ADVANCED APPLICATIONS OF CARDIAC COMPUTED TOMOGRAPHY FOR THE DIFFICULT-TO-IMAGE PATIENT

by

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Abstract

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Throughout the development of computed tomographic (CT) imaging the challenges of capturing the heart, with its perpetual, vigorous motion, and in particular the tiny detail within the coronary arteries, has driven technological progress. Today, CT is a widely used and rapidly growing modality for the investigation of coronary artery disease, as well as other cardiac pathology. However, limitations remain and particular patient groups present a significant challenge to the CT operator.

This thesis adds new knowledge to the assessment of these difficult-to-image patients. It considers patients with artefact from coronary artery calcification or stents, examining the remarkable diagnostic performance of high definition scanning, as well as material subtraction techniques using dual energy CT, alongside ways in which current technology might be revisited and refined with the use of alternative image reconstruction methods. Patients with challenging heart rate or rhythm abnormalities are considered in three studies; how to achieve diagnostic image quality in atrial fibrillation, the safety of an aggressive approach to intravenous beta-blocker use prior to coronary imaging, and the development of patient information to address anxiety as a source of tachycardia and motion artefact. Finally, the novel application of a single

source, dual energy CT scanner to additional cardiac information is considered, with studies of myocardial perfusion CT and delayed iodine enhancement imaging, to identify ways in which non-coronary imaging might be exploited to more thoroughly evaluate a patient's coronary artery status.

These findings are presented in the context of developing technology and together offer a range of potential options for operators of cardiac CT when faced with a difficult-to-image patient.

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Abbreviations

ACCURACY	Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography study
AF	Atrial fibrillation
AHA	American Heart Association
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CMR	Cardiac magnetic resonance (scan or imaging)
CTCA	CT coronary angiography
CTDI	Computed tomography dose index
DECT	Dual energy computed tomography
DLP	Dose-length product
DSCT	Dual source computed tomography
EBCT	Electron beam computed tomography
ECG	Electrocardiography
ESC	European Society of Cardiology
FAME	Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention study
FBP	Filtered back projection
HDCT	High definition computed tomography
HU	Hounsfield units
ICA	Invasive coronary angiography
ICRP	International Committee on Radiological Protection

IR	Iterative reconstruction
kVp	Kilovolt peak
LNT	Linear no-threshold
mA	Milliampere
MBIR	Model-based iterative reconstruction
MDCT	Multi-detector row computed tomography
mGy	MilliGray
mSv	Millisievert
MRI	Magnetic resonance imaging
MTF	Modulation transfer function
NICE	National Institute of Health and Clinical Excellence
PCI	Percutaneous coronary intervention
PROTECTION I	Prospective Multicenter Study on Radiation Dose Estimates of Cardiac CT Angiography I study
rMPI	Radionuclide myocardial perfusion imaging

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Publications and Presentations

The following publications and presentations were undertaken during the period of study, relevant to the research in this thesis:

Publications

Clayton B, Roobottom C, Morgan-Hughes G. CT coronary angiography in atrial fibrillation: a comparison of radiation dose and diagnostic confidence with retrospective gating vs prospective gating with systolic acquisition. *Br J Radiol* 2015; 88: 20150533

Clayton B, Raju V, Roobottom C, Morgan-Hughes G. Safety of intravenous β-adrenoceptor blockers for computed tomographic coronary angiography. *Br J Clin Pharmacol* 2015;79(3):533-6

Clayton B, Morgan-Hughes G, Roobottom C. Transcatheter aortic valve insertion (TAVI): a review. *Br J Radiol* 2014;87:20130595

Clayton B, Roobottom C, Morgan-Hughes G. Assessment of the myocardium with cardiac computed tomography. *Eur Heart J Cardiovasc Imaging* 2014;15(6):603-9

Clayton B, Morgan-Hughes G. Pacing via a patent foramen ovale: computed tomographic identification of unusual lead positioning. *Europace* 2014;16(9):1395

Clayton B. Aetiology of cardiac arrest in a 'trauma patient': Exploiting trauma CT for concomitant cardiac assessment. *Injury Extra* 2014;45:15–7

Author – Chapter 7 and Contributing Author – Chapter 8, in:
The Royal College of Physicians, the British Society of Cardiovascular Imaging, The Royal College of Radiologists. *Standards of practice of computed tomography coronary angiography (CTCA) in adult patients*. London: The Royal College of Radiologists, 2014

Presentations

Clayton B, Read J. Referral advice for CT Coronary Angiography (CTCA): Simple educational interventions that improve diagnostic yield. Association for the Study of Medical Education. Annual Scientific Meeting 2013

Clayton B, Raju V, Roobottom C, Morgan-Hughes G. Intravenous beta-blockers are safe at high dosages for CT coronary angiography. British Cardiovascular Society Annual Conference. *Heart* 2013;99 Suppl 2:A1-141

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At no time during the registration for the degree of Doctor of Medicine has the author been registered for any other University award without prior agreement of the Graduate Committee.

Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment. This programme of study was financed with the aid of a grant from the cardiology department research funds at Derriford Hospital, Plymouth, and carried out in collaboration with Plymouth Hospitals NHS Trust.

The study of high-definition CT in chapter 2.2 was designed, and data was collected, by Dr Sri Iyengar around a concept proposed by Dr Gareth Morgan-Hughes while all subsequent work, including the sub-study, was entirely my own. The data analysis for the phantom study was supported by Andrew Bailey, who also created the box plots, but all other work on the study is my own.

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Section 1 – Background and rationale

1. Introduction

At his Nobel Lecture in 1979 Sir Godfrey Hounsfield, the British inventor of computed tomography (CT) remarked on experiments performed in which detectors had traversed the heart in cardiac diastole, synchronised by an electrocardiograph. He alluded to the "special conditions of scanning" which might make it possible, one day, to image the coronary arteries.[1] Cardiac, and particularly coronary, CT imaging has always been one of the most challenging applications of this modality, with the requirement to accurately visualise tiny abnormalities within structures just a few millimetres across in the only perpetually moving organ in the human body.

Although cardiac imaging developed with electron beam CT (EBCT) it was the introduction of multi-detector row CT in the late 1990s that began the rapid development of cardiac-capable CT scanners.[2] Over the last twenty years technology has developed at an astonishing pace, such that coronary arteries which were barely visible on early multi-slice CT systems can now be readily and accurately analysed, down to the composition of plaque within the arterial wall. Indeed, most modern developments in CT technology have been driven by the unique challenges presented by imaging the heart.

This chapter is not intended to be a textbook on the principles of cardiac CT. However there are some particularly important principles which have guided the development of modern CT technology – CT needs to balance image quality with radiation dose, optimising diagnostic performance whilst maintaining acceptable safety. The drive to reduce the dose of radiation to which a patient is exposed has driven many of the

advances in cardiac CT to date, and the importance of dose will remain for further advances in the foreseeable future. It therefore seems prudent to outline the major issues with both radiation safety and image quality relevant to cardiac CT.

1.1 Electrocardiographic gating

To achieve diagnostic image quality, cardiac motion must be minimised, capitalising on moments of relative cardiac standstill, usually in mid-diastole or, at higher heart rates, end systole. Cardiac CT therefore uses electrocardiographic (ECG) triggering, or 'gating' (Figure 1). Early multi-detector CT used retrospective gating, whereby imaging is performed continuously over multiple cardiac cycles (Figure 1A). The required phases of the cardiac cycle are subsequently extracted for analysis to ensure that only the periods of interest are examined but, for most studies, the remainder is not required. In other words, over 3 or 4 heartbeats lasting a number of seconds only a few milliseconds of data are used. Dose modulation, where radiation exposure is reduced during the phases of the cardiac cycle least likely to be useful but maximised during the diagnostic phases, (Figure 1B) can reduce the radiation dose from standard retrospective CT by half.[3]

Subsequent development led to the introduction of prospective gating. Here, the scanner uses a 'step and shoot' approach, acquiring a single volume through the heart in one cardiac cycle, using the next one or more cycles to move the patient through the scanner, before taking the next volume in another cycle. This is repeated until the entire volume is acquired, which is then 'reassembled' by the scanner (Figure 1C). While this requires good heart rate and rhythm control, to ensure that imaging occurs at the same point in the cardiac cycle for each volume, it exposes the patient to

significantly less radiation. The impact of gating techniques on radiation dose is discussed further below.

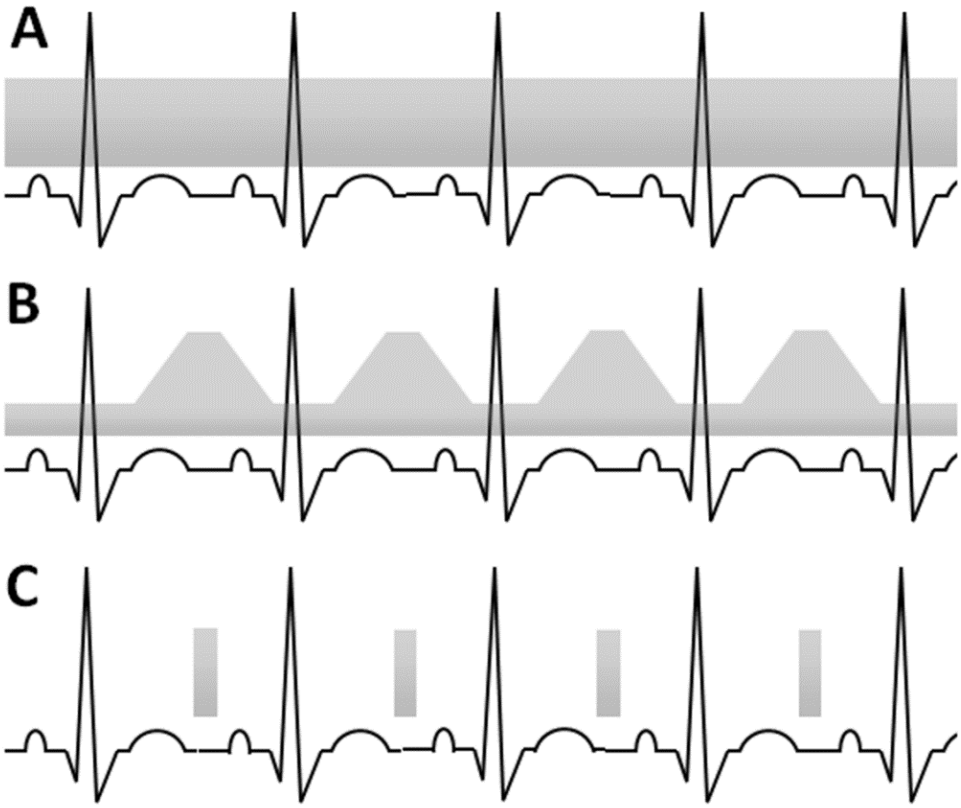

Figure 1
Electrocardiographic gating. The grey bars represent the delivery of radiation to the patient. A – retrospective gating without dose modulation, B – retrospective gating with modulation, C – prospective gating.

With the new generation CT scanners comes a further development in gating technology which somewhat hybridises the existing methods.[4] High-pitch retrospective gating is one such technology. Standard retrospective scanning uses a very low pitch – the ratio of the table speed to detector width – to ensure complete data capture, which results in significant oversampling.[5] With dual-source scanners, which have two x-ray sources within a single gantry, the whole heart can be examined in half the time. This means that, if cardiac diastole is long enough, an entire heart

volume can be acquired in a single cardiac cycle. This dramatically reduces the radiation exposure to the patient while maintaining resolution.[6]

1.2 Resolution

Achieving optimal image resolution is key to maintaining diagnostic image quality. For general CT this includes spatial resolution and contrast resolution.

Spatial resolution is the ability of the scanner to distinguish substances of different sizes. It is determined by factors such as the number of samples, the image reconstruction method, and reconstruction field of view. With helical scanning, the pitch is also important. The recommended detector size for cardiac CT is 0.625 mm or less.[4] It is easier to achieve resolution in the x-y axis (the axial plane) but z-axis resolution, in the craniocaudal or longitudinal direction is more challenging and is significantly influenced by the detector size and geometry.[7] The term isotropic resolution describes the situation where x-y and z-axis resolution are both equal and is important to allow three-dimensional visualisation in any plane without loss of spatial resolution. Spatial resolution is measured either in line pairs per centimetre, which reflects the number of pairs of equally sized lines that can be discriminated from each other within a one centimetre region of interest, or as MTF, or modulation transfer function. The latter concept describes the degradation in performance of a scanner as the spatial frequency (e.g.: number of line pairs per centimetre) increases. At the time of writing the current recommended minimum spatial resolution is 12.5 line pairs per centimetre at 10% MTF.[4]

Contrast resolution is the ability to discriminate between an object and its background or other objects. In cardiac CT these features are particularly important, to evaluate sub-millimetre structures such as coronary lumen and atheromatous plaque, and to distinguish between tissue densities or intravascular contrast. Contrast resolution improves with increasing tube current (and therefore radiation dose) but can also be influenced by reconstruction methods, patient habitus and detector sensitivity. All of these affect noise, which ultimately detracts from contrast resolution.[8]

The challenge specific to cardiac CT is the addition of temporal resolution – the ability to 'freeze' cardiac motion to ensure imaging free from artefact. While ECG gating is important to identify the periods of least cardiac motion, it is still challenging to achieve image acquisition during these phases. The length of diastole varies in a non-linear fashion according to heart rate[9] and shortens rapidly as heart rate rises. To achieve diagnostic image quality across multiple phases of the cardiac cycle the temporal resolution should be around 50 ms.[8] Fluoroscopy, used for invasive coronary angiography, has a temporal resolution in the order of 10 milliseconds or less.

Temporal resolution with CT is limited predominantly by gantry rotation time. By using partial scan reconstruction scanners only require data from a 180° rotation (plus the fan beam angle) – a half-scan – but resolution is still dependent on the time taken for this to occur. Various methods have been used to improve this further. When retrospective gating it utilised, with helical scanning throughout multiple cardiac cycles and low pitch (resulting in slice overlap) multi-segment reconstruction becomes

possible. Small amounts of data can be utilised from each cardiac cycle until sufficient data is available to create a half-scan.[10]

Another alternative to reduce the time taken to complete a half-scan is to increase the number of x-ray tubes. By using two x-ray sources only a quarter of a rotation is required, and thus one new generation CT scanner employs this approach (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany), such that with a rotation time of 330 ms it can achieve an effective temporal resolution as short as 83 ms.[11]

1.3 Radiation

A recurring issue considered in the previous section is the balance between improved resolution and radiation dose. The rapid growth in the use of CT, both for cardiac and general imaging examinations, has contributed to an increase in the use of ionising radiation. Technological developments, the need for surveillance of established disease, and wider appreciation of the merits of detailed, cross-sectional imaging from both clinicians and patients have driven this demand,[12]such that the United States saw a sixfold increase in medical radiation exposures over the 25 years to 2006.[13] Since a seminal report in 2001[14], further, large scale analyses have demonstrated the potential long term risk of radiation, particularly in children[15,16] and a multitude of similar studies are expected in the next few years[17].

When therapeutic radiotherapy is excluded, somewhere between 19 and 40% of, medical radiation exposure is due to cardiological diagnosis or therapeutics.[18,19] The risk from cardiac computed tomography (CT) has been of particular interest and

concern – radiation exposures from cardiac CT have traditionally been considered significant,[18] leading to criticism of the technique[20] and, in line with the overall growth of this modality[19], the volume of cardiac CT scans has also increased dramatically in recent years.[18]

In fact the dose of radiation a patient receives from an individual exposure has fallen substantially in recent years,[19] but this may not always be reflected in discussions about the risk from CT imaging.[12] A recent position paper from the European Society of Cardiology (ESC) suggested that prescribers and practitioners of imaging techniques may lack awareness or understanding about radiation, potentially threatening longer term public health.[19]

Broadly, there are two effects on biological tissues from ionising radiation. Deterministic effects are localised tissue reactions, which arise due to serious cell damage or death, and generally occur predictably beyond a given dose threshold.[21] Examples of these effects include cutaneous erythema, desquamation or ulceration, hair loss, or cataract formation, and their severity increases proportionally to the dose received. Although rare for most diagnostic imaging procedures, they may occur during fluoroscopically-guided interventional procedures, or poorly planned radiotherapy. One highly publicised example from the United States highlighted cerebral CT perfusion studies which left patients with a circumferential band of hair loss.[22]

While clearly alarming for patients it is perhaps the other sequelae, stochastic effects, which are the most concerning public health issue.[18] These increase the future likelihood of adverse events, rather than the severity of a particular occurrence. Arising due to radiation-induced mutation, they are binary in nature – they will either occur or they will not – and may increase the risk of malignancy in later life. There is a lag of five to 10 years before the development of most solid tumours and at least 2 years for leukaemias,[18] making direct causal attribution challenging. The stochastic effects of radiation are described as 'linear no-threshold' (LNT), implying that, in contrast to deterministic effects, the risk increases continuously, in a linear fashion, but without a clear dose threshold or safe lower limit.[23] Theoretically, genetic mutation may also affect the progeny of the index patient. The risk of any genetic disease has been estimated at 0.3-0.5% per Gray for each first-generation offspring[21], although these assessments are based on extensive experimental, rather than direct, *in-vivo*, evidence.[18] This is notably different from *in-utero* exposure, where epidemiological data supports the proposition of an increased rate of childhood cancer.[24]

Ironically, radiation also increases the risk of developing cardiovascular disease. Higher rates of stroke are seen following radical radiotherapy for head and neck cancers,[25] while breast cancer therapy appears to confer a significant, long-term risk of cardiovascular mortality.[26] Radiation appears to promote atherosclerosis, with lipid accumulation and plaque rupture both possible,[27] possibly due to tissue injury and repair.

Measurement of radiation dose

The quantification of radiation dose is not altogether straightforward. A plethora of terms exist to describe the way radiation is generated and disseminated, its absorption, and its effect on biological tissue. The term 'radiation exposure' may have colloquial interpretations but, strictly, means the amount of ionisation created in air, measured as the total charge of positive or negative ions produced by radiation in 1kg of dry air.[21]

To estimate the potential risk of an imaging investigation to patients, the absorbed dose – the amount of energy delivered to tissues – must be established. Absorbed dose from CT is measured using the CT dose index (CTDI). This describes the dose delivered in a single axial slice, dividing the total absorbed dose by the width of the x-ray beam. This is less meaningful in a clinical scan, which often involves a series of slices of a given thickness, often with overlaps or gaps and therefore for practical application the volume CTDI ($CTDI_{vol}$) is preferred. This provides an estimate of the dose in a given volume by a particular scan protocol and, importantly, facilitates comparison of the performance of a centre or individual with recognised standards[28] or other institutions.

Neither parameter considers the length of the scan in the longitudinal plain (or *z* axis); clearly important when considering the total patient dose. The dose-length product (DLP) is the $CTDI_{vol}$ multiplied by the scan length in centimetres. It more closely resembles the dose received by an individual patient, although it is important to

appreciate that it is still computationally derived from standardised phantom sizes and measurements, mathematical assumptions and calculations[21].

Estimating the potential risk of harm requires further consideration. Tissues vary considerably in their propensity for malignant transformation and some tissues are more sensitive to radiation than others. The same radiation dose applied to a brain has far less potential to induce carcinogenesis than that absorbed by breast tissue. To accommodate this, conversion factors are utilised to 'normalise' localised irradiation relative to whole body exposure[29] and facilitate comparison between examinations. This measurement, the effective dose (E), can be calculated through Monte Carlo simulations, or estimated as the product of a surrogate conversion factor (*k*) and the DLP[30], and is measured in milliSieverts (1 Sv = 1 J/kg).

There are advantages to using effective dose to describe potential risk: it is relatively simple,[28] accounts for tissue sensitivity, and allows comparison to a variety of non-medical radiation exposures, and between imaging modalities.[31] This last benefit may be particularly useful when explaining risk to laypersons. Unfortunately effective dose also has significant limitations, ignoring important patient-specific factors such as obesity,[28] age and gender and still relying on numerous statistical assumptions. The same is true of the tissue weightings themselves, which are broad approximations, averaged for age and gender.[18] Thus the actual dose received by a patient may be three times higher or lower than the estimated E value.[32] Experts recommend that E should therefore be retained for broad estimates of dose for populations, based on the

order of magnitude, rather than assuming it to be a precise measure of an individual's risk.

There are specific issues with effective dose and cardiac CT. New generation scanners increasingly employed for cardiac CT utilise novel image acquisition techniques, which have not been calculated into the standard dose models. Changes in scatter, coverage and other factors may need to be re-evaluated, and meanwhile the use of effective dose calculations and conversion factors is questionable.[33] In addition, there is concern about the most widely used conversion factor for cardiac CT. The International Commission on Radiological Protection (ICRP) currently recommend the 'chest' conversion factor of 0.014 to calculate the effective dose from the DLP. However in addition to the heart, the organs receiving the highest doses with cardiac CT are the breasts, part of the lungs, liver, and oesophagus[21] and breast tissue in particular is highly sensitive to radiation. Furthermore, considering the thoracic volume as the whole chest does not accurately depict the coverage of cardiac CT, which covers the mid-chest to the upper abdomen.[34] For these reasons, the chest factor significantly underestimates the dose from cardiac CT[33,35] and analyses suggest doubling this (to 0.028) to achieve a more representative assessment.[36]

Estimation of risk

Estimation of the risk of radiation stems largely from the Life Span Study (LSS), a cohort of around 100 000 survivors of the Hiroshima and Nagasaki atomic bombs[37]. This study estimated the likely radiation exposure to individuals and has subsequently observed them for more than 50 years. The incidence of cancer and other pathology

has been extensively studied, providing statistical expectations of an individual's risk following a given exposure and assessing tissue sensitivity from which ICRP weightings are derived.[29]

The appropriateness of these extrapolations is not without controversy. Unlike patients, who usually experience repeated, low-dose radiation exposures, targeted to limited anatomy, over days or even years, participants in the LSS received an initial, high, whole-body dose, over a few seconds, with subsequent exposure over days to months. The radiation is heterogeneous, and confounders such as toxins and carcinogens from blast debris exist.[38] That said, large epidemiological studies,[14] including recent work[16,39] demonstrate remarkable parity with LSS predictions.

Further debate arises from the extrapolation of LSS data to 'linear no-threshold' (LNT) principle described above. LNT was conceived as a tool for occupational radiation protection, rather than to predict biological harm in patients and some authors claim that there is insufficient data to support its use in this fashion.[40] A number of studies, in a range of environments, have considered whether lower dose radiation carries a risk of carcinogenesis at all, or may even be hormetic. These include patients with occupational, radiographic or therapeutic exposure, as well as patients from the Japanese atomic bomb and Chernobyl disasters[38]. It is proposed that where radiation causes the production of oxidative free radicals, known to induce malignancy, at a rate similar to biological processes then they present very little risk, and that only when very high doses of radiation are encountered are immune defence mechanisms overwhelmed.

Controversy arises from projections of mathematical data, difficulty attributing causality and the need for long-term, confounder-free follow up, not entirely achievable from the Life Span Study or other registries. Furthermore, as the risks of radiation reduce in a population with an already high level of cancer, greater numbers of participants are required for follow-up, in order to identify additional events with statistical confidence[41]. While the issue remains contentious, with some major organisations declaring safety at even quite moderate doses[42], most international advisory boards persist with the LNT principle, acknowledging its limitations[18,43], until such a time that further evidence is forthcoming[23]. Meanwhile it may at least draw attention to the need for careful radiation protection measures[44].

The disagreements about LNT are fundamental to the debate about the risks of medical radiation. The vast majority of medical exposures are considered to be low, or ultra-low dose (less than 50mSv in a single examination), particularly in comparison to the very large doses experienced by the atomic bomb survivors. There is little evidence specifically considering small exposures, not least because of the aforementioned study design challenges, and so risk has to be based on extrapolation and inference.[18] Most studies which do analyse medical exposures consider much higher radiation doses than current practice would confer,[18] and due to the latency period between exposure and sequelae even very recent analyses can overestimate the risk of modern practice. That said, recent, large studies appear to suggest a link between medical radiation and future cancer risk. So far these have mainly been in children,[15,16] unreflective of the majority of patients undergoing cardiological

investigation or treatment. One analysis has considered the radiation exposure from cardiac examinations in adults admitted to hospital with myocardial infarction,[45] approximating exposure based on the type and number of cardiac procedures for each patient. Using subsequent health insurance claims, the authors suggested an increased risk of 3% for every 10 mSv exposure, but the study was hampered by a number of methodological limitations,[18] including failing to adjust for important confounders, reliance on insurance claims databases as a sole source of subsequent diagnoses and a lack of detail regarding both patient baseline and outcomes. They also ignored the risk of *not* undertaking investigation or treatment.

Justification of risk

One major concern of proponents of imaging irrespective of dose is the potential failure to diagnose important pathology.[46] For many conditions the risk of death from missed diagnosis is greater than the potential harm from imaging[47] and with cardiovascular disease the leading cause of death worldwide[48] this is particularly relevant to cardiac imaging.

The roles of imaging are to confirm, refine or refute the clinical diagnosis, add to risk stratification, guide or facilitate therapy, and evaluate disease progression or treatment. Investigations should be targeted to the individual patient[49] according to the diagnostic or therapeutic goal. Selecting an investigation using ionising radiation should only occur if there is no other suitable test to adequately answer the clinical question and after "thoughtful consideration of the patient".[50] Clinicians might also consider local expertise, previous investigations and the likely investigative yield[49].

The risk of *not* undertaking a test may be sufficiently low to justify an alternative strategy, but might equally make it clear that the radiation risk is justified.[51] One clear example would be the exposure to radiation from fluoroscopy of a patient suffering an ST-elevation myocardial infarction – in this case, the need to undertake diagnosis and treatment of the occluded coronary artery is justifiable on the basis that failure to revascularise the myocardium is likely to lead to death or permanent disability and other therapies are less effective. Appropriate use guidance is available from specialist bodies,[52] but ultimately the risk assessment needs to be dynamic,[19] adjusted to the individual situation. It has been estimated that between one-fifth and half of all CT requests could be changed for a test without radiation or simply cancelled.[53]

One further consideration is non-transferability of risk. This means that one patient's risk from an exposure cannot transfer the potential risk of future malignancy to another. This is relevant in the reporting of population statistics, such as at the start of this chapter, commenting on the increased use of medical imaging. Such increases should only be averaged over the number of patients being imaged, and not an entire population. These groups may differ – imaged patients may be sicker and older than the general population – thereby altering the balance of risk, [51] although this, too, is contentious.[45]

As with all medical procedures, discussion with the patient is key to the appropriate selection of investigations. Patients can guide the choice[49], and may have their own opinion as to what constitutes acceptable risk to them. Furthermore, through the

process of providing clear information to patients, clinicians may further explore their own rationale for choosing a particular test. There are risks associated with most tests, all of which need to be considered, along with the patient, for the 'least worst', and most suitable, test to be selected.

