Chapter 3

Non-Invasive Imaging of Coronary Artery Disease — The Expanding Role of Coronary Computed Tomographic Angiography in the Management of Low- to Intermediate-Risk Patients and Dealing with Intermediate Stenosis

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Additional information is available at the end of the chapter

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Abstract

Non-invasive anatomic imaging modalities play a crucial role in the diagnosis of coronary artery disease (CAD), particularly in the case of the symptomatic patient presenting in the emergency department.

Some of the key issues of discussion will be the appropriate use of coronary computed tomography (CT) in the anatomical assessment of CAD, the prognostic information that this assessment holds and how the role of CT may evolve in the coming years.

The aim of this chapter is to summarise and evaluate the current best non-invasive anatomical strategies of CAD imaging, notably in those with a low to intermediate pre-test risk of CAD and those with an intermediate luminal stenosis.

Keywords: Coronary artery disease, computed tomography, imaging, intermediate stenosis

1. Introduction

The British physician William Harvey described the heart as, "the household of Divinity which, discharging its function, nourishes, cherishes, quickens the whole book and is indeed the foundation of life."[1] In Harvey's words, together with his wider body of work, he en-

capsulates three simple truths; it is the heart's role to pump the blood that it is the role of the blood vessels to circulate the blood and it is the blood that sustains living tissue. These assertions may seem obvious, but they are just as pertinent now as when they were first penned in the 17th century. The reason for this is clear, the leading cause of mortality in the developed world is coronary artery disease(CAD). CAD is a narrowing of the lumen of the arteries that supply blood to the heart resulting in a 'failure' of the circulation to deliver blood to the heart.[2] Modern medical imaging allows the physician to accurately assess the extent to which the coronary arteries are narrowed (anatomical imaging), and to what extent this narrowing results in a 'failure' to circulate the blood (functional imaging).

It is an undisputed fact that the current best method for imaging the burden of CAD is invasive coronary angiography (ICA). This fact is reflected in its ubiquitous use in clinical practice today; figures from 2004 show that 201,000 of these procedures were undertaken in the United Kingdom, an increase of 7% from the previous year. Whilst the risks may be small – a mortality of 0.07% and a radiation exposure risk lower than other imaging procedures [3] – it would not be safe, practical or cost effective to offer every patient with symptoms of CAD to ICA. Furthermore, up to 40% of the patients who do go on to have elective ICA are found to have sub-clinical stenosis in all coronary arteries.[4,5] This highlights the inadequate and inaccurate information provided by orthodox first-/second-line investigations in the assessment of symptomatic patients with suspected CAD.

There is an increasing body of evidence which suggests that non-invasive anatomical imaging modalities have a crucial role to play in the diagnosis of CAD, particularly, in the case of the symptomatic patient presenting in the emergency department. That is, not to say that non-invasive imaging will completely supplant ICA, but it may, and in some instances already has been proven to be clinically useful in the right patient group, at the right stage of the patient pathway [6, 7, 8]. One such promising imaging modality, which will be evaluated in explicit detail in the course of this review, is CT. Some of the key issues of discussion will be the appropriate use in anatomic assessment of CAD, the prognostic information that this assessment holds and how the role of CT may evolve in the coming years.

The aim of this chapter is to summarise and evaluate the current best non-invasive anatomical strategies of imaging CAD. The main focus will be to unveil the best to approach the two less well understood (and sometimes overlapping) cohorts of CAD symptomatic patients: those with a low to intermediate pre-test risk (10–29%) of CAD and those with CAD, who have an intermediate amount of luminal stenosis (40–69% of the luminal cross-sectional area).

2. What is CAD? Blood haemodynamics and myocardial demand

Coronary artery disease has one main consequence: it limits blood flow to the myocardium. When this happens, CAD can cause an imbalance between the myocardial oxygen demand and the rate of delivery of oxygen by the blood, leading to tissue hypoxia. The overall process is a broad spectrum of conditions known as ischaemic heart disease. In 1772, when Wil-

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liam Heberden described an 'uncomfortable sensation' while walking and called it angina, he was describing a manifestation of ischaemic heart disease (Figures 1 and 2).[2]

- The flow of the blood to heart is summarised by Darcy's law: *flow=pressure/resistance* [9]
- In coronary artery disease (CAD) the reduction in flow is as a result of an increase in resistance.
- The resistance in blood vessels is frequently described by a mathematical law called Poiseuille's law.
- Poiseuille's law demonstrates that the resistance to a fluid flowing through a tube, assuming laminar flow, is inversely proportional to the radius to the power of four. [2][1]
- However, the relationship between the amount of vessel occlusion, resistance and flow, is a great deal more complicated than this when applied to CAD.
- It is of paramount importance that a more nuanced physiological account of blood hemodynamics in CAD is understood when interpreting imaging of suspect lesions.

Figure 1. Darcy's law and Poiseuille's law

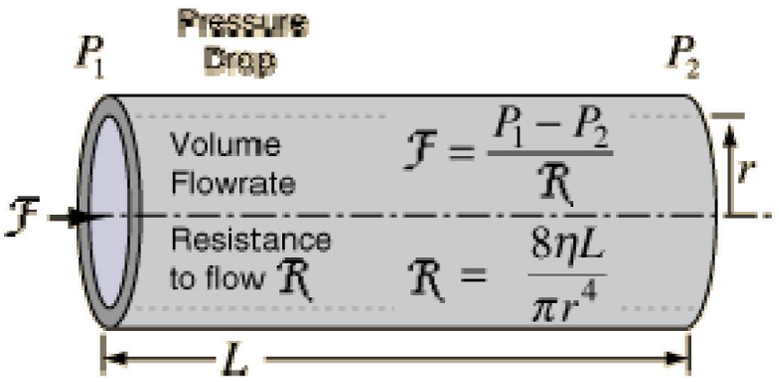

Figure 2. Schematic representation to show Darcy's law (volume flow rate) and Poiseuille's law (resistance to flow) in a rigid tube, assuming laminar flow. *adapted without permission*[42]

The situation presented by traditional thinking, derived from animal experimental models in the 1970s, is that CAD is not deemed to be flow limiting at all, when 60% of the lumen cross-sectional area is occluded and is only deemed to be obstructive to flow during stress

when 70% of the luminal cross-sectional area is blocked (Figure 3).[10] The relationship between the percentage of obstruction and flow forms the basis for much of the findings in anatomical imaging, such as CT coronary angiography (CTCA). For example, it is a well-reported fact that sub-clinical stenosis (<50%). CAD is associated with a very low myocardial infarction event rate.[7]

