

Risks and Benefits of Coronary Computed Tomography Angiography: A Review

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PAU.: Risks and Benefits of Coronary Computed Tomography Angiography: A Review. Multislice computed tomography coronary angiography (CTA) is a noninvasive radiology technique that provides high-resolution images of the coronary artery. It has high sensitivity and specificity for coronary stenosis and can be used to rule out significant coronary artery disease (CAD), thereby avoiding the risk of invasive coronary angiography. There is a danger that CTA may be overused as a screening test for CAD in healthy subjects, thereby exposing the patients to the dangers of adverse reactions to iodinated contrast agents and cancer induction from radiation exposure. Consensus document has been published for clinical guidance on when it is appropriate to order a CTA. Comparative studies with stress nuclear myocardial perfusion imaging (MPI) have shown that significant coronary atherosclerosis demonstrated on CTA may not be associated with ischemia in the same region on MPI. Functional stress testing with exercise or pharmacological agents may be indicated as supplement to CTA for prognostic stratification and assessment for revascularization. (*J HK Coll Cardiol* 2007;15:67-73)

Cancer induction, contrast reaction, coronary computed tomography angiography, functional stress testing, invasive coronary angiography

摘要

冠狀動脈的多排CT血管成像(CTA)是一項非侵襲性的放射技術，它可以為冠狀動脈提供高質量的圖像。此項技術對於冠狀動脈狹窄具有很高的敏感性和特異性，可以排除嚴重的冠心病(CAD)，並由此避免侵襲性冠狀動脈造影的操作。然而在健康人群的冠心病篩選中，CTA可能有過度運用的風險，由此病人將面臨碘造影劑的副作用，並且放射照射本身還可誘導腫瘤的發生。何時需要進行CTA檢查的臨床指導意見已經出版成文。比較研究顯示核素心肌灌注造影(MPI)能夠清晰地顯示冠狀動脈的硬化程度，而在相同部位CTA檢查中卻可能並不表現缺血。運動或藥物的心臟應激功能檢測可以作為CTA的補充，作為治療預後的分層選擇和血管重建後的評價。

關鍵詞：腫瘤誘導 造影劑反應 冠狀動脈CT血管成像 功能應激檢測 侵襲性冠脈造影

Introduction

Rapid advances in multislice computed tomography (MSCT) technology in the past few years have made MSCT coronary angiography (CTA) an attractive alternative to conventional invasive coronary

angiography (ICA). The attractiveness of CTA lies in its ability to rule out significant coronary artery disease (CAD), thereby avoiding unnecessary ICA. Advances in CTA required the development of protocols consistent with rapid incremental improvements in CT technology. Parameters such as gantry rotation time, breath holding, heart rate control, ECG gating, scanning parameters, multiplanar image reconstruction, image field of view and contrast injection techniques are taken into consideration.¹ With proper patient selection and appropriate protocols in the use of a new generation of 64-slice CT scanners, sensitivity of 83% to 99% and specificity of 93% to 98% in comparison with ICA have

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been reported. The high negative predictive value of 95% to 100% confirms the value of CTA in ruling out significant CAD.² It has been proposed that even though the effective radiation dose from CTA is higher than ICA, the risk of mortality from radiogenic and non-radiogenic risks combined in ICA (0.02% and 0.11% respectively) yields a 0.13% overall risk, which is nearly twice as high as the radiogenic mortality risk of 0.07% from CTA.³

Patient Selection

To undergo CTA, patients must be able to lie still, follow breath-holding instructions (6 to 20 seconds) and have no irregular rhythm and no contraindication to iodinated contrast agents. They should be able to tolerate beta blockers if necessary to lower the heart rate to around 60 per minute and nitroglycerine to enhance image quality. Heavy calcification (calcium score 400 or more) or presence of stent in the coronary arteries may obscure the lumens. Analyses is usually limited to segments with diameter of over 1.5 mm. A new advance in technology for 64-slice CTA is to use 2 sets of X-ray tubes and detectors (dual source) instead of one to improve temporal resolution and reduce the problems caused by motion artefacts.⁴ 256-slice CTA with 0.5 mm collimation and expanded field of view has been developed, which has the potential to visualize wall motion, ejection fraction, myocardial perfusion in addition to the evaluation of coronary arteries with the same injection of iodine, resulting in less radiation exposure to the patient.⁵

