Abstract

Background: Multi-detector computed tomography has advanced enormously and now enables non-invasive evaluation of coronary arteries as well as cardiac anatomy, function and perfusion. However, the role of cardiac MDCT is not yet determined in the medical community and, consequently, many clinically unnecessary scans are performed solely on a self-referral basis.

Objectives: To prospectively evaluate the role of a cardiologist consultation and recommendation prior to the scan, and the influence on the diagnostic yield of cardiac MDCT.

Methods: In our center a CT service was initiated, but with the prerequisite approval of a cardiologist before performance of the CT. Each individual who wanted and was willing to pay for a cardiac CT was interviewed by an experienced cardiologist who determined whether cardiac MDCT was the most appropriate next test in the cardiovascular evaluation. Subjects were classified into three groups: a) those with a normal or no prior stress test, no typical symptoms and no significant risk factors of coronary artery disease were recommended to perform a stress test or to remain under close clinical follow-up without MDCT; b) those with an equivocal stress test, atypical symptoms and/or significant risk factors were allowed to have cardiac MDCT; and c) those with positive stress test or clinically highly suspected CAD were advised to go directly to invasive coronary angiography. CT findings were categorized as normal CAD (normal calcium score and no narrowings), < 50% and > 50% CAD.

Results: A total of 254 people were interviewed, and in only 39 cases did the cardiologist approve the CT. However, 61 of the 215, despite our recommendation not to undergo CT, decided to have the scan. Assessment of the 100 cases that underwent MDCT showed a statistically significant better discrimination of significant CAD, according to the cardiologist's recommendation: MDCT not recommended in 3/54 (6%) vs. MDCT recommended in 12/39 (31%) vs. recommended invasive coronary angiography in 4/7 (57%) ($P < 0.001$).

Conclusions: Detection of coronary calcification, as well as MDCT angiography can provide clinically useful information if applied to suitable patient groups. It is foreseeable that MDCT angiography will become part of the routine workup in some subsets of patients with suspected CAD. Selection of patients undergoing

Coronary artery disease is the leading cause of mortality and morbidity in the western world. Although mortality has decreased in recent years, we still urgently need other ways to detect and stratify patients. Advances in medical imaging now offer physicians multiple tests that can be used to investigate patients with cardiovascular disease. Coronary angiography is currently the gold standard for the diagnosis of CAD, though there is a small but not negligible risk of complications and discomfort from the procedure. In recent years, multi-detector computed tomography angiography has emerged as a new alternative to invasive angiography for evaluation of individuals suspected of having CAD. Several studies were performed comparing the ability of MDCT to detect angiographic coronary lesions [1].

With the rapid technological advances in MDCT, reliable non-invasive evaluation of coronary vessels and bypass grafts is feasible [2]. MDCT also allows the evaluation of coronary calcium score and cardiac global and regional function, and provides highly detailed information on the aorta, pulmonary artery and veins, lungs and mediastinum [1-4]. Supportive findings of regional abnormalities in myocardial enhancement, function and thickness indicate its usefulness also for assessing infarcted myocardium [5-7].

In part, because of the scarcity of large-size outcome studies, there are no universally accepted absolute indications for cardiac MDCT angiography. How clinicians, hospital managers and funding bodies will adapt to this new technology is still unclear [5].

Many of the scans performed in outpatient settings are performed on a self-referral basis. As occurs worldwide, there are no clear indications and guidelines as to who should have the scan. In our center, a tertiary academic care facility, when the cardiac MDCT service started we decided to include a cardiologist in the service. Prior to performing the scan, the approval of an experienced cardiologist was needed.

The aim of the present study was to prospectively assess the role of the cardiology consultation and recommendation before the scan with regard to the selection of the best patient population to undergo MDCT

Patients and Methods

After completion of a comparative study [7], we initiated a cardiac MDCT service. Letters were sent to primary care physicians, public lectures were held, and an advertising campaign was run in the media. We established a hotline number so that the public could call for information. A trained team explained what the test was and how much it cost and those who were willing to have the scan were referred for an interview with a cardiologist.

Cardiology consultation

An experienced cardiologist examined the individuals scheduled for the cardiac MDCT. They were referred either through the hotline or directly by a primary care physician. Patients referred to the scan directly by their cardiologist were not included in this study.

Study groups

We prospectively divided the population into three study groups:

- Individuals with normal or no prior stress test and/or with no typical symptoms and/or no or one risk factors were advised not to have the CT scan. This group was informed about risk modification and current CAD prevention guidelines.
- All those with equivocal or un-interpretable exercise electrocardiographic stress test or unable to have such a test, atypical symptoms and chest pain or significant risk factors were advised and permitted to have the scan.
- Individuals who had a positive stress test or a high suspicion of CAD (usually typical effort angina and risk factors) were advised to go directly to coronary angiography and not MDCT.