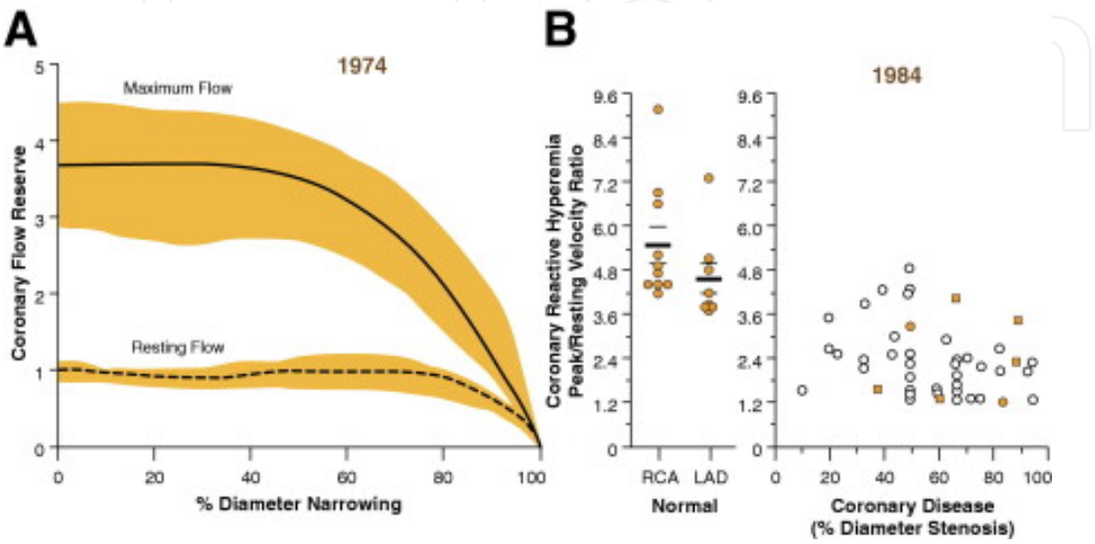

Figure 3. A graph derived from animal experiments in the 1970s, showing the relationship between the amount of vessel occlusion and flow at rest and during stress. It can be seen that flow is affected at a lower threshold of diameter narrowing during exercise than during stress. This was originally cited as the cause of angina described by Heberden in the 18th century. However, it is now known that the relationship between percentage of vessel narrowing and coronary flow is a more complicated process than this experiment implied [10] *graph adapted without permission*

The problem with the traditional thinking and the experimental models, from which it was derived, is that the animal experiments were done on healthy coronary arteries, which were externally compressed at one point along the coronary artery. Equating the flow demonstrated in an externally compressed coronary artery to that in an equally stenosed, diseased coronary is wrong for two main reasons. Firstly, the pathophysiological process that causes CAD does far more than physically 'block' the vessel. Secondly, CAD can exist 'diffusely' along a great portion of the vessel and still have profound haemodynamic consequences. For example, one can use ICA to demonstrate that diffuse disease with narrowing as little as 38% can cause as much as a 65% decrease in coronary flow reserve (Figure 4). The implications of this for imaging are clear; an anatomical assessment of coronary artery stenosis is useful information, however, this test alone cannot comprehensively assess the extent or be the best approach to tackle CAD.[11]

3. Atherosclerosis (Figures 5–7)

As highlighted earlier, CAD results in a narrowing of the coronary arteries. The narrowing of these coronary arteries can cause a limitation of blood flow and therefore oxygen supply

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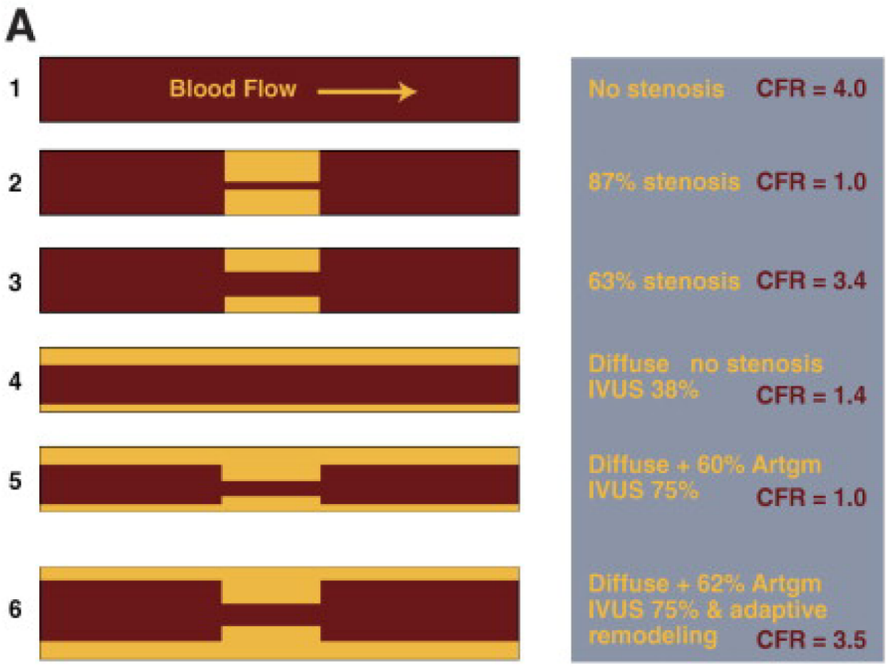

Figure 4. A schematic representation that illustrates the limitations of anatomic imaging by Artgm (arteriogram) and IVUS (intravascular ultrasound) during invasive coronary angiography. The recorded value of blood flow, measured by CFR, is severely at odds with the findings using only anatomic measurements. *Adapted without permission*[11]

(ischaemia) to the myocardium. The cause of this 'narrowing' is a poorly understood chronic inflammatory process called atherosclerosis.[2]. Atherosclerosis, literally meaning 'hard gruel', is a more complicated process than the development of an atherosclerotic plaque, which thickens the vessel wall, intruding and obstructing the vessel lumen. The reason for this atherosclerosis is that the healthy coronary artery cannot be thought of as simply an inert tube through which blood flows. [2, 9] In fact, the healthy artery must be thought of as three layers of differing function: the tunica intima, tunica media and tunica adventitia.

The intima must be recognised as more than simply a mechanical barrier which encloses the blood; it is involved in metabolism, signalling and through a combination of both, and it plays a crucial role in haemodynamics of blood flow. The way it does this is twofold:

1. The intima plays a role in producing anti-thrombotic molecules, lowering the tendency of blood to clot, therefore lowering its viscosity and the resistance to flow.

2. The intima produces signalling molecules, which alters the contractility on smooth muscle cells and therefore controls the size of the coronary artery lumen. In health, the intima triggers vasodilatation of the arterial lumen during exercise and therefore increases the myocardial blood flow to meet the demand.

During the process of atherosclerosis, for reasons beyond the scope of this chapter, the intima lining cells fail to perform their normal role in regulating the flow of blood at a local level. As a result, endothelial cell dysfunction arising from atherosclerosis causes both

inappropriate vasoconstriction and loss of normal anti-thrombotic properties (thus increasing blood viscosity).[2] This is relevant to imaging because the relationship between how much of the luminal cross-sectional area of a coronary artery is occluded is not always directly proportional to flow limitation. Therefore, imaging modalities that merely acquire anatomical information cannot provide haemodynamic information specific to the individual.