Risks of CTA

Heart disease has ranked second to cancer as a major cause of death in Hong Kong for over four decades, and sudden death may be the first symptom of CAD. A screening test which has a high negative value is therefore very appealing to health-conscious individuals. As more facilities for MSCT are becoming available and the cost per CTA examination is coming down to the affordable level (about four to six thousand

Hong Kong dollars), there is a danger that CTA may be overused as screening tests for asymptomatic patients with no significant risk factors of CAD, thereby exposing them to the dangers of (1) contrast reaction, (2) excessive radiation exposure and (3) false positive test result with the risks of invasive coronary angiography that follows. The worst possible complications are fatal reaction to iodinated contrast agents and fatal cancer induction such as leukemia from excessive radiation exposure.

Adverse Reactions to Iodinated Contrast Agents

Adverse reactions to iodinated agents range from mild allergic reaction such as itchiness to life threatening emergency such as anaphylactic shock. Renal toxicity is a well known complication. The risk for adverse reaction is 4% to 12% with ionic contrast agents and 1% to 3% with nonionic contrast agents, and the risk for severe adverse reaction is 0.16% with ionic contrast agents and 0.03% with nonionic contrast agents. The death rate, one to three per 100,000 contrast administration, is similar for both ionic and nonionic agents.⁶ Previous reaction to contrast agents, asthma, and allergies are factors associated with an increased risk of developing adverse reaction. Pretreatment of such patients with corticosteroid and diphenhydramine decreases the chance of adverse reactions. Prompt recognition of adverse reactions allow them to be treated immediately. Using the smallest dose possible with low-osmolar, nonionic agents also reduces the relative risk of reactions. Contrast-induced nephropathy may be decreased by ensuring adequate hydration and discontinuation of nephrotoxic medications such as metformin before contrast administration.⁷

Cancer Risk from Radiation Exposure in CTA

The unit of measurement for effective dose of radiation is millisievert (mSv). Different tissues and organs in the body have different sensitivity to radiation exposure, and the actual dose to different parts of the

body during an X-ray procedure also varies. The term effective dose is used when referring to the dose averaged over the entire body. The average exposure to natural background radiation (from external terrestrial radiation, cosmic radiation and radioisotopes within the body) is about 1 mSv per person per year at sea level. This does not include the background radiation of about 1.2 to 2.0 mSv per year delivered to the lungs from radon gas in buildings. The maximal permissible levels that are recommended by the National Council on Radiation Protection and Measurements (NCRP) in the United States for people exposed to radiation (other than background radiation and from medical applications) are 1 mSv per year for the general public and 50 mSv per year for radiation workers employed by nuclear-related industries.

The risk of cancer after low doses of ionizing radiation has been studied in survivors of atomic bombs in Japan, in nuclear workers, and in diagnostic X-rays.⁸⁻¹⁰ The lowest dose of X- or gamma radiation for which good evidence of cancer risk exists is approximately 10-50 mSv for an acute exposure and 50-100 mSv for a protracted exposure.¹¹ Coles et al reported the effective radiation doses from various coronary diagnostic image studies as follows: ICA (5.6 mSv), CTA (14.7 mSv), calcium score scanning (2.6 mSv), positron emission tomography (PET) scan (8.0 mSv), single-photon emission computed tomography (SPECT) imaging with 201 thallium (18.0 mSv), (10 to 12 mSv with technetium 99 sestamibi).¹² Hausleiter et al estimated the effective dose from 16-slice CTA is 6.4 mSv and that from a 64-slice CTA is 11.0 mSv.¹³ Modulation techniques gated to ECG may reduce the radiation exposure of CTA by about 40-60%.

The US Food and Drug Administration cautioned that typical values cited for radiation dose should be considered as estimates that cannot be precisely associated with any individual patient, examination, or type of CT system. The actual doses from a procedure could be two or three times larger or smaller than the estimates. For comparison, the typical effective dose for a chest X-ray is 0.02 mSv, skull X-ray (0.07 mSv), screening mammogram (0.13 mSv), lumbar spine (1.3 mSv), IV urogram (2.5 mSv), upper GI exam (3.0 mSv), barium enema (7.0 mSv), CT head (2.0 mSv), CT

abdomen (10.0 mSv).¹⁴ The estimated dose range received by Japanese survivors of atomic bombs, who have demonstrated a small but definite risk of fatal cancer, is 5 to 20 mSv.