Optimising technique to reduce dose

Justifying patient exposure to ionising radiation is only half of the consideration, simply deciding if it is an appropriate means of achieving the clinical goal, in the context of the individual patient and with knowledge of the risks, benefits and alternatives. The next step is to ensure that the procedure is optimised, using the smallest amount of radiation that provides diagnostic image quality.[40] The historically high radiation exposure from cardiac CT[18] has led to great radiation awareness in the cardiac imaging community[40] and demand for radiation reduction strategies has led to a number of technological developments.

Acquisition techniques

Major progress was made in terms of radiation reduction with the developments in ECG gating which were discussed earlier. The introduction of dose modulation reduced the then-high doses of radiation by half.[3] Most current scanners employ prospective gating, where the scanner predicts the relevant cardiac phase based on the ECG and acquires data only at those points (Figure 1C). This method requires good heart rate control, to ensure that the optimal phases of the cycle are sufficiently long and consistent, and it is therefore unsurprising that the administration of beta-blockers to patients prior to CT can facilitate dose-reducing techniques.[54]

Further dose reduction can be achieved by modifying the tube energy (kV). Modern cardiac CT techniques use 100 kV for most patients, sparing the traditional 120 kV for patients with a larger body habitus. Some centres use 80 kV for sleight patients. Radiation dose is proportional to the tube voltage, squared,[21] and introduction of a reduced tube energy protocol reduces radiation dose by half again.[34,55]

Combined, these changes can facilitate an 80% dose reduction compared to un-modulated, retrospective techniques (Figure 2).[3] Retrospective studies do retain a role, particularly where cardiac motion is vigorous or unpredictable, such as in patients with tachycardia or arrhythmia.[52] Even here, however, improvements are being made and the latest generation of cardiac-capable scanners can obtain images very rapidly, achieving doses as low as 14% of standard scans, even in patients with higher heart rates.[56] New generation technologies also confer improved dose efficiency, with larger detectors requiring fewer rotations for each acquisition, and thus less wasted penumbra.

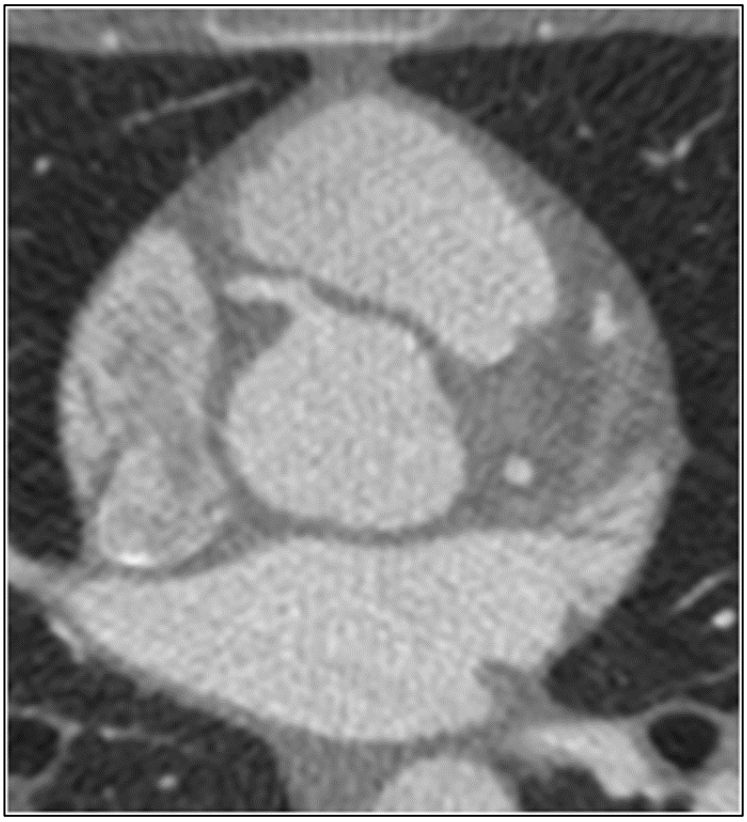

Figure 2
CT coronary angiography in a young adult to exclude vasculitic complications. The patient's body mass index was 22 kg/m^2. The entire scan was undertaken using 80 kV, 250 mA on a prospective protocol with 'zero padding', with a dose length product of 26 mGy·cm.

Reconstruction

The major limitation of reducing tube energies to save dose is the subsequent increase in noise[57] – lower energy photons are less likely to penetrate tissue, instead being scattered. Noise is also an issue inherent to the process of image reconstruction using the original method of filtered back projection. With this technique, the passage of x-rays through a structure creates attenuation profiles called ray sums, a process known as forward projection. These profiles are then projected back across the image space. This cycle is repeated at a number of different angles to create the composite, back projected, image. In the course of this image construction significant artefact is introduced and this needs to be removed using a filter, or kernel. The filters are

mathematically modelled on the CT process and, for computational simplicity, include many simplified assumptions about the scanning process, for example the size and shape of the x-ray beam and focal spot, which are assumed to be infinitely small points. This makes data processing easier at the expense of accuracy, and introduces noise. Recently, novel reconstruction techniques have been developed with more sophisticated mathematical modelling, performed repeatedly on the filtered data via a series of iterations. These iterative reconstruction (IR) processes result in fewer assumptions and less noise and while this does not reduce dose directly, it facilitates the use of lower tube energies while maintaining an acceptable level of image noise, because the noise from the reconstruction process has been reduced.[34] IR also improves tissue analysis characteristics, particularly the reduction of artefact, so image quality may even improve despite the reduced dose.[57] The introduction of IR into cardiac CT imaging has facilitated a halving of the radiation dose.[34]

The next logical development is to attempt to accurately model the entire CT acquisition process. Model-based reconstruction is computationally demanding, making no assumptions about the scanner or physical characteristics of the scan, but instead modelling each detail of the optics of the CT system accurately, with the promise of dramatically improved image quality for even less dose. Early work applying these techniques to thoracic imaging have suggested that some CT procedures may be achievable for a radiation dose comparable to a plain chest radiograph[58] and may improve the visualisation of coronary plaque.[59]

Service evaluation

With even controversial evidence of potential harm but various options to mitigate this, scrutiny of cardiac imaging providers is an essential component of both safety and quality improvement programmes.[53] As postulated, dose reduction cannot be at the expense of diagnosis, as this would render the investigation futile, but ensuring doses are kept as low as reasonably possible is vital. Radiation doses for particular examinations vary considerably between centres[60] and the landmark PROTECTION 1 study confirmed that cardiac CT was no different.[61] The investigators identified a 6-fold difference in dose between sites, according to the available technology and image acquisition protocols. Centres embarking on active quality improvement programmes can derive significant reductions in dose.[62] Together, these findings suggest that significant improvements in both technique and dose optimisation could be made, and the move by national authorities to survey and report on the undertakings of their members[63] will begin to facilitate this. A programme of education, for providers and patients, multi-professional collaboration, audit and further research into the effects of radiation and techniques to optimise safety are required.[40]

1.4 Dual energy CT

The arrival of dual-energy computed tomography has provided a plethora of novel CT applications, not least for cardiac imaging. The ability to simultaneously interrogate the same structures with two x-ray energies simultaneously not only improves the assessment of solid state materials such as coronary plaque or myocardial scar but, by exploiting the properties of contrast, also makes feasible the assessment of perfusion and blood flow characteristics.

Conventional multidetector CT generates a continuous stream of polychromatic Bremsstrahlung from the rotating anode.[64] The programmed tube voltage selected by the operator refers to the maximum energy of the photons produced, below which there is a spectrum of lower energies. The use of filters can enable further refinement of the x-ray beam, but this remains polychromatic, with the average x-ray energy of the beam approximately one-third of the maximal tube voltage (kVp).

The passage of x-rays through tissue depends on both the energy of the photons and the interaction thereof. The photoelectric effect, which increases with the atomic number of a material, is of little consequence traversing most intrathoracic structures, but in dense calcification or intravascular contrast, significantly increases photon absorption. This effect is exploited by the use of substances exhibiting the maximal photoelectric influence (up to that of caesium, due to its electron shell configuration) with the use of contrast materials containing iodine or barium. While the photoelectric effect with calcium is less than these heavier metals, due to an emptier electron K shell, it remains greater than that of organic material, nitrogen or oxygen.

Of course the varying attenuation properties of different materials are what provide the delineation between tissue structures required to make CT imaging feasible. However, the lower energy photons required to maximise the contrast between materials are absorbed by heavier substances such as calcium and iodine, such that the x-ray beam is ‘hardened’. This reduces the tissue contrast beyond the structure and may also change the apparent overall material property; creating artefacts overlying the soft tissue which hinder accurate analysis.

Dual energy CT (DECT), or spectral imaging, uses two distinct photon spectra in an attempt to better interrogate tissues, gaining the benefits of contrast at lower energy and of overcoming artefact with higher energy. The use of 80 and 140 kilovoltage peaks (kVp) provides maximal difference and least overlap between spectra, within clinically useful and technically achievable parameters. Below 80 kVp most spectra will be excessively absorbed and technological limitations currently prohibit routine use of greater energies than 140 kVp.

Image acquisition techniques

Current systems generate images using the entire profile of detector fluorescence created by photon arrival. There is no clinically available technology to identify the energy of these photons as they arrive at the detector, although this may be available in future,[64][65] for example by using multi-layer detectors. This means that at present scanners must either use two distinct x-ray sources with paired detectors, or vary the timing of generation and detection of particular spectra in order to distinguish between them.

This is of particular relevance to cardiac CT, where temporal resolution is of prime importance. The near-constant motion of the cardiac structures requires almost simultaneous acquisition of data at the respective energies to ensure a consistent region is accurately imaged. This prohibits the application of sequential imaging to cardiac CT, whereby a scan is undertaken twice, at different tube energies.

Both alternative methods are currently employed in DECT scanners. Dual source imaging uses the two-source/two-detector approach. With rapid gantry rotation, two energy spectra can be used simultaneously, although the precise accuracy of this is theoretically questionable, as the orientation of image acquisition or timing thereof, must be distinct.[66] Furthermore, the need to fit two sources and detectors into the gantry requires miniaturisation of the second system, which significantly limits the potential field of view. One further limitation of this approach to dual-energy imaging is the risk of scatter, with the potential for photons from one detector to be received by that of the other. Modern scanner iterations employ computing technologies to recognise and compensate for this phenomenon.

It is possible to image the body using a single source and still achieve dual energy analysis. X-ray tubes are capable of rapid oscillation between energy spectra,[67] the timing of which can be analysed so that detected photons can be appropriately attributed. Traditionally, this meant that the gantry rotation speed had to be slowed to permit sufficient time for data acquisition. Newer detector materials permit acquisition with kVp alternating at 5 kHz,[67] reducing the temporal resolution so important to cardiac imaging. This method may incur a greater dose penalty, due to its inability to utilise dose reduction features such as tube current modulation or optimal filtration.[64]

Monochromatic imaging & material decomposition

Two major outputs from dual energy CT have been utilised for a wide range of clinical applications. Images can be produced as if they were generated from a pure,

monochromatic beam of photons of a single energy (keV), rather than from the reality of a polychromatic beam with a designated peak energy (kVp). Virtual monochromatic images can be synthesised at a range of keV values, which can reduce beam hardening artefact and improve the measurement of attenuation.[66] Clinically, high keV images can be used for reducing artefact from metal implants, calcification or pools of contrast, while lower keV datasets improve soft tissue contrast to allow visualisation of soft tissue[68] or atheroma.

Basis material decomposition has been explored for almost 40 years.[69] This technique exploits the different attenuation coefficients of substances at differing photon energies and, by referencing the attenuation effects of known substances, for example iodine and water, is able to model other materials. This permits the identification of particular materials such as bone, or vascular calcium, which can then be subtracted from the image[70], or may facilitate the identification of the composition of stones[71], or even the characteristics of tumours.[72] By subtracting iodine it is possible to generate both an enhanced and a 'virtual' non-enhanced dataset from a single contrast acquisition.[66]

In systems using rapid energy switching, basis material decomposition is performed in the projection domain, but with dual source systems, where the two datasets are not as closely temporally aligned, this occurs in the image domain.[66] While reconstruction of the raw data generally confers better image quality, it relies on precisely aligned datasets, which are not always achievable with dual source

technology.[73] To date there has been little research comparing what, if any, impact these differences have on the clinical application of these technologies.

1.5 Calcium

The presence of coronary calcium is a well established marker of the potential for intraluminal coronary atheroma, but it is also a major limiting factor for cardiac CT. Increasing awareness of coronary calcium among radiologists has led to its presence being reported in non-cardiac investigations (Figure 3), particularly in smokers or those with dyspnoea undergoing thoracic CT. It presence and distribution are now crucial to image quality with modern cardiac CT, particularly for coronary imaging. Its relevance to clinical practice and its influence on technological developments are fundamental to this thesis and so a brief overview of coronary calcification will be outlined here.

Various studies have examined the relationship between the calcium score and both radiological[74] and histological[75] measures of atherosclerotic plaque burden, including at invasive coronary angiography.[76,77] The location of plaque does not necessarily correspond directly to clinically relevant stenosis, due to compensatory remodelling of affected arteries[78] (Figure 4). In addition, most acute coronary events occur due to soft plaque rupture rather than stenosis, which is less likely in calcified artery, but there is evidence that calcified plaques colocalise with the more rupture-prone atheroma.[79] This is particularly important for the negative predictive value of calcium scoring. Because calcification occurs late in the healing phase of atherosclerosis, non-calcified plaque and stenosis may be present in patients without coronary calcium. In particular, younger or diabetic populations,[80] where this

process may not have yet occurred or occur slowly due to poor healing, may have rates of significant atheroma as high as 20%.[81]

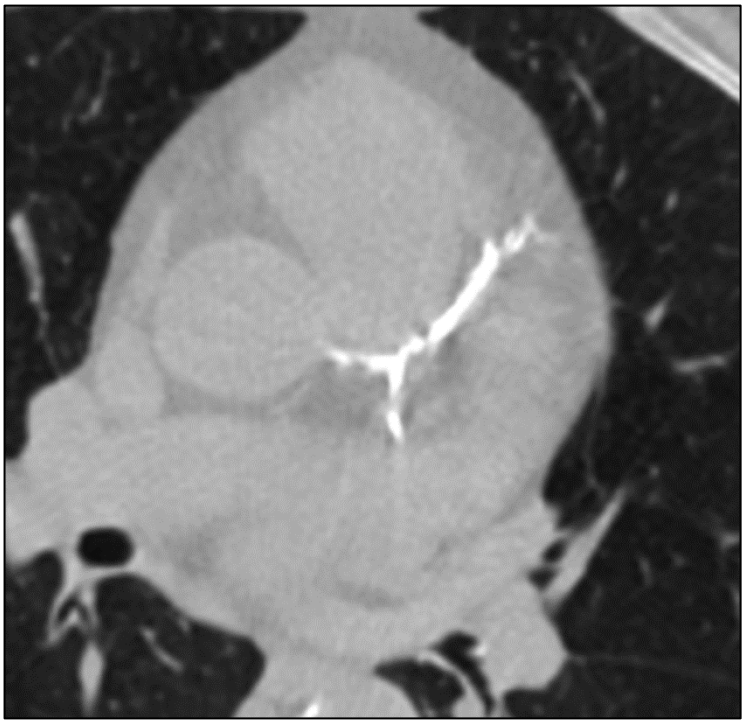

Figure 3
Incidental coronary calcification. Image from an ungated CT pulmonary angiogram demonstrating the incidental presence of extensive calcification of the left main stem, left anterior descending and proximal circumflex arteries

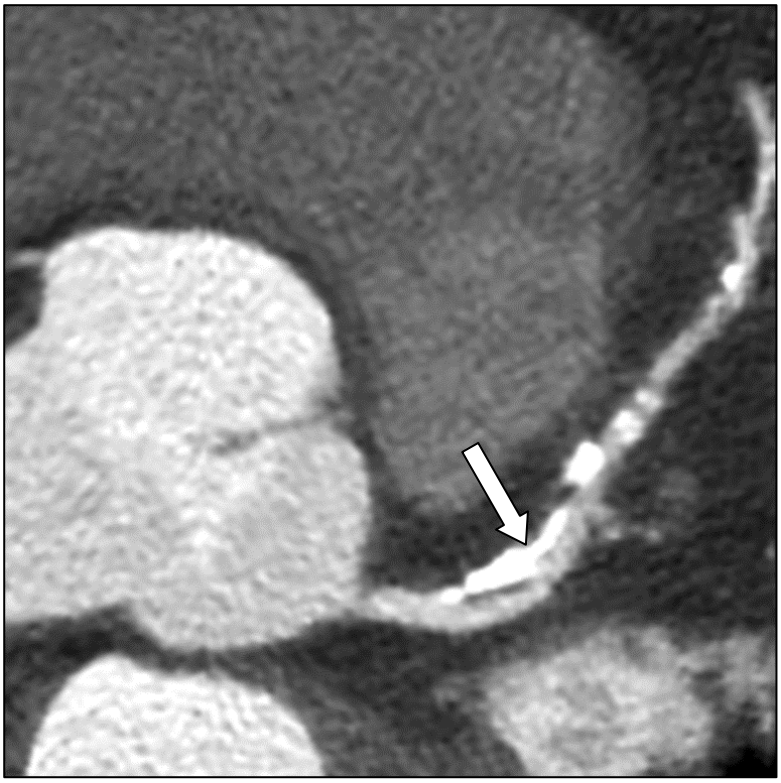

Figure 4
Expansile remodelling of calcified coronary atheroma (arrow). Despite a large plaque there is little impingement on the coronary artery lumen.

The presence of coronary calcium is therefore reflective of overall vascular health rather than demonstrating specific culprit lesions. Measurement of the burden of arterial calcium is utilised widely in the assessment of patients presenting with chest pain of potential cardiac origin, and features in international guidelines for this purpose.[82,83] There is also evidence supporting its use for prognostication in asymptomatic patients. The presence of any coronary calcium is associated with a significantly higher rate of death, myocardial infarction or need for coronary revascularisation than having none,[84,85] and the degree of risk correlates with the overall arterial burden.[86][87]

The most widely used method of quantifying coronary calcium is the Agatston score, using a standardised, ECG-gated, non-contrast acquisition, which has been in use for

over 20 years.[88] Although based on evidence from electron-beam CT (EBCT) its validity has broadly been accepted in modern multi-slice scanners[82,89] despite only limited evidence[90] and a lack of robust clinical trials. Most CT technology employs semi-automated software to calculate the Agatston score with minimal effort to provide a numerical value.

Artefact from calcification

As previously mentioned, the landmark study examining the utility of 64-multidetector row CT was ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography).[91] A subgroup analysis of patients with severe coronary artery calcification (Agatston score more than 400 units) demonstrated significant drop off of the accuracy of CT, a phenomenon which has been replicated repeatedly. One large systematic review and meta analysis found that for patients with an Agatston score between 400 and 1000 the per-patient sensitivity of CT to detect significant atheroma was 0.99 but the specificity was 0.84. With Agatston scores above 1000 sensitivity was maintained at 0.98 but the specificity fell to 0.51.

The reason that CT performance falls in the presence of calcium is the metal's density and the artefacts that it creates. Recalling the explanation of dual energy CT above, lower energy x-rays are important to help differentiate between different materials but are readily absorbed by dense structures, including calcium. This has the effect of 'hardening', or increasing the energy of, the x-ray beam. This reduces the available

contrast in the tissues surrounding the calcium and creates image artefacts that can be misinterpreted or can obscure the area of interest.

The other major limitation is partial volume artefact, where tissues of markedly differing density are projected onto the same voxel. The scanner is unable to differentiate between the structures and the image created depicts the highest density material. This can lead to overestimation of the volume of calcium present, known as 'blooming' artefact (Figure 5). Partial volume artefacts have been reduced in general CT with improved spatial resolution, but cardiac imaging requires such resolution at the very limits of scanner technology and the small structures and measurements involved means that blooming artefact remains a problem, particularly with conventional scanner technology.

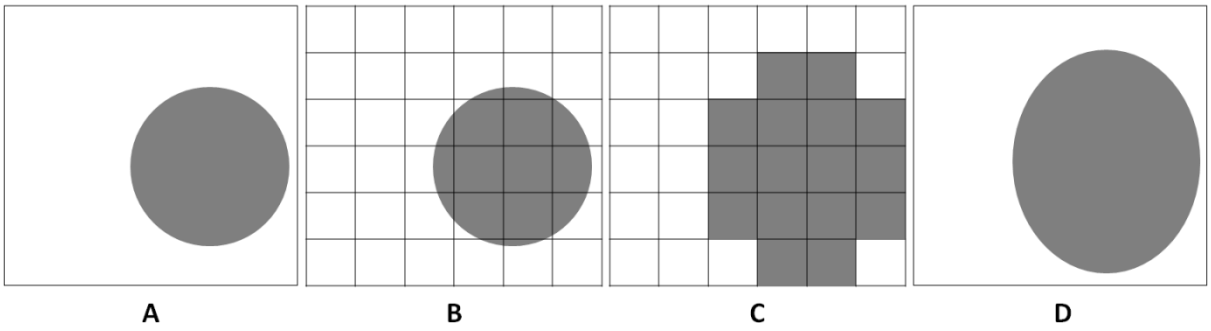

Figure 5
Schematic representation of the principles of partial volume, or blooming, artefact. A highly dense object is scanned (A) and the CT scanner creates an image in a series of voxels (B). If each voxel represents the smallest volume that the scanner can distinguish then voxels which only partially contain high density material may be misinterpreted as entirely containing high density material (C). Even if filtering is applied, the result is a much larger image than the object itself (D).

1.5 Current uses of cardiac CT

The use of cardiac CT is increasingly widespread and the breadth of indications is also expanding. At the time of writing there are two sets of international appropriate use criteria in existence; from the United States[92] and Korea[93] (Tables 1 and 2). Written in 2006 and 2015, respectively, they reflect the rapid progress in CT technology over that 9 year period.

The predominant application of cardiac CT is for non-invasive coronary angiography. There is currently no other modality which can achieve sufficient image resolution in a non-invasive manner and the risks of coronary angiography are increasingly apparent and do not appear reducible.[94] The risk in patients with coronary artery bypass grafts are higher still.[95] CT is also significantly cheaper than invasive angiography.[96]

There is not universal agreement on the patients who should undergo a CT angiogram. Both international appropriate use guidelines recommend its use in patients of intermediate risk[92,93] – that is to say, those patients in whom the clinical history and risk factor profile place them in an intermediate pre-test stratum for the risk of obstructive coronary artery disease.[97] In the United Kingdom, NICE Clinical Guideline 95 recommends CT for use only in patients deemed at low clinical risk.[82] This is mainly due to the limited positive predictive value of CT in patients in the higher risk groups, due in turn to the high prevalence of severe coronary calcification in this cohort. This is particularly relevant as NICE Diagnostics Guideline 3, recommending the use of new generation CT scanners for the difficult to image patient, did not revisit

these criteria and therefore the recommended use of new technology for challenging patients is limited to coronary artery assessment in this low risk group.[98]

American 2006 Guideline[92]
Coronary artery assessment ✓ Chest pain, with intermediate pre-test probability ✓ Chest pain, with equivocal stress test ✓ Assessment of coronary anomalies ? Chest pain syndromes in patients who have previously undergone coronary artery bypass grafting or percutaneous coronary intervention ? Chest pain with low pre-test probability, or intermediate probability and unsuitable for exercise tolerance test ? High-risk, asymptomatic patients ✗ Asymptomatic patients of low or intermediate risk
Cardiac anatomy ✓ Pulmonary vein anatomy prior to ablation for atrial fibrillation ✓ Cardiac venous anatomy prior to biventricular pacing ✓ Repeat cardiothoracic surgery – to assess access and risk of iatrogenic injury ✓ Complex or vascular congenital heart disease ✓ Evaluation of cardiac masses (as a second line investigation) ✓ Anatomical assessment of the pericardium (as a second line investigation)
Cardiac (myocardial and valvular) function ? Left ventricular in the context of heart failure or coronary artery disease (as a second line investigation) ? Native and prosthetic valvular function (as a second line investigation)

Table 1

Abbreviated summary of the ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 Appropriateness Criteria for Cardiac Computed Tomography. ✓- Appropriate indication; ? – Uncertain appropriateness; ✗- Inappropriate indication.

Korean 2015 Guideline[93]
Coronary artery assessment ✓ Chest pain, with low to intermediate pre-test probability ✓ Chest pain syndromes in patients who have previously undergone coronary artery bypass grafting ✓ Chest pain syndromes in patients who have previous undergone percutaneous coronary intervention to the left main stem, or other major artery more than 3 mm diameter ✓ Chest pain syndromes with normal coronary arteries at invasive angiography ✓ Chest pain requiring triple rule out* ✓ Chest pain following equivocal or discordant stress testing ✓ Assessment of heart failure (if low risk of coronary artery disease) ✓ Screening prior to non-coronary cardiac surgery ✓ Prior to complex percutaneous coronary intervention, including chronic total occlusions ✓ History of Kawasaki's disease ? Screening of asymptomatic individuals if intermediate risk ? Investigation of ventricular tachycardia ? Investigation of syncope ✗ Chest pain, with high pre-test probability ✗ Inappropriate for the assessment of the aetiology of new atrial fibrillation
Cardiac anatomy ✓ Pulmonary vein anatomy prior to ablation for atrial fibrillation ✓ Cardiac venous anatomy prior to biventricular pacing ✓ Other percutaneous cardiac procedures (such as device closure), to confirm anatomy ✓ Repeat cardiothoracic surgery – to assess access and risk of iatrogenic injury ✓ Complex or vascular congenital heart disease ✓ Evaluation of cardiac masses ✓ Anatomical assessment of the pericardium
Cardiac (myocardial and valvular) function ✓ Left ventricular function where other imaging modalities are unsuitable ✓ Right ventricular function ✓ Valvular function (as a second line investigation) ✓ Prosthetic valve dysfunction ? Left ventricular function as a first line test in the context of heart failure or coronary artery disease ? Myocardial viability where other modalities are not suitable

*Triple rule out: the exclusion of obstructive coronary artery disease, acute aortic syndrome and pulmonary emboli in a single examination

Table 2

Abbreviated summary of the Korean Guidelines for the Appropriate Use of Cardiac CT.
✓- Appropriate indication; ? – Uncertain appropriateness; ✗ - Inappropriate indication.