Another reason why a good understanding of the pathophysiology of atherosclerosis is important is because the composition of the atherosclerotic plaque itself is having an incremental role in interpreting the significance of imaging findings. [4, 7, 8, 12] During the process of atherosclerosis, 'bad' cholesterol, low-density lipoproteins, accumulate under the intimal wall; these lipids quickly become oxidised and are engulfed by tissue macrophages forming 'foam cells'. Another thing that happens, not necessarily in a sequential order, is that smooth muscle cells are moved away from their native sites in the media and these migrate into the intima. These smooth muscle cells secrete extracellular matrix forming a fibrous plaque, which often have high calcium concentrations.[2] Misleadingly, this calcium does not always concentrate at the site of maximal stenosis and calcified plaque only represents approximately 20% of the total coronary atherosclerotic burden. Therefore, calcium can be considered a good marker of CAD and its absence is an excellent marker of no CAD [13], but it cannot diagnose obstructive CAD. [6] [12] The relative proportions of fibrous tissue to lipid also determine the vulnerability of the plaque to rupture. This is crucial in risk stratification when assessing CAD.

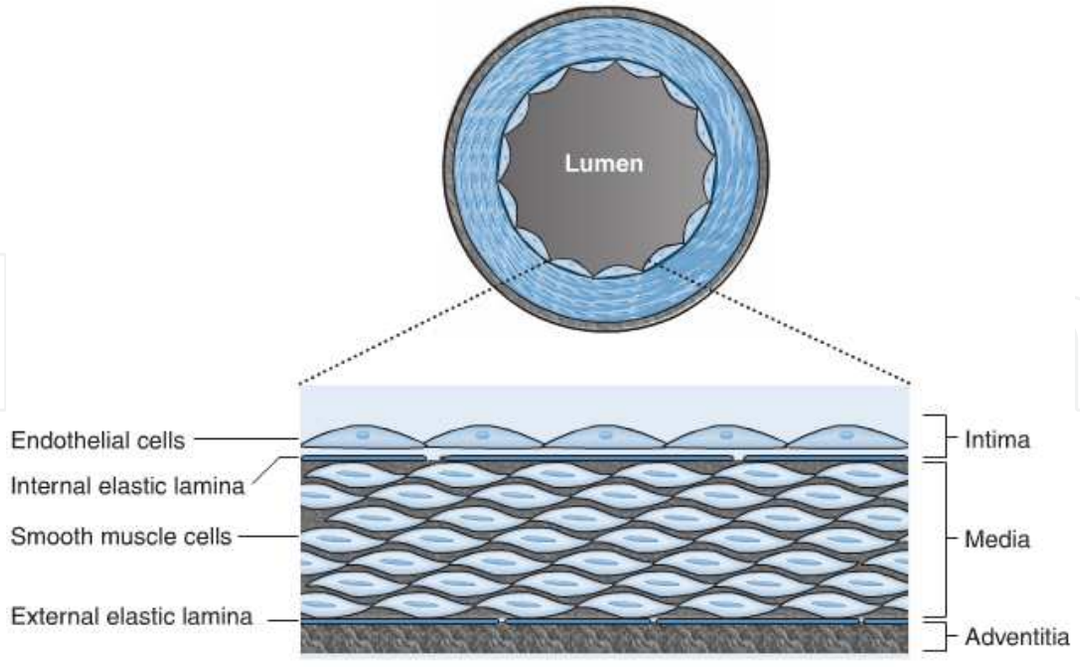

Figure 5. The three layers of artery wall: tunica intima, media and adventitia. The media contains smooth muscle cells. During the process of atherosclerosis, these can migrate into the intima and elaborate fibrous ECM. The adventitia is composed of connective tissue, nerves and lymph. *adapted without permission*[2]

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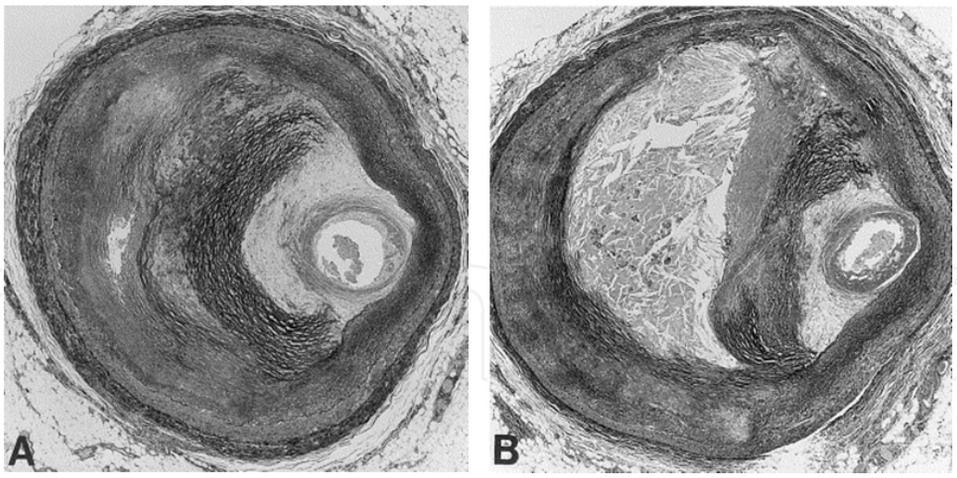

Figure 6. A micrograph showing that atherosclerotic plaques are not homogeneous in their composition. The figure illustrates two stenotic plaques of differing morphology a) plaque consisting of hard, collagen rich sclerotic tissue b) A plaque many comprised lipid-rich atheromatous core, separated from the vessel lumen by a thin fibrous cap. *Adapted without permission*[45]

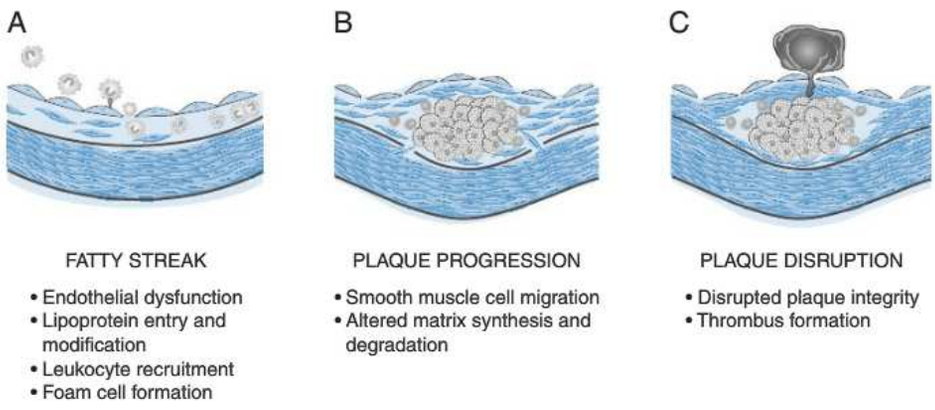

Figure 7. Schematic showing the pathological development of Atherosclerosis and the factors that contribute during each phase. One of the key aims going forward in anatomic imaging is to identify plaques which are at high risk of rupture as seen in C *adapted without permission*[2]

4. Anatomic imaging: The evolving role of coronary CT in the management of chest pain (Figures 8–12)

CT has come a long way since the first clinical scans in 1971. It is now estimated that over 4 million scans are performed annually in the UK and one of the recent successful applications of CT has been the emergence of CT coronary angiography (CTCA) in the management of chest pain.[4] A moving object, such as the heart, was thought impossible to image by CT as the discrete nature of the imaging process meant early scanners had poor temporal resolution. However, with the advancement in CT technology, particularly the development

of greater number of detector row and more rapid gantry rotation, CT can now accurately evaluate structures in constant motion like the heart and coronary arteries due to its superior spatial and temporal resolution. [4, 14] CTCA involves visualising the coronary arteries directly with sub-millimetre isotropic spatial resolution and using this anatomic information on stenosis severity to determine the true extent of CAD.