MDCT scan protocol and image reconstruction

Patients were not pretreated routinely with beta-blocking agents. When the heart rate was above 70/min, 5–10 mg i.v. metoprolol was administrated several minutes before the scan. Datasets were acquired with a Brilliance™ 16-slice scanner (Philips Medical Systems, Cleveland, USA). For ECG-gated calcium scoring the following imaging and reconstruction parameters were used: collimation 8 × 3 mm, kVp 120, mAs 55, rotation time 0.42 sec, slice width 3 mm, and increment 24 mm. For ECG-gated coronary angiography the following imaging and reconstruction parameters were used: detector collimation 16 x 0.75 mm, voltage 120–140 kV, effective current 400–500 mAs, relative pitch 0.2–0.3, rotation time 0.42 sec, reconstruction slice width 0.75 mm, and increment 0.5 mm. Between 120 and 130 ml non-ionic iodinated contrast material (Ultravist®, 370 mgI/ml, Schering AG, Germany) was injected at a rate of 4 ml/sec using a power injector. No saline flash was used. The scan delay was determined using the Bolus Pro Ultra™ tracking technique: when a threshold of 150 HU was reached in the descending aorta at the inferior level of the carina, a delay of 5–6 seconds was applied before the scan was initiated. Scans were performed during a single breath-hold and lasted 20–30 seconds. Axial datasets were reconstructed from ECG-gated raw data at 0%, 40%, 45%, 50%, 70%, 75% and 80% of RR interval.

MDCT image interpretation

For each patient, post-processing reformations and measurements were performed on a Brilliance Extended Workspace™ workstation (Philips Medical Systems) by an attending radiologist with 4 years experience in cardiac imaging. CT coronary angiographic images were reformatted using curved multi-planar reformations through the lumen of the coronary vessels. On the basis of established cardiology practice, the minimal diameter of stenotic coronary lesions was measured using manually positioned electronic calipers and compared with the maximal diameter of the closest proximal normal arterial segment. Coronary artery segments were graded as normal, less than 50% diameter stenosis or greater than 50% diameter stenosis. According to accepted cardiology practice, diameter stenoses ≥ 50% were regarded as significant.

MDCT scan results

The results were divided into three subgroups: a) no evidence of CAD, as reflected by calcium score of zero, and normal coronaries on CT coronary angiography; b) non-significant CAD, which included minor irregularities or *any* calcium even without evidence of narrowings; and c) significant CAD, evidenced by narrowings (> 50%) in the coronary arteries.

MDCT report

An experienced radiological team analyzed all the scans, which were presented and discussed in a joint meeting, and the final recommendation was written by the cardiologist. The clinical data, physical and laboratory findings, other cardiac tests, and MDCT findings were taken into account.

Follow-up

In cases where coronary angiography was recommended, the patients were contacted and the catheterization results were compared to the CT findings.

Results

A total of 928 calls were received by the hotline number in the first 6 months of its operation, and 254 people who wanted and were willing to pay for coronary CT were interviewed by a cardiologist. The interview included a careful evaluation, review of all past medical documents, a brief physical examination, laboratory tests and ECG.

In 39 cases the cardiologist approved the cardiac MDCT and in 215 cases the recommendation was not to perform the scan. However, 61/215 people (28%) – despite our recommendation not to – decided to have the scan. Analysis of the first 100 MDCT scans (from both groups) performed in our center is presented.

In the overall study population, no CAD and a calcium score of 0 were found in 39% of cases. More than 50% narrowing was found in 18%. Coronary lesions of less than 50% narrowing or any calcium score was found in 44%.

The MDCT findings based on our recommendation are shown in Table 1. There was a significantly ($P < 0.01$) better discrimination of CAD between the groups based on the cardiologist's recommendation. Furthermore, when assessing significant CAD alone (> 50%), the significance was even greater. Only 3 of 54 patients (6%) for whom the cardiologist did not recommend

Table 1. CT findings according to cardiologist's recommendation vs. all study groups

	Cardiologist's recommendation							
CT findings	No CT	%	CT	%	Angio-graphy	%	All study patients*	%
Number	54		39		7		100	
Negative	33	61	5	13	0	0	38	38
< 50%	18	33	22	56	4	57	44	44
> 50%	3	6	12	31	3	43	18	18

