Current perspectives
Non-invasive coronary angiography with multislice computed tomography. Technology, methods, preliminary experience and prospects

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The recent technical developments in multislice computed tomography (MSCT), with ECG retro-gated image reconstruction, have elicited great interest in the possibility of accurate non-invasive imaging of the coronary arteries. The latest generation of MSCT systems with 8-16 rows of detectors permits acquisition of the whole cardiac volume during a single 15-20 s breath-hold with a submillimetric definition of the images and an outstanding signal-to-noise ratio. Thus the race which, between MSCT, electron beam computed tomography and cardiac magnetic resonance imaging, can best provide routine and reliable imaging of the coronary arteries in clinical practice has recommenced.

Currently available MSCT systems offer different options for both cardiac image acquisition and reconstruction, including multiplanar and curved multiplanar reconstruction, three-dimensional volume rendering, maximum intensity projection, and virtual angioscopy.

In our preliminary experience including 176 patients suffering from known or suspected coronary artery disease, MSCT was feasible in 161 (91.5%) and showed a sensitivity of 80.4% and a specificity of 80.3%, with respect to standard coronary angiography, in detecting critical stenosis in coronary arteries and artery or venous bypass grafts. These results correspond to a positive predictive value of 58.6% and a negative predictive value of 92.2%.

The true role that MSCT is likely to play in the future in non-invasive coronary imaging is still to be defined. Nevertheless, the huge amount of data obtainable by MSCT along with the rapid technological advances, shorter acquisition times and reconstruction algorithm developments will make the technique stronger, and possible applications are expected not only for non-invasive coronary angiography, but also for cardiac function and myocardial perfusion evaluation, as an *all-in-one* examination.

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Introduction

Ischemic heart disease is the cause of 13.7% of all deaths in industrialized countries: it was responsible for 600 000 deaths in Europe in 1998, approximately 50% of which were without symptoms prior to the fatal event[1,2]. The current gold standard for the definition of the presence and severity of coronary heart disease remains catheter-based selective coronary angiography. In 1998, 1 291 000 coronary angiographies were performed in the United States; in Italy, in 2001, 179 000 were performed. In line with the European average, 63.5% of these were not followed by percutaneous transluminal coronary angioplasty (PTCA) and were therefore carried out exclusively for diagnostic purposes[3-5].

Although selective catheterization of the coronary arteries is at present relatively safe as an invasive diagnostic method, at least in the structures where it is performed in large numbers[6], research into alternative methods of coronary imaging that are non-invasive, reliable, repeatable and cost-effective has for years posed a challenge to cardiologists and, more generally, to those involved in imaging diagnostics.

At the beginning of the ’90s, the use of ultra-fast electron beam computed tomography was first proposed for the study and prognostic evaluation of coronary calcifications[7-10]. Its more recent use in coronary imaging[11,12] remains so far limited by the high incidence of motion artifacts that reduce the interpretability of the images[13,14]. Moreover, the high cost of the equipment with respect to conventional scanners, and the utility of electron beam computed tomography being essentially linked to the study of the heart, have greatly limited, particularly in Europe, its diffusion and application in the clinical context.

Another non-invasive technique that has recently become available for coronary imaging and appears very promising is magnetic resonance imaging[15-19]: it has the advantage of not requiring ionizing radiation and can be performed without injection of iodine contrast media. The low signal-to-noise ratio (even though counterbalanced by the signal's high dynamic range) and moderate spatial resolution – even with the latest devices that use high magnetic field intensities, high gradients and faster sequences of acquisition – still restrict the use of magnetic resonance imaging in the investigation of the coronary anatomy to an area of preclinical research.

Recent technological developments in computed tomography have led to the development of scanners with multiple rows of detectors designed to simultaneously acquire from 4 to 16 tomographic sections at a speed of < 0.5 s, i.e. multislice computed tomography (MSCT). These characteristics of spatial and temporal resolution enable submillimetric image acquisition in a few seconds over a relatively wide region of interest (such as the heart). Moreover, the development of retrospective electrocardiographic systems of synchronization (ECG gating) enables off-line image reconstruction, overcoming the problem of cardiac motion. This technological evolution of computed tomography, a diagnostic tool considered up to a few years ago as having reached its full "maturity", has thus opened up the possibility of non-invasive coronary imaging and has a diagnostic potential such as to render its widespread clinical application in cardiology possible[20-32].