While assessment of coronary artery disease remains the major application for cardiac CT,[99] its use is of course not restricted to arterial pathology. Playing to its strengths, CT is therefore commonly used to rule out ischaemic heart disease as a cause of cardiomyopathy, either with calcium scoring[100] or, considering the limited sensitivity of calcium scoring due to the wide slice thickness used, lower prevalence of calcific disease in young and diabetic patients[80] particularly, and its inability to confirm stenotic coronary disease, CT coronary angiography. Both 16-slice[101] and 64-slice CT[102,103] can discriminate between ischaemic and non-ischaemic causes in patients with a dilated cardiomyopathy phenotype, with one meta-analysis suggesting a pooled summary estimate of 98% sensitivity and 97% specificity for the diagnosis of ischaemic cardiomyopathy using CTCA.[104] The gross morphology is non-specific, with ventricular dilatation and dysfunction, myocardial thinning and, although less commonly, intramyocardial fat, and so can make this distinction otherwise challenging.[105]

The widespread use of both contrast angiography and unenhanced imaging for coronary assessment means that there is extensive work examining the consequences of ischaemia and infarction with CT. Rudimentary blood flow imaging, simply observing myocardial density following contrast delivery, can be achieved with standard CT[106] and areas of hypoattenuation can often be seen in patients with significant CAD. This is not entirely straightforward as apparent hypoperfusion may be the result of beam-hardening artefact, which is best refuted using multiphase examination, but doing this increases the radiation exposure. Further evaluation of ischaemic sequelae can be achieved by undertaking deferred scanning, at an interval following contrast

administration. Delayed enhancement can be identified in a similar manner to late gadolinium enhancement with cardiac MRI. In combination with CTCA, the presence of scar adds additional accuracy to the diagnosis of ischaemic cardiomyopathy.[103] At present, assessment of myocardial viability with CT is predominantly a research tool and there is uncertainty about recommending its use in clinical settings.

In 2010 an expert panel of the American College of Cardiology also outlined potentially emerging uses for CT.[7] These included improved assessment of coronary atheroma, both in terms of the overall vascular burden of atherosclerotic plaque and the identification of 'vulnerable' plaque, which may be at greater risk of rupture. It also suggested myocardial assessment for hypoenhacement following myocardial infarction, which has just been described. Finally the statement acknowledged that there remained a lack of consensus about the use of CT for screening asymptomatic patients with a high pre-test probability of coronary stenosis, and the use of the triple rule out test, a single-examination assessment for coronary artery disease, acute aortic syndrome and pulmonary emboli.

1.6 Approaching the 'difficult-to-image' patient

The 'difficult-to-image' patient was a concept illustrated by the National Institute of Health and Clinical Excellence (NICE) in its 2013 technology appraisal of 'new generation' scanners.[98] The development of scanners had, to this point, been largely comparable between manufacturers with each iteration of scanner offering additional detector rows or image slices.[107] The range of new generation scanners has seen notable diversity in technology including novel detector materials, improved spatial

resolution, improved temporal resolution and wider detector coverage to address previous technological limitations.[98]

It is an interesting concept as it suggests two somewhat paradoxical ideas about the current capabilities of cardiac CT – that it is so advanced as to make its widespread use conventional, and yet it is insufficiently advanced as to allow its unrestricted application to all patients and situations. In practice of course this simply reflects the development of the technology, but it might be argued that the fact that NICE has identified a small group of patients in which imaging with CT remains challenging is in fact illustrative of just how far CT has been developed and how widely it can be used.

In particular NICE identified spatial resolution, low contrast detection, noise artefacts and higher levels of radiation to be the major shortfalls of conventional scanners and reflected this in its list of the patients in whom imaging with conventional scanners has been demonstrated to be challenging. These include:

- obesity
- high levels of coronary calcium (calcium score greater than 400)
- arrhythmias
- high heart rates
- stents
- previous coronary artery bypass grafts

These can be further grouped into broad themes or difficulties and it is useful to combine the technological limitation with its *in vivo* challenges in order to understand

the clinical importance of these issues. The difficulties of coronary calcification, due to limited spatial resolution, beam hardening artefact and partial voluming (or blooming) have been discussed previously. The same issues arise in patients with previous bypass grafts, where evaluation of both the surgical grafts and the native coronary arteries is required. In fact, the former are generally well visualised with conventional CT[108–111] but the native vessels tend to be heavily calcified, limiting the diagnostic performance of CT in this cohort. Stents present similar challenges, in that the high-density materials used to construct them leads to significant beam hardening and blooming artefacts which prohibit satisfactory visualisation of the coronary lumen, particularly in smaller stents.[112] The consideration of all such artefact and its detriment to coronary visualisation will be considered.

High heart rates and arrhythmia may also be linked in terms of the technological challenges they present. These are generally motion artefact and misregistration artefact. The former is encountered in patients with relative tachyarrhythmias where the heart rate cannot be suitably controlled – such clinical scenarios may include patients in whom beta-receptor antagonist drugs (beta-blockers) are contraindicated, patients with atrial fibrillation where the high heart rate may be relatively refractory to pharmacotherapy or situations where it is difficult to isolate part of the cardiac cycle where cardiac motion is minimised. This last issue is one reason that retrospective gating may be preferred in some patients with tachycardia, despite its higher radiation burden, as phase selection can be achieved more reliably. The issue of misregistration artefact arises due to the need to image an entire organ with detectors that do not fully cover it, instead relying on accurate imaging in ‘slabs’ through the heart over a

number of cardiac cycles which are then digitally assembled to create a whole heart reconstruction. Again, atrial fibrillation can be challenging as it is difficult to predict the timing of cardiac motion in such an irregular, chaotic arrhythmia.

Obesity presents a number of challenges for CT operators. Image quality is impaired[113] due to increased photon attenuation and scatter by fat, which leads to increased image noise. As discussed in chapter 1.2 above, reducing noise in this context requires an increase in photons reaching the detector, which can be achieved by increasing the tube energies. This in turn increases the radiation exposure to the patient. Furthermore, by improving the penetration power of photons (by increasing the kVp) the effects of beam hardening are accentuated.[114]

In addition to identifying solutions to these specific problems, an alternative approach would be to change the way in which we use CT. The use of CT to examine the heart beyond the coronary arteries has already been outlined and assessment of the myocardium can give clues about the underlying coronary vessels. For example, the identification of abnormal myocardium due to scarring following infarction, or the abnormal uptake of contrast medium due to impaired downstream tissue perfusion can both highlight problems with coronary artery patency. Following on from this, it may be possible to generate so-called functional information, that is to say information about the working of the heart and its blood supply rather than its anatomical appearance, from CT images.

This thesis will consider initial explorations into all of these approaches.

Section 2 – Artefact from high-density material

2. High-definition CT

2.1 Introduction

By rapidly altering the x-ray focal spot in the horizontal, or *z* axis, (a technique referred to as focal spot 'wobble'), the high definition scanner can acquire significantly more data with each gantry rotation, thereby improving spatial resolution. The use of novel image reconstruction methods, now widely recognised to facilitate a reduction in the ionising radiation requirements of CT,[115] can be incorporated into high-definition CT (HDCT) scanning to offset the otherwise increased dose necessitated by higher tube energies. Furthermore such iterative reconstruction algorithms also reduce image noise compared to traditional filtered-back projection (FBP) techniques (see Chapter 1), which may provide additional image quality optimisation.

While appealing, these concepts have not been widely explored in clinical practice. This study therefore aimed to investigate the diagnostic performance of HDCT with dose optimisation and iterative reconstruction in the evaluation of significant coronary artery disease, using invasive coronary angiography (ICA) as the reference standard.

2.2 The study

Materials and methods

Patients and design

This study was a prospective, diagnostic accuracy trial, conducted at a single, high-volume, tertiary cardiothoracic centre (Derriford Hospital, Plymouth, UK). Consecutive patients undergoing invasive coronary angiography, with a high pre-test risk of coronary artery disease (as assessed by a consultant cardiologist), previously treated

(percutaneously or surgically) coronary disease, or stable patients admitted with an acute coronary syndrome were screened and enrolled. Exclusion criteria were patient under 40 years old, those requiring immediate percutaneous coronary intervention, elevated serum creatinine (>135 mmol/L) or estimated glomerular filtration rate <30ml/min/1.73m^2, contrast induced nephropathy, permanent or persistent atrial fibrillation, New York Heart Association class III or IV heart failure, severe aortic stenosis, contraindication to beta-blockade, pregnancy or body mass index >33/m^2. Patients unable to hear or understand English were also excluded.

The study was undertaken in accordance with the Declaration of Helsinki and approved by our instutitional research and development team and a committee of the UK National Research Ethics Service, and was registered as a clinical trial (NCT01946737). Patients provided informed, written consent.

Blinding

Following the clinical reporting of both investigations, the images were anonymised, assigned study numbers and stored digitally offline for investigative reporting. ICA images were reported by two experienced, independent readers. HDCT images were reported by two other, independent readers with extensive CTCA experience. Discrepancies were resolved by consensus.

Procedures

ICA was undertaken in accordance with standard clinical practice (Allura XPer FD10, Philips Healthcare, Best, Netherlands). Each coronary artery was visualised in at least

two orthogonal planes using standard projections, with additional views undertaken for overlapping segments or unusual anatomy. Stenosis assessment was facilitated with proprietary quantitative coronary analysis software (View Plus, Sanders Data Systems, California, USA).

All patients underwent two sequential CT acquisitions (coronary artery calcium scoring and coronary angiography) within 28 days of ICA with a 64-slice high definition scanner (Discovery HD-750, GE Healthcare, Milwaukee, USA). Patients with a heart rate greater than 60 beats per minute received intravenous metoprolol, in 2.5 – 5 mg aliquots to a maximum of 60 mg, to achieve a target heart rate of less than 60 beats per minute. Calcium scoring was performed using prospective ECG gating in 3-4 sets of non-overlapping, axial slices with 4 cm z-axis coverage, 80, 100, or 120 kV tube voltage according to body mass index and 300 mAs tube current. CTCA was performed in high definition mode using prospective ECG gating, 350 ms gantry rotation speed, 64 x 0.625 mm slice collimation, 100 kV tube voltage, and fixed tube current according to body mass index (BMI < 22.5 kg/m^2: 450 mA, BMI 22.5 – 24.9 kg/m^2: 500 mA, BMI 25.0 – 27.4 kg/m^2: 600 mA, BMI 27.5 – 30 kg/m^2: 700 mA, BMI >30 kg/m^2: 800 mA). Additional tube-on time (padding) of up to 200 ms was used at the discretion of the supervising clinician for patients with heart rate variability, according to standard departmental protocol, with 100 ms added for heart rate variability or 200 ms for heart rate 60 – 65 bpm despite beta blockade. A multi-phase contrast injection protocol was used with 100 ml (125 ml for patients with coronary bypass grafts) of Optiray 350 (Ioversol, Mallinkrodt Inc, MO, USA), initially at 6.5 ml/sec reducing to 5.5 ml/sec over 17 seconds, followed by 70 ml of saline flush at 5.5 ml/sec, using a

standardised protocol. Raw CT data was reconstructed using a combination of 40% Adaptive Statistical Iterative Reconstruction (ASIR) and 60% filtered back projection.

Assessment was undertaking using the standardised, American Heart Association coronary model in both modalities.[116] All coronary artery segments larger than 1.5 mm diameter were evaluated for stenoses which were graded using an ordinal scale (normal, < 50% stenosis [mild], 50 to 70% stenosis [moderate], greater than 70% stenosis [severe] and absence of opacification [occluded]). Segments with more than one stenosis were graded according to the greatest stenosis. Segments distal to an occlusion were excluded from the analysis. Inter-reader differences in stenosis assessment were resolved by a third expert in the relevant modality.

On CT, all coronary artery segments were assessed for image quality using a 4-point Likert scale: 4 = good image quality, no artefacts; 3 = adequate image quality; 2 = suboptimal image quality; 1 = non-diagnostic). All segments of non-diagnostic image quality were labelled as significantly stenosed on an intention-to-diagnose basis.

The primary outcome was the diagnostic accuracy of the high definition CT protocol to detect moderate stenoses (>50%) as defined by invasive angiography, which is the general degree of accuracy assessed by most diagnostic coronary imaging studies. Further analyses evaluated the diagnostic accuracy for severe stenosis (>70%, which may be more specific for functionally significance, although it is now widely accepted that stenosis alone is a poor predictor of functional significance[117]) and the radiation dose. The radiation dose was recorded from the scanner dose report, expressed as

dose-length product (DLP) in milligray-centimetres. The effective dose was calculated using a cardiac-specific conversion factor in accordance with previously published data from our institution.[36]

Statistical analysis

Patient demographics were assessed graphically for distribution and presented using means or medians as appropriate. Mortality was compared using Fisher's exact test. Diagnostic accuracy was calculated for four groups: all stented segments (per-segment), for all patients with stents (per-patient), for all native segments in patients with previous bypass grafts (per-segment), and for all patients with previous grafts (per-patient). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were all calculated with 95% confidence intervals. Two-tailed P values <0.05 were considered significant. Cohen's kappa was used to compare intermodality agreement, and interobserver agreement for CTCA. Statistical analysis was performed using MedCalc (v13.2, MedCalc Software, Belgium).

Patient follow-up

Clinical outcomes were evaluated at one year, using the hospital admissions system and the patient's clinical notes.

Results

Of 486 patients screened for inclusion in the study, 350 patients were eligible according to the study criteria. 48 patients did not consent and two patients, who were excluded due to dysrhythmia on the day of the CTCA, withdrew consent. Thus 300 patients were included in the final analysis. No patient was excluded due to suboptimal CTCA scan, on an intention to diagnose basis.

Table 3 illustrates the baseline characteristics of the patients included in the study. The prevalence of significant coronary artery disease, defined by the presence of at least one stenosis of $\geq$ 50%, was 69%. 215 (72%) patients had a high pre-test probability of significant coronary disease and 85 (28%) patients had established coronary artery disease which was previously treated either percutaneously or surgically (62 patients had stents, 20 had coronary bypass grafts and three had both).

The median time between CTCA and ICA was 12 days (range 1 – 28). There were no serious adverse events and all patients completed the study protocol, undergoing unenhanced, low-dose calcium score scanning and prospectively-gated CTCA. This required aggressive heart rate control with 206 (69%) patients requiring intravenous metoprolol prior to the scan and 49 patients (16%) receiving more than 30 mg. A small proportion (10%) of scans required additional tube-on time (padding), to enable evaluation of multiphase dataset, reducing the number of non-diagnostic studies due to beat-to-beat heart rate variability during image acquisition. Full CTCA characteristics are described in Table 4.

Patient baseline characteristics	**Value**
Age in years – median (interquartile range)	66 (60-73)
Gender – Male (%) / Female (%)	225 (75%) / 75 (25%)
Body mass index - median (interquartile range) < 20 – n (%) 20-24.9 – n (%) 25-29.9 – n (%) ≥30 – n (%)	27 (25-28) 7 (2%) 79 (26%) 176 (59%) 38 (13%)
Chest pain Unstable angina - n (%) Stable or single episode - n (%)	 24 (8%) 276 (92%)
Hypertension - n (%)	278 (93%)
Diabetes - n (%)	35 (12%)
Hypercholesterolemia - n (%)	248 (83%)
Smoking Current - n (%) Past history - n (%) Non-smoker - n (%)	 123 (41%) 102 (34%) 75 (25%)
Family history of CAD - n (%)	85 (28%)
NYHA Status Class I – n (%) Class II – n (%)	 227 (76%) 73 (24%)
Previous heart failure – n (%)	15 (5%)
Previous stroke – n (%)	3 (1%)
Previous myocardial infarction – n (%)	44 (15%)
Previous percutaneous intervention – n (%)	65 (22%)
Previous Coronary bypass grafting – n (%)	23 (8%)

Table 3

Baseline characteristics of patients included in the study of high definition CT coronary angiography.

CTCA characteristics	Value
Time from ICA to CTCA in days – median (interquartile range)	12 (1-24)
Heart rate Baseline – median (interquartile range) Acquisition – median (interquartile range) Beat-to-beat variability at acquisition – n (%)	 65 (58-74) 57 (52-60) 37 (12%)
Beta-blocker Previous oral – n (%) Intravenous – n (%)	 119 (40%) 206 (69%)
Beta-blocker dose – median (interquartile range) ≤10 mg – n (%) 11-30 mg – n (%) >30 mg – n (%)	9 (0-21) 88 (29%) 69 (23%) 49 (16%)
Agatston calcium score – median (interquartile range) <400 - n (%) 400-999 - n (%) ≥1000 - n (%)	587 (110-1435) 121 (40%) 71 (24%) 108 (36%)
Tube current – mA – median (interquartile range)	800 (740-800)
Padding – median (interquartile range) None – n (%) 100 msec – n (%) 200 msec – n (%)	 269 (90%) 1 31 (10%)
Dose length product – milligray-centimetre (mGy·cm)	151 (150-253)
Effective dose – milliSieverts (mSv)	4.2 (4.2-7.1)

Table 4
Characteristics of acquisitions for high definition CT coronary angiograms

The median radiation dose for CTCA was 151 mGy-cm (IQR 150-253) which translated to a median effective dose of 4.2 mSv (IQR 4.2-7.1) using a CTCA specific conversion factor (k = 0.028 mSv/mGy·cm).

For the primary outcome measure data was analysed on patient, coronary vessel and coronary segment levels. The image quality was excellent in a majority of coronary artery segments. 4248 coronary artery segments were analysed on both ICA and CTCA. 4116 (96.9%) segments demonstrated diagnostic quality on CTCA, while 132 (3.1%) segments were considered non-diagnostic. The diagnostic performance of CTCA on a

per-patient and per-vessel basis is detailed in Tables 5 and 6. For 50% stenosis the per-vessel sensitivity of HDCT was 96.1% (95% confidence interval 93.8 – 97.7), specificity 98.8% (97.8 – 99.5), positive predictive value 97.9% (96.0 – 99.0) and negative predictive value 97.8% (96.5 – 98.7).

Patient Level	**50% stenosis**			**70% stenosis**	
	Value	*95% CI*		*Value*	*95% CI*
Sensitivity	97.0	93.8 – 98.9		98.9	96.0 – 99.8
Specificity	97.9	92.5 – 99.7		93.4	87.5 – 97.1
PPV	99.0	96.4 – 99.8		96.6	91.6 – 98.1
NPV	93.9	87.1 – 97.7		98.3	93.9 – 99.7

Table 5
Accuracy of high definition CT coronary angiography on a per-patient basis.

Vessel Level	**50% stenosis**			**70% stenosis**	
	Value	*95% CI*		*Value*	*95% CI*
Sensitivity	96.1	93.8 – 97.7		98.8	96.9 – 99.7
Specificity	98.8	97.8 – 99.5		96	94.4 – 97.2
PPV	97.9	96.0 – 99.0		90.2	86.6 – 93.0
NPV	97.8	96.5 – 98.7		99.5	98.8 – 99.9

Table 6
Accuracy of high definition CT coronary angiography on a per-vessel basis. The vessels have been assessed as left main stem, left anterior descending, circumflex and right coronary arteries. Branch vessels are included in the main vessel analysis.

The weighted Kappa value for agreement between two independent readers on high-definition CTCA was 0.99.

2.3 Discussion

This study demonstrates that with high definition technology, CT coronary angiography is a highly accurate diagnostic test, comparable to invasive coronary angiography, with sensitivity and specificity greater than 95% for 50% stenosis at both patient and vessel level.

Furthermore, HDCT maintains its accuracy across a range of vessel stenoses. Differentiating between moderate and severe lesions is frequently challenging in clinical practice, but the sensitivity and specificity remain above 95% for all four levels of stenosis (mild, moderate, severe, occluded) on a per-vessel analysis. Importantly, this accuracy has persisted despite evaluating patients with extensive coronary disease, a cohort previously considered less suitable for CTCA due to vessel artefact from calcification or stents[91,118] where international guidelines are unable to make firm recommendations.[92]

The advantages of CTCA to the interventional cardiologist are clear. In patients with a low pre-test probability of coronary artery disease, CTCA has been shown to provide safe and rapid exclusion of disease, avoiding the risks of unnecessary interventional procedures. Now, for high-risk patients, therapy can be pre-planned and targeted. The same is true for patients with coronary bypass grafts where decisions can be made prospectively regarding the need to intervene percutaneously on grafts or native arteries, and assistance gained with locating or avoiding particular vessels.

One of the major limitations in the uptake of CT as a mainstream investigative modality has been its limited positive predictive performance and, consequentially, its use in patients with a high pre-test probability of significant coronary artery disease has not been recommended.[119–121] This does influence the risk-benefit ratio of CT, as the diagnostic yield in lower risk populations is less. Of course, assessing the accuracy of CT in a cohort with a high, *a priori* risk of coronary artery disease is not directly comparable to assessing the same technology in a cohort with a lower

prevalence of disease because of the effect on the positive predictive value, but the maintenance of a high negative predictive value in this setting is extremely reassuring.

Radiation exposure remains the main disadvantage to CT, as discussed in the earlier chapters. The median dose-length product (DLP) in our study was 150.8 (interquartile range 150.0 – 252.5). This equates to a median effective dose of 4.2 mSv (4.2 – 7.1), which is comparable to previously published studies using 64-slice scanners.[122][118] The effective dose is not as low as those published in several recent studies[123,124] due to the use of a more appropriate conversion factor, validated at our institution previously.[36] This is comparable to a median effective dose of 6.3 mSv (4.2 – 8.2) for ICA at our institution, which is likely to underestimate exposure during graft studies. It should be noted that our department already utilises aggressive dose-reduction strategies, including widespread use of prospective gating, patient-adjusted tube energy and heart-rate reduction, which may contribute to this modest dose range. In the Prospective Multicentre Study on Radiation Dose Estimates of Cardiac CT Angiography in Daily Practice I (PROTECTION I) study, the median radiation dose was 12 mSv and prospective ECG-gating and 100-kV tube voltage were used in 6% and 5% of patients, respectively.[125] In the ACCURACY trial examining dose reduction strategies, the median dose fell from 21 to 10 mSv, with prospective ECG-gating and 100 kV tube voltage used in 0% and 43% of patients, respectively.[122] In contrast in our study all scans (100%) were performed using prospective ECG gating and 296 (99%) at 100 kV tube voltage.

It is possible that the upper limit on body-mass index of 33 kg/m^2 may also have reduced the radiation dose of our cohort. The mean BMI in the ACCURACY study was 31.4 kg/m^2 which is clearly higher than the median average of 27 kg/m^2 in our study (Table 3). Nonetheless, comparison to the later PROTECTION I study is favourable, with a median BMI in the prospectively gated arm of 28.5 kg/m^2, suggesting that BMI alone is unlikely to be the sole factor in radiation reducing.

This study has a few limitations. Overall the patient recruitment is largely reflective of real-world requirements and our exclusion criteria align with common contraindications to CTCA. Furthermore, no patient was excluded on the basis of a suboptimal scan or non-diagnostic coronary segment. However, patient selection remains an important consideration for successful CTCA. Heart rate and variability are important factors and while diagnosis is possible despite rate-controlled AF and other dysrhythmias such patients were excluded from this study, as were patients where heart rate control would be challenging due to beta-blocker intolerance.

The study was conducted in a high-volume, tertiary centre and the CTCA reporters have extensive experience with cardiac CT. While this does not diminish the accuracy of the technique, it should be considered when developing new services elsewhere. That said, the intra-observer agreement in this study was very high (weighted kappa 0.99). Along with the very low proportion of non-diagnostic coronary segments (3.1%) this suggests that the technique should be highly reproducible.

The use of ICA as the reference standard also begets difficulty. ICA is not a 'gold standard' test as it has its own limitations. It cannot evaluate extra-luminal disease, including expansile remodelling, coronary segments are not always fully imaged and visual assessment of stenoses can be somewhat subjective. The use of QCA attempts to mitigate this but still ignores features such as serial stenoses or long segments of disease. Of course anatomical stenosis does not correlate perfectly with haemodynamic significance, as demonstrated by the FAME trial,[117] and as yet CT cannot provide robust perfusion analysis, although this is under development.

This is the first study to comprehensively evaluate the accuracy of HDCT in a clinical population. The findings support the wider use of CTCA for the evaluation of coronary artery disease and may question the use of ICA as a first-line diagnostic modality where contemporaneous intervention is not being planned.

Subset analysis – patients who have undergone prior revascularisation

2.4 Introduction

As previously considered, patients who have previously undergone coronary revascularisation are particularly challenging to image with CT, with artefact, from stent metal or heavy calcification in the native vessels of patients who have undergone coronary artery bypass grafting (CABG), impairing image quality. Current guidance from the European Society of Cardiology highlights both the potential utility of CTCA for the evaluation of patients following revascularisation, as well as its weaknesses, notably pronounced coronary calcification.[126]

In the United Kingdom, the National Institute of Health and Care Excellence (NICE) now recommends the use of new generation CT scanners "for first-line evaluation of disease progression, to establish the need for revascularisation, in people with known coronary artery disease in whom imaging with earlier generation CT scanners is difficult".[98] While the performance of conventional multidetector-row CT has been extensively evaluated, there are relatively few studies examining the accuracy of new generation technology for the assessment of revascularised patients. The aim of this study was therefore to assess the accuracy of high-definition CT in patients who have previously undergone coronary revascularisation, in a subset of the previously described study.

Materials and methods

The methodology has been described earlier in this chapter. This prospective study was approved by the UK National Research Ethics Service and was conducted in a

single, high-volume, tertiary teaching hospital. All patients gave informed, written consent. The methodology has been described previously. Of this study population, 66 patients had undergone prior revascularisation, 41 with percutaneous coronary intervention (PCI) and 21 with CABG and 4 with both.

The ICA and CTCA images were pseudonymised and reported on a segment-by-segment basis, using the American Heart Association 17-segment coronary model, by two independent experts for each modality (each with over 5 years' experience), blinded to the other imaging results. Discrepancies were resolved by a third, independent expert. Contiguous stents were considered as a single entity, and all segments containing stents were analysed (e.g.: two, adjoining stents crossing the first diagonal would be recorded as a single stent but analysed for both proximal and mid-left anterior descending segments). Segments beyond an occlusion were not assessed. Significant disease was defined as the presence of moderate (≥50%) or severe (≥70%) stenosis. All non-diagnostic segments were labelled as significantly stenosed on an intention-to-diagnose basis. No segment was excluded on the basis of size or image quality.

Results

Demographics

All recruited patients completed the study, undergoing both imaging techniques. Sixty-six patients with prior revascularisation were identified. Fifty-three (80%) were male and the median age was 67 years (range 43 – 82). The mean body mass index was 26 kg/m^2 (standard deviation 3.3). The median Agatston calcium score in patients without

coronary stents was 1628 (interquartile range 373 – 2800). The median dose-length product was 192 mGy.cm (IQR 150.5 – 247.9) giving an effective dose of 5.4 (IQR 4.2 – 6.9) using a cardiac-specific conversion factor of 0.028.[31] The smallest stent was 2.5 mm in diameter.