Based on experimental studies, it is believed that the most important type of lesions induced by ionizing radiation is breaks in double-stranded DNA, resulting in induction of point mutations, tumour-suppressor gene inactivation, or chromosomal translocation. The mutation in cancers and their growth characteristics are not distinguishable from spontaneously occurring cancers of the same sites, and have long latent periods. This explains why there are many uncertainties in the risk estimation of cancer from low doses of ionizing radiation, (unlike for example, mesothelioma and its association with asbestos exposure). Radiation protection agencies such as the International Commission on Radiological Protection (ICRP) have adopted the hypothesis that there is no safe lower limit or threshold to the cancer-causing (stochastic) effect of low dose ionizing radiation in their approach to risk management.¹⁵

The US Food and Drug Administration Center for Devices and Radiological Health estimated that a CT examination with an effective dose of 10 mSv may be associated with a 1 in 2000 chance of developing fatal cancer.¹⁴ ICRP estimated that CTA with an effective dose of 14.7 mSv has a risk of fatal cancer induction rate of 1 in 1400. Invasive coronary angiography (5.6 mSv) has a fatal cancer risk of 1 in 3600 and calcium scoring scan (2.6 mSv) has a fatal cancer risk of 1 in 7700. The BEIR VII report in 2006 doubled the cancer risk of a 10 mSv CT to 1 in 1000.⁸ The risk in children is even higher with a reported chance of 1 in 550. BEIR VII reported that the malignancies most associated with X-ray exposure are leukemia, thyroid and breast cancer. The latent period between exposure and the development of cancer was reported as 2 to 5 years for leukemia and 10 to 20 years for solid tumours. In comparison, the natural risk of developing fatal cancer in the US population is about 1 chance in 5. In Hong Kong, the natural risk of developing fatal cancer for the general population is about 1 in 3. In other words, the risk of developing cancer from CT radiation exposure is much smaller than the natural risk of cancer. Nevertheless,

this small increase can become a public health concern if large numbers of the general population undergo increased numbers of CT screening procedures that have no certain health benefit. For individuals in whom interventional radiology procedures are life-saving, the risks associated with radiation exposure are secondary in importance. One area in which the risk of radiation exposure is clearly unjustified is CTA screening of healthy asymptomatic individuals with low risk factors for CAD.

Strauss et al (Memorial Sloan-Kettering Cancer Center, New York) made a calculation on the risk-benefits of CTA and concluded that 'the risk of radiation has its reward.' They contented that if the entire 18,800,000 people comprising the 50 to 55 year-old population were screened for CAD using CTA, the increase in the number of fatal cancers would be 14,900. If this screening were repeated every 5 years until the population reached the age of 70, the aggregate risk would be increased by about threefold to 42,900. Because the average age of patients with their first myocardial infarction is 65.8 for men and 70.4 for women and because 94% of these patients would have over 75% stenosis in at least one vessel, these sequential CTA procedures could identify patients with significant stenoses before their initial events. If this procedure prevented even 10% of the estimated 355,000 sudden deaths from CAD each year, the trade off would be well worthwhile.³

On the other hand, if we consider that over half of the patients who died of sudden death from CAD had coronary lesions that are less than 50% stenosed, due to rupture of soft, non-calcified vulnerable atheromatous plaques resulting in sudden platelet aggregation and thrombosis of the coronary artery, the benefit of CTA and subsequent interventions in reducing the rate of sudden cardiac deaths may be over-estimated. As yet the place of identifying the vulnerable plaques with CTA and its clinical applications are uncertain. For example, Boden et al found in the COURAGE study (which was presented in ACC 07 in March in New Orleans) that among patients with stable coronary disease, treatment with percutaneous coronary intervention (PCI) was not associated with a difference in death or myocardial infarction compared with

intensive medical therapy through 5 years of follow-up.¹⁶ To combat CAD for the health of the community, priority should be given to prevention through control of the risk factors of CAD.

When Is It Appropriate to Do a CTA?