Technology and methodology of cardiac multislice spiral computed tomography

Evolution of scanners for computed tomography. In first-generation computed tomographic systems, the X-ray generator was mechanically rotated and produced a thin ray that, once having passed through the patient, was captured by a single detector. The physical connection between the tube and power supply cord was such that the tube itself could not rotate in a continuous mode and, after each single scan was acquired, the system had to rotate inversely back to the starting position. Axial sections of a thickness of the order of 1 cm could be acquired in not less than 1 s. The bed on which the patient lay moved forward with each scan, to a degree corresponding to the space between two contiguous sections. The thickness of each single section and the gap between contiguous sections made reconstruction of images on planes other than the axial one very difficult; moreover, dynamic contrast-enhanced studies were impossible due to the long duration of single image acquisition (Fig. 1A).

At the end of the '80s, the adoption of "slip-ring" technology overcame the need for a physical connection between the power supply cord and radiogenic tube, permitting the continuous rotation of the tube-detector system. With the patient's table moving continuously, instead of single sections one could now obtain a spiral scan of a volume. The far shorter scanning times of these systems, which were given the name "spiral computed tomography", and the possibility of acquiring contiguous sections without gaps between one another constituted the premises for dynamic contrast-enhanced studies and for image reconstruction on planes other than the axial one (Fig. 1B).

First-generation conventional and spiral computed tomography have a single row of detectors. Latest-generation tomographic systems, i.e. MSCT scanners, have from 4 to 16 rows of detectors. The increased number of detectors, together with the scanner's increased rotation speed (up to 120 revolutions/min) means that a large volume of the body can be scanned in an extremely short space of time (e.g. the entire chest can be studied during a single breath-hold), or a small volume scanned with very thin sections (up to 0.4 mm), with spatial reconstructions that are virtually isotropic (i.e. voxels $0.5 \times 0.5 \times 0.5$ mm)[33] (Fig. 1C).

Electrocardiographic gating and acquisition protocols. To overcome the problem related to cardiac motion, images must be reconstructed utilizing data acquired during different consecutive cardiac cycles, in selected phases of the R-R interval, typically during late diastole when the cardiac motion is negligible. In "absolute" ECG gating, the data used for image reconstruction correspond to a fixed time interval after the R wave (absolute delay) or to a fixed interval before the R wave (absolute reverse delay). In "relative" ECG gating, the acquisition for each single beat corresponds to a specific fraction of the RR interval. It has been shown that the absolute-reverse type of gating improves image quality with respect to the absolute delay type, since it is able to reduce the impact of arrhythmias and more generally that of the RR interval variability[2,34,35]. All systems allow for the selection of different reconstruction windows required for the visualization of different coronary artery branches due to their non-synchronous motion. As a matter of fact, the reconstructed images are defined as iso-phasic, since they refer to the same phase of different cardiac cycles. In order to reduce radiation exposure, some systems allow, by means of gating, for a reduction in the X-ray intensity during those phases of the cardiac cycle not utilized for image acquisition (typically systole and protodiastole) (Fig. 2).

If the duration of diastole is long enough, for a scanner rotation speed of 2 revolutions/s (gantry rotation time of 500 ms), the data obtained from a single row of

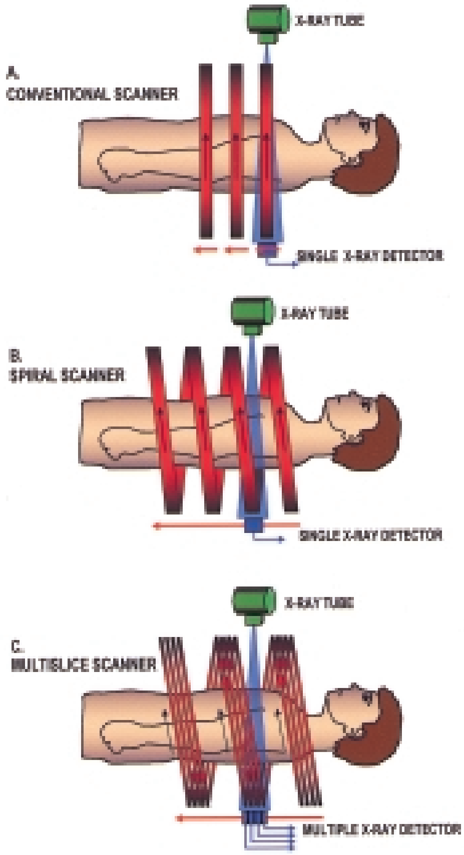

Figure 1. *Technological evolution of scanners for computed tomography.* A: *conventional scanner. Acquisition of single sections during each single rotation of the X-ray generator and detector system; the bed moves forward in a discontinuous mode between one scan and the next, in the time needed to bring back the X-ray generator and detector system to the starting position.* B: *spiral scanner. The generator and single detector system rotate around the patient at the same time as the bed moves continuously, giving rise to a spiral scan.* C: *multislice scanner. The generator and multiple detector system permit the acquisition of several contiguous spiral scans contemporaneously.*