Accuracy

Eighty-three stented, and 244 native, vessel segments were analysed. The prevalence of moderate stenosis (≥50%) was 9.6% in the stent group, 43.6% in the native coronary group and 34.9% combined. The prevalence of severe stenosis (≥70%) was 4.8%, 39.4% and 30.6% respectively. The accuracy of CTCA to detect moderate or severe stenosis, for each method of revascularisation and combined, was very high (Table 7). The per-patient sensitivity, specificity, PPV and NPV, for all patients, were all 100% for severe stenosis and 97.2%, 100%, 100% and 94.7% respectively for moderate stenosis. Agreement between high-definition CT and invasive angiography was very good (combined kappa 0.95, weighted kappa 0.97).

	Per segment		Per patient	
	50% stenosis	**70% stenosis**	**50% stenosis**	**70% stenosis**
Stent assessment				
Sensitivity	87.5% (47.4 – 97.9)	75% (20.3 – 95.9)	96.4% (81.6 - 99.4)	100% (86.2 - 100)
Specificity	100% (95.2 – 100)	98.7% (93.1 – 99.8)	100% (80.3 - 100)	100% (83.0 - 100)
PPV	100% (58.9 – 100)	75% (20.3 – 95.9)	100% (87.1 - 100)	100% (86.2 - 100)
NPV	98.7% (92.9-99.8)	98.7% (93.1 – 99.8)	94.4% (72.6 - 99.1)	100% (83.0 - 100)
Native vessels				
Sensitivity	99.1% (94.8 – 99.8)	100% (96.2 - 100)	100% (85.6 - 100)	100% (85.6 - 100)
Specificity	97.8% (93.7 – 99.6)	96.6% (92.2 - 98.9)	100% (16.5 - 100)	100% (16.5 - 100)
PPV	97.2% (92.1 – 99.4)	95.1% (88.9 - 98.4)	100% (85.6 - 100)	100% (85.6 - 100)
NPV	99.3% (95.9 – 99.9)	100% (97.4 - 100)	100% (16.5 - 100)	100% (16.5 - 100)
Combined				
Sensitivity	98.3% (93.8 – 99.7)	99.0% (94.6 – 99.8)	97.2% (88.9 - 99.7)	100% (92.1 - 100)
Specificity	98.6% (95.9 – 99.7)	97.3% (94.3 – 99.0)	100% (81.3 - 100)	100% (83.8 - 100)
PPV	97.4% (92.6 – 99.4)	94.3% (88.1 – 97.9)	100% (92.4 - 100)	100% (92.1 - 100)
NPV	99.1% (96.6 – 99.9)	99.6% (97.5 – 99.9)	94.7% (73.9 - 99.1)	100% (83.8 - 100)

Table 7
Accuracy of high definition CT coronary angiography in patients who have had previous coronary revascularisation, expressed as percentages, with 95% confidence intervals. PPV – positive predictive value, NPV – negative predictive value

The weighted kappa for interobserver agreement between the expert CT readers was 0.99 for the entire study population.

Clinical follow-up

At one year, 79% of patients had been managed medically, comprising 73% of patients with existing stents and 92% of patients who had undergone previous CABG (Table 8).

Mortality in previously revascularised patients was 6%, compared to 3.6% for the total study population (p = 0.28). One from each group (stents and bypass grafts) had died from metastatic malignancy and another in the group with previous bypass grafts died following diverticular perforation. All three were receiving medical management. One patient in the stent group died post-operatively following CABG with mitral valve repair.

Strategy	All	Previous stent	Previous CABG
Further revascularisation	19.7% (13)	24.4% (11)	8.0% (2)
Medical management	78.8% (52)	73.3% (33)	92.0% (23)

Table 8
Onward management of all patients who had previously undergone coronary revascularisation, following their subsequent investigation. Data for one patient with a stent unavailable

2.5 Discussion

This subset analysis suggests that high-definition CT is highly accurate in the assessment of patients who have undergone previous coronary revascularisation who present with chest pain. The combined, per-segment sensitivity, specificity, PPV and NPV for 70% stenosis are 99.0%, 97.3%, 94.3% and 99.6% respectively, and are all 100% on a per-patient basis. The median dose-length product of 192 is considerably less than the benchmark from standard 64-multidetector row CT identified in one major, multicentre study.[61]

High-definition CT is a new generation technology[98] which utilises both novel hardware and image reconstruction methods, to improve image quality and diagnostic accuracy. It uses a ‘flying focal spot’, which increases the data sampling with each gantry rotation, thereby providing more data for image reconstruction and greatly

improved spatial resolution. Image reconstruction is performed using enhanced mathematical modelling of the scan process, undertaking recurrent adjustments to filtered-back project data in an iterative fashion (Adaptive Statistical Iterative Reconstruction). This results in reduced image noise and blooming artefact, which also permits radiation dose reduction.[36,127,128]

CTCA versus ICA

It is important to consider the justification for referring patients to CT rather than ICA. Previous presumption has been that the likelihood of recurrent disease is so high as to warrant an invasive strategy, where revascularisation can be attempted at the same sitting if appropriate. Our data suggest that, in fact, the vast majority of patients do not require further revascularisation with 79% of our cohort, and 92% of those with bypass grafts, receiving medical management. Even in patients with stents, where repeat revascularisation is more likely, slightly fewer than one in four required such intervention. An important caveat is that patients presenting acutely who required immediate PCI were excluded from the study. These conclusions should therefore only be applied to patients investigated in an elective, outpatient fashion.

This low rate of intervention alters the perceived risk-benefit ratio of invasive angiography. Drug-eluting coronary stents have significantly reduced the frequency of restenosis, with major trials suggesting a prevalence of 5-10%[129,130] and a 'rule-out' approach, utilised so successfully in patients without known CAD, may therefore be appropriate. This is reflected in studies of clinical populations being investigated for in-stent restenosis, where the prevalence of significant disease is in the order of 13-26%

(Figure 6).[112] The use of CT for 'rule-out' assessment is already incorporated into international guidelines for the evaluation of left main stem stents.[126] Conventional CT and even alternative, new-generation technology, has been limited in this group, with reasonable negative predictive, but poor positive predictive, values in the order of 100% and 67% respectively with a 16-slice scanner,[131] and 83-100% and 12.5-23% respectively using dual-source techniques.[132,133]

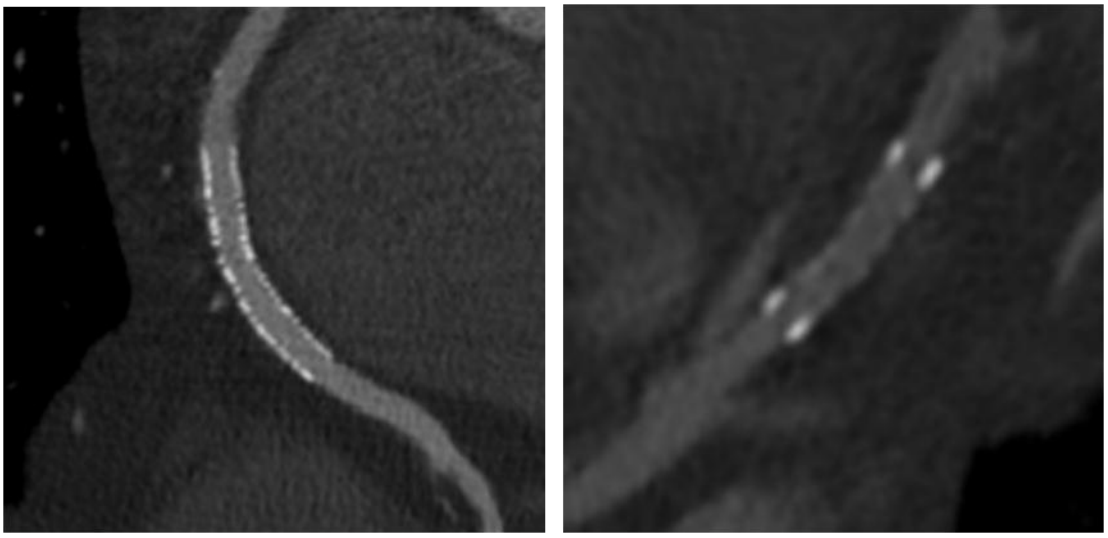

Figure 6
Normal appearances of coronary stents. The left hand image is a modern, platinum-chromium, drug eluting stent ('Promus Element', Boston Scientific, Marlborough, MA, USA). The right hand image is an older, stainless steel, bare metal stent ('Teneo', Biotronik, Berlin, Germany). Both are free of intimal hyperplasia or in-stent restenosis.

Graft studies may also be best suited to CT. Invasively these can be challenging and prolonged and the risk of iatrogenic stroke from ICA is three times higher in patients with previous CABG than those without.[95] Conversely, there is a wealth of evidence demonstrating excellent diagnostic accuracy in bypass graft assessment using CT.[108–111] CT also positively impacts on downstream care, with demonstrable benefit to surgical procedure time, rates of peri-operative myocardial infarction and intensive care stay, in patients undergoing repeat cardiac surgery.[134]

Other new generation technology

Although NICE has recommended new-generation technology for the assessment of all difficult to image patients they may not be equal. Indeed, the guideline acknowledges that differences in the technological advances with each new generation scanner may provide different benefits, depending on the reasons for imaging being difficult.[98]

Dual-source CT scanners and those with wide detector arrays[135] can both achieve rapid image acquisition, and so logically reduce artefact due to misregistration or cardiac motion. This is important in graft studies where large volume acquisition is required. However, assessment of the grafts alone does not provide the whole story and the ESC guidelines recommend evaluation of the native coronary arteries also.[126] There are few studies to have considered this, but wide-bore detectors appear to struggle with sensitivity, specificity, NPV and PPV for non-grafted vessels just 83%, 77%, 77% and 83% respectively in one large study.[135] DSCT appears to fare better, with one study demonstrating 99%, 96%, 94 and 99% respectively.[136] To our knowledge, no previous study has examined the use of high-definition CT in this population, and overall there is very little prior evidence for firm conclusions to be drawn about any technology in this group.[96]

The existing evidence base is somewhat larger for stent assessment, comprising over 30 single-centre studies and at least two meta-analyses. As with conventional CT indications, most studies demonstrate reasonable negative predictive value with limited positive prediction. Pooled sensitivity, specificity, PPV and NPV has been estimated at 87%, 84%, 68%, and 98% respectively.[137] As with native arteries in

post-CABG patients, large bore detectors do not appear to add significant benefit, with the positive predictive value remaining low, between 54 and 77%,[138–140] with sensitivity as low as 59%.[138] Dual-source scanners again seem to perform somewhat better, achieving sensitivity and positive predictive values approaching, and up to, 100% in recent studies.[141–145] Nonetheless, the positive predictive values in these studies remain poor, between 14 and 89%. One previous study has examined the use of high-definition CT in comparison to both a conventional scanner and ICA.[123] While no significant difference could be identified between scanners, the authors acknowledge that their study was underpowered, and the performance of high-definition CT compared to ICA was very good, with per-stent sensitivity, specificity, positive and negative predictive values of 96, 95, 90 and 98% respectively. Importantly in this study, all stents were included irrespective of image quality.

Limitations

This study has a number of limitations, some in addition to the main analysis described previously. The sample size is relatively small. Furthermore, the low prevalence of recurrent disease in the stent group makes firm conclusions as to the positive predictive value of CTCA difficult (as evidenced by the broad confidence intervals in the per-stented segment group), although its ability to exclude significant disease is apparent. Similarly, the very high rate of significant disease in the native vessels of patients who have undergone CABG somewhat limits comprehensive assessment of the negative predictive value of high-definition CT in this group. Nonetheless, the samples are comparable to previous similar studies, and this cohort represents the first evaluation of native vessels in patients with prior CABG to use high-definition imaging.

The study uses an anatomical measure, invasive coronary angiography, as its gold standard. There is now widespread acknowledgement of the limitations of anatomical testing[146] and fractional flow reserve is a more robust method for decision making regarding revascularisation, with patient outcome data to support this approach.[117] However, CT is presently an anatomical test and it is therefore appropriate to compare this to the current anatomical gold standard.

While our exclusion criteria were reflective of real world requirements and limitations of CTCA, and are commensurate with current clinical practice, current limitations of CT technology necessitated the exclusion of patients with dysrhythmias, those where heart rate control was not possible, patients unable to breath-hold for at least 20 seconds, and those with BMI >33 kg/m^2. Importantly, however, no patient was excluded on the basis of suboptimal scan or non-diagnostic images. The study was undertaken in a single, high-volume, tertiary centre and by reporters with extensive cardiac CT experience. Although this does not diminish the accuracy of the technique, it should be considered when developing newer services in smaller volume centres. On the other hand, the inter-observer agreement in this study was very high (weighted kappa of 0.99) which may suggest that the technique is robust and highly reproducible.

Conclusions

Our results suggest that high definition CT offers exceptional diagnostic accuracy, comparable to ICA. This is a subset analysis and the small populations must be considered. Nonetheless, high definition CTCA appears to be a promising tool for the

evaluation of patients who have undergone prior coronary revascularisation, and, given the low proportion of patients requiring further intervention, may obviate the need for ICA as a first-line diagnostic test.

3. Dual-energy CT for the subtraction of calcium

3.1 Introduction

To recap from chapter 1, dual-energy CT (DECT) is a novel technology currently being explored for use in cardiac imaging. The heart is interrogated using two x-ray spectra simultaneously, either from two x-ray sources or using novel detectors with a single source,[65] and the attenuation of each spectrum by particular materials is measured. The latter technique requires novel detectors, capable of distinguishing between different signals, 0.25 milliseconds apart, without artefact from the detector afterglow experienced with traditional materials, so that the two energy spectra can be emitted from a single anode almost simultaneously, using rapid tube voltage switching.[67]

The datasets from each spectrum can then be compared to ensure that errors due to beam hardening are reduced. Processing the data in the projection domain, both peak kilovolt (kVp) projections are processed to generate measurements according to the density of two basis materials which would be required to produce the observed attenuation. Based on known mass attenuation coefficients of these materials, final image sets can be produced at simulated, monochromatic tube energies, that depict objects as if they have been subjected to a specified photon energy, rather than a polychromatic beam[147] (virtual monochromatic images). Lower keV images can be used to improve tissue differentiation or enhance intravascular contrast, while higher keV images can help to reduce blooming artefact. The purported improvement in a material's identification, based on its attenuation coefficients, and transformation into a linear combination of the two basis materials (material decomposition), might also provide the opportunity for subtracting particular materials from each other, such as

calcium from iodine. The use of a single x-ray source may have theoretical advantages over dual-source systems, due to the improved temporal association of each dataset.

To date, this technology has had relatively little evaluation in clinical practice. While the utility of monochromatic data analysis has been assessed in terms of noise and image quality,[147] the accuracy of images generated by single source, dual-energy CT has yet to be considered in a population with significant coronary calcification. We therefore undertook a feasibility study to examine the potential benefits and limitations of virtual monochromatic, and material decomposition (calcium subtraction), images for the assessment of patients with calcified coronary artery disease, and to assess their potential diagnostic accuracy in comparison to invasive angiography.

3.2 The study

Materials and methods

This prospective study was approved by a committee of the UK National Research Ethics Service and registered as a clinical trial (NCT 01816750). All participants gave informed, written consent. Thirty patients were recruited at a single, high-volume, tertiary cardiothoracic centre from a population undergoing invasive coronary angiography (ICA) on clinical grounds. Only patients with evidence of coronary calcification, visible at angiography or on previous cross-sectional imaging, were included. The exclusion criteria were patients under 50 years old, body mass index >30kg/m^2, allergy to iodinated contrast media, contraindication to intravenous beta-blockade, estimated glomerular filtration rate <30ml/min, or pregnancy. Patients

requiring urgent revascularisation before CT scanning could take place were also excluded. Of all the patients approached (consecutively) six declined to participate.

Reference standard

The reference standard for the study was invasive, catheter angiography (ICA), which was performed as per standard clinical protocol using digital angiography (Allura XPer FD10, Philips Healthcare, Best, Netherlands). Each coronary artery was viewed in at least two orthogonal planes. Images were later reported by two angiographers (each with more than 5 years experience of ICA), blinded to the clinical data and CTCA results. Images were assessed according to the modified AHA 15-segment model[148] and each segment was scored based on the presence and degree of stenosis in this fashion: <50% (mild), 50<70% (moderate) or ≥70% (severe). Variations in results were resolved by a third, independent angiographer.

CT protocol

CTCA was performed using a single source, dual-energy scanner (Discovery CT750 HD, GE Healthcare, Milwaukee, WI). Patients with a resting, pre-scan heart rate of >65 beats per minute received intravenous metoprolol (Betaloc, AstraZeneca, London, UK) in 5mg aliquots (up to 40mg) to achieve a heart rate of <65 beats per minute. A non-enhanced scan was performed for the purposes of calcium scoring. Angiography was undertaken in dual-energy mode (rapid kV switching between 80 and 140 kV) using vendor-programmed tube settings according to the patient's body mass index (Table 9). Scans were acquired using prospective ECG gating, centred around 75% of the R-R interval. Where heart rate control remained inadequate despite beta-blockade up to

200 milliseconds of padding (additional 'tube-on' time, to cover more of the cardiac cycle) was utilised and the centre point was moved to 60% of the R-R interval, to acquire both systolic and diastolic phases. Iodinated contrast (Optiray 350, Covidien, MA, USA) was administered as a 100 ml, multiphase bolus at an initial rate of 6.5 ml/s, followed by a 50 ml saline flush and the scan was triggered manually upon opacification of the ascending aorta, with a seven second scan delay.

BMI (kg/m^2)	**Preset No.†**	**Tube voltage (kV)***	**Tube current (mA)***	**Bowtie filter**
<20 – 22.9	62	108	600	Small cardiac
23.0-26.9	65	112	640	Small cardiac
27.0-30.0	64	112	640	Medium cardiac

Table 9
*Tube parameters for dual energy presets (manufacturer-specified) and their use according to body mass index.BMI – body mass index. †Manufacturer programmed, non-modifiable tube parameters, selected by choosing the appropriate preset *These values are approximated as an average resulting from rapid switching between 80 kVp and 140 kVp.*

Image analysis

Following the scan the images were reconstructed using 50% iterative reconstruction (Adaptive Statistical Iterative Reconstruction, GE Healthcare), as recommended by previous studies[147], and transferred to a workstation (Advantage Workstation 4.6, GE Healthcare). They were anonymised and subsequently reported by two independent experts (each with more than 10 years experience of CTCA), blinded to the clinical data and the results of the invasive angiogram, using the 15-segment model as before. Scans were analysed as virtual monochromatic datasets at 60, 100 and 120 keV, and using 'calcium subtraction' (iodine-hydroxyapetate material density subtraction). Previous work has suggested that 65-75 keV confers highest image

quality[7], which also approximates to the mean photon energy of a 120 kVp polychromatic beam, while higher monochromatic energies may reduce blooming artefact from calcific deposits. Monochromatic and material density subtraction image sets were evaluated independently, with more than 6 weeks interval between each read.

Lesions were graded using the same descriptions as for ICA and differences between the readers were resolved by consensus. The non-enhanced scan was used to calculate an Agatston calcium score using semi-automated software on the workstation.

Statistical analysis

Distributions in patient demographics and scan features were assessed graphically, with subsequent metric or parametric techniques selected accordingly.

Descriptive statistics were used to describe the accuracy (including sensitivity, specificity, negative predictive value [NPV] and positive predictive value [PPV]) of CT versus ICA, with 95% confidence intervals for both moderate and severe stenoses. Comparisons were made on a per-segment, per-vessel and per-patient basis, the vessels comprising the left main stem, left anterior descending artery, circumflex artery, and right coronary artery. Branches of each vessel were included in the assessment of the major vessel from which they arose. Cohen's kappa was calculated to describe the agreement between the two modalities.

Results

All patients underwent CTCA, without complication or adverse incident, within three months (median 5.5 days) of ICA. One study was subject to significant motion blur due to contrast-induced tachycardia and respiratory motion, and was non-diagnostic. All the segments of all remaining patients were included in the analysis, irrespective of image quality. In total, 403 segments in 86 vessels were analysed.

Eighty percent of the study subjects were male, with a mean age of 69.2 (range 53 – 85) years and a mean body mass index of 28.6 (range 21.6 – 30) kg/m^2. Calcified coronary plaque was identified in all patients and the median Agatston calcium score was 964 (interquartile range 304.5 – 1840.5) units. The mean volume CT dose index ($CTDI_{vol}$) for the entire examination was 17.9, dose-length product 197 mGy cm^{-1}, giving an effective dose of 5.5 mSv (cardiac conversion factor 0.028[36]).

The per-segment, per-vessel and per-patient prevalence of moderate stenosis was 24%, 59% and 86%, and the prevalence of severe stenosis was 15%, 51% and 83%, respectively.

The sensitivities, specificities, PPV and NPV of the virtual monochromatic image sets are illustrated in Table 10, with 95% confidence intervals. The accuracy of this technique for the identification of moderate and severe stenosis was 0.88 on a per-segment basis, 0.84 and 0.86 respectively on a per-vessel basis, and 0.93 and 0.97 respectively on a per-patient basis. The weighted kappa statistic between ICA and CTCA was 0.71, suggesting good agreement between the two methods.

	Per segment	Per vessel	Per patient
≥50% stenosis			
Sensitivity	0.76 (0.66 – 0.84)	0.78 (0.64 – 0.89)	0.93 (0.76 – 0.99)
Specificity	0.92 (0.89 – 0.95)	0.93 (0.80 – 0.98)	1.00 (0.19 – 1.00)
Positive predictive valve	0.76 (0.66 – 0.84)	0.92 (0.79 – 0.98)	1.00 (0.86 – 1.00)
Negative predictive value	0.92 (0.89 – 0.95)	0.79 (0.65 – 0.90)	0.50 (0.08 – 0.92)
≥70% stenosis			
Sensitivity	0.73 (0.60 – 0.83)	0.78 (0.61 – 0.90)	1.00 (0.85 – 1.00)
Specificity	0.91 (0.87 – 0.93)	0.94 (0.84 – 0.98)	0.83 (0.36 – 0.97)
Positive predictive valve	0.58 (0.47 – 0.70)	0.90 (0.74 – 0.98)	0.96 (0.79 – 0.99)
Negative predictive value	0.95 (0.92 – 0.97)	0.86 (0.74 – 0.94)	1.00 (0.48 – 1.00)

Table 10
Diagnostic accuracy of monochromatic imaging on per-segment, per-vessel and per-patient level analyses for moderate (≥50%) and severe (≥70%) stenoses with 95% confidence intervals

The per-segment sensitivity, specificity, PPV and NPV (and 95% confidence intervals) of the material decomposition image sets were 0.67 (0.57 – 0.76), 0.82 (0.77 – 0.86), 0.54 (0.45 – 0.63) and 0.88 (0.84 – 0.92) respectively for moderate stenosis, and 0.70 (0.57 – 0.80), 0.79 (0.75 – 0.83), 0.40 (0.31 – 0.49) and 0.93 (0.89 – 0.96) respectively for severe stenosis. The overall accuracy was 0.78 for both moderate and severe stenosis.

3.3 Discussion

This study demonstrates that the use of virtual monochromatic images from single source, dual-energy CTCA is feasible in patients with severe coronary calcification and further investigation of its diagnostic performance is merited. The use of calcium subtraction techniques from material decomposition image sets provided highly inconsistent calcium subtraction (Figures 7 & 8) and were not considered to be useful for further analysis, thus combined analysis using both techniques was not attempted.

The poor image quality appeared to be due to image noise, with resultant misidentification of calcium and excessive subtraction.

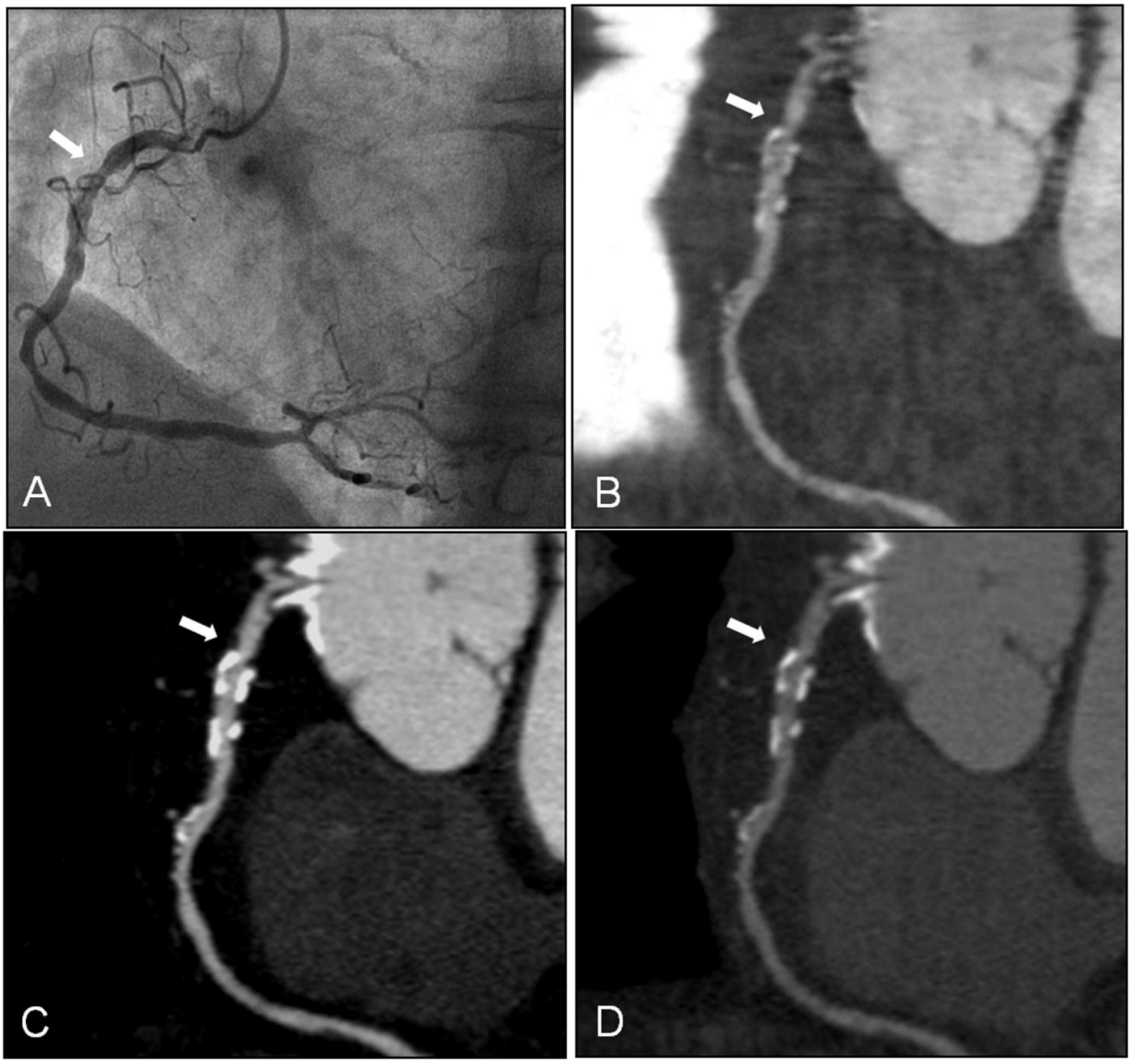

Figure 7
Dual energy assessment of the calcified lesion – 1. Example of the image set of a patient with a calcified stenosis of the proximal right coronary artery. Panel A illustrates the stenosis (beginning at the arrow) with comparative, invasive angiography. Panel B is the material decomposition (calcium-subtracted) image. Panel C is the same image reconstructed as a virtual monochromatic image at 60 keV (approximately equivalent to the mean energy of a 100 kVp polychromatic beam) and demonstrates greater calcium blooming than Panel D, which is reconstructed at 100 keV.