* Without cardiologist's input and recommendation, i.e., all studied patients

Table 2. Patients characteristics according to findings

	No narrowings or calcium	< 50%, or any calcium	> 50%	*P*
N	38	44	18	
Age (yrs)c	52.2 ± 11.2	58.8 ± 9.1	62.7 ± 12.1	0.14
Gender (male)	13 (66)	37 (84)	18 (100)	< 0.01
Mean calcium score	0	90 ± 155	790 ± 1202	< 0.001
Diabetes	2 (5)	5 (11)	2 (11)	NS
Hypertension	12 (32)	22 (50)	10 (55)	NS
Dyslipidemia	18 (47)	26 (59)	11 (61)	NS
Smoking (past or present)	8 (21)	10 (23)	3 (17)	NS
Family history of ischemic heart disease	13 (34)	16 (36)	8 (44)	NS

MDCT had significant (> 50%) coronary narrowing vs. 12 of 39 (31%) ($P < 0.001$) for whom the cardiologist did recommend the scan. Those with coronary narrowing were older, male and had a higher calcium score [Table 2].

Discussion

Advances in imaging technology now provide a spectrum of diagnostic tools to investigate heart and vascular disease. However, much less is known about which test performs best in which circumstances and which test has the greatest impact on improving treatment. MDCT coronary angiography, while very promising with regard to the detection of coronary stenoses, definition of "soft plaque," assessment of left ventricular function and congenital coronary anomalies, and evaluation of cardiac structures, has limited data supporting its use for many clinical applications, especially regarding its role in patient care algorithms [1-3,6]. The only guideline we currently have is the appropriate criteria for cardiac CT (and magnetic resonance imaging) published by the American College of Cardiology, American College of Radiology, Society of Cardiovascular Computed Tomography, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. In the present study we show that an interview with a cardiologist, which serves as a "gatekeeper," prior to cardiac MDCT is an important barrier and can significantly improve the yield of this test. To the best of our knowledge, this is the first study to examine this practice and report this approach.

Can cardiac MDCT deliver the goods?

With the improving temporal and spatial resolution of mechanical MDCT scanners, coronary artery imaging is entering the clinical realm. Several investigations [6-16] [Table 3] have been conducted on the accuracy of MDCT angiography in cases of known or suspected CAD. Although these studies differed in methodology and patient characteristics, all compared rates of detection of coronary lumen obstruction > 50% with MDCT and with invasive angiography, examined patients already medicated with beta-blockers, excluded those who had cardiac arrhythmias, and reported analyses of sensitivity, specificity, and positive and negative predictive values, Findings for sensitivity ranged from 82% to 100%, and for specificity 78% to 98%. The real strength of cardiac MDCT was found to be its negative predictive value, which in the most recent studies ranged from 95% to 97% among patients deemed to be at intermediate to high risk of CAD. The technology has advanced and most centers have slice scanners of 64 or more, allowing higher quality images.

In the coming years we will be able to utilize non-invasive techniques to gain information on the condition of patients [17-22]. However, especially for outpatient settings, there is a potential for uncontrolled utilization and stimulation of downstream testing and treatment such as unwarranted coronary revascularization. This has raised substantial concern among government and private payers as well as leading specialists in evidenced-based cardiovascular medicine. As MDCT becomes clinically available, the health care community needs to understand how to incorporate these advances into acceptable clinical care [6].

Table 3. Sensitivity, specificity, and negative predictive value of recent studies comparing 16- and 64-slice MDCT with invasive coronary angiography for detection of coronary artery stenoses

Author	N	Sensitivity	Specificity	Negative predictive value	Not evaluable	Comment
Martuscelli et al. [8]	64	89%	98%	98%	16%	16-slice CT (500 ms rotation)
Morgan-Hughes et al. [9]	58	83%	97%	97%	2%	16-slice CT (500 ms rotation)
Hoffmann et al. [10]	103	95%	98%	99%	6%	16-slice CT (420 ms rotation)
Mollet et al. [11]	51	95%	98%	99%	0%	16-slice CT (375 ms rotation)
Kuettner et al. [12]	72	82%	98%	96%	7%	16-slice CT (375 ms rotation)
Achenbach et al. [13]	50	93%	95%	99%	5%	16-slice CT (375 ms rotation)
Ghersin et al. [7]	66	80%	89%	97%	3%	16-slice CT (375 ms rotation)
Garcia et al [14]	238	89%	65%	99%	29%	16-slice CT (375 ms rotation)
Leschka et al [15]	57	94%	97%	99%	0%	64-slice CT (375 ms rotation)
Leber et al. [16]	59	80%	97%	99%	0%	64-slice CT (330 ms rotation)
Raff et al. [17]	70	86%	95%	98%	12%	64-slice CT (330 ms rotation)

Real life experience

In our patient population with 100 scans, significant narrowings defined as > 50%

were found in 18%. This is remarkably high. In this study, 4 of 7 patients (57%) in group 3, who should have gone straight to catheterization based on the cardiologist's recommendation, had less than 50% stenosis on MDCT. Equally intriguing is that 3 (6%) of the patients who were in group 1 had significantly obstructive CAD.