detectors can permit the reconstruction of an entire section. In this case, the temporal resolution in the various systems is around 250 ms: this mode of image reconstruction limited MSCT cardiac investigation to subjects with a heart rate < 60-65 b/min and not infrequently required the use of pre-medication with beta-blockers.

For subjects with a higher heart rate, to obtain higher temporal resolutions (up to 80-85 ms) the algorithms used envisage the reconstruction of each single section with data deriving from different rows of detectors that scan the same section of the heart anatomy in successive contiguous cardiac cycles (Fig. 2). Algorithms that permit an increase in the temporal resolution are the more effective the less they reduce the spatial resolution. Commercial firms have made the reconstruction algorithms available for up to 4-slice systems, with biphasic type reconstructions (utilizing 2 rows per cycle). But subsequent competition between the various manufacturers (and the consequent huge sums invested in the development of increasingly complex software) has led to "protection" of these algorithms, so that basically only their performance characteristics are now disclosed. A recent further advance in the gating systems developed by one manufacturer of latest-generation scanners permits automatic multiphase image reconstruction: images are reconstructed using the "best" sections of the entire diastolic interval considered, without the operator having to proceed by trial and error in selecting the various phases of the available RR interval (Imaging Physics Section of the Medical Physics Department at St. George's Hospital, Tooting, London - Medicines and Healthcare products Regulatory Agency [MHRA], UK, available at http://www.infoscan.org).

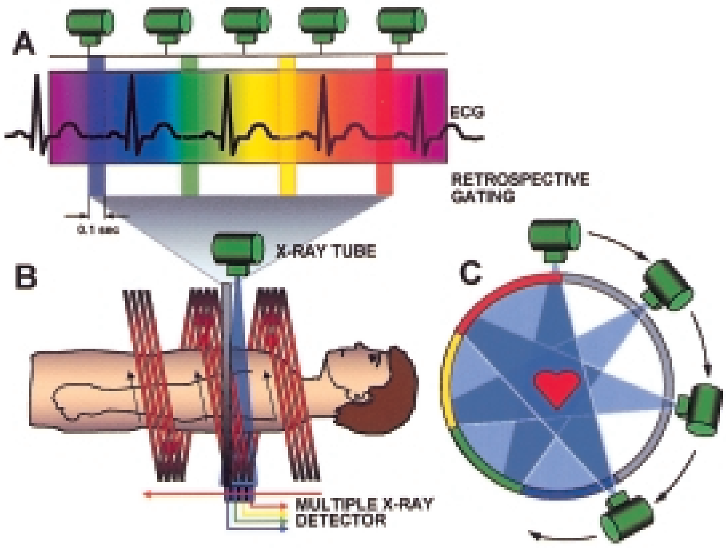

Figure 2. *Electrocardiographic synchronization (gating) used by multislice tomographic systems.* A: *schematic representation of the modality of acquisition during contiguous cardiac cycles.* B *and* C: *each segment is reconstructed from partial acquisitions by each detector (the example refers to a 4-detector system represented in blue, green, yellow and red).*

Modes of image reconstruction. The modalities of reconstruction and visualization of the data acquired are diverse, but surprisingly common to the various MSCT systems currently available.

Multiplanar reconstruction. Multiplanar reconstruction allows not only axial sections, such as conventional scanners provide, but also sagittal and coronary sections and virtually all the infinite intermediate planes.

"Curved" multiplanar reconstruction. "Curved" multiplanar reconstruction makes it possible to represent, on the same plane, the curvilinear plane formed by the infinite planes intercepting the vessel lumen (Fig. 3A): with such a display it is possible to "flatten out", on a single plane, the full length of the vessel maintaining its dimensional and morphological characteristics, so overcoming the geometric limits of conventional – typically projective – coronary angiography (Figs. 3B and 4B).

