 4. The 64-slice CT curved MPR reconstruction displays calcified plaques in the left circumflex (A). The corresponding cross-section shows a calcified plaque (B).

Table 3. Potential scenario in which MSCT might represent the imaging gatekeeper in the detection of stenoses. If a stenosis is detected in patients with suspected coronary ischemia, assessment of ischemia is requested by means of provocative tests. Depending on the induced ischemia, CCA and revascularization may follow



cur. In the absence of coronary atherosclerosis further imaging may not be needed. If a stenosis is detected, assessment of ischemia is requested by means of provocative tests. Depending on the ischemia induced, CCA and revascularization may follow (Table 3).

However, the task to compare MSCT with CCA may be difficult since the two techniques show different features while preserving the peculiar properties of the information they can deliver. The use of a quantitative algorithm in MSCT would be of paramount importance since the comparison is performed with a quantitative CCA. Moreover, MSCT could be the first-step tool in the detection of plaques (overall image-based quantification of CAD), while MRI or catheter based techniques may better characterize lesions when CT provides a roadmap. However, this is only a potential scenario since, until now, preventive percutaneous coronary intervention has never demonstrated to alter plaque biology and primary prevention with an intensive medical treatment may overcome the need of an imaging tool. It is indeed controversial if absolute HU values are valid in determining the plaque composition and in identifying the corresponding tissue. Intra-coronary attenuation significantly modifies the attenuation of plaques (51). A calibration factor may probably be introduced in the future to address this issue. Moreover, prospective trials on follow-up of non-stenotic soft plaques are needed to prove these research findings. Therefore, it is wiser to consider MSCT in the same perspective of CCA, unless important data on the prognostic relevance of plaque become available.

Conclusion

MRI needs an improvement in image quality and diagnostic accuracy, which may be obtained with the introduction of high magnetic field and blood pool contrast agents. Non invasive coronary MSCT is a fast, relatively inexpensive, patient-friendly tool to diagnose coronary artery stenoses. Efforts have to be made in order to reduce radiation exposure. In selected patient populations coronary MSCT might replace CCA, by maintaining the same indications, unless important data on the prognostic relevance are available. Promising initial steps have been taken in non invasive plaque imaging.

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