- CT became possible in 1917 when the mathematician, J.H. Radon proved that the 2D distribution of an object can be determined exactly, if the integral values along any number of lines passing through the same layer are known.
- It was realised that the same principle was true of 3D objects.
- The practical implications of this in medicine were not realised until the English engineer, Hounsfield showed that by measuring attenuation x-rays fired from different angles in a plane perpendicular to the scanning subject (although theoretically any arbitrary plane can be used) one can gather the line integrals necessary to reconstruct an image in 3D.
- He called this technique CT.
- CT visualises the body as composed of a series of finite slices.
- Modern CT scanners use multiple x-ray beam collimators, which convert the x-ray beam into a 'fan' beam, covering the individual body section or slice.
- Multiple detectors measure the difference between the known primary intensity of the x-ray sheets and their attenuated intensity having passed through different tissues. [14]
- X-ray beam generators and detectors spin 360 degrees around the scanning subject collecting many thousands of attenuation intensities from different angles within the same plane.
- These attenuation intensities are used to create a discrete number of cubic volume elements or voxel. Each individual voxel is described by its individual CT number or Hounsfield unit.
- [15] The intensity of radiation recorded at all the detectors during the scan is equal to the integration of all the CT numbers of the voxels.
- This is called the ray sums. The ray sums can be solved simultaneously to obtain the co-ordinates of each voxel in three dimensions and pair it to its exact attenuation properties, thus eliminating the superimposition that occurs in conventional radiography.
- Each individual voxel is then combined to produce a thin sliced, three-dimensional image.

Figure 8. A brief summary of the Physics of CT

$$HU = 1000 \times \frac{\mu x - \mu_{water}}{\mu_{water}}$$

Figure 9. CT number (Hounsfield) equation – the equation used to calculate the voxel intensity

5. A Mandate for CTCA (Figure 13)

Traditionally, a patient presenting with chest pain in the emergency department with a clinical history indicating CAD, but with no ECG changes or troponin-plasma irregularities, would be sent for an exercise treadmill test (ETT). The weaknesses of ETT are encapsulated

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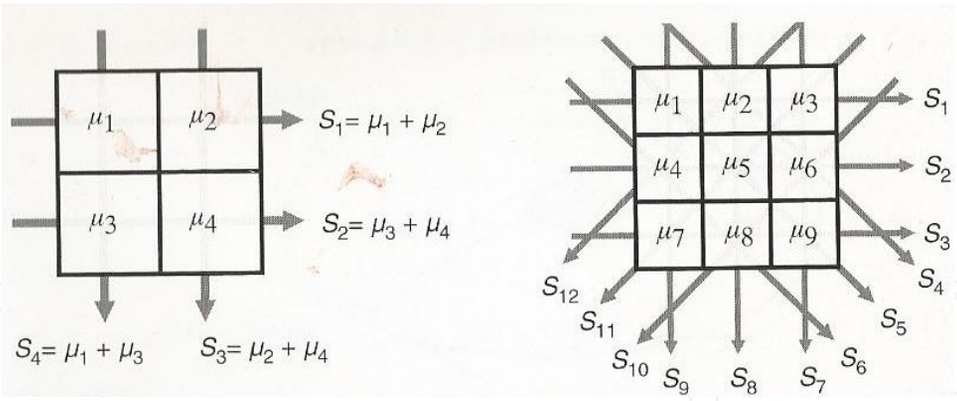

Figure 10. Schematic demonstrating how the ray sums are acquired in the simplest image matrices possible (2 × 2 and 3 × 3). There are N squared unknown values of attenuation for an N × N image matrix. The ray sums can then be solved as simultaneous linear equations to find the attenuation values of each voxel. *Image adapted without consent*[14]

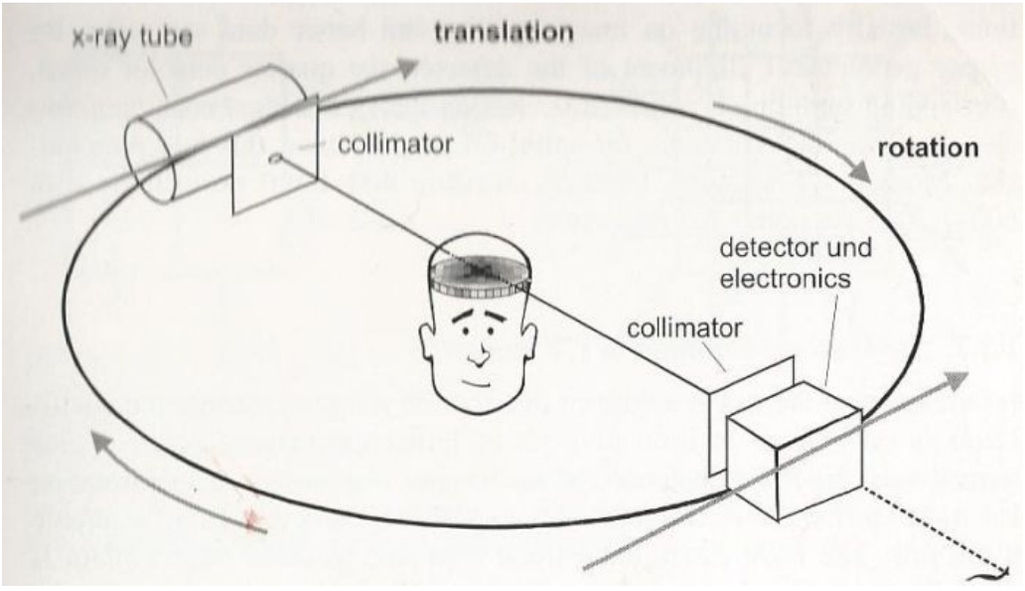

Figure 11. In a single plane, perpendicular to the scanning subject, the x-ray tube, and detector acquire attenuation values 360 degrees around the scanning subject (thus the scanning subject is the axis of rotation). This allows a single 'volume' slice to be obtained. Slices can be combined to form a 3D image visualised from any angle. *image adapted without consent*[14]

in a meta-analysis conducted by Patel et al, reviewing a sample of 398,978 cases of chest pain admissions with unknown CAD. The results show that 59% of the positive tests had no obstructive CAD and 28% were false negatives when ICA was performed. This level of inaccuracy is unacceptable, regardless of the fact that ETT is inexpensive and readily available; it is no better than flipping a coin at positively predicting flow-limiting CAD. The findings of Patel et al also illustrate that in the established patient pathway only 37.6% of patients referred to ICA were found to have obstructive CAD. The overall conclusion of the study was that "better strategies for risk stratification...to increase diagnostic yield of cardiac catheterisation in routine practice" are necessary [17]