Three-dimensional reconstruction ("volume rendering"). This method of visualization generates the most spectacular images. The pseudo-colors and shading used by the reconstruction algorithms are designed to provide "life-like" three-dimensional images (Figs. 4A, 4C, 4D and 4E).

Reconstruction of the maximum intensity projection. Images of opacified coronary vessels are highlighted by the representation algorithms, while the contrast signal coming from the cardiac cavities and other structures with different X-ray absorption is dampened. The reconstruction is of a three-dimensional type on a single plane and the images thus obtained are strikingly similar to those provided by conventional coronary angiography in the left anterior oblique and right anterior oblique projections.

Virtual angioscopy. In this technique, the reconstruction algorithms give rise to virtual images with the intravascular visualization of the coronary walls. A route through the vessel is defined, allowing a sort of navigation from the origin to the most distal parts of the vessel. The images are appealing for the potential study of the morphological and surface features of stenoses and their spatial relationships with the coronary branches[36] (Fig. 4F).

Diagnostic reliability. Since latest-generation computed tomographic scanners have only just recently become available for use in clinical research, and since the software used for image reconstruction is continually being updated, the diagnostic reliability of MSCT in non-invasive coronary assessment is at present still under investigation. Table I[20,23,25,26,37-42] reports the data currently available in the literature regarding the technique's sensitivity and specificity compared to conventional coronary angiography in detecting critical coronary stenoses. It should be noted that the data published to date largely refer to 4-slice systems, equipped with first-generation ECG gating that enabled technically

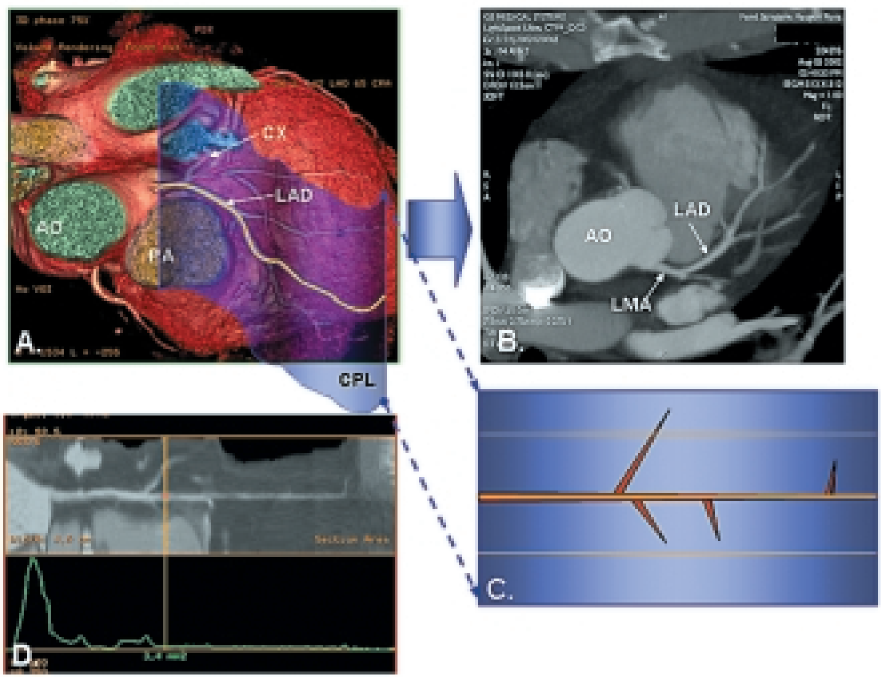

Figure 3. *Modality of multislice spiral computed tomographic image reconstruction.* A: *the curved plane that intercepts the coronary vessel, identified semi-automatically by algorithms of recognition based on the contrast density, is represented on a single plane* (B). *Other algorithms of reconstruction enable a rectilinear visualization of the principal coronary axis* (C and D), *for a better analysis of the vessel lumen. AO = aortic root; CPL = curved plane; CX = circumflex coronary artery; LAD = left anterior descending artery; LMA = left main artery; PA = pulmonary artery.*