To answer this question, the American College of Cardiology Foundation (ACCF) in conjunction with the American College of Radiology and related Societies have recently published their consensus on the appropriateness of cardiac computed tomography and cardiac magnetic resonance imaging.¹⁷ The section on CTA for chest pain syndrome is summarized as follows:

1. The use of CTA for evaluation of chest pain syndrome is considered appropriate if the patient is (1) symptomatic, (2) has an intermediate pre-test risk of CAD and 3) has one of the following: (a) has an uninterpretable ECG and is unable to exercise, (b) has no ECG changes and serial cardiac enzymes were negative while under observation for acute coronary syndrome, or (c) has previously an uninterpretable or equivocal stress test (exercise, perfusion, or stress echo). Uninterpretable ECG refers to ST-segment depression of 0.10 mV or greater in resting ECG, complete LBBB, WPW syndrome, or paced rhythm.

'Symptomatic' means that the patient has chest pain syndrome which includes chest pain, chest tightness, burning, dyspnea, shoulder pain, jaw pain, and perhaps pain radiating to the back as well.

'Pre-test Probability of CAD' is evaluated as follows and is based on the characteristics of the chest pain, as proposed originally by Diamond and Forrester in 1979:¹⁸

- 1) Typical Angina if it is: (a) substernal (b) provoked by exertion or emotional stress and (c) relieved by rest and/or nitroglycerin.
- 2) Atypical Angina if the chest pain or discomfort has only 2 out of 3 of the characteristics of typical angina.
- 3) Nonanginal Chest Pain if chest pain or discomfort has only one or none of the 3 characteristics of typical angina.

An intermediate pre-test probability of CAD also takes sex and age into consideration and is calculated as follows:

Pre-test probability of CAD is Intermediate for (a) men 30-39 with typical angina and (b) men 40 and above with atypical angina or nonanginal chest pain.

Pre-test probability of CAD is Intermediate for (a) women 40-49 with typical angina, (b) women 50-59 with atypical angina, and (c) women 60 and above with nonanginal chest pain.

The rationale for this strategy is that a majority of patients in this group will have negative finding from CTA, and they will be spared from the risks of ICA.

2. The use of CTA for the evaluation of chest pain syndrome is considered inappropriate if the patient is symptomatic and has (a) high pre-test probability of CAD, or (b) there is ECG ST elevation or positive cardiac enzymes while under observation for acute coronary syndrome, or (c) if previous evaluation for chest pain syndrome showed evidence of moderate or severe ischemia on stress test (exercise, perfusion, or stress echo). Pre-test probability of CAD is considered high (a) for men aged 40 and above with typical angina and (b) for women aged 60 and above with typical angina.

Here, the rationale is that these patients have a high likelihood of significant CAD and will be better served by going straight for ICA, thereby avoiding extra expenses and extra radiation from CTA.

3. The use of CTA is also considered inappropriate for asymptomatic patients with low or moderate risk of coronary heart disease (CHD) based on the Framingham Risk Score.^{19,20} The Framingham risk stratification for CHD is based on age and 5 other risk factors: high LDL cholesterol, low HDL cholesterol, hypertension, diabetes and smoking. There are different sets of criteria for men and women. The risk is 'high' if the total points indicate that the 10 year risk of CHD is greater than 20%, 'moderate' if the risk is between 10% and 20%, and 'low' if the probability is <10%. The risk of CTA is not justified if the pre-test likelihood of CHD is not high.

A rough calculation of risks for CHD (without referring to the CHD prediction score sheet) is as follows: For men age 60 and above, 'high' is 2 out of 5 risk factors present; and 'moderate' is 1 out of 5 risk factors present. For women aged 60 and above, 'high' is 3 out of 5 risk factors present; and moderate is 2 out of 5 risk factors present.

4. The appropriateness of CTA is considered uncertain if the patient is asymptomatic but has high CHD risk according to the Framingham score. Opinion was divided whether the patients should just receive intensive risk reduction medical therapy, or undergo stress testing (exercise, perfusion or stress echo) or CTA.

CTA or Stress Testing?