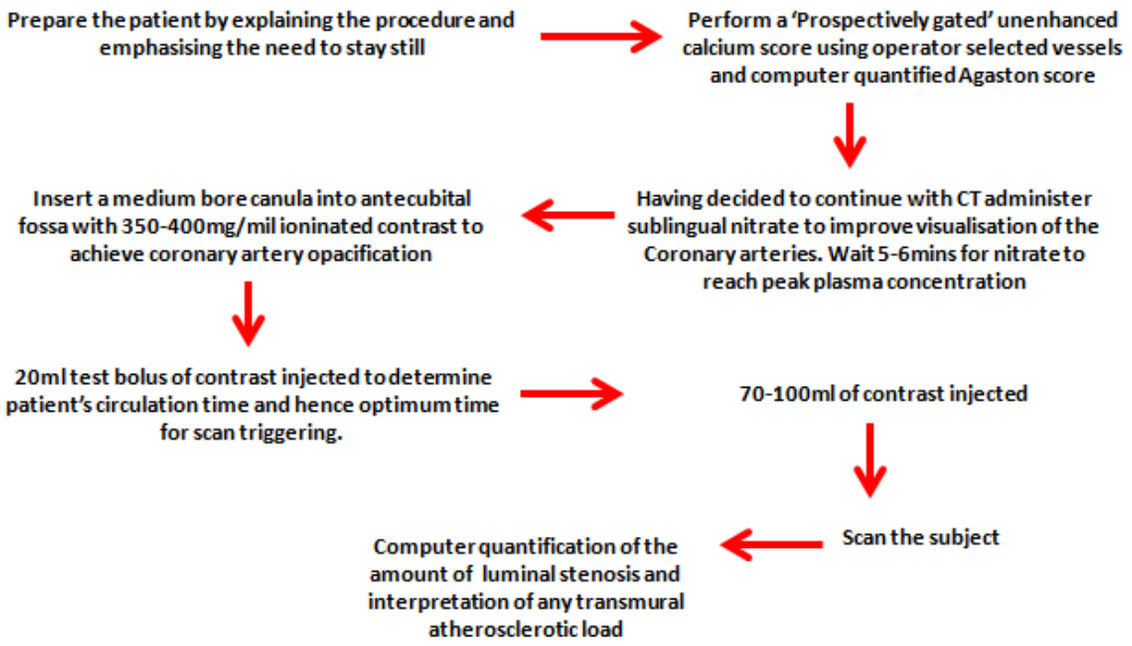

Figure 12. A flow diagram to show the procedure of calcium scoring and full-blown, contrast-enhanced CTCA. *Original figure: information adapted*[7]

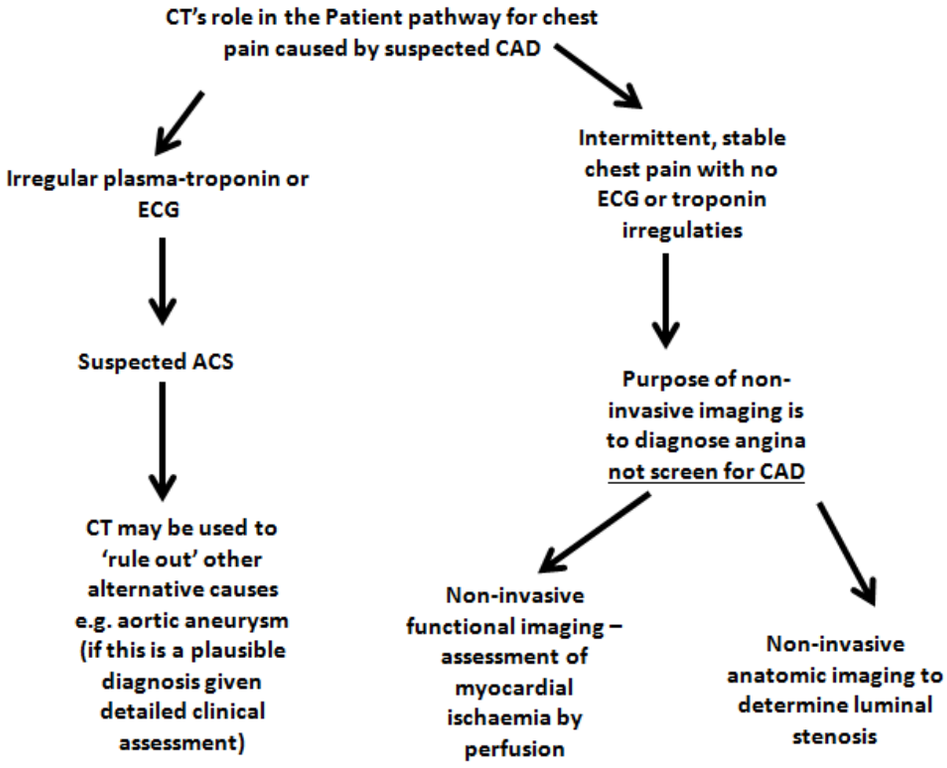

Figure 13. Flow diagram illustrating CT's current role in the management of chest pain in the UK does not extend beyond a 'rule out' in the intermediate stenosis group. It currently has no role in suspected ACS in the UK. *original figure, information adapted*[7]

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The mandate for CT, if proven to work, is clear; too many patients, who do not need it are being sent for ICA. This is expensive and unnecessarily increases the patient's risk of complication. ICA has a serious complication rate of about 1/1,000[12]. Importantly, indecisive testing also increases the amount of time a patient spends in the waiting room. The CT coronary angiography for systematic triage of acute chest pain patients to treatment (CT-STAT) and randomised controlled trial (RCT) showed that as compared with the conventional pathway, a patient evaluated with CTCA can expect to wait on average less than 4 h at a cost, which is on average $1,500 cheaper compared with the healthcare provider.[18] Another large-scale RCT (n = 1,365), which compared the traditional care group with that who received CTCA after first line tests, found that there were 26.8% fewer (95% CI 21.4–32.2) unnecessary admissions in the CCTA group. In addition, there were fewer negative invasive angiograms and a greater number of patients who were correctly identified as having obstructive CAD. [19] In fact, the health economic model, using ICA as the reference standard, shows that at a pre-test probability of 50% or lower, CTCA results in a lower cost per patient with a true positive diagnosis.[15] Annually, there are 6 million presentations for chest pain, only 20% of these receive a diagnosis of CAD, and a large number are hospitalised unnecessarily. In 2006, the bill for non-specific chest pain in the UK came to £11.2 billion.[8] On the issue of assessing chest pain for patients in the emergency department, medicine can and should do better than ETT. The evidence shows CTCA is far superior on the basis of time and expense [18].

6. How can CTCA be used and does it work?

CTCA has advanced to the stage that it is now advocated by 'National Institute for Clinical Excellence (NICE) Guidance 95' for patients with a low–intermediate risk of CAD (10–29%). [7] The main reason CTCA has taken on this new role is because of its high negative predictive value and thus the exceptional ability to rule out CAD (Figures 14–16). [20, 8, 4, 6, 21]

- Pre-test probability is calculated using an algorithm, which involves 12 lead ECG, typicality of symptoms, age, sex and risk factors.
- It should also be noted that the RCT evidence out there is based on the use of at least 64 MDCT scanners and therefore the result findings are not applicable to centres that do not have this facility available. There is a lack of RCT evidence on the accuracy of the newer 320 MDCT scanners, exclusively.
- Accuracy of CTCA varies according to the level of disease prevalence and the level at which anatomic imaging defines luminal obstruction as haemodynamically significant.