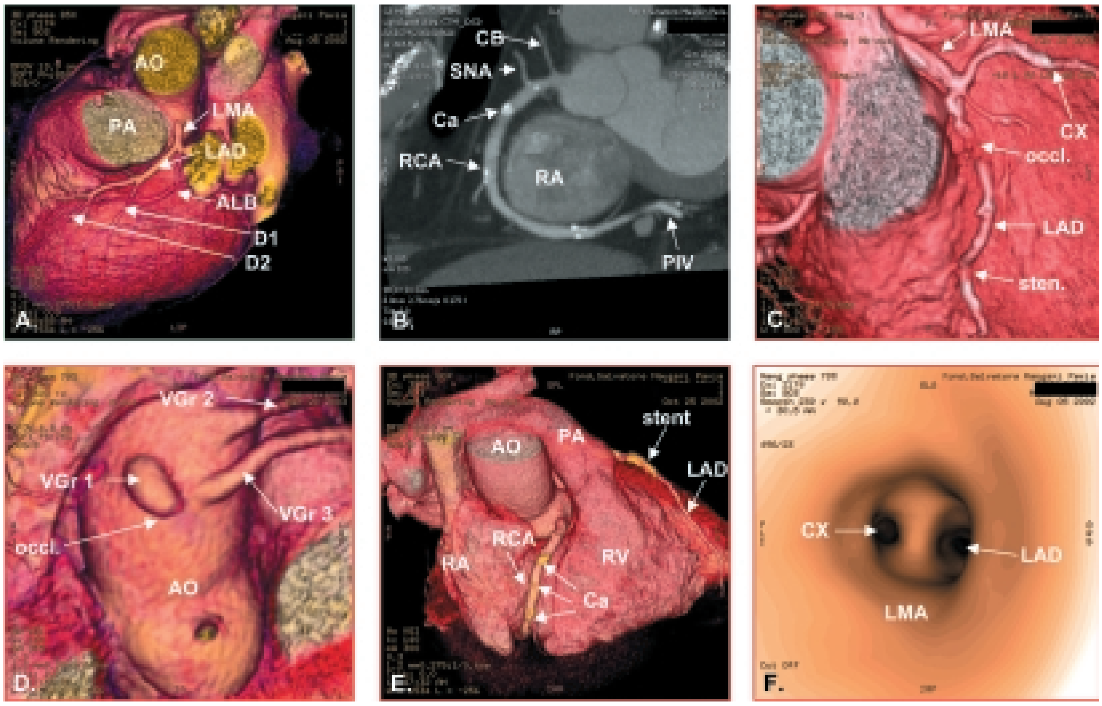

Figure 4. *Mode of presentation of multislice spiral computed tomographic images.* A: *three-dimensional reconstruction (volume rendering) of the heart; the pseudo-colors and shading enable a life-like view not only of the coronary arteries but also of the various cardiac structures and arterial and venous connections. The volume rendering technique has been used to remove the pulmonary trunk, to allow the visualization of the left main (LMA) and left anterior descending (LAD) arteries.* B: *curvilinear maximum intensity projection of the right coronary artery (RCA) with multiple calcifications along its course.* C: *occlusion of the proximal portion of the LAD followed by a significant stenosis.* D: *volume rendered reconstruction of three venous coronary bypass grafts; one of them (VGr 1) shows a proximal occlusion.* E: *volume rendered reconstruction of a LAD with a stent in its middle tract; the RCA, despite the detection of three calcifications, does not show significant stenoses.* F: *example of virtual angioscopy with a three-dimensional reconstruction of an intracoronary image of the branching of the LMA, from the perspective of the LMA. ALB= antero-lateral branch; AO = ascending aorta; Ca = coronary calcification; CB = conus branch; CX = circumflex coronary artery; D1, D2 = first and second diagonal branches; PA = pulmonary artery; PIV = posterior interventricular artery; RA = right atrium; RV = right ventricle; SNA = sinus node artery.*

Table I. Diagnostic accuracy and feasibility of coronary multislice spiral computed tomography (CT) compared to conventional selective coronary angiography in detecting significant coronary stenoses.

Author	No. CT slices	No. patients	Feasibility (%)	Criteria for stenosis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Achenbach et al.[20], 2001	4	64	68	50	91	84	59	98
Nieman et al.[25], 2001	4	31	73	–	91	97	–	–
Knez et al.[26], 2001	4	44	94	50	78	98	84	96
Nieman et al.[23], 2002	4	53	70	50	82	93	66	97
Nieman et al.[37], 2002	16	59	97	70	95	86	97	80
Kopp et al.[38], 2002	4	102	70-90	50	86	96	76-81	98-99
Bohme et al.[39], 2003	–	102	74	50	71	93	–	97
Kaiser et al.[40], 2003	16	42	62	50	49	82	53	79
Gerber et al.[41], 2003	4	27	80	–	65	78	–	–
Ropers et al.[42], 2003	16	77	96	50	92	93	82	81
Total no. patients		601						
Mean value			79.4		80.2	90.3	74.7	90.7