Economic issues

Rapid technological advances and new clinical applications in cardiovascular imaging technology, coupled with increasing therapeutic options for cardiovascular disease, have led to explosive growth in cardiovascular imaging. In fact, in the United States, diagnostic imaging services reimbursed under Medicare's physician fee schedule grew more rapidly than any other type of physician service from 1999 to 2003. In the present study, we found that only one of the six patients who contacted us was ultimately approved by an experienced cardiologist to have the test. If such a private imaging center implements our recommendation, their income from coronary MDCT angiography will decrease by 80% or more.

Radiation issues

Several imaging modalities are available for the optimal management of patients with cardiovascular disease. When assessing any imaging technique, radiation dose must be considered along with the value of the imaging technique. Coronary MDCT angiography is associated with 7–12 mSv (one chest X-ray is equivalent to 0.02 mSv) [23-25]. Yet, it should be remembered that the effective dose of dual isotope scan – an image modality frequently used in cardiac patients – is higher (~15-25 mSv) than both cardiac CT and diagnostic heart catheterization (~5-7 mSv). The physician should carefully weigh which test should be recommended to each patient [2].

In our population, we advise most patients to perform a treadmill stress test or risk modification measures – both associated with no radiation – or on the other hand, avoid the unnecessary exposure from a diagnostic-only test and go directly to invasive coronary angiography, a diagnostic but also an interventional procedure.

Limitations

In our study there is no confirmation of the presence/absence of coronary stenoses by a coronary angiogram. This would have been particularly interesting in group 2 and in verifying the value of the CT < 50% stenosis.

This work was based on a 16-slice scanner, an outdated machine today. The results might be different in newer scanners, especially the motion artifacts, and the number of "inconclusive" segments which was totally reduced in newer scanners.

The restriction of patients to those who "were willing to pay" creates a selection bias. The patients who were willing to pay may have more severe symptoms than those who were interested but not willing to pay. Similarly, those who were not willing to pay may have represented a lower socioeconomic class that might have a higher or lower incidence of disease. However, we present the "real life" situation that occurs in many places worldwide.

Future perspective

The demand for coronary MDCT angiography is expected to continue to increase. It is foreseeable that CT angiography will become part of the routine workup in some subsets of patients with suspected CAD [17-25]. The question remains as to which test is suitable for which patient and what if any is the role of the cardiologist consultation before the CT scan.

In summary

Detection of coronary calcifications, as well as coronary MDCT angiography, can provide clinically useful information if applied to suitable patient groups. Cardiac MDCT holds much promise for patients and for the cardiovascular community. More research will be needed to address these issues and to determine exactly when the test is useful and what the best screening method is prior to the scan. This is especially true as this is an evolving field with limited evidence. Our data suggest that an interview by a cardiologist prior to coronary MDCT should be considered an integral part of routine clinical practice and should be recommended. This may also be done by primary care physicians, internists and other physicians capable of determining the pretest probability.

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Not being able to govern events, I govern myself

Michel de Montaigne (1533-1592), one of the most influential writers of the French Renaissance. Montaigne is known for popularizing the essay as a literary genre although he was admired more as a statesman than as an author

Capsule

Farnesylation of lamin A leading to progeria

Children with the rare disorder Hutchinson-Gilford progeria syndrome (HGPS) develop a constellation of health problems typically seen in the geriatric population, including severe atherosclerosis and osteoporosis, and most affected individuals die as teenagers. The disease-causing mutation lies in the LMNA gene, which encodes the nuclear scaffold protein lamin A, and it results in the production of an unprocessed form of lamin A that aberrantly retains a farnesyl lipid anchor and induces structural changes in the cell nucleus. The observation that farnesyltransferase inhibitors (FTIs: drugs that inhibit the enzyme that attaches the farnesyl tail to proteins) partially reversed the nuclear changes in cultured cells and ameliorated disease symptoms in mouse models of HGPS led to the initiation of a clinical trial to test these drugs in children with the disease. New results suggest that the concept motivating this clinical trial may require revision. To test the hypothesis that the HGPS-associated lamin A is toxic because of its farnesyl group, Yang and team generated mice expressing a mutant version of lamin A that contained not only the disease-causing mutation but an additional mutation that prevented the protein from being farnesylated. Surprisingly, these mice developed the same spectrum of HGPS-like phenotypes as did mice expressing the farnesylated protein, albeit in a milder form. Thus, farnesylation of lamin A is unlikely to be a major contributor to the pathogenesis of HGPS, and the mechanism underlying the therapeutic efficacy of FTIs in the earlier preclinical studies remains unclear.

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