Figure 14. A note on methodology of the trials

- A key strength of EVASCAN, which is not seen in many other studies of this kind, is that non evaluable segments were not excluded from the analysis, or as they are in other studies, assumed to be stenosed; falsely elevating the negative predictive value (NPV) and specificity.
- One of the EVASCAN study limitations was that currently, stenosis analysis is more often performed by more crude qualitative assessment in clinical practice rather than the quantitative approach taken in research.[20] For this reason, the findings of EVASCAN should be evaluated with caution when applied to the clinical setting.
- A weakness of CTCA pointed out by all major RCT study findings is that diagnostic accuracy of CTCA is limited in distal vessels or in vessels that are narrower than 1.5 mm due to its limited spatial resolution (0.5 mm) which is still by far inferior to that of the invasive angiograph (0.2 mm)[27].
- All studies pointed toward the need for further study on the 'real life' management of patients with chest pain. It is hoped that this could help to define a precise role for CCTA in symptomatic patients with CAD and determine exactly what benefit it can provide to specific patient groups rather than using ICA

Figure 15. Strengths and weaknesses of the EVASCAN study methodology

Study Name	Degree of stenosis severity assessed	Disease Prevalence	Study Number	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive value
CORE 64[22]	>50%	51%	N=291	85	90	91	83
ACCURACY [25]	>70%	13.9%	N=231	91	84	51	99
ACCURACY OF 64 SLICE CTCA [26]	>50%	68%	N=360	99	64	86	97

Figure 16. A table summarising the data concerning the accuracy of 64 MDCT at various disease prevalence and degrees of stenoses, considered flow limiting

One of the most definitive RCTs conducted to evaluate the accuracy of CTCA at detecting or ruling out >50% stenosis is the EVAluation of CT SCANner (EVASCAN) study, which included the largest sample of intermediate–high risk stable symptomatic patients, to date. Considering the low–intermediate group forms, the greatest proportion of individuals presenting with symptomatic CAD in the emergency department (ED) is 50–70% [19], EVASCAN's study sheds light on a previously under-investigated and crucial patient group. EVASCAN examined population with a prevalence of CAD of 54%, in a study sample of 757, using a 64 slice multi-detector row CT scanner. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) compared with ICA as the reference standard were 91%, 50%, 68% and 83%, respectively.[20] At 83%, EVASCAN's negative predictive value concords with the CORE 64 RCT [22], which also examines CTCA's effec-

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tiveness at detecting CAD severity compared with the gold standard of ICA. At a lowly 68%, the positive predictive value (PPV) of CTCA is badly affected by CT's facility to systematically over-estimate stenosis severity due to local accumulation of non-obstructive local foci of calcium.

The results of EVASCAN and CORE 64 must be contextualised. Both look at the ability of CT to determine haemodynamically obstructive CAD, based on a 'binary', > or <50% stenosis severity. For reasons highlighted earlier, 50% stenosis is quite a low boundary to be considered flow limiting across the board. Whilst the inability to account for other physiological factors in flow limitation is an inherent weakness of anatomical CTCA, ruling out CAD exclusively on the basis of a 50% stenosis severity is bound to be less accurate than using the 70% threshold. For this reason, NICE guidance advocates the use of the >70% threshold in the assessment of flow limitation.[23]

The challenging question of, "what extent of luminal obstruction should be assumed to be flow limiting?" has recently been tackled by a few small-scale RCTs. These RCTs call for a re-evaluation of the binary classification of stenosis severity as flow limiting/not flow limiting according to a single cut-off threshold. These studies demonstrate the potential clinical usefulness of a more quantitative, tiered approach to evaluating stenosis severity. These studies also illustrate that stenosis severity can be accurately 'graded' by CTCA and this 'grading' shows excellent correlation with flow limitation (r = 0.82), assessed by ICA.[24] Further large-scale RCTs are needed to evaluate the usefulness of this graded approach in risk stratification and prognostic outcome. More evidence is also needed to determine the exact effectiveness of anatomical CTCA in assessing flow limitation in the intermediately stenosed group (40–69%).

The ACCURACY RCT illustrates CTCA's excellent ability to rule out CAD in populations of low prevalence of CAD with a negative predictive value of 99%.[25] At the other end of the spectrum, ACCURACY of 64 shows that CTCA can accurately rule out CAD in populations with a high prevalence of CAD with an NPV of 98%.[26] These results demonstrate that it is feasible to use CTCA in populations at high and low risk of the disease. Something that needs to be considered from a research perspective is that 99% rule out is extremely impressive and far more encouraging than ETT. However, from a clinical perspective 1 mistake in every 100, given the high turnover of chest pain patients in the ED, could prove to be very costly in terms of lives lost. Therefore, while it is feasible to use CTCA in the rule out of obstructive CAD in both of these patient populations, it does not necessarily provide clear clinical benefit over ICA, the gold standard to which CTCA is being compared with, in terms of accuracy of the 'rule out'.

The overall findings of EVASCAN, and associated RCTs, illustrate that in populations with a low prevalence of disease and using a 70% stenosis as a threshold for flow limitation, CTCA can be used to a great effect to rule out flow-limiting CAD. This is why EVASCAN and other studies call for clinicians to recognise the importance of the pre-test probability. In low to intermediate pre-test probability of CAD (10–29%), where the disease prevalence of obstructive CAD will be low, it is more cost effective, safer than and almost equally as accurate as the gold standard ICA at ruling out CAD. The reason CTCA's use cannot be extend-

ed to high pre-test risk population (>61%) is because in spite of the high NPV, a patient will receive no benefit from receiving CTCA.[7] In this high-risk group, a rule-in test is required, and CCTA's unimpressive PPV and ICA's added benefit of being able to revascularise straight away, if the culprit lesion is shown to be flow limiting, makes it more cost effective than CCTA in this patient group.

7. Prognostic value of CTCA

The focus thus far has been to assess to what extent CT can accurately identify obstructive CAD and the monetary and time-saving benefit CT can offer. It is also crucial to follow up patients after diagnosis by CTCA and record their outcomes that is. given a negative finding on CT, what proportion of patients still go on to have major adverse coronary event (MACE)?