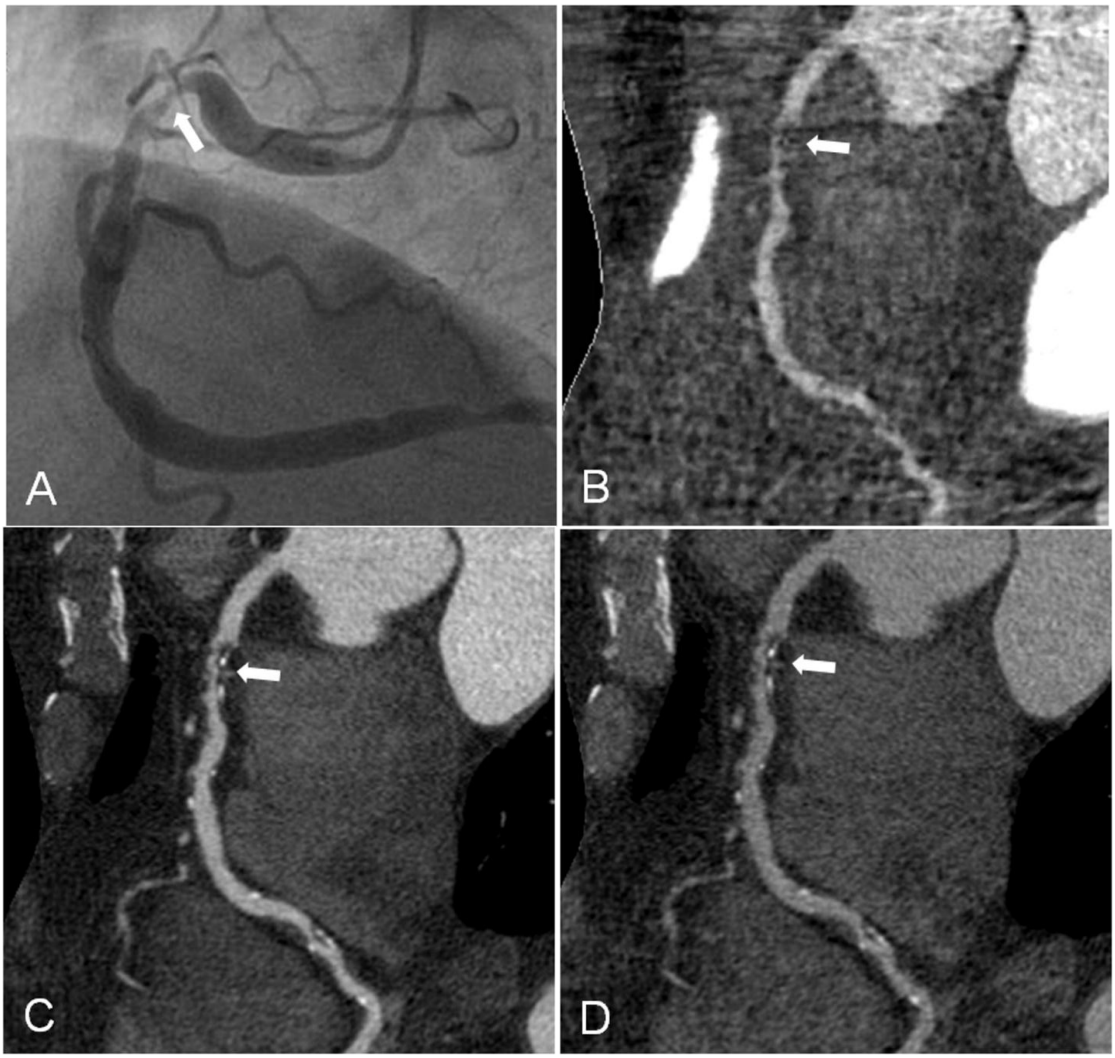

Figure 8
Dual energy assessment of the calcified lesion – 2. Severe stenosis of a proximal right coronary artery at invasive angiography (Panel A). The material decomposition image (Panel B) accurately subtracts the two small calcified deposits. With the low burden of calcific deposits there is no advantage of high keV images (Panel D) compared to low keV (Panel C), and the lower energy images improve intravascular contrast visualisation (C).

Just six years ago the landmark ACCURACY study demonstrated the value of 64-multidetector row CT (MDCT) with per-patient sensitivity, specificity, PPV and NPV of 0.95, 0.83, 0.64, and 0.99 for the identification of moderate stenosis, and 0.94, 0.83, 0.48, and 0.99, for severe stenosis[91]. In a subgroup of patients with severe coronary artery calcification (Agatston score >400 units), the specificity fell to 0.53. A more recent subgroup analysis from the CorE64 study, in patients with a calcium score $\geq$600,

found that the sensitivity, specificity, positive and negative predictive values were 0.96, 0.56, 0.94 and 0.63 respectively,[119] limited due to blooming artefact, while a large systematic review gave pooled, per-patient sensitivity as 0.98 – 0.99 and specificity as 0.51 – 0.84 (two categories of Agatston score, 400-1000 and >1000) for 64-MDCT.[149]

The appeal of CT for the investigation of coronary artery disease is clear. Invasive angiography carries a small, but important, risk of mortality and morbidity[95], while CT is both cost effective[96] and convenient, and can demonstrate plaque composition both within and out of the vessel lumen. Even in the presence of severe coronary calcification, ascertaining the presence or absence of obstructive disease can predict the need for revascularisation and the likelihood of death. In one recent analysis only 11% of patients with a calcium score >600 required revascularisation, and all of these had severe, underlying stenosis identified at CT.[150] However, conventional CTCA techniques have struggled to maintain their diagnostic performance in patients with extensive calcification.[119] This study adds to existing evidence that novel imaging methods may be able to overcome such difficulties, permitting access to non-invasive anatomical imaging to a wider patient group.[151] Importantly in this study, no patient was excluded on the basis of artefact from calcification.[152]

Few studies of new-generation CT scanners have been undertaken to explore imaging in patients with extensive coronary calcification.[151] Initial exploration of dual source techniques was disappointing, with one of two studies from the same centre reporting “limited accuracy” with a PPV of just 70%,[153] and the second seeing an

overestimation of mild stenosis leading to a PPV of 61%, despite the per-vessel prevalence of moderate stenosis of just 17%.[154] One more promising study demonstrated sensitivity, specificity, PPV and NPV all above 90% on segment- and vessel-based analysis, but with a similarly low disease prevalence (19%) and having excluded segments where artefact from calcium impacted on image quality.[152] Results from studies of dual-source CT (DSCT) in the aforementioned systematic review suggested a pooled sensitivity and specificity of 0.96 – 0.97 and 50.0 – 84.0 respectively, for calcium scores of 400-1000 and >1000.[149]

There are some theoretical advantages of single-source over alternative dual-source techniques. With two sources located distinctly from each other there must be gantry rotation between each kVp acquisition. This reduces the temporal association of each kVp dataset. Furthermore, because this data is not entirely coincident it must be reconstructed in the image, rather than projection, domain which may impair image quality.[155] Whether these differences in technology translate into meaningful clinical discrepancies remains to be seen.

Our study has some limitations. It included patients with heavy coronary calcification, who therefore had a high pre-test likelihood of significant coronary artery stenosis. The high positive predictive value of this test should be interpreted accordingly, although this does not detract from the potential benefits of this modality in such a patient group. This feature of our cohort also accounts for the apparently poor, per-patient, NPV for moderate stenosis – only four patients had a ‘negative’ CT. The wide

confidence intervals at the per-patient level prohibit definitive conclusions being drawn about test accuracy.

The radiation dose is significant. In order to ensure the feasibility of the technique we aimed to avoid noise limitation as a priority and so used tube presets with higher currents and fewer BMI strata than previous studies.[147] We used a cardiac-specific conversion factor[36] double that of most earlier studies, and when this variation is considered the dose is comparable to,[152] or less than,[156] other dual-energy studies and akin to contemporary practice,[36] particularly in the context of calcified disease.

One patient was excluded from the analysis due to the occurrence of contrast-induced tachycardia, which rendered the images completely uninterpretable. Our study protocol did not permit repeat imaging and no meaningful estimation could be made of any coronary segment. This is an acquisition difficulty rather than one related to the novel technology.

Finally, this remains a pilot study and, while demonstrating the ability to generate interpretable images with satisfactory patient tolerance at an acceptable radiation dose, firm conclusions as to the diagnostic abilities of this technology require further, large scale analyses. While we have attempted to make broad comparisons with existing technologies and previous studies, head-to-head comparison is required to confidently assess the diagnostic benefit of dual-energy techniques.

Overall this initial study suggests that the use of single-source, dual energy CT for the assessment of severely calcified coronary arteries is feasible, and demonstrates acceptable accuracy compared to conventional technology, which may be worthy of further evaluation in a clinical population.

4. Image reconstruction methods

4.1 Introduction

A range of novel technologies has been developed to improve the assessment of calcified coronary arteries, some of which have been explored in the preceding chapters. Iterative reconstruction (IR) is one further method which may improve diagnostic accuracy, using more complex mathematical processing of the statistical facets of image acquisition, combined with filtered back projection data, to minimise image noise (see chapter 1.3). The use of IR is becoming widespread, not least due to the apparent ability to keep noise constant, or even reduced, while also reducing radiation dose.[57] While these techniques improve image quality, their effect on diagnostic accuracy is less clear. Recent work in abdominal imaging has examined IR techniques with liver lesions, which are typically low density, and raised concerns that low-contrast detectability may be impaired when the radiation dose is also reduced.[157] Further studies with thoracic CT suggest similarly questionable results at very low radiation doses,[158] although this is inconsistent and IR does seem to provide acceptable results for some pathologies.[159] IR has been examined in small cohorts of patients to consider coronary stenosis assessment and plaque composition,[160] where it appears to reduce blooming artefact.[161]

As of 2012, model-based iterative reconstruction (MBIR) techniques have also been developed. As previously discussed, these methods use more accurate modelling of the scanner system optics, avoiding assumptions about the scanner or the physical properties of the image acquisition process. By modelling these processes from scratch and thereby avoiding hybridisation with filtered back projection, which is inherently

flawed due to these mathematical assumptions, these purport less noise. They offer the possibility of ultra low-dose scanning, with some exploratory chest CT imaging reaching doses comparable to chest radiography.[58] As with statistically modelled reconstruction methods, the question remains one of accuracy and while there is a plethora of analysis considering image quality, there is a paucity of data examining the accuracy of these techniques. Some recent work in this area has evaluated the delineation of vessels[162,163] and the assessment of vascular diameter[164,165] with various types of iterative reconstruction. These studies have examined large, non-calcified vessels.

To date a single study has examined the application of MBIR to cardiac CT.[166] This *in vivo* work studied 42 patients using standard and ultra-low dose CT, the latter employing tube current of 150 – 210 mA and 80 – 100 kV dependent on body mass index. The mean dose length product was 14.9 mGy cm – a dose reduction of 82% - with no statistically significant difference in image quality. Because MBIR is not yet commercially available the scans needed to be reconstructed off-site with the manufacturer. Furthermore, only 48% of patients had coronary calcium and the median calcium score for the whole study population was 141. There was no assessment of the accuracy of the reconstruction algorithm. My preliminary investigations suggested a marked improvement in image quality using MBIR (Figure 9).

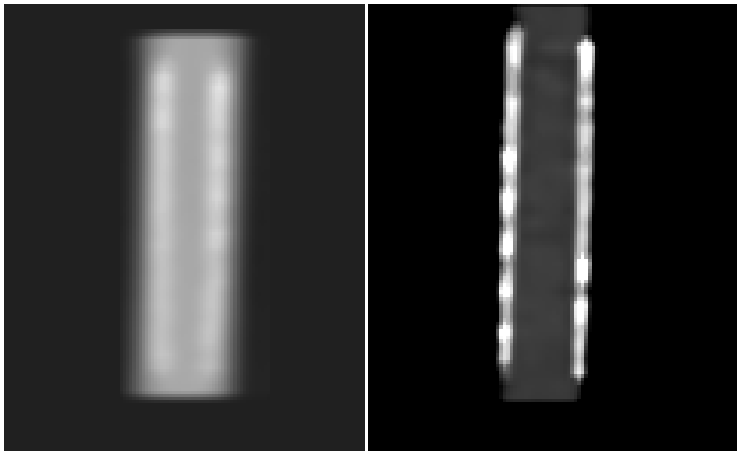

Figure 9
Preliminary examination of a single in vitro *coronary artery phantom containing a drug-eluting stent. The same image has been reconstructed using iterative reconstruction (left) currently used in clinical practice (50% blending with filtered back projection) with a novel model-based iterative reconstruction method (right).*

Of interest, some recent work has also considered more straightforward options of improving accuracy in the context of calcified stenosis. CT scanners come with a variety of reconstruction algorithms, or 'kernels'. These are the filters through which the back projected data is reconstructed and each one does this variably, to balance spatial and contrast resolution. They are generally classified according to the degree of 'smoothness' they confer, and are useful for specific indications. Softer, smoothing kernels tend to facilitate the visualisation of low-contrast structures at the expense of spatial resolution, while sharper, edge-enhancing kernels are often used to identify high-contrast boundaries, for example between soft tissue and bone. These in particular appear to improve stent assessment, both in terms of visibility[167] and detection of in-stent re-stenosis.[168] Some kernels also adjust Hounsfield values of various tissues. As previously discussed, filtered back projection is far less computationally demanding (and therefore faster) than both iterative and model-based reconstruction techniques, and optimisation of this process may be just as useful if appropriate kernels are selected.[169]

The optimal imaging strategy of the calcified coronary lesion has not been evaluated, despite its importance as the limiting factor for the accuracy of CT coronary angiography. In order to further consider the range of techniques available for coronary analysis we assessed the accuracy of existing reconstruction methods and a new model-based iterative reconstruction process at evaluating dense stenosis in coronary phantom models.

4.2 The study

Materials and methods

Coronary phantoms

Coronary segment phantoms (Fuyo Corporation, Tokyo, Japan) were constructed at 2.5, 3.0 and 3.5 mm (+/- 0.02 mm) luminal diameter using acrylonitrile butadiene styrene (which has a density of 40 HU). Models of both concentric circular and irregular (crosshair) morphology were precision machined high density polyvinyl chloride (950 HU) to simulate calcified plaque, to create mild (25%), moderate (50%) and severe (75%) concentric luminal stenoses for each segment diameter. We measured the mean density of intraluminal contrast in 100 consecutive patients with calcified disease. The phantom segments were filled with intravenous contrast (Omnipaque 300, GE Healthcare AS, Oslo, Norway), diluted to a density of approximately 450 HU, to correlate with these clinical targets. In total, 18 variations of coronary anatomy were studied.

Imaging protocol

Each coronary segment was placed into a 32 cm CTDI phantom to simulate surrounding tissue and were individually imaged longitudinally, parallel to the z-axis, using a standardised protocol (100 kV, 420 mA, pitch 0.2, 400 ms gantry rotation time) with a 64-MDCT scanner (Discovery CT750 HD, GE Healthcare, Milwaukee). This standardised protocol was selected as, at the time of investigation, model-based iterative reconstruction was not available for use in imaging protocols using ECG gating. The images were undertaken in both standard and high-definition modes and were not touched between these acquisitions. The images were then reconstructed using filtered back projection, iterative reconstruction (Adaptive Statistical Iterative Reconstruction, GE Healthcare), model-based iterative reconstruction (Veo, GE Healthcare), and with standard or edge-enhancing kernels (Bone, GE Healthcare), according to the reconstruction method. We reconstructed these in 0.625 mm thickness slices at 0.5 mm intervals. In all, 11 combinations of reconstruction techniques were assessed (Table 11).

Scan mode	Reconstruction method	Kernel
Standard	Filtered back projection	Standard
	Iterative reconstruction – 30% blending	Standard
	IR – 50% blending	Standard
	IR – 70% blending	Standard
	IR – 100% blending	Standard
	Filtered back projection	Edge-enhancing
	IR – 50% blending	Edge-enhancing
	IR – 100% blending	Edge-enhancing
	Model-based iterative reconstruction	N/A
High-definition	IR – 50% blending	Standard
	IR – 50% blending	Edge-enhancing

Table 11
Scanner parameters investigated using coronary artery phantoms

Image analysis

The circular concentric stenoses were analysed quantitatively for assessment of stenosis. The segment was examined in an axial plane to visualise the luminal cross section. This was bisected through the centre in a horizontal plane, parallel to the x-axis, and measurements of the Hounsfield unit density were taken at 0.1 mm intervals along this line using the workstation software (Advantage Workstation 4.6, GE Healthcare). This allowed the construction of a graphical illustration of the cross-section, plotting density against distance (Figure 10). Maximum and minimum luminal diameters were measured precisely from this graph, and the difference between these recorded, to give a quantitative measure of the clarity of the lumen. The degree of error was calculated as a proportion of the mean diameter at CT compared to the known manufactured diameter.

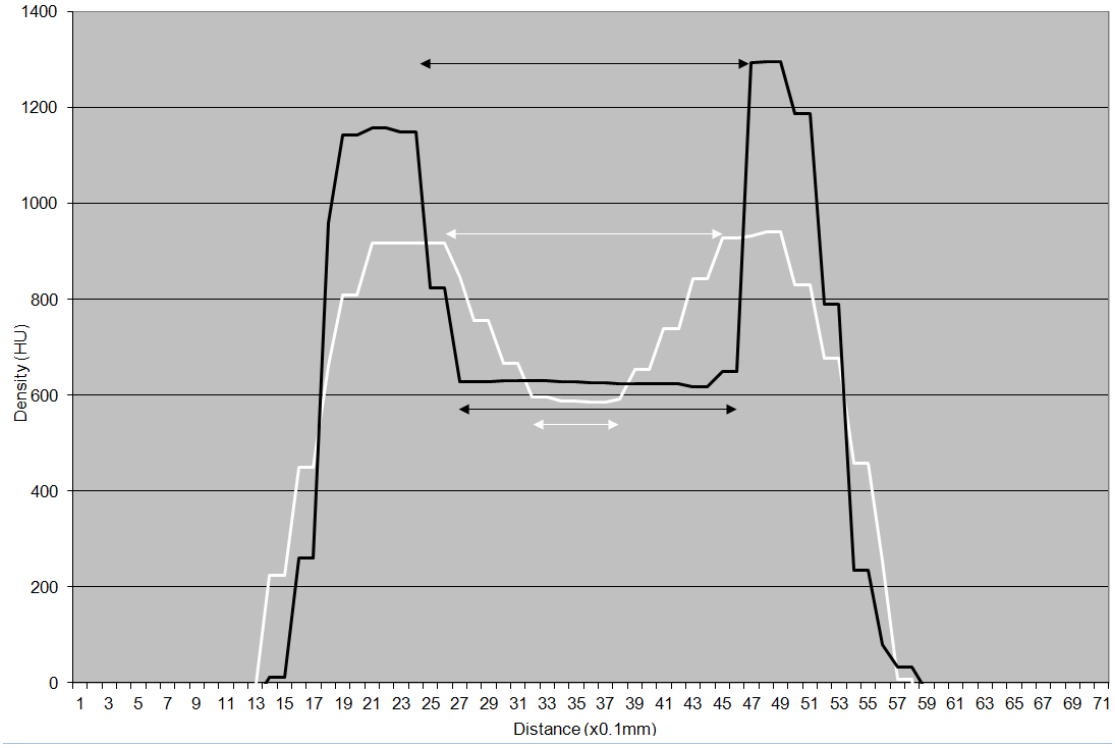

Figure 10.1

Graphical cross section of the same coronary segment demonstrating densities reconstructed using model-based iterative reconstruction (black) and 50% Adaptive Statistical Iterative Reconstruction blending and a standard kernel. The peaks illustrate the high-density 'plaque' with the centre portion demarcating the contrast-filled lumen. The arrows show the maximum and minimum diameter of the lumen using each technique.

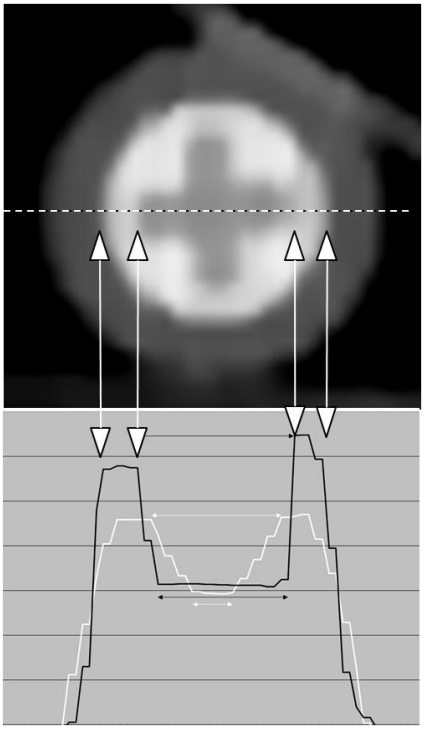

Figure 10.2

Illustrative diagram demonstrating the generation of Figure 10a from the image. The phamtom was bisected with density measurements every 0.1 mm.

The irregular stenoses underwent visual analysis by two experienced readers of CT coronary angiography each with more than 10 years experience of cardiac CT). Each image was rated using a Likert scale to describe the clarity of the lumen and estimation of stenosis: 1 – no lumen visible; 2 – lumen barely visible, impossible to establish shape; 3 – lumen visible, uncertainty about shape; 4 – lumen fairly clear, shape distinguishable but stenosis uncertain; 5 – lumen shape easily identifiable and stenosis assessable. Differences between the readers were aligned by consensus.

Statistical analysis

For the quantitative assessments, the degree of error was calculated for each parameter (reconstruction method or kernel) and the mean was derived. These were compared graphically in a boxplot and analysed using the Friedman test as a non-parametric analysis of variance. As the Friedman test suggested that a significant difference was present a Wilcoxon signed-rank test for paired data was used to compare groups. Due to the sample size, and that the data does not look plausibly normal, a non-parametric Wilcox signed-rank test was employed. A full pairwise analysis was performed between each group, allowing for the multiple testing using a Benjamini and Hochberg correction. Two-tailed P values <0.05 were considered significant.

We also analysed the data on an 'as-scanned' basis, comparing combinations of reconstruction method and kernel. These clinical combinations were also compared using the Freidman test, followed by pairwise analysis, again using a Benjamini and Hochberg correction.

Qualitative assessment was scored for each image (nine stenoses, 11 reconstruction methods). The mean scores were analysed using a non-parametric Wilcox signed-rank test and interobserver variability was assessed using Cohen's kappa.

Statistics were performed using R (version 3.0.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Nine coronary segments, comprising three vessel sizes (internal diameters of 2.5, 3.0 and 3.5 mm) with three degrees of high density stenosis (mild, moderate, severe) were analysed. The segment with an internal diameter of 2.5 mm and severe stenosis (residual luminal diameter 1.3 mm) could not be assessed using the standard kernel as the lumen was completely obliterated by artefact (Figure 11). This segment was therefore excluded from the quantitative analysis. Of note, the error of all methods of reconstruction increased markedly in this segment, suggesting that structures this small may not be sufficiently visible using this technology.

For the quantitative assessment, the error for each reconstruction method is detailed in Table 12. With regards to the qualitative assessment, the kappa statistic for interobserver agreement was 0.91 (weighted 0.95, confidence interval 0.86 – 0.98) suggesting excellent agreement. The image quality scores are presented in Table 13.

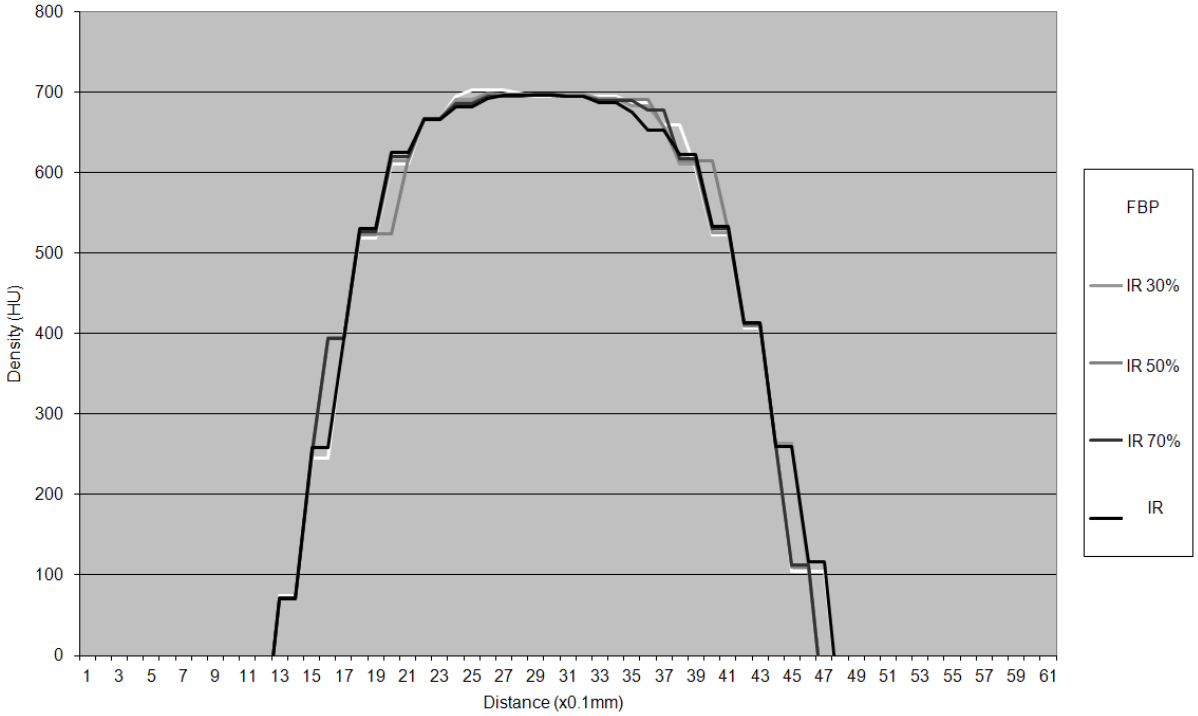

Figure 11

Cross section through the 2.5mm coronary segment with severe stenosis. No lumen can be identified. Grey scale lines represent filtered back projection and various levels of iterative reconstruction blending (30%, 50%, 70% and 100%).

Reconstruction method			Stenosis			Vessel size			Total
Mode	**Recon**	**Kernel**	**Mild**	**Moderate**	**Severe**	**2.5 mm**	**3.0 mm**	**3.5 mm**	**Mean**
Std	FBP	Std	0.520	0.583	0.394	0.518	0.530	0.491	0.512
Std	IR 30%	Std	0.531	0.581	0.394	0.492	0.549	0.497	0.516
Std	IR 50%	Std	0.531	0.574	0.394	0.492	0.549	0.491	0.513
Std	IR 70%	Std	0.567	0.565	0.394	0.524	0.549	0.496	0.514
Std	IR 100%	Std	0.532	0.577	0.394	0.518	0.536	0.490	0.515
Std	FBP	Edge	0.238	0.234	0.367	0.482	0.218	0.140	0.280
Std	IR 50%	Edge	0.288	0.254	0.367	0.520	0.230	0.160	0.303
Std	IR 100%	Edge	0.244	0.204	0.329	0.416	0.215	0.147	0.259
Std	MBIR	N/A	0.162	0.220	0.344	0.324	0.256	0.146	0.242
HD	IR 50%	Std	0.520	0.606	0.394	0.518	0.539	0.147	0.520
HD	IR 50%	Edge	0.253	0.241	0.301	0.420	0.229	0.146	0.265

Table 12

Summary of quantitative error for each reconstruction parameter, given by degree of stenosis, vessel size and total mean. Std – standard, HD – high-definition, Edge – edge-enhancing kernel, FBP – filtered back projection, IR – iterative reconstruction (ASIR), MBIR – model-based iterative reconstruction, N/A – not applicable (kernels are not used for MBIR)

Reconstruction method			Image quality score
Mode	**Recon**	**Kernel**	
Std	FBP	Std	1.8
Std	IR 30%	Std	1.6
Std	IR 50%	Std	1.6
Std	IR 70%	Std	1.7
Std	IR 100%	Std	2.0
Std	FBP	Edge	3.3
Std	IR 50%	Edge	3.4
Std	IR 100%	Edge	3.4
Std	MBIR	N/A	4.0
HD	IR 50%	Std	1.6
HD	IR 50%	Edge	3.6

Table 13

Image quality for each reconstruction parameter. Std – standard, HD – high-definition, Edge – edge-enhancing kernel, FBP – filtered back projection, IR – iterative reconstruction (ASIR), MBIR – model-based iterative reconstruction

Kernels

The mean error for the standard kernel across all other parameters was 0.524. The mean error for the edge enhancement kernel was 0.277. The edge enhancement kernel resulted in significantly less error than the standard kernel (p 0.012, figure 12). Kernels cannot currently be specified with MBIR, but overall this too was significantly more accurate than non-MBIR methods with standard kernels (error 0.242, p 0.012). The edge-enhancement kernel was not statistically significantly different to MBIR (p 0.547). The range of measured densities appears higher using edge-enhancement kernels with high-definition scanning, but this did not affect edge definition or error.

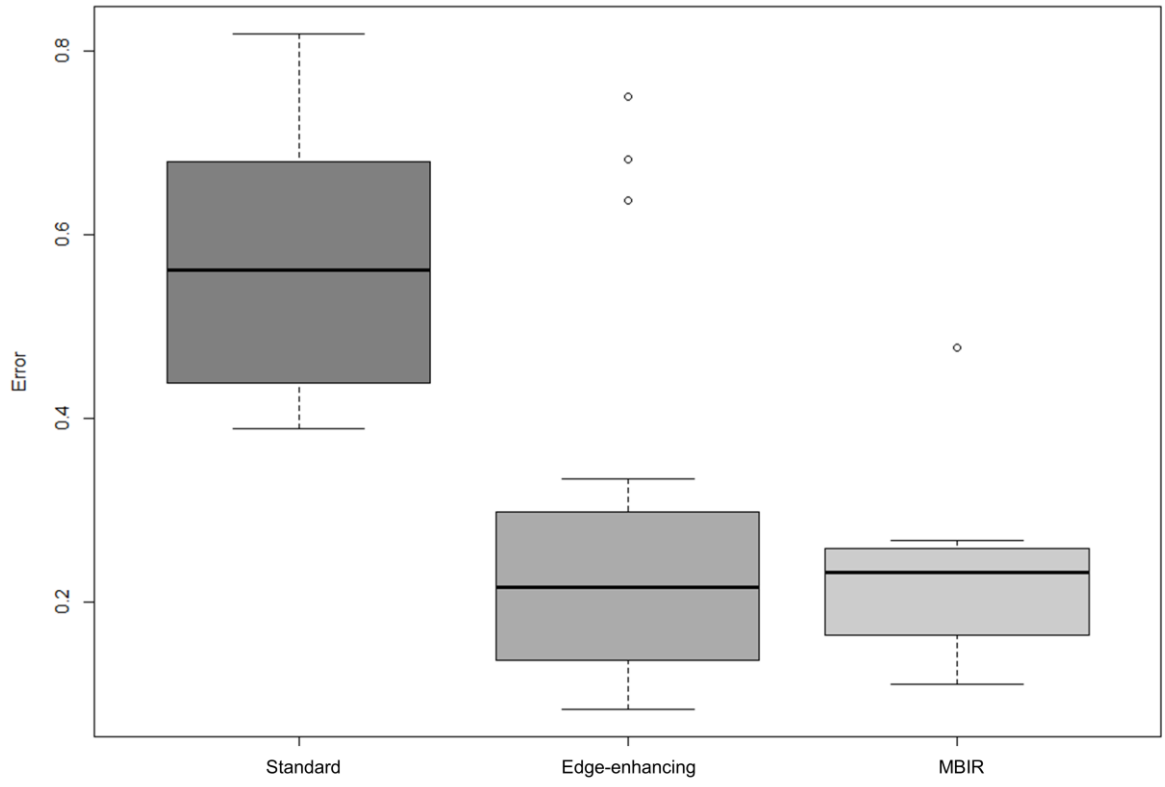

Figure 12
Box plot comparing mean errors by kernel type, and with model-based iterative reconstruction

Subjective lumen visibility was also higher with both model-based iterative reconstruction (mean score 4) and edge-enhancement kernels (3.4) than with standard kernels (1.7).

Reconstruction methods

The mean errors for the each reconstruction method were: FBP – 0.389, ASIR – 0.432, MBIR – 0.242, demonstrating that there were significant differences between them ($p = 0.0008$). Pairwise testing suggested differences between all three groups (Figure 13), with MBIR significantly more accurate than both ASIR ($p = 0.012$) and FBP ($p = 0.016$), but also with FBP more accurate than ASIR ($p = 0.012$).

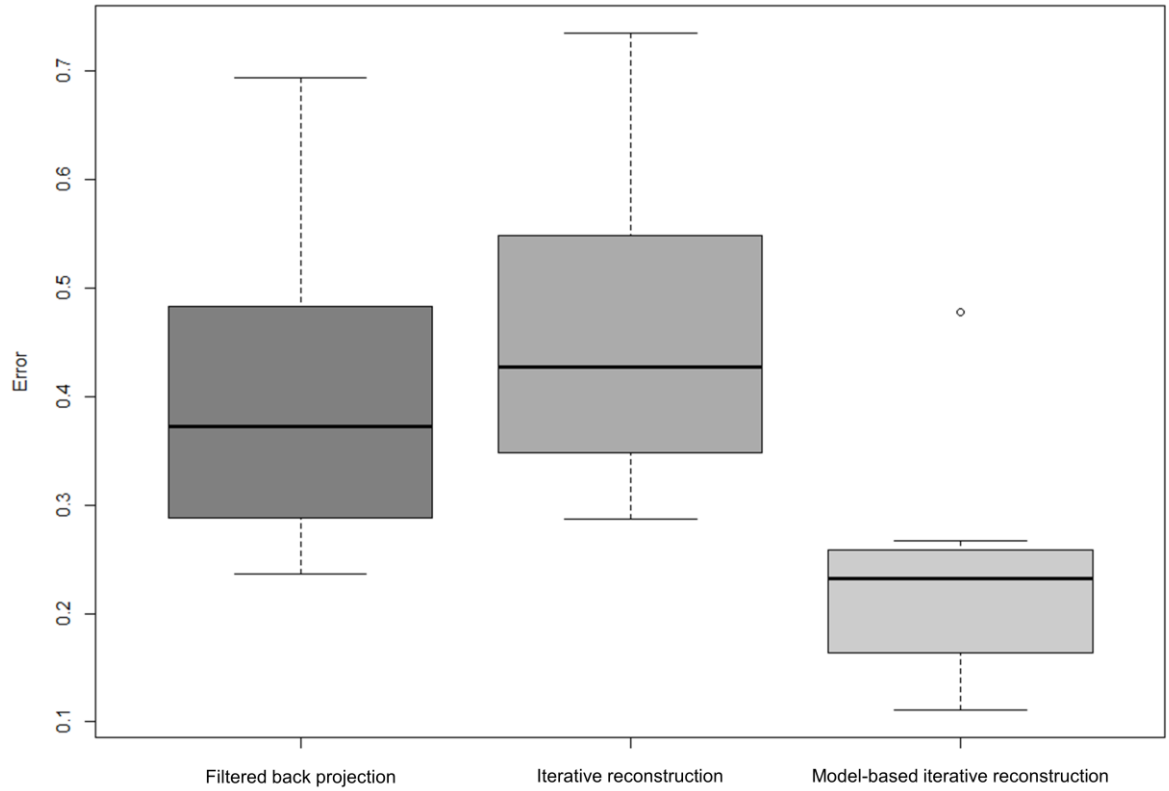

Figure 13
Box plot comparing image reconstruction methods.

MBIR was scored highest for lumen visibility with a mean of 4. FBP was better than all levels of ASIR combined (2.6 vs. 2.3) but similar to ASIR with 100% blending (2.6 vs. 2.7). This suggests that there may be subtle differences between each level of ASIR, which is corroborated by the increasing visibility seen with increasing blending of ASIR (Table 14).

% ASIR blend	0 (FBP)	30	50	70	100
Mean score	1.8	1.6	1.6	1.7	2

Table 14
Mean lumen visibility score for levels of ASiR using standard reconstruction kernel

Scanning mode

The mean error for high-definition scanning and standard scanning were 0.369 and 0.372 respectively. There was no significant difference between these groups (p = 0.476). This is reflected by the measured graphs (Figure 14) and the mean visibility score, which was 2.6 for high-definition acquisition and 2.5 for standard methods.

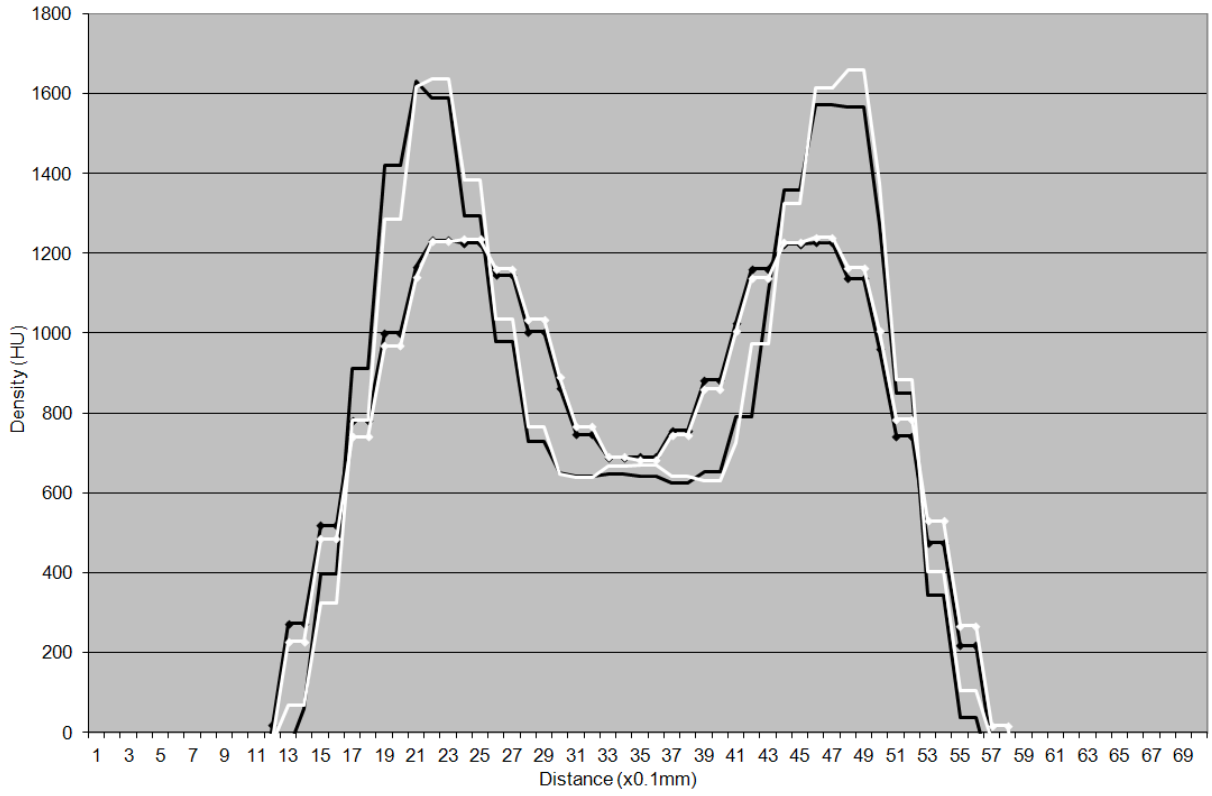

Figure 14
3.5mm vessel with severe stenosis comparing HD (white) with standard (black) acquisition, using edge-enhancement (smooth line) and standard (dotted line) kernels. There is no clear difference between HD and standard scan modes.

Clinical combinations

Combining reconstruction techniques in a manner commensurate with routine clinical practice demonstrated similar results. At 5% significance there are statistically significant differences between the standard reconstruction kernel and both the edge-enhancement kernel and MBIR (Figure 15, Table 15).

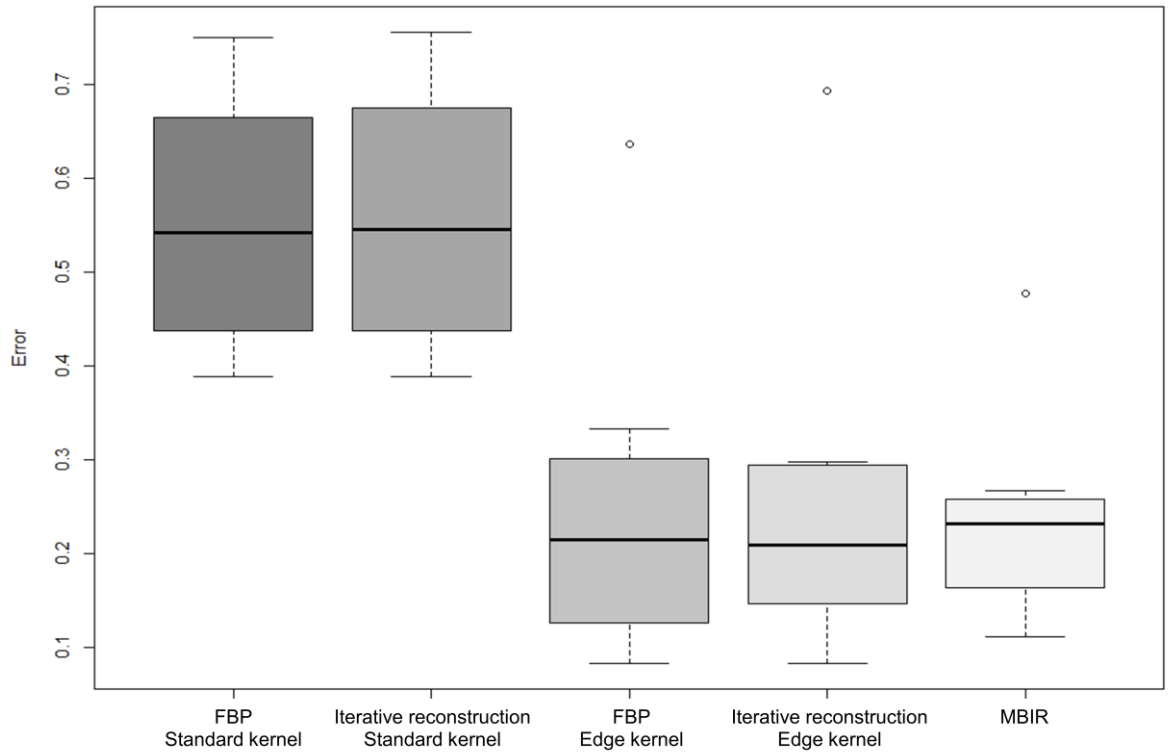

Figure 15
Box plot comparing clinical combinations of reconstruction method and kernels

Reconstruction method		*FBP*	*FBP*	*ASiR*	*ASiR*
	Kernel	*Standard*	*Bone*	*Standard*	*Bone*
FBP	*Standard*	-			
FBP	*Bone*	0.013	-		
ASiR	*Standard*	0.655	0.013	-	
ASiR	*Bone*	0.013	0.655	0.013	-
MBIR		0.013	0.673	0.013	0.638

Table 15
p values for error comparisons of clinical combinations of reconstruction methods. FBP – filtered back projection, ASIR – Adaptive Statistical Iterative Reconstruction

4.3 Discussion

Arterial wall calcification represents a major challenge to successful, accurate CT coronary angiography. This phantom study suggests that model-based iterative reconstruction may prove to be of significant benefit in the assessment of calcified coronary arteries (Figure 16). Blooming artefact, caused by partial voluming at the interface between very high and much lower tissue densities, and beam hardening, appears to be reduced, resulting in greatly improved delineation of structures. This finding is consistent with previous work by others examining the accuracy of MBIR in larger, non-calcified vessels.[165]

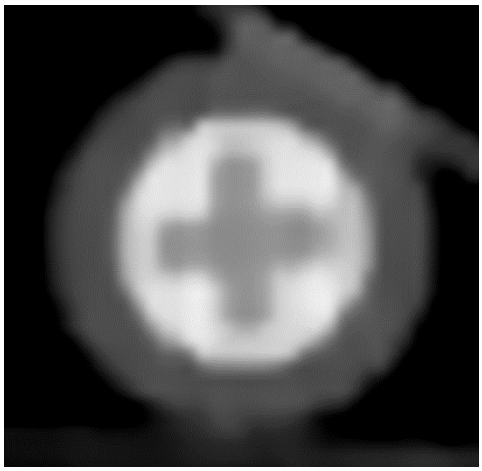

Figure 16
3.5mm vessel with moderate, irregular stenosis reconstructed using MBIR. The smallest internal diameter of this vessel phantom is 0.48 mm.

Our study also highlights the importance of reconstruction kernels and suggests that there may be a need to adjust these in light of findings for each patient. This rapid and widely available adjustment to reconstruction comes with no additional burden to the patient, in terms of either scans or radiation dose, and may improve the accuracy of the imaging when highly calcified vessels are encountered. This will need specific assessment in patients with mixed morphology plaque to ensure that the increase in noise does not adversely impact on the interpretation of the remainder of the image,

although the simplicity and aforementioned benefits of reconstruction kernels would readily permit an edge-enhanced image set to be produced alongside standard imaging.

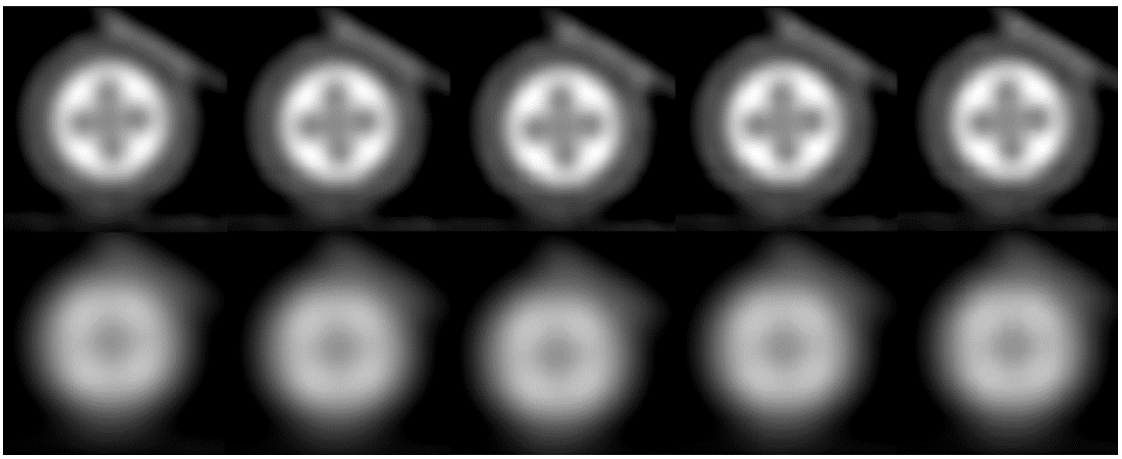

Figure 17
The effect of ASIR and edge enhancing kernels. The same coronary segment reconstructed with (from left to right) FBP, 30% ASIR, 50% ASIR, 70% ASIR, 100% ASIR and using edge-enhancement (top) and standard (bottom) kernels.

In this study, with our static x-ray dose (fixed mA protocol), the iterative reconstruction algorithm did not alter the diagnostic accuracy in this setting (Figure 17), and only high levels of iterative blending conferred any advantage in lumen visibility and assessment. Further work will be required to establish whether accuracy can be maintained using iterative reconstruction despite a reduction in dose. Although the use of novel reconstruction methods is touted as a method for improving image quality, in clinical practice it is often used to facilitate a reduction in radiation dose, while maintaining a particular image quality level. It will be important to evaluate whether IR offers superior maintenance of image quality in the face of reducing radiation dose, in comparison to conventional techniques.

Importantly, the study considers the accuracy of the various reconstruction methods, rather than just interpreting image quality. A plethora of studies have already confirmed that iterative reconstruction improves image quality, including in coronary imaging,[59] but far less work has been undertaken to consider its impact on diagnosis. The improvements in image quality with MBIR have been confirmed in a previous study at our institution investigating thoracic CT[170] and a small study examining its use in cardiac CT,[166] a finding which has also been seen in our analysis. While these previous studies confirmed the visually appealing nature of MBIR, it also suggested that the diagnostic acceptability of this method is high, which has been further corroborated by our work.

This study does have a number of limitations which need to be considered. In order to ensure exact parity between acquisition and reconstruction techniques, and facilitate precise analysis, coronary segments with known dimensions and stenoses must be repeatedly scanned in the same position. Quite clearly this cannot be achieved in patients, not least due to the radiation dose, and cardiac and respiratory motion, and therefore this study relies on phantoms. The vessel and its composition do limit the direct applicability of these findings to a patient population. The use of a CTDI (CT dose index) phantom may also limit some of the findings. The coronary segments are surrounded by a thin layer of air inside cavities within the phantom. This adds an additional tissue interface which is not present *in vivo*, although of course the heart is surrounded by intrapulmonary air. Whether this has a significant impact on the reconstruction algorithms is not clear, but altering the surrounding soft tissue may introduce noise, which these techniques are intended to reduce. A further limitation is

that our scans were undertaken without ECG gating and using helical acquisition. This was essential to ensure compatibility with MBIR, which is not yet available for clinical use with ECG gating. At our centre the vast majority of clinical studies are carried out with prospective gating and this again somewhat limits our findings. That said, previous analyses have shown that prospective gating improves image quality,[171] and so we may have in fact underestimated the usefulness of MBIR, and the impact of gating is likely to affect all scanning and reconstruction techniques equally. Finally, despite attempts to make the assessment of the coronary lumen entirely objective, some element of subjectivity was present, particularly in segments where the image quality was poor (Figure 18).

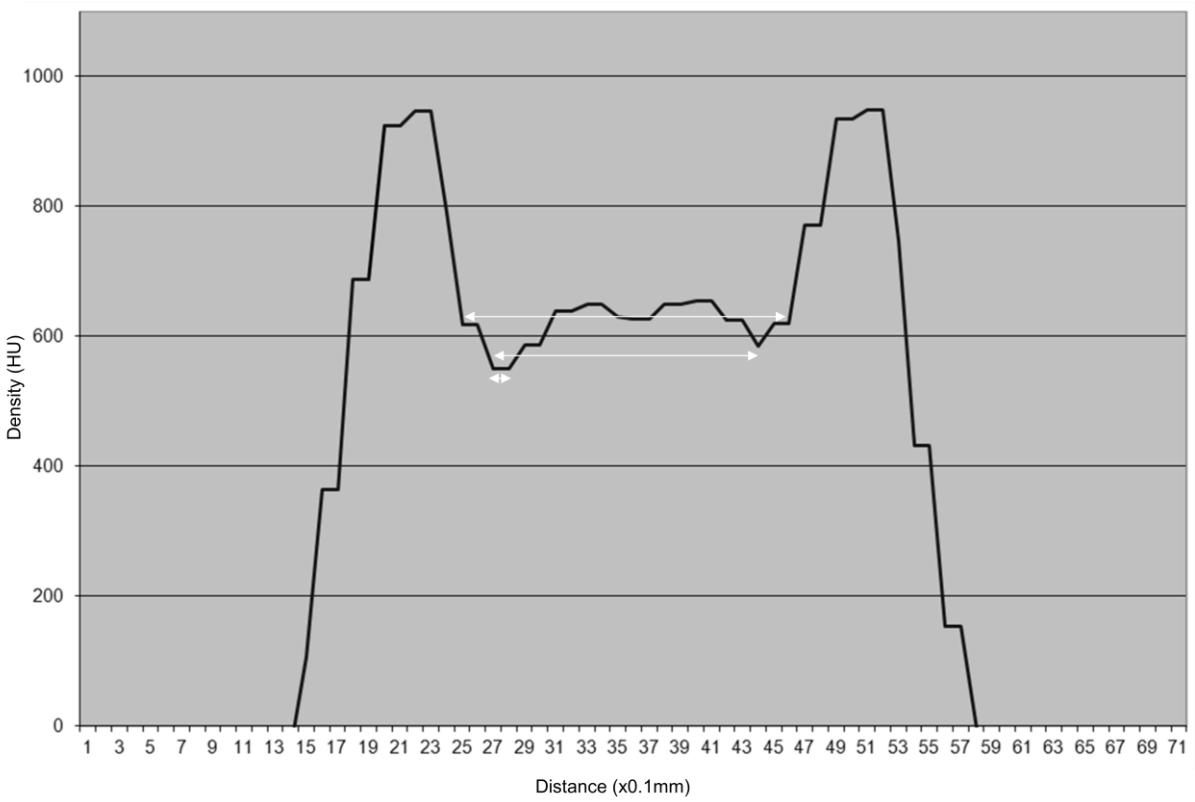

Figure 18
Limitations of objectivity with assessment of phantom diameter. If the distance representing the lowest density is used then, strictly, the bottom arrow represents the measurement which should be taken. Applying some subjectivity one of the other two arrows is likely to be more representative. While these do vary the maximum variation is less than 0.4 mm which is unlikely to have a significant impact on the overall results.

The use of three decimal places may give a false impression of the accuracy of measurement. The Hounsfield unit density was measured at 0.1 mm intervals across the image and the degree of error was therefore calculated as a submillimeter proportion. Nonetheless, the image has been acquired by 0.625 mm detectors, with the reconstruction process creating variations below this interval and while these tiny alterations are the focus of this study it is unlikely that genuine differences at less than 0.1 mm can be identified with this methodology. Furthermore the clinical relevance of any such variation is dubious.

Despite these limitations, we have ensured that consistency is maintained with each scan acquisition. We have assumed a perfect environment, without cardiac motion and with presumed breath hold, while keeping scanner settings constant, in order to minimise confounding factors as much as possible. Furthermore, we have examined coronary segments simulating concentric calcification, which is a particularly challenging scenario for the current generation of CT scanners. The major residual limitation is undoubtedly the current clinical applicability of these findings. It is clear that further *in vivo* studies are required in patients to examine the effects of reconstruction kernels on diagnostic accuracy but at present model-based iterative reconstruction is not available for clinical use in cardiac CT studies.[166]

Our study therefore raises a number of questions for future research. The effects of reducing radiation dose and increasing surrounding soft tissue need to be explored. Further reconstruction kernels should be examined in a clinical setting, ideally with correlation with reference standards, to identify the optimal choice, and patient-

specific protocols may need to be considered. In particular the benefit of high-definition scanning over standard acquisition with edge enhancement kernels may need to be established (Figure 19). Additional scan parameters, particularly tube energy (kV), should also be assessed, as well as cardiac motion, and studies are ongoing at our institution using a beating heart phantom for this purpose. Future studies should continue to explore the diagnostic accuracy of these techniques, in comparison to accepted CT methodology or (preferably) the reference standard of invasive coronary angiography, rather than just measurements of subjective visual appeal.

Finally, this study has highlighted that current methods using standard algorithms may not be suitable for the analysis small, calcified vessels. Minimum vessel sizes may need to be stipulated for particular reconstruction techniques to ensure that diagnostic reliability can be maintained.

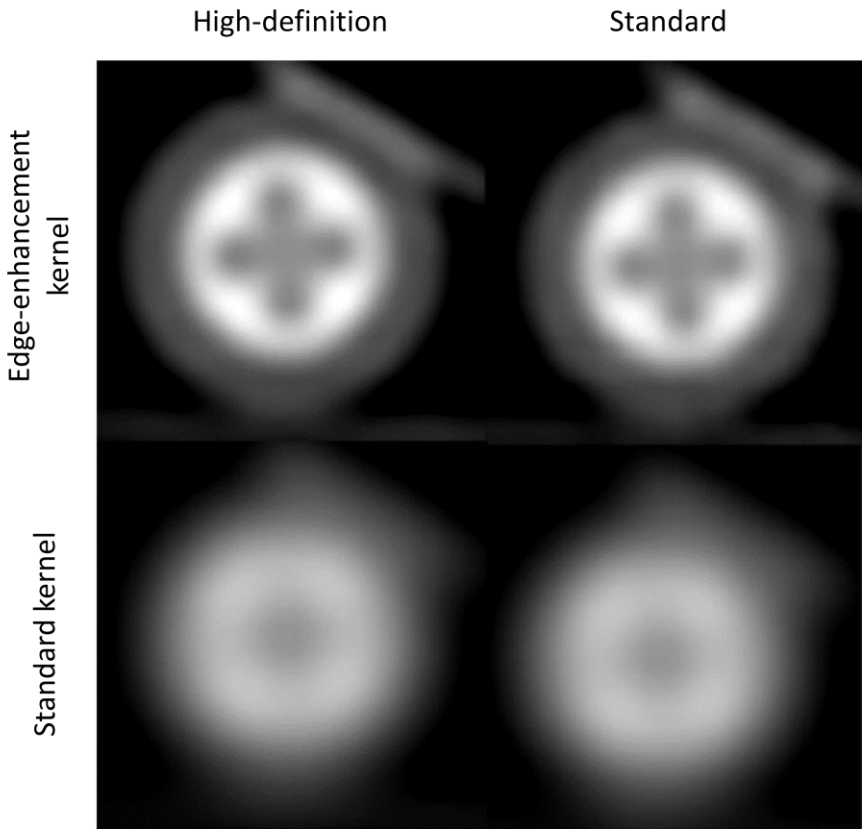

Figure 19

The effect of high definition scanning and edge enhancement kernels. The same coronary segment imaged in high definition (left) and standard (right) modes and reconstructed using edge enhancement (top) and standard (bottom) kernels. 50% iterative reconstruction (ASIR) was used for all images.

Section 3 – Patients with poorly controlled heart rate or rhythm

5. Imaging patients with atrial fibrillation

5.1 Introduction

Patients with atrial fibrillation (AF) often have both R-R interval variation, and persistent relative tachycardia, making CT imaging challenging and degrading image quality. The prevalence of coronary artery disease in patients with AF is extremely high, particularly in those referred for CTCA, with estimates of more than 80% having any disease.[172] Furthermore, mortality in these patients is more than double that of patients without AF, predominantly due to underlying cardiac pathology.[172] Accurate coronary imaging is therefore of potentially great benefit.

The conventional method for imaging patients with fast, or irregular, heartbeats is with retrospective ECG gating, where image acquisition occurs constantly throughout a number of cardiac cycles and suitable cycle phases are retrospectively extracted for image analysis.[173] While this allows the maximum flexibility, to overcome variation in the length of R-R interval and facilitate assessment of the phases with the least motion blur, the cost in terms of radiation exposure is high. In patients in sinus rhythm, prospective gating, where the x-ray tube is turned on for a brief moment at a predetermined phase of the cardiac cycle, results in better image quality with a radiation dose reduction of more than 75%.[174] The usual preference is to image in diastole, where coronary motion is at its least, but the unpredictable R-R interval and shorter duration of diastole in tachycardia make this difficult in AF.

Some studies have considered acquisition of images earlier in the cardiac cycle. End-systole (or more precisely, the period of isovolumetric relaxation which immediately

follows) offers a small window of relative cardiac and coronary stability, which has been exploited to image both the aorta[175] and the coronary arteries in patients with AF.[176,177] This seems intuitive, due to the reduced time from detection of the R wave to scanning which, in combination with aggressive heart rate control,[178] would minimise the opportunity for interruption by the next ventricular contraction. Studies of 'systolic triggering' have been limited, demonstrating improvement in both image quality and radiation dose but still with only moderate image quality in more than one-third of patients.[177]

This study examined the transition from retrospectively gated scanning to prospectively gated, systolic triggering as our default method of acquisition for patients in atrial fibrillation. Analysis was undertaken to examine CTCAs before and after the introduction of this technique, with the primary outcome measure being radiation dose and the secondary measure being diagnostic confidence.

5.2 The study

Materials and methods

Study methods and ethical review

All CT scans were undertaken at a single, tertiary referral centre. The study was reviewed by our institutional Research & Development board and registered locally as a clinical service evaluation. Further ethical review was waived due to the retrospective nature of the study and informed consent was not required.

Patient selection

We reviewed the Clinical Radiology Information System to retrieve image sets on two groups of 25 consecutive patients with atrial fibrillation undergoing cardiac CT. One group was selected from patients immediately prior to September 2013, when we began prospective gating in AF, and the second group comprised 25 patients immediately after this change. Patients were excluded where image quality was suboptimal for reasons other than heart rate or rhythm (failure to breath-hold, contrast timing error, etc.). Demographic information and scan acquisition data were extracted from the clinical report, which is recorded contemporaneously at the time of image acquisition, and the scanner data sheet.

Image acquisition and reconstruction

The CT acquisition protocol was as follows. Patients with a minimum heart rate of >50 beats per minute and a maximum heart rate of >60 beats per minute received intravenous metoprolol, titrated in 5 mg aliquots.[178] Imaging was performed on a 64-detector row CT scanner (Discovery CT750, GE Healthcare, USA), with either prospective or retrospective gating. For prospective ECG gating with systolic triggering (45% R-R interval), 100 milliseconds of padding (additional tube-on time either side of the R-R interval) were applied, as per standard departmental protocol when imaging patients with heart rate variability. 0.625mm slices were taken at 0.5mm intervals to cover the cardiac volume. Retrospectively gated acquisition was undertaken without dose modulation with the pitch set to 0.2. In both cases tube parameters were adjusted according to patient BMI, with the same parameters selected regardless of gating mode. 100ml ioversol (Opivist 350, Covidien, Dublin) was administered (125ml

for bypass graft studies) at a reducing rate, commencing at 6.5ml/sec, followed by a saline bolus. Aside from the gating mode, all other acquisition parameters were consistent between the groups.

Images were reconstructed in a standard fashion, using a 50/50 blend of filtered back projection (FBP) and iterative reconstruction (Adaptive Statistical Iterative Reconstruction, GE Healthcare) and standard kernel, at 5% phase intervals, including the 45% (of the R-R interval) phase.

Image analysis

The images were anonymised in a random fashion and reviewed, blinded, by two expert readers, each with more than 10 years experience of cardiac CT. These were reviewed for stenosis assessment and diagnostic confidence. The latter was recorded on a 5-point Likert scale for each coronary segment, thus: 5 – excellent image quality with minimal motion artefact, not affecting diagnosis, 4 – mild motion artefact but diagnostic confidence maintained, 3 – moderate artefact with little diagnostic doubt, 2 – significant motion artefact with diagnostic uncertainty, correlative imaging essential, 1 – study uninterpretable due to motion artefact. Segments graded 3 or greater were considered to be diagnostic for the purposes of the study.

Outcome measures

The outcome measures were image quality by gating method and total study radiation dose. The secondary outcomes were diagnostic confidence by patient and artery.

Statistical analysis

Statistical analysis was performed using SPSS Statistics 21 (IBM Corp., New York). Chi squares were performed for categorical variables and Mann Whitney U testing for continuous variables, with a significance level of 0.05. Image quality scores were analysed on a per-patient and per-vessel basis, both by lowest image quality score and by mean image quality score, tested with the Kruskal-Wallace Test for independent samples. Post-hoc power was estimated using G*Power 3.1.9.2 .[179]

Results

Fifty patients were identified, having excluded three for non-AF reasons (two failed to breath-hold, one poor contrast timing due to contrast pump failure). The patient demographics are presented in table 16. There was no significant difference in gender, BMI, heart rate (absolute or degree of variability) or calcium score between the two groups.

	Prospective	**Retrospective**	**p value**
Mean age (years)	66 (SD 43 – 88)	62 (SD 43 – 82)	0.11
Male	80%	68%	0.18
Bypass graft studies (n)	1	1	0.31
Median calcium score	113 (IQR 31 - 287)	25 (IQR 0 – 129)	0.41
Mean BMI (kg/m^2)	28 (SD 19 – 38)	29 (SD 17 – 40)	0.74
Mean high heart rate (bpm)	89 (SD 47 – 130)	90 (SD 52 – 129)	0.73
Mean low heart rate (bpm)	61 (SD 29 – 93)	62 (SD 39 – 83)	0.50
Heart rate variation	30%	30%	0.65

Table 16
Baseline demographics for patients in the AF study. SD –standard deviation from the mean, IQR – interquartile range

The radiation dose was significantly higher for patients in the retrospectively gated group than those being scanned using prospective gating. The mean $CTDI_{vol}$ was 17.58

in the prospectively acquired group and 50.82 in the retrospectively acquired group (p <0.01). The mean dose-length product was 212 mGy.cm compared with 761 mGy.cm respectively (approximately 2.9 mSv versus 21 mSv using a 0.028 cardiac-specific conversion factor[36]).

Seven hundred and fifty seven coronary artery segments were evaluated for image quality (373 in the prospectively gated group and 384 in the retrospectively gated group). The proportion of diagnostic segments was 85% and 63% respectively (p <0.001). At a patient level, image quality was better in the prospectively gated group than the retrospectively gated group regardless of whether it was based on a mean of every analysed segment (3.78 versus 3.09, p = 0.02), or the lowest rated segment within each patient (2.36 versus 1.64, p = 0.01). Image quality was better in the prospective group for analysis of each major coronary vessel.

We undertook a post-hoc estimation of power for the primary outcome of radiation dose. This was calculated assuming an α-error probability of 0.05 and a calculated effect size of 2.2. The power of the study was calculated at 1.0.

5.3 Discussion

This study demonstrates that the use of end-systolic, prospective gating can significantly reduce the radiation exposure for patients in AF undergoing CT coronary angiography, and that image quality is at least comparable to retrospectively gated studies. Importantly this can be achieved using standard CT technology without the need for dual-source or wide detector array scanners.

The use of CT in patients with AF is expanding considerably. In addition to the identification of CAD, which is highly prevalent in this cohort,[172] CT is increasingly used for the evaluation of the heart prior to AF procedures, to identify left atrial or pulmonary venous abnormalities,[180] the proximity of at-risk structures,[181] or for fusion with intraprocedural, electrophysiological maps.[182] The exclusion of coronary disease is important where class Ic antiarrhythmic drugs are being considered.[183] Finally, patients with paroxysmal AF may be referred in good faith due to sinus rhythm at the time of consultation, but arrive for their CTCA in AF.

Various methods have been employed to facilitate coronary imaging in AF. Reducing average heart rate and heart rate variability in patients with atrial fibrillation improves image quality[184] and some authors have even considered inducing short periods of asystole for fluoroscopic imaging.[185] In recent years a number of technological advances have improved the temporal resolution of CT, helping overcome the difficulties of heart rate variability while maintaining radiation dose reduction. Wide-detector scanners can image the heart in a single heartbeat, although the appropriate phase of the cardiac cycle must still be decided.[186] This either has to be accurately chosen, or else the entire cardiac cycle must be imaged, which adds to the x-ray exposure time and therefore radiation dose.[187] The ability to dose-modulate for more than one target phase is being tested[188], but again the phases must be chosen prospectively to benefit maximally from radiation reducing techniques. The improved temporal resolution of dual-source scanners should also be of benefit when imaging patients with a tachyarrhythmia[189] and the diagnostic accuracy of these scanners

appears promising when compared to ICA, even without attempts at heart rate control[190] but results are variable[191] radiation dose remains a significant issue[190,192] and the technology has not always been compared to conventional scanners.[188,191]

This study is limited by its retrospective nature. The patient and scan information, including scanner settings and radiation dose, is all collected prospectively but given the clinical nature of the decision to scan there may well be some selection bias. Some patients may not have been scanned at the operator's discretion. However, there is no reason for the decision making threshold to have varied following the switch to prospective gating and the remarkable similarity in patient demographics suggests that the impact of selection bias is likely to be very small. Furthermore, there may be limitations due to the inability to completely blind the image analysis to the gating method. This is inherently discernible to any experienced reader from a single phase examination, even before multiple phases are used (there will be more phases available from retrospective acquisition). Firm conclusions about the superiority of the diagnostic confidence of prospectively gated studies may therefore be questionable.

Due to limitations in our scanner technology it was not possible to prospectively select the timing of acquisition using the time from the R peak. Instead, the scan was triggered at a specified phase of the R-R interval, based on the scanner's calculation of preceding R-R intervals. In atrial fibrillation, where there is significant R-R variation, this approach may be less accurate. Furthermore it cannot be adjusted in cases where the activation time is prolonged, such as with bundle branch block or extrinsic pacing.

While we reconstructed images based on absolute time from the R wave, acquisition in this fashion would be preferable, as utilised in other studies.[191]

In summary, although CT diagnosis is highly achievable in atrial fibrillation, the radiation dose remains high.[193] Because such patients are difficult to image, most major literature has excluded those without rate-controlled sinus rhythm, resulting in a relative paucity of data for such groups, and their exclusion from clinical access to this useful modality. For patients in sinus rhythm image quality is superior with prospectively gated studies[174] and the routine use of prospective gating in AF therefore offers the potential for both dose reduction and improved diagnostic accuracy.

6. The use of beta-blockers for cardiac CT

6.1 Introduction

The use of beta-blockers to facilitate high image quality remains pertinent to cardiac CT. The use of these drugs is important in atrial fibrillation, as discussed in the previous chapter, and in sinus rhythm. We have now explained the use of systolic data acquisition in atrial fibrillation but in sinus rhythm this usually occurs during cardiac diastole, when cardiac motion is minimised or briefly ceased, and lower heart rates prolong this phase, which reduces image artefacts. Slower heart rates also facilitate the use of optimal radiation-reducing techniques;[173] for example at higher heart rates, the scanning time is increased to include more of the cardiac cycle in order to identify an optimally motion-free phase, or to allow the analysis of multiple phases, to overcome the otherwise limited image quality.

The use of beta-blockers to achieve heart rate control is well established, most commonly with metoprolol,[194] although centres vary widely in their choice of agent, administration route, and dose. Although recent European data suggests a trend towards increasingly aggressive use of beta-blockade,[194] there is little literature documenting the safety of this approach, and guidelines for practitioners have recommended conservative dosing regimens.[54,195] While defensively safe, such protocols result in a substantial proportion of patients failing to meet the target heart rate,[54,196] with the potential implications of poorer image quality and greater radiation exposure.

We pursue aggressive heart rate control with intravenous metoprolol tartrate (Betaloc, AstraZeneca UK Ltd., Luton), in an off-label fashion, due to its favourable pharmacological characteristics, including rapid onset, predictability and short half-life (average 3.5 hours, range 1 – 9 hours)[197] compared to alternative agents. To evaluate the safety of our practice, a retrospective data analysis was performed.

6.2 The study

Materials and methods

The study was reviewed by the Research & Development department at our institution and registered locally as a clinical audit. Further review and the need for informed consent were waived.

The records of all patients undergoing CT coronary angiography on clinical grounds over a 3 year period (July 2010 – June 2013) at our tertiary cardiothoracic centre were examined to establish beta-blocker usage and the occurrence of immediate complications. Patients undergoing non-coronary assessment, and those referred from outside the hospital catchment area, were excluded. All adverse incidents where treatment or monitoring is required (such as contrast allergy) are recorded in the clinical report, produced contemporaneously to the scan. We reviewed all clinical reports and the hospital admissions database was interrogated for readmissions within 48 hours.

Beta-blocker administration

The decision to administer intravenous metoprolol is taken by the supervising physician at the time of the scan, and administered by them. Advanced life support facilities are immediately available. The target heart rate is <65 beats per minute, and ideally <60 beats per minute[2], during a breath-hold (which provides physiological augmentation to bradycardia in most patients) with no pre-defined, maximum dose; metoprolol is administered in 5mg boluses at one-minute intervals and titration is continued provided an observable impact on heart rate is being achieved. While the patient's three-lead electrocardiogram is continuously monitored throughout administration we do not routinely record or monitor the patient's blood pressure.

Most standard contraindications are observed,[197] including: allergy to the drug or its excipients, high-grade atrioventricular block (first degree block with a PR interval >260 milliseconds, any second or third degree block), severe or decompensated heart failure, or severe peripheral vascular disease. We also exclude patients with severe aortic stenosis. We treat the concomitant use of verapamil as an absolute contraindication to intravenous metoprolol, but not diltiazem, and we will administer a modest dose of metoprolol (up to 10 – 20 mg), cautiously with the latter. The use of oral beta-blockers is not considered when deciding to use intravenous beta-blockers, other than as reassurance of the patient's likely tolerance.

Patients with asthma are counselled about the potential risk, but are offered beta-blockers if they are not using high-dose inhaled $beta_2$-agonists, have not required corticosteroid therapy within the last year, and have no other indications of poor

control or risk factors for severe exacerbation (e.g.: previous critical care admission). Chronic obstructive pulmonary disease is not a contraindication to the use of beta-blockade, although we avoid intravenous administration where patients have a significant bronchospastic component, requiring regular, high-dose bronchodilator therapy. Patients with such a relative contraindication or caution are offered an informed choice, comprising careful use of metoprolol, scanning with increased radiation dose, or an alternative imaging modality. Inpatients with acute illness, such as sepsis or potential pulmonary embolus, do not undergo rate-control.

Following the scan patients are observed for at least 20 minutes prior to discharge (i.e.: beyond the time to peak onset). Vital signs are not routinely monitored.

Results

We identified 3098 consecutive patients meeting the inclusion criteria. In 68 cases the use or dosage of beta-blockers could not be verified. 1159 patients (37%) did not receive beta-blockers due to satisfactory baseline heart rate, or contraindication. 1871 patients received intravenous metoprolol with a dose range of 2.5 – 70 mg (median dose 15 mg, interquartile range 10 – 25) (Figure 20). 901 (29%) patients received more than the licensed dose of 15 mg (noting that there is no formal licence for the use of metoprolol for cardiac CT). 129 patients received intravenous metoprolol despite a resting heart rate $\leq$65 bpm, with a median dose of 6mg (interquartile range 5 – 10). No complications or adverse incidents were reported in this cohort. There were no unplanned hospital admissions within 48 hours of the CT.

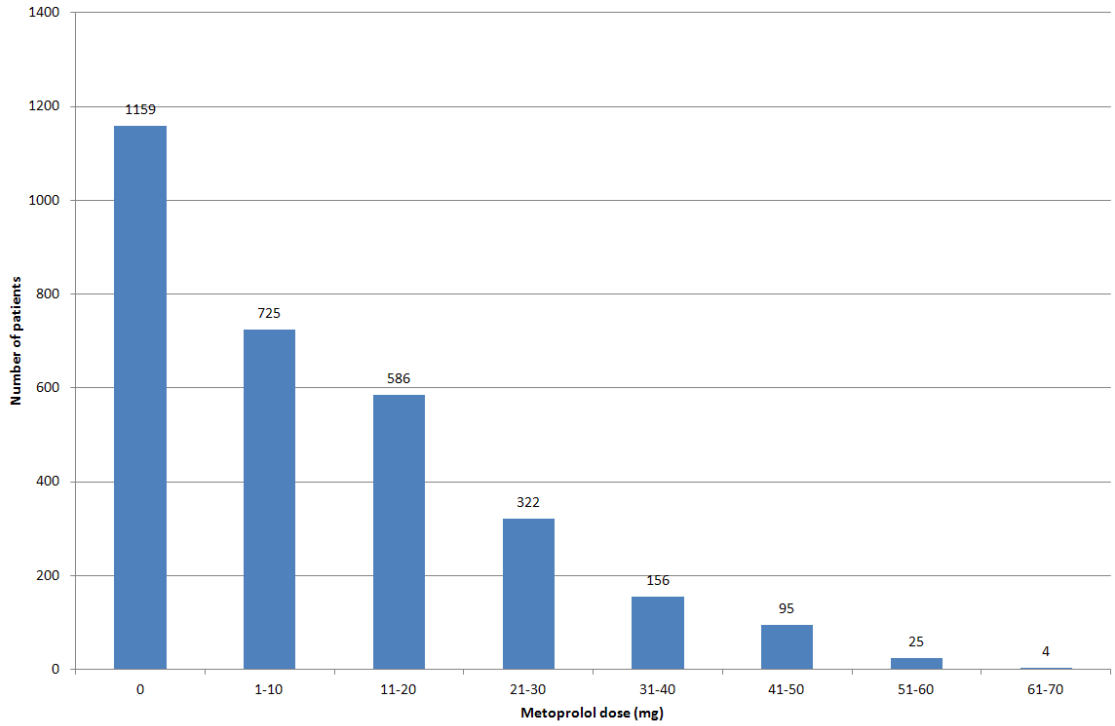

Figure 20
Administration of intravenous metoprolol. Number of patients within each dose range of IV beta-blocker.

Out of all 1871 patients there was one adverse incident. Brief loss of consciousness occurred, without sequelae, in an outpatient under investigation for atypical chest pain and syncope, who had received 15 mg metoprolol prior to CT. The patient fully recovered and was discharged from hospital following a short period of cardiac monitoring, ultimately being diagnosed with reflex syncope. No other complications or adverse incidents occurred and no other patients required any medical treatment.

6.3 Discussion

Our data, comprising the largest analysis of real-world practice in this setting, suggest that the off-label use of intravenous beta-blockers to facilitate cardiac CT is safe. Complications are rare, provided that due consideration and appropriate patient assessment is undertaken, on an individual basis. We have also demonstrated, in a

small subset, that beta-blockers can be used at doses above that currently recommended for other indications[7] in selected patients. As cardiac CT becomes increasingly widespread, the ability to achieve safe heart rate control has important implications for both image quality, and potentially therefore for the need for additional downstream testing, and for radiation exposure.

The low rate of complications and side effects compared to the expected frequencies seen in clinical trials and surveillance needs careful consideration. This is a retrospective analysis and therefore there is an inherent risk of reporting bias, although the data has been collected prospectively for clinical purposes and so recall bias has been reduced. Most of the common side effects of metoprolol are minor, such as dizziness, headache or nausea, which patients may not report or may attribute to the iodinated contrast media administered during the final phase of imaging. The use of a single dose of metoprolol is also likely to be relevant, with side effect profiles being generated from patients taking longer term, generally oral, therapy and side-effects such as weight loss and fatigue are much less relevant. While bradycardia will be reported as an adverse incident in the context of arrhythmia or myocardial infarction (and occurs commonly), relative bradycardia is of course the objective when using metoprolol for cardiac CT. Perhaps the significance in this analysis is the absence of any patients requiring intervention for profound, symptomatic or compromising bradycardia.

Our judicious use of beta-blockers in patients with bronchospastic disease, and avoidance in acutely unwell patients also avoids many of the other side effects we

would expect to see in such cohorts, whereas intravenous metoprolol is generally used for patients suffering acute myocardial infarction or arrhythmia, both of which can cause significant clinical instability and even death – we experienced no complications in any of these groups. Finally, postural disorders are also considered to be a common side effect of intravenous metoprolol, although with syncope occurring rarely.[197] Even with our single adverse event, the rate of postural symptoms is low. This is likely to be due to a combination of mild or self-limiting symptoms not being reported by patients and not requiring medical intervention, the use of a one-off dose, and mitigation by the use of intravenous contrast which provides a 100 – 125ml fluid bolus and may contribute to intravascular volume expansion.

The majority of other side effects are considered to be uncommon (incidence 0.1 – 0.9%) rare (incidence 0.01 – 0.09%) or very rare (incidence <0.01%),[197] and may not occur in a sample size such as ours. That said, our service has over ten years of experience of cardiac CT and now scans around 2000 patients per year, with similarly low rates of complication reported anecdotally.

The use of intravenous beta-blockers has been demonstrated to be an effective measure for controlling heart rate prior to CT coronary angiography.[198] While some studies have suggested that injectable formulations may be less effective than oral administration, the protocols have generally been restricted to much lower doses than we describe here, and use in clinical practice.[54] This study provides data to answer previously unanswered questions about the safety of intravenous beta-blockers in this setting, at doses far higher than for more conventional indications. In combination

with improving temporal resolution in scanner hardware this should facilitate the inclusion of a wider range of previously difficult-to-image patients.

7. The patient experience as a factor in optimising cardiac imaging

7.1 Introduction

It is clear therefore that temporal resolution can be optimised by both pharmacological preparation of the patient and by careful attention to scanning technique, to include as many patients as possible. Nonetheless, this may be challenging to achieve in an anxious patient, where autonomic drive elevates the heart rate, and consequently additional radiation exposure is required to optimise the chances of diagnostic images.[199] Indeed, the efficacy of intravenous beta-blockade has been shown to decline with increasing dose – the concept of diminishing returns – with some patients remaining tachycardic despite significant doses of these drugs.[198]

Poor patient selection and preparation have thus been shown to increase the radiation burden to the patient, as well as to increase the rate of non-diagnostic scans, leading to patients needing additional, alternative testing.[200] This can be distressing for patients and increases downstream costs for healthcare providers. Poor patient awareness is also known to increase the anxiety of attending for a test.[201] It is perhaps unsurprising therefore that observational evidence suggests that patients with higher levels of pre-CT anxiety ultimately have scans of lower image quality and that pre-procedural anxiety is higher in patients who have already undergone invasive angiography,[200] presumably because they anticipate a similar experience. Meanwhile, improved patient information and understanding has been shown to improve outcomes in a wide variety of hospital settings.[202–204] Evidence from cardiac catheter angiography suggests that the use of alternative information formats can reduce patient anxiety and improve patient satisfaction, as well as improving their

understanding of the technical requirements of a test.[205] The latter may also contribute to how well a patient prepares for a test – for example, patients who do not understand the requirements for cardiac CT, particularly the need for a slow heart rate, will often consume caffeine, stop their heart-slowing drugs, or even run or cycle to their appointment.

Outside the cardiology setting, it is suggested that the addition of video information to written information significantly improves pre-procedural anxiety[204] and we therefore evaluated the impact of this method of conveying information to patients on how well they are prepared to undergo CT coronary angiography and the effect this might have on the outcome of their investigation.

7.2 The study

Materials and methods

Ethics and consent

The study was approved by our institutional research and development board, and by a committee of the UK National Research Ethics Service, and was prospectively registered as a clinical trial at clinicaltrials.gov (NCT 02156973). All participants provided informed, written consent to undertake an anxiety questionnaire and to allow their image sets and data to be included in the study, although to minimise reporting bias due to demand characteristics they were not specifically aware of the role of the information film.

Inclusion and exclusion criteria

All adult patients attending for CT coronary angiography were screened. Patients were excluded if they were unable to provide informed, written consent for any reason, were attending for a non-coronary CT scan, had previously undergone cardiac CT, or were hospital inpatients.

Sample size

Previous similar work has identified a significant effect size when introducing videos before potentially stressful clinical procedures. One study identified a large effect size (>0.9) in a group of women attending for colposcopy.[204] Given that our investigation is less invasive, we have chosen a smaller effect size for our sample size calculation, in order to ensure we recruit sufficient patients (medium effect size, based on Cohen[206]). With an effect size of 0.5, for 80% power and with significance defined as $p \leq 0.05$, the sample size is 59 patients in each group. Allowing for a 10% non-return or withdrawal rate, our sample size will therefore be 130 patients. This calculation also assumes correction with asymptotic relative efficiency in the event of a non-normal distribution – this allows for the use of an appropriate, non-parametric test if necessary, by ensuring that the study power is not compromised in such an event.

Procedures

Patients attending for CT coronary angiography in our institution all receive an information leaflet with their appointment letter, which outlines the steps they need to take prior to coming to the scan (see Appendix 1). In addition they are given a brief verbal description of the scan by the radiographer immediately before it is undertaken,

as standard care. All patients attending during the study period were offered the opportunity to complete an abbreviated Speilberger State-Trait Anxiety Index (STAI) questionnaire, which has previously been validated for use in outpatient settings,[207] to gauge levels of pre-procedural anxiety. Participants subsequently underwent CT coronary angiography according to standard departmental protocols.

Once the control group were recruited, and following a delay to ensure crossover did not occur, all subsequent patients were given the opportunity to view a short patient information film prior to their scan. This film was produced by a local university prior to commencement of the study, in collaboration with cardiologists and radiologists from our institution, having spoken to patients about their experiences of undergoing cardiac CT. The film demonstrates the pre-procedure preparation required, the scan room, scanner and anticipated patient experiences. The film is available on the hospital website and on YouTube with the URL provided to patients with their patient information leaflet (available at: tinyurl.com/derrifordheartct). Patients who did not access the internet were able to view the film in the waiting room prior to the scan. These patients were then invited to take the STAI questionnaire and underwent their CT coronary angiography in the usual way.

The CT scans in both groups were completed using the same protocols in a standardised fashion. Scans were undertaken using a 64-MDCT scanner (Discovery CT750-HD, GE Healthcare, Milwaukee, USA). Patients with a heart rate greater than 60 beats per minute received intravenous metoprolol, in 2.5 – 5 mg aliquots to a maximum of 60 mg,[178] to achieve a target heart rate of <60 beats per minute.

Calcium scoring was performed using prospective ECG gating in three or four sets of non-overlapping, axial slices with 4cm z-axis coverage, 100kV tube voltage and 100 mAs tube current. CT angiography was then performed using prospective ECG gating, 350 ms gantry rotation speed, and 64 x 0.625mm slice collimation. Standard or high-definition mode[124] was used at the supervising doctor's discretion based on the load and distribution of coronary artery calcium, or the presence of coronary stents. Fixed tube parameters adapted to the patient's body mass index were used according to Table 17 with minimal radiation exposure time (zero padding) as a default. Patients with heart rate variability or a probable acquisition heart rate of greater than 65 beats per minute received up to 200 ms of padding to allow multi-phase data reconstruction. A dual-phase contrast injection protocol was used with 100 ml (125 ml for patients with coronary bypass grafts) of Optiray 350 (Ioversol, Mallinkrodt Inc, MO, USA) followed by a 70 ml saline flush using a standardised protocol. Raw CT data was reconstructed using a blend of 40% iterative reconstruction (Adaptive Statistical Iterative Reconstruction, GE Healthcare) and 60% Filtered Back Projection.

Body mass index (kg/m^2)	**kV**	**mA**	**mA HD**
<20	80	250	500
20 – 22.4	100	270	600
22.5 – 24.9	100	300	700
25 – 27.4	100	360	800
27.5 – 29.9	100	420	830
30 – 34.9	120	390	830
>35	120	480	N/A

Table 17
Scan parameters for patient information film study. kV – kilovoltage peak, mA – milliamperes, mA HD – milliamperes used when high definition mode selected (note this option is not available for patients with a body mass index of 35 kg/m^2 or greater)

The images were anonymised in a random fashion and reviewed, blinded, by two expert readers, each with more than 10 years experience of cardiac CT. Image quality

was recorded on a 5-point Likert scale for each coronary segment, thus: 5 – excellent image quality with minimal motion artefact, not affecting diagnosis, 4 – mild motion artefact but diagnostic confidence maintained, 3 – moderate artefact with little diagnostic doubt, 2 – significant motion artefact with diagnostic uncertainty, correlative imaging essential, 1 – study uninterpretable due to motion artefact. Segments graded 3 or greater were considered to be diagnostic for the purposes of the study.

Outcome measures

The primary outcome measure was the self-reported level of anxiety in patients attending for CT coronary angiography.

The secondary outcome measures were the patient's pre-scan heart rate, the requirement for intravenous beta-blockers, the required use of additional tube-on time ('padding'), image quality and radiation dose (dose length product).

Statistics

Statistical analysis was performed using SPSS Statistics 21 (IBM Corp., New York). The distribution of data was assessed graphically. Continuous variables were analysed with an unmatched t-test or the independent samples Kruskal-Wallace test. Categorical variables were analysed using Chi-squares unless there were categories with an expected count of less than 5 results, where Fisher's exact test was used. Image quality was analysed within each Likert category and as a binary variable (diagnostic or not

diagnostic), as was heart rate (more than 65 beats per minute, or not). Two-tailed P values of less than or equal to 0.05 were considered significant.

Results

Participants

130 patients were recruited to the study, 11 patients having declined to participate. Two patients underwent non-coronary cardiac CT and were excluded. Three further patients were excluded as they had not answered all of the questions on the STAI questionnaire. Of the remaining 125 patients, 61 were in the control group and 64 in the intervention group. The baseline characteristics for the study participants are presented in Table 18. There were no significant differences between two groups.

	Control	**Intervention**	**p value**
Male	35 (57%)	31 (48%)	0.37
High-definition mode	11 (18%)	18 (28%)	0.21
Age (mean)	60 years	62 years	0.50
BMI (mean)	28 kg/m^2	28 kg/m^2	0.88

Table 18
Baseline characteristics for patient information film study

Outcomes

The self-reported anxiety level, assessed using the Speilberger State-Trait Anxiety Index was significantly lower in the group who had seen the patient information film compared to those who had not (Table 19). There was no significant difference in pre- or intra- scan heart rate, required use of 'padding', required dose of intravenous beta blocker, image quality or radiation dose between the two groups.

	Control	Intervention	p value (95% confidence interval)
STAI score[1]	33.20	31.25	0.04 (-7.36 – -0.11)
Pre-scan heart rate[1]	73.3	71.3	0.39 (-6.47 – 2.53)
Scan heart rate[1]	61.6	60.3	0.49 (-4.90 – 2.35)
>65 bpm (n)	*14 (23%)*	*12 (19%)*	*0.66*
Beta-blocker dose[2]	10 mg (0 – 20)	10 mg (5 – 20)	0.15
Use of padding (n)	9 (15%)	10 (16%)	1.00
Image quality[2]	4 (3 – 4)	4 (3 – 5)	0.56
Diagnostic (n)	*54 (89%)*	*59 (92%)*	*0.77*
Dose length product[2]	151 (91 – 192)	151 (112 – 225)	0.40

Table 19
Outcome variables for patient information film study. [1]mean and standard deviation, [2]median and interquartile range.

7.3 Discussion

This study suggests that the use of a patient information film may improve the anxiety experienced by patients attending for CT coronary angiography. Despite this, there was no significant impact on patient heart rate and as such the use of beta-blockers, the need for additional tube-on time and ultimately the radiation dose was therefore comparable. This suggests that while a patient information film may be useful in improving the patient experience of cardiac CT, it may not be effective at reducing heart rate significantly.

There are however a number of factors which may be relevant which have not been explored in this study. The degree to which anxiety affects heart rate cannot be demonstrated and it is likely that this study is underpowered to identify subtle differences. Most patients (79%) underwent diagnostic scans with a heart rate within the target range and only 12 studies were not of diagnostic quality and, following on from the previous chapter, our centre utilises an aggressive approach to the use of intravenous beta-blockade, in all patients.[178,198] Given this high rate of diagnostic

imaging and widespread use of beta-blocker, it is perhaps unsurprising that a further improvement cannot be demonstrated with a small reduction in pre-scan anxiety.

While a better understanding of an experience may improve a participant's anxiety about what is to come[204,205], this finding is not universal. Some studies have demonstrated that despite improved knowledge and recall of information, anxiety has not been reduced.[208,209] There may be a number of different reasons for this fact, which may limit the applicability of this study. It is widely recognised that the causes and response to anxiety vary between different social and cultural environments[210,211] and it would be logical to assume that addressing anxiety would therefore need contextualisation to local cultures. This study was conducted in a single centre in a predominantly white, British population with a higher than average age demographic.[212] The information film was produced following consultation with patients who had experienced cardiac CT and therefore contained information pertinent to the anxieties of the local population.

Future studies would be useful to explore which features of the information film patients found most beneficial, and to compare its usefulness at our centre with other environments. It would be useful to establish whether additional benefit can be found in patients with a resting heart rate above 65 beats per minute, or whether it is useful in patients who report no anxiety on arrival for the test. This may clarify whether it is of any benefit in helping to achieve diagnostic images in the difficult-to-image patient. Finally, a larger study may help determine if there is any measurable difference in

heart rate, beta-blocker use or radiation exposure, although given the apparent magnitude any impact is unlikely to have a useful clinical implication.

Section 4 – Additional information in the diagnosis of coronary artery disease

8. Ischaemia testing with cardiac CT

8.1 Introduction

There is an alternative strategy when faced with a patient in whom diagnostic, sub-millimetre imaging is unlikely to be feasible. Rather than identifying coronary artery stenosis itself, the heart can be imaged in an attempt to identify the consequences of atherosclerotic disease. For patients presenting with chest pain this means generating information about the blood flow to the myocardium or the physiological effects of blood flow reduction. Such information is the target of all other non-invasive imaging modalities used for the investigation of coronary artery disease and considers either the flow of blood into and out of the myocardium, or the abnormal behaviour of the myocardium as a consequence of poor perfusion, or both. Stress echocardiography can identify regional abnormalities in myocardial wall motion during cardiac stress compared to rest. Cardiac magnetic resonance (CMR) imaging and radionuclide myocardial perfusion imaging (rMPI) also examine myocardial wall motion but in addition use contrast or radioactive tracer, respectively, to permit visualisation of blood as it passes into and out of the tissue. All of these modalities use a pharmacological agent to induce cardiac stress, simulating exercise, and some can also be performed with a patient using an exercise bicycle.

It is also possible to use non-imaging tests to identify the ischaemic consequences of reduced myocardial blood flow. Exercise tolerance testing has been a mainstay of cardiology for decades[213] using electrocardiographic changes which occur due to the abnormal way in which ischaemic myocardium transmits electrical impulses. In the United Kingdom exercise tolerance testing has all but ceased as a primary diagnostic

test for the investigation of patients presenting for the first time with symptoms of potential myocardial ischaemia following guidelines from NICE in 2010.[82] The problem with the exercise ECG is that the electrical changes within myocardial tissue occur late on in the ischaemic process.[214] Modalities which identify the mechanical consequences of ischaemia – left ventricular dysfunction – are therefore more sensitive. Even before ischaemia leads to ventricular wall motion abnormality it is possible to identify the variation in blood supply to the myocardium with perfusion imaging, which may increase the sensitivity further.[215] The current reference standard is the measurement of fractional flow reserve at invasive angiography, which measures the drop in pressure which occurs as blood crosses a stenosis.

Functional, or ischaemia, testing adds to anatomical data obtained with invasive, or CT, angiography. In patients with diffuse, or multi-vessel, coronary disease the correlation of symptoms and a demonstrable, regional reduction in blood flow can help to identify the 'culprit' lesion. It is also important to acknowledge that the anatomical degree of a stenosis is a poor predictor of its capability to cause ischaemia and undertaking revascularisation in this setting confers risk without benefit.[117]

In comparison to CMR[216] or rMPI,[217] CT performance is limited for predicting ischaemia on the basis of stenosis alone. This is not altogether surprising and its accuracy compares to catheter angiography,[218] with well known limitations[117] in inferring blood flow from visual estimates of stenosis.[146] The desire to add physiological information to the highly accurate anatomical assessment which can be made with CT is therefore compelling. This is particularly useful if assessment can be

achieved without the need for such precise image quality. Because changes in blood flow or myocardial motion are larger than coronary lumen, techniques require far less stringent spatial resolution. Rudimentary blood flow imaging, simply observing myocardial density following contrast delivery, can be achieved with standard CT[106] and areas of hypoattenuation can often be seen in patients with significant CAD and does add to the accuracy of CT in patients with coronary atheroma,[219] particularly where this is calcified. However, this is not entirely straightforward as apparent hypoperfusion may be the result of beam-hardening, particularly in the basal segments where the proximity of highly attenuating, contrast-filled blood pools in the left heart and descending aorta can cause artefact. This is best refuted using multiphase examination, but this of course increases the radiation exposure to the patient. Nonetheless, CT assessment in this manner performs well compared to rMPI[220,221] and may be more sensitive.[106] It can be challenging to distinguish fixed from reversible perfusion defects with conventional CT, exacerbated by the proposition that iodinated contrast may act as a coronary vasodilator, eliciting a degree of coronary steal.[222] Because of this, 'rest' CTCA undertaken without a pharmacological stressor may identify perfusion defects seen at both rest and stress with rMPI.[223,224]

Dual energy CT (DECT) may be useful in improving the accuracy of CT perfusion scanning, offering two potential advantages over single energy techniques. Firstly, particularly with the use of monochromatic images, beam hardening artefacts can be reduced, improving diagnostic confidence in the presence of hypoattenuating myocardium. Furthermore, DECT improves the assessment of iodine with the creation of colour maps, again increasing diagnostic accuracy.[225] These utilise the improved

contrast resolution of low kV scanning with the reduced noise and artefacts of higher kV images to improve the differentiation of normal and iodinated myocardium, which can help with the visualisation of hypoperfused regions.[226]

This has been extensively explored by a number of studies,[226] and although there has been no direct comparison made between conventional and dual energy scanners, the novel technology does appear to offer improved performance[219,227] comparable to that of both rMPI and CMR. In one study examining patients with acute chest pain, the sensitivity, specificity, negative predictive value and positive predictive value were 93%, 99%, 92% and 96% respectively compared to CMR, and 94%, 98%, 92% and 94% respectively compared to rMPI.[228] A more recent study compared a dual-energy CT angiography and perfusion protocol to FFR, finding 100% sensitivity, 66% specificity, 100% NPV, 74% PPV, with 82% accuracy for a combination of a significant (>50%) stenosis and a territorial perfusion defect.[229] Such results are broadly comparable to a number of other studies in patients with symptoms or corroborative imaging findings, demonstrating again that DECT offers an exceptional ability to rule-out disease with rather more limited positive predictability, but comparable accuracy to conventional perfusion imaging.[224,230,231]

The diagnostic performance of single-source, dual energy CT with rapid kV switching has not been evaluated to date. This has some theoretical advantages over the dual source systems which have undergone extensive investigation (see Chapter 1.4). We therefore undertook a preliminary investigation of the performance of a single source, dual energy CT scanner for the assessment of myocardial perfusion.

8.2 The study

Materials and methods

The study was performed in a prospective fashion, with prior approval by a committee of the UK National Research Ethics Service. It was registered as part of a larger clinical trial of the applications of single source, dual energy cardiac CT (NCT 01816750). All participants gave informed, written consent. All patients with a positive myocardial perfusion scan, having been imaged on standard clinical grounds, between March 2013 and May 2014 were screened against the study criteria.

The exclusion criteria were patients under 50 years old, body mass index >30kg/m^2, allergy to iodinated contrast media, contraindication to intravenous beta-blockade, estimated glomerular filtration rate <30ml/min, or pregnancy. Patients requiring urgent revascularisation before CT scanning could take place were also excluded.

This study was started during a transitional period for stress imaging at our centre. The growth of CT at our tertiary centre has taken a significant proportion of patients and the hospital has recently expanded its cardiac MRI service. NICE recommend the use of CMR, rMPI or stress echocardiography based on local expertise and service access and so the choice of a specific modality is somewhat variable between centres and referrers.[82] During the study period the CE-MARC trial, the largest examination of stress perfusion MRI in the assessment of coronary artery disease to date, was published. This study suggested superiority of CMR over rMPI,[232] which was further led to the expansion of our MRI service at the expense of nuclear medicine. Nuclear medicine remains particularly important for patients with renal dysfunction,

particularly as the use of gadolinium contrast media is contraindicated in renal failure due to the risk of nephrogenic systemic fibrosis. This means that a significant proportion of patients being referred for rMPI at our centre have renal dysfunction, which is an exclusion for our study due to the risk of contrast-induced nephropathy. This further limits the ability to recruit from this modality. As such, we revised our initial target of 20 patients to five-to-10, in order solely to assess the feasibility of the workflow and patient experience, with the subsequent intention of conducting a larger study comparing CT to cardiac MRI. The amendments to the study protocol were approved by the Research Ethics Committee.

rMPI protocol

The rMPI scans were undertaken over two attendances, one week apart, according to standard departmental protocol. A Millenium VG Hawkeye (GE Healthcare, Milwaukee) gamma camera was used. A weight-adjusted dose of technetium (99mTc) tetrofosmin (Myoview, GE Healthcare) was used on each occasion, with the stress acquisition undertaken at the first visit and the rest acquisition at the second.

Following the scan the images were reported by one of two nuclear medicine consultants, each with more than 5 years experience of nuclear cardiology.

CT protocol

All patients underwent stress perfusion CT scanning between 1 day and 1 year after the MPI-SPECT, using the standardised Stress Perfusion CT protocol described below. CTCA was performed using a single source, dual energy scanner (Discovery CT750 HD,

GE Healthcare, Milwaukee, WI). Patients were weighed and measured and a body mass index (BMI) calculated. Intravenous cannulae were inserted into both arms, to allow the administration of the pharmaceutical stressor and iodinated contrast medium separately. The patient's baseline heart rate and blood pressure were recorded.

An infusion of adenosine was commenced at the rate of 140 µg/kg/min. Patients were closely observed to ensure hyperaemia was achieved – where this did not occur, or where patients had consumed caffeine prior to the scan, the rate of adenosine was increased to 210 µg/kg/min, commensurate with recognised practice.[233] Blood pressure monitoring occurred at no less than 1 minute intervals throughout the administration of adenosine. Once hyperaemia was been achieved the stress CT was undertaken. Iodinated contrast (Optiray 350, Covidien, MA, USA) was administered as a 100 ml, multiphase bolus at an initial rate of 6.5 ml/s, followed by a 50 ml saline flush and the scan was triggered manually upon opacification of the ascending aorta, with a seven second scan delay. The scan was conducted using prospective ECG gating, without additional tube-on time, irrespective of heart rate. The following parameters were used: slice acquisition 64 × 0.625 mm, z-axis coverage 40 mm with an increment of 35 mm, gantry rotation time 350 ms, 80 – 140 kV fast switching tube voltage, with tube current according the manufacturer-specified settings (see Table 9, Chapter 3). The adenosine infusion was terminated immediately following the scan and the patient allowed to recover.

Fifteen minutes later the patient's heart rate and blood pressure were assessed. Where the heart rate was below 65 beats per minute (bpm) no further medication was administered. For those patients with heart rates above 65 bpm, intravenous metoprolol (Betaloc, AstraZeneca, London, UK) was be administered slowly in boluses of 2.5 mg (up to a maximum of 40 mg) to obtain a heart rate less than 65 bpm (as per standard clinical practice).[178,198] It is expected that occasionally the patient's heart rate will not respond adequately to beta-blockade. A resting scan was then performed, using the same scan parameters as before. Where the patient's heart rate control was inadequate despite beta-blockade up to 200 milliseconds of padding was utilised and the centre point was moved to 60% of the R-R interval, to acquire both systolic and diastolic phases.

Following the scan both image sets were reconstructed using 50% iterative reconstruction (Adaptive Statistical Iterative Reconstruction, GE Healthcare), as recommended by previous studies,[147] and transferred to a workstation (Advantage Workstation 4.6, GE Healthcare).

Results

Seven patients were recruited for the study. All patients underwent both the rMPI and CT protocols. There were no adverse events. The group comprised five men and two women. The median age was 66 years (interquartile range 64 – 72.5 years) and the median body mass index was 26 kg/m^2 (IQR 24.8 – 30 kg/m^2).

The median $CTDI_{vol}$ was 30.9 mGy (IQR 25.75 – 33.5 mGy) and the dose length product was 372 mGy·cm (329.25 – 412 mGy·cm).

There were 10 perfusion defects identified at rMPI. There was concordance with CT in five of these, with two 'false positive' and three 'false negative' results. When compared to the angiographic testing strategy there were eight concordant results with one false positive and two false negatives.

The imaging of each patient is summarised below, with examples of the images obtained. Key: LMS – left main stem, LAD – left anterior descending artery, Cx – circumflex artery, RCA – right coronary artery, PCI – percutaneous coronary intervention

Patient 1

Gender	Male
Age	72 years
Body mass index	25 kg/m^2
Previous medical history	Previous PCI to RCA
Total dose ($CTDI_{vol}$/DLP)	22 mGy / 403 mGy·cm
rMPI diagnosis	Inferior, mild reversible perfusion defect Fixed anterior perfusion defect but without regional wall motion abnormality – suggestive of artefact
Perfusion CT findings	Reversible inferior perfusion defect, fixed anteroseptal perfusion defect with reversibility in a larger, adjacent anterior territory
Onward management	Patient underwent PCI to the LAD, but the RCA was managed medically
Comments	This patient did not undergo functional testing during the invasive angiography. The LAD stenosis is clearly more severe, visually, and the operator elected to stent this vessel, although this does not match with the severity of the defects according to the perfusion study

Table 20
CT Perfusion Patient 1 Summary.

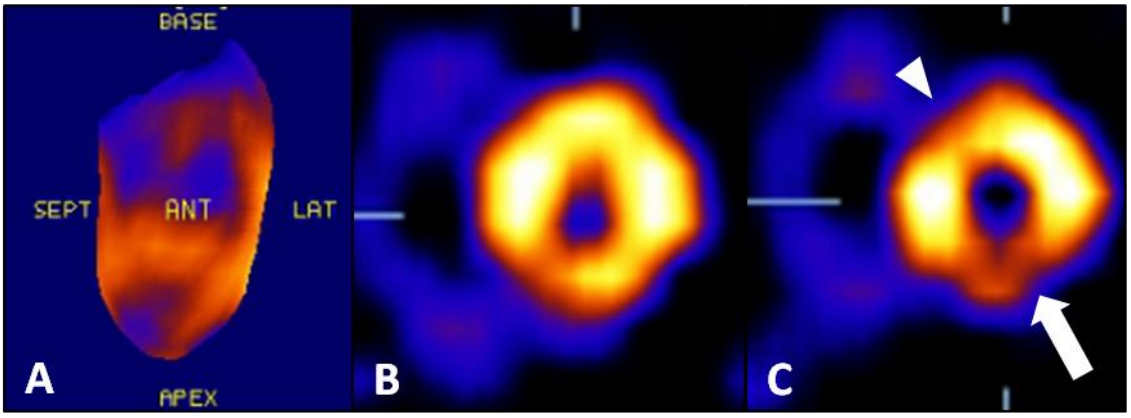

Figure 21.1
CT Perfusion Patient 1 – rMPI. A – LV outline at stress. B – basal cross-section through the left ventricle at rest. C – corresponding basal cross-section through the left ventricle at stress demonstrating modest anterior (arrowhead) and marked posterior (arrow) perfusion defects.