Criteria for stenosis = diameter reduction considered for significant stenosis; CT slices = number of detectors of the multislice spiral CT system; NPV = negative predictive value; PPV = positive predictive value.

sufficient image acquisition only in selected patients, i.e. with spontaneous or beta-blocker-induced bradycardia. Data on the diagnostic accuracy of 8-slice systems are not yet available in the literature. There exist only a few preliminary studies on the diagnostic accuracy of 16-slice systems: it is claimed that with these systems it is possible to obtain an isotropic volumetric image reconstruction, i.e. with "voxel" dimensions that are submillimetric and equal in the three spatial axes[37,42,43]. Few studies have investigated coronary stents: data recently published indicate the capacity of MSCT to detect stent occlusions[44]; so far, the technique would seem of scant utility in identifying intrastent restenosis[45]. We may speculate that the further increase in spatial resolution with 16-slice MSCT systems will permit, through short-axis sections of the vessel and of the stent, the distinction between the vessel wall, prosthesis, plaque and coronary lumen. In contrast, the findings on venous and arterial grafts already suggest an excellent diagnostic capacity of MSCT[46-48], with a sensitivity of around 95% in diagnosing graft disease and a specificity in the range of 92-100% (Table II)[48-55].

Preliminary study

One hundred and seventy-six patients at our Institute underwent coronary MSCT with a Light Speed Ultra System (General Electric Medical Systems, Milwaukee, WI, USA): of these patients, 116 had had recurring symptoms of angina after revascularization procedures (51 after bypass surgery and 65 after PTCA); in 57 patients the examination was performed in the context of a diagnostic work-up for suspected ischemic heart disease, i.e. typical angina pectoris or exercise test or myocardial scintigraphy positive for asymptomatic coronary artery disease (CAD); in 3 patients the examination was performed for the etiological definition of dilated cardiomyopathy. A subgroup of 39 patients underwent conventional selective coronary angiography within no more than 4 weeks of MSCT.

The baseline heart rate was < 70 b/min in 128 patients (72%); 101 were on long-term treatment with beta-blockers. In our study, intravenous beta-blocker premedication was limited to a subgroup of subjects in whom a significant reduction of the RR interval during the intravenous infusion of contrast medium was predictable by testing for prolonged apnea (5% of patients).

MSCT images were acquired during a single breath-hold, at full inspiration and after gentle hyperventilation. Contrast enhancement was obtained with the injection of 130 ml of iodine contrast agent in an antecubital vein. The mean breath-hold time was 20 ± 5 s. The average investigation time was < 16 min; reconstruction and evaluation of MSCT studies at the workstation took about another 50 min.

In our series, the overall feasibility was 91.5% (161/176 patients). In 15 patients (8.5%), the examination could not be evaluated due to the poor quality of image acquisition and consequently of image reconstruction. In particular, the image quality was not of a diagnostic level in 11 patients on account of motion artifacts due to a sudden increase in heart rate during infusion of the contrast agent or to an incorrect breath-hold (Fig. 5A), in 2 patients owing to the presence of extensive coronary calcifications, in 1 patient owing to insufficient contrast enhancement in the arterial phase (the patient had a severely depressed ejection fraction), and in 1 patient owing to an extensive masking effect of the coronary arteries by the venous network (Fig. 5B).

In 51 patients with previous bypass surgery, 6 grafts (5.6%) out of a total of 108 (58 venous, 50 arterial) were not assessable: 3 due to artifacts generated by the metal clips, 2 to artifacts caused by breathing motion, and 1 due to insufficient contrast concentration within the graft during acquisition. The findings concerning the 102 assessable grafts were as follows: in 39 left internal mammary artery grafts on the left anterior descending artery 2 occlusions and 1 critical stenosis were detected; in 5 right internal mammary artery grafts on the left anterior descending artery or obtuse marginal branch 1 occlusion and 1 critical stenosis were found; a radial artery graft on the obtuse marginal branch was occluded. With regard to the 57 venous grafts, 8 occlusions and 3 critical stenoses were detected. These MSCT findings concerning occlusions or critical stenosis of the graft were all confirmed at subsequent conventional coronary angiography.