In the course of evaluating a patient with chest pain and intermediate risk of CAD, current guidelines from the American College of Cardiology and American Heart Association suggest that noninvasive testing may be of use for both diagnostic and prognostic purposes.²¹⁻²⁶ Logically one should start with the basic and most economical test, such as a regular stress exercise ECG with attention to functional capacity, heart rate response during and after exercise, and ventricular ectopy, which are more important predictors of risk than ST segment depression.²⁷ Many physicians, however, are attracted by the innovation of CTA. Fear of missing a significant coronary lesion leading to sudden death is a potent incentive but no tests are ever fool-proof. CTA provides direct visualization of coronary stenosis but provides no adequate information on the hemodynamic significance of the stenotic lesions. In other words, it identifies atherosclerosis but not ischemia. No long term prognostic data are yet available for CTA with the exception of coronary calcium score. On the other hand, there are ample data for prognostic stratification with the various forms of stress testing.

In a study comparing CTA with stress myocardial perfusion imaging (MPI) using gated SPECT with technetium 99, with both tests completed within 30 days of each other, Schuijff et al found that 90% of the patients with normal CTA also had normal MPI; but in patients

with obstructive CAD (luminal stenoses of 50% or more) on CTA, 50% were found to have normal MPI. The latter finding indicates that CTA and MPI provide different information on CAD, namely atherosclerosis versus ischemia.²⁸ In the accompanying editorial, Dorbala et al wrote that the enthusiasm for CTA as a potential noninvasive tool for guiding patient management decisions is tempered by a growing awareness that CTA may be limited in defining physiologic significance of coronary stenosis. Therefore in patients with obstructive CAD on CTA, MPI would be necessary to identify appropriate candidates for ICA and revascularization, since revascularization would not yield benefit in patients who have no objective evidence of ischemia, or only small amounts of ischemic myocardium. The substantial radiation burden from combined evaluation with CTA (7 to 12 mSv) and MPI (15 mSv) needs to be considered.²⁹

In another study, patients with acute chest pain (at low risk of acute coronary syndrome after initial assessment in an emergency center) were randomized into two groups: (1) initial CTA, followed by nuclear stress MPI if indicated and (2) nuclear stress MPI. CTA was able to establish or exclude CAD as the cause of chest pain in nearly 75% of cases. Patients with intermediate lesions of unclear hemodynamic significance (defined as stenosis = 26% to 70%) or non-diagnostic CTA scans underwent nuclear stress MPI. Patients with insignificant lesions on CTA or MPI were sent home. Patients with a stenosis of 70% or more and those with abnormal MPI underwent ICA, and ultimately 95% had a correct and definitive diagnosis. The patients randomized to primary nuclear stress MPI who had normal tests were immediately discharged (95% of patients), and those with an abnormal MPI test results underwent ICA. No major adverse events were reported in either group of patients who were sent home during 6 months of follow-up, indicating the safety of such measures.³⁰

The initial CTA approach was associated with the necessity for 25% of patients to undergo radiation exposure twice (15 to 28 mSv), with a further 4 to 6 mSv for the 10% of patients referred for ICA. An alternative, if initial CTA does not give a definitive diagnosis, would be to use other stress tests that avoid

radiation exposure such as exercise ECG, dobutamine stress echo, or magnetic resonance stress testing. A benefit of the CTA approach in the assessment of acute chest pain in the emergency setting is that other potentially fatal conditions such as acute coronary occlusion, aortic dissection and pulmonary embolism may be picked up or excluded (triple rule-out). This would require a CT scan protocol with a large field of view allowing global evaluation of thoracic structures, and the draw back is that it would compromise the evaluation of the coronaries and might lead to misinterpretation of coronary lesions.³¹

It is clear that CTA and stress testing are complementary diagnostic tools in the investigation of patients with chest pain and intermediate likelihood of CHD. One cannot replace the other. The technology of MSCT is still progressing. 256-slice CTA, hybrid machines such as PET/CT and SPECT/CT are now available, and further studies will be necessary to determine how best to use these new diagnostic techniques. Their cost-effectiveness also need to be addressed. Referring physicians should be educated on the hazards of radiation exposure in CTA and nuclear scans. Patient disclosure of radiation risks for CTA and nuclear MPI study should be adopted. The possibility of alternative methods of clinical evaluation and stress testing which do not involve the risks of contrast reaction and radiation exposure should be discussed with the patients.

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