A recent meta-analysis (n = 9,592), with a median 20-month follow-up, showed that the risk of MACE following a negative test on CTCA is 0.17% per year, a figure that is comparable with the baseline rate (0.15% per year). In patients with abnormal findings on CTCA, there is a risk of MACE of 8.8%, 40 times more than the risk in the general population.[27] Another meta-analysis (n = 3,670), which performed similar analysis over a longer mean follow-up period (21.6 months), found a tenfold higher risk in patients with "any detectable coronary stenosis by CTCA compared with subjects without coronary stenosis".[28]

A recent case–control study went into more detailed analysis at the potential for CT to stratify risk. It was found that, by grading coronary stenosis using a segmental stenosis score, and following up after 52 months, those with a score up to 5 (less severe stenosis) had an event-free survival of 85%, whereas those who had a score >5 had an event-free survival of just 20%. The same study also found that those with an intermediate degree of the stenosis (40–69% ruled out as flow limiting) showed an event-free survival between those with normal coronary arteries and those with obstructive CAD.[29] This study conceded that it could not be sure that the higher number of deaths in this group was because of the non-obstructive CAD, developing into obstructive CAD, or because of non-obstructive CAD plaque rupture, and highlighted, "early identification of non-obstructive CAD with CTCA is clinically important because it may lead to a more aggressive strategy of cardiovascular risk factor control and modification of clinical follow-up."[29] It is for exactly this reason that prognostic information obtained by CTCA is so useful; rather than widespread distribution of primary and secondary interventions, targeted aggressive treatment can be handed to the patients who need it the most.

8. Prognostic value of CTCA: Calcium scoring

Calcium scoring is a tool available for cardiac CT (Figures 17 and 18), which can be performed immediately, without the use of contrast and without the use of high doses of radia-

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tion, in order to stratify for cardiac risk. It works on the basis that coronary artery calcium (CAC) has excellent x-ray attenuation properties and is a quantifiable marker of atherosclerotic plaque. However, the quantity of CAC is poorly correlated with the degree of stenosis, so its presence should not be extrapolated to be a good predictor of flow limitation.[8]

- A calcium score of zero is indicative of no detectable calcium
- NICE recommend that symptomatic low-intermediate (10–29%) risk patients should be offered CAC scoring
- In a score between **1** and **400** , the recommendation is to proceed to formal CTCA
- In a score that exceeds **400**, with no alternative explanation, the recommendation is to proceed to ICA[7] as CTCA is less effective in patients with significant calcification [30]

Figure 17. NICE Recommendations on the calcium score

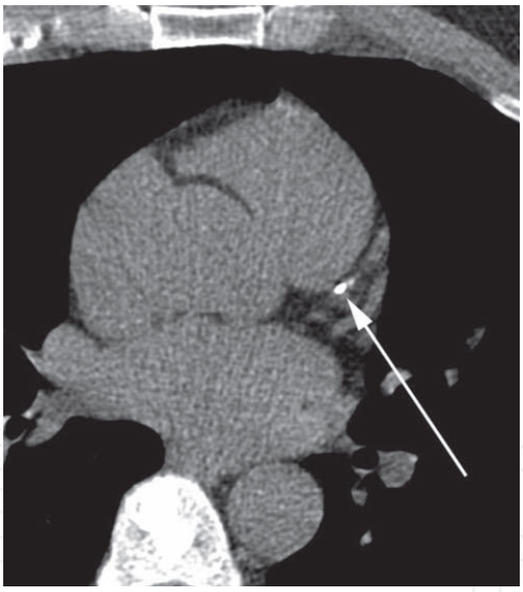

Figure 18. An unenhanced calcium score showing low degree calcification in proximal left anterior, descending artery. The patient was thus referred to CTCA. *Figure adapted without consent*[7]

A calcium score of zero has a 12-year-survival of 99.4% and a score of 100–400 Agatston units has a lifetime risk ratio of myocardial infarction of 4.3 compared with those with a calcium score of zero. Despite the excellent prognosis of a CAC score of zero, its use is not indicated for the purpose of screening as the likelihood of finding stenosis in low-risk patients (using the Framingham score) is too low to warrant imaging.[12] The CAC score is best deployed in the intermediate-risk population.[7] A serious consideration which requires the

physician's meticulous attention is the calcific distribution; a relatively low overall calcium score may be taken more seriously if it is found in the 'spotty distribution' of calcium.[30]

Another aspect of the calcium score in risk stratification is the patient's age. Whilst no coronary calcium is an excellent marker of prognosis, the true false negative rate is not really known and controversy surrounds the ability of CAC to rule out non-calcified fibrolipid plaque.[7] In a meta-analysis of 10,355 symptomatic patients, testing the ability of CAC scoring to detect significant CAD compared with ICA, results showed as high as 2% of the patients had significant CAD with no detectable calcium and CAC scoring had a poor overall specificity of just 40%.[31] These individuals (significant CAD with no CAC) tend to be younger than 50 years of age and particular diligence must be taken with patients in this age group. Worryingly, the presence of this non-calcified plaque is higher in patients with serious acute coronary syndrome (ACS) rather than stable angina.[12]

9. Prognostic value of CTCA: Plaque composition

An advantage of CTCA, and an area of great promise, is the ability to provide more information about the coronary artery than just the luminal information offered by ICA. CTCA can offer insight into the degree of mural plaque burden and the plaque sub-type, which is beyond ICA without the use of intravascular ultrasound.[4]

Broadly speaking, CTCA can identify three types of plaque: calcified, non-calcified and mixed. Comparison with intravascular ultrasound during ICA shows that CTCA can correctly identify 95% of the calcified plaque, 83% of the non-calcified plaque and 84% of the mixed plaque. The accuracy for the identification of non-calcified plaque is lower for the same reason; CAC scoring is a poor predictor of obstructive CAD: CTCA systematically overestimates CAC due to the high attenuation properties of calcium and the partial volume effect. However, it is hoped that one day CTCA will be able to unlock useful prognostic information about the chance of CAD plaque rupture, and therefore detect and direct medical intervention.[12]

It has already been highlighted that 90% of the ACS is caused by plaque rupture [2] and up to two-thirds of MIs occur from disruption of plaque that causes less than 50% stenosis. [12] Currently, CTCA would result in the discharge a patient with chest pain at this intermediate degree of stenosis and any further functional testing that would be performed (stress testing or ICA) is unlikely to show any signs of ischaemia. [12]

Plaques at the risk of rupture have a specific morphology called 'thin-capped fibroatheroma'. These have a lipid-rich, necrotic core with a thin fibrous cap. The most important property in the risk of rupture of plaques is the thickness of the fibrous cap; the thinner the fibrous cap, the greater the risk of rupture. Currently, the spatial resolution of CT is limited to 330 μm and, by definition, the fibrous cap is less than 65 μm in thickness. The current limits of CT suggest that being able to visualise 'at risk' fibrous caps is impossible. However, these 'fibroatheromas' have slightly different attenuation properties to more stable, fibrous

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lesions. Although there is still much progress to be made, promise remains in the ability of CTCA to distinguish the attenuation properties of the lipid-rich core in the hope of recognising and quantifying the risk of rupture in vulnerable plaque. [30, 12]

10. CT in the assessment of Fractional Flow Reserve(FFR): The future

ICA has been referred to many times throughout the course of this chapter as the 'gold standard' in the assessment of CAD (Figure 19). In order to define a precise role for anatomic CTCA, in the assessment of CAD, one must first understand the process of ICA, what useful information it gathers and whether it is within the capability of CTCA to gather similar, useful information.