Table II. Diagnostic accuracy and feasibility of coronary multislice spiral computed tomography (CT) compared to conventional selective angiography in the evaluation of coronary artery bypass graft patency.

Author	No. CT slices	No. patients	Feasibility (%)	Criteria for stenosis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Ropers et al.[48], 2001	4	65	100	50	75	92	71	93
Smekal et al.[49], 2002	16	15			100	100		
Kim et al.[50], 2002		31			100	98		
Pasowicz et al.[51], 2002	4	57			92	95		
Silber et al.[52], 2003	4	74			100	96		
Ropers et al.[53], 2003	16	34		50	100	100		
Yoo et al.[54], 2003	4	42	100		98	100	98	
Ko et al.[55], 2003	4	39	97	70	93	99	93	99
Total no. patients		357						
Mean value			99		94.8	97.5	87.3	96

Criteria for stenosis = diameter reduction considered for significant stenosis; CT slices = number of detectors of the multislice spiral CT system; NPV = negative predictive value; PPV = positive predictive value.

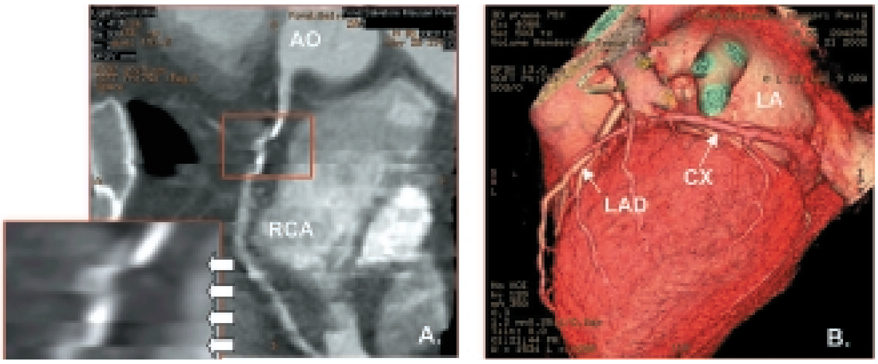

Figure 5. *Technical artifacts in multislice spiral computed tomographic coronary imaging.* A: *evident artifacts due to the breathing motion during acquisition produce, in an image reconstructed with maximum intensity projection, a series of gradations* (arrows) *which prevent a satisfactory assessment of the right coronary artery (RCA).* B: *this volume-rendered three-dimensional image does not allow an adequate visualization of the left anterior descending artery (LAD) and circumflex coronary artery (CX) due to the masking effect of the venous network. AO = ascending aorta; LA = left atrium.*

In the subgroup of 39 patients who underwent conventional coronary angiography by way of control soon after coronary MSCT, considering a standard subdivision of the coronary tree into 12 segments, out of a total of 468 segments, 377 segments (80.6%) were adequately evaluable at MSCT. In these segments, the sensitivity of coronary MSCT in identifying critical lesions (> 70% of the lumen diameter) with respect to conventional coronary angiography was 80.4% and the specificity 80.3%. In this preliminary experience, the positive predictive value was 58.6%, while the negative predictive value was 92.2%.

Future perspectives

Just as for all recently introduced imaging tools undergoing fast technological development, the role of cardiac MSCT in the clinical setting, both in terms of its diagnostic accuracy with respect to the preexisting reference methods and in terms of the diagnostic work-up, has still not been defined. Nevertheless, on the basis of the currently available literature, the possible fields of application of coronary MSCT could be outlined as follows:
a) evaluation of arterial or venous graft patency after surgical myocardial revascularization;
b) evaluation of restenosis after PTCA;
c) assessment of CAD progression in subjects with known ischemic heart disease;
d) screening for CAD, in subjects > 45 years before non-coronary heart surgery (to date these subjects, according to widespread clinical practice, generally undergo conventional coronary angiography as a preoperative screening procedure for the presence of CAD);
e) evaluation of symptomatic subjects at low risk for CAD with negative or inconclusive diagnostic tests for coronary insufficiency;
f) evaluation of asymptomatic subjects at high risk for CAD, with negative or inconclusive diagnostic tests for coronary insufficiency;
g) follow-up of graft coronary heart disease in heart transplant patients.

To summarize, these are all clinical situations which constitute indications for the investigation of the coronary anatomy in a clinical context that does not include the option of, or immediate need for, a contemporary interventional procedure.

We may speculate about a series of complementary indications related to the primary prevention of CAD and to the investigation of atherosclerotic plaque development and evolution, but the real diagnostic significance and role of these will be established only on the basis of a more extensive use of MSCT in the scenario of population studies (Fig. 6).

Furthermore, the huge amount of data acquired by cardiac MSCT, thanks to its characteristics of spatial and temporal resolution at present concentrated mainly in the production of coronary angiograms, may also be used to obtain a detailed morphological definition of the chambers and structures of the heart as well as an accurate assessment of its dimensions, volumes and functional parameters[56-58].

According to recent observations, MSCT also permits, in patients with recent acute myocardial infarction, the identification of the areas of low contrast density[59]. Moreover, with MSCT it is possible to define the extent of reperfusion after acute myocardial infarction, a clear concordance having been observed with the results obtained at myocardial tomoscintigraphy in determining the site and volume of scar tissue[60]. The same group highlighted a worse clinical outcome in patients who at MSCT scanning of myocardial perfusion show an early perfusion defect after acute myocardial infarction which still persists at later evaluation. The assessment of the coronary flow has also been attempted by analyzing the appearance of contrast enhancement in the myocardium by means of dynamic scans with prospective ECG gating: the method was able to differentiate regions with normal flow regimes, in the order of 0.73 ± 0.20 ml/kg/min, from hypoperfused regions[61].

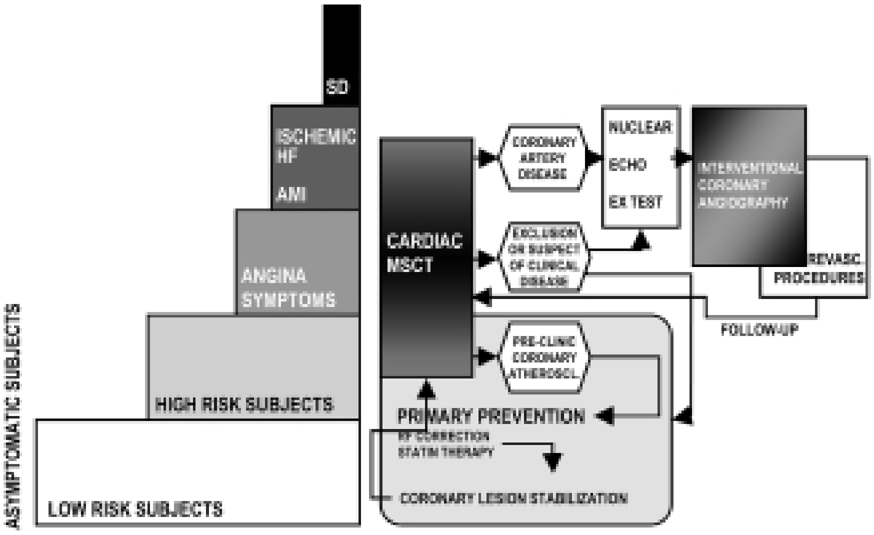

Figure 6. *Possible future perspectives regarding the role of cardiac multislice spiral computed tomography (MSCT) in the diagnostic work-up of ischemic heart disease. AMI = acute myocardial infarction; HF = heart failure; RF = risk factors; SD = sudden death.*

If the diagnostic potential of MSCT – not only in coronary angiography but also in relation to the morphology, and to the analysis of ventricular function and myocardial perfusion – will be validated in a clinical scenario in terms of its feasibility and reliability, we could foresee a real revolution in the diagnostic work-up of CAD. With a single non-invasive contrast-enhanced examination it would be possible to obtain a wealth of information comparable (if not superior in terms of its power of resolution and operator-independence) to that of echocardiography for the morphology and indices of cardiac function, to that of myocardial scintigraphy for myocardial perfusion data, and to that of traditional (non-interventional) coronary angiography for the coronary anatomy and, prospectively, the atherosclerotic plaque anatomy. In addition, the data obtained at MSCT on the identification and quantification of coronary vessel calcifications could provide additional prognostic information which would otherwise not be obtainable – a notion, in fact, already amply supported by the literature[62,63]. The convergence of different indirect diagnostic tests into a single non-invasive cardiac imaging test, performed moreover, with scanners that represent the next step in the technological evolution of "conventional" computed tomographic systems now widespread and existing in almost all radiology departments, would tilt the balance in cost/benefit terms in favor of the use of MSCT for the assessment of ischemic heart disease[64].

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