- ICA, or, as it is more simplistically known, coronary angiography involves 'cardiac catheterisation'
- Cardiac catheterisation is the process where the femoral or brachial artery (most commonly on the left side) is punctured and a long, thin, flexible, hollow, tube-like device (a catheter) is fed in a retrograde fashion through the circulatory system to the heart and coronary arteries
- The movement of the catheter tip is guided by an x-ray machine and injections of contrast are used to enhance visualisation of the vasculature. [33] This allows the physician to directly visualise the degree of coronary artery stenosis in real time
- FFR is calculated by measuring the ratio of pressure proximal to and distal to a stenotic lesion during vasodilator induced hyperaemia

Figure 19. The procedure of ICA

One of the major advantages of ICA is the ability to perform percutaneous coronary intervention (PCI) in an attempt to restore normal flow to the obstructed coronary artery. This assumption was called into question by the COURAGE RCT trial, which compared the outcomes of elective, stable angina patients with those who received optimised medical therapy (anti-platelet therapy and statins) when compared with PCI. The findings of this study were that, "as an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction or other major cardiovascular events when added to optimal medical therapy."[32]

The COURAGE trial was followed up by the COURAGE nuclear substudy, which took into account the extent of ischaemia on perfusion imaging, using the same two treatment alloca-

tions. The substudy found that revascularisation did lead to a decrease in ischaemia and a decrease in adverse cardiac events.[27] The results of the two trials were not incongruent. When taken together, they imply that there is a lack of revascularisation benefit, identified on anatomical grounds exclusively. In order to effectively identify patients who require revascularisation, some other test, which directly measures haemodynamic consequences of stenosis, is required. The test that has been developed and proven to be clinically useful is the fractional flow reserve (FFR). It has been found that if FFR > 0.75, PCI can be deferred without increased patient risk, despite an angiographic appearance of significant stenosis. Moreover, the cardiac event rates were lower in patients with FFR > 0.75 who did not have PCI than patients who did have PCI. [27, 33, 34]Finally, the evidence supports the fact that there is no benefit in revascularising, unless the haemodynamic consequences of stenosis are known.

The relevance to CTCA is that with modern 320 detector row CT scanners, one can also measure FFR (Figure 20) by applying fluid mechanical modelling to CCTA images, with no extra radiation exposure and no change to the normal CCTA procedure.[35]

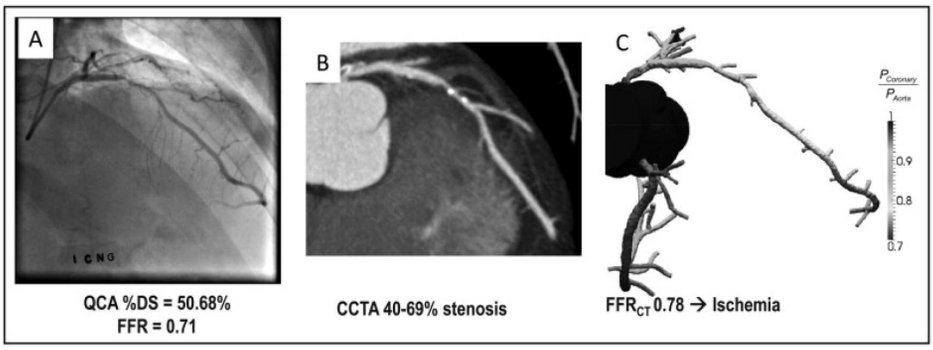

Figure 20. A) An invasive coronary angiogram of LAD artery. QCA – Quantified coronary angiography (maximal quantified stenosis) is 50.68% showing it is an intermediately stenosed lesion. Invasively measured fractional flow reserve (FFR) is 0.71, which indicates this lesion is causal of ischaemia B) Conventional CCTA concurs with the findings on ICA that the lesion is in the intermediately stenosed group and C) Combined function and anatomical image of LAD artery. The shading corresponds with the FFR at that point along the coronary artery. FFR measured by CCTA is 0.78, which by this study's definition (ischaemia if FFR<0.8) is an ischaemia causing lesion. This highlights the combined ability of anatomic and, new, functional CCTA to diagnose a lesion as flow limiting despite the fact it is only modestly stenosed (50.68% by QCA) [35]

How best could we use the anatomical information obtained by CCTA and apply it to the haemodynamic consequences of CAD on blood flow? The group of patients this has posed a particular problem for is the intermediate stenosis group (40–69%). Within this group CTCA has, as yet, been unable to unlock the haemodynamic consequences of CAD through an anatomical approach.

Recent evidence has shown early promising signs; using CTCA measured FFR can produce a diagnosis of ischaemia in lesions of intermediate stenosis severity with a PPV (compared with ICA measured FFR) of 82.4% and a NPV of 90.6%.[35] CTCA measured FFR, in combination with anatomical imaging, has been shown to increase the accuracy of the diagnosis of

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ischaemia in lesions of all types by 25%. Another potential benefit is that in instances of multi-segment stenoses, the culprit lesion(s) can be correctly identified. [35] The findings of these studies are based on a very small cohort (n = 60) and need to be shown to be reproducible on a larger scale. Furthermore, the potential to use CCTA measured FFR should not be seen as a challenge to ICA and its potential benefits, compared or in conjunction with stress-testing modalities, need to be fully evaluated before its precise role can be defined.

11. Conclusion

This chapter has aimed to show that the process and manifestations of CAD are nuanced; therefore, what is required is a far more detailed analysis than the current diagnosis of, or the 'ruling out' of, the ACS.

CTCA has been shown to be a cost effective, quick and accurate means of managing patients with acute chest pain, and it has been established that for CTCA to be used effectively, it must be targeted at the right patient group (10–29% pre-test probability). The prognostic information that can be garnered by CTCA is useful; however, the role of the prognostics in the direction of primary and secondary intervention requires further study in order for its precise use in risk stratification and direction of primary, secondary and tertiary interventions.

The findings demonstrate that the role of CTCA is not to supplant ICA as the gold standard in the investigation of CAD in a similar way that CT pulmonary angiography has its invasive counterpart. The current role of CTCA must be viewed as a means to avoiding unnecessary invasive angiography and the associated risks that come with it in the right patient population. There is no longer a role or a need for ETT in the assessment of patients with acute chest pain.[36]

Whilst the focus of this chapter is purely upon the merits of anatomical assessment of CAD, it must be noted that the role of cardiac CT in the management of chest pain in the ED is evolving.[37] Growing evidence is emerging about the possibility of a 'one-stop shop' approach where the anatomy, physiology and perfusion of the heart and coronary arteries, as well as assessment of pulmonary embolism and aortic aneurysm, are all used to diagnose the cause of chest pain in one study.[38] This has been reflected by a readiness of centres in the USA to use the modern 320 MDCT scanners in the emergency department assessment of chest pain.

The potential of using CTCA to determine FFR in the diagnosis of ischaemic heart disease is also an exciting development and has the potential to expand the role of CTCA further by elucidating the haemodynamic significance of the intermediate stenosis. Another avenue of much research lies in the attempt to increase the accuracy of CAD assessment of stable, symptomatic, intermediate-risk patients, by combining the anatomical approach of CTCA alongside myocardial perfusion imaging by CT.[27] What is clear is that CTCA, and CT more broadly, has and will continue to have an expanding role in safeguarding the function of the heart that William Harvey breathlessly outlined for the first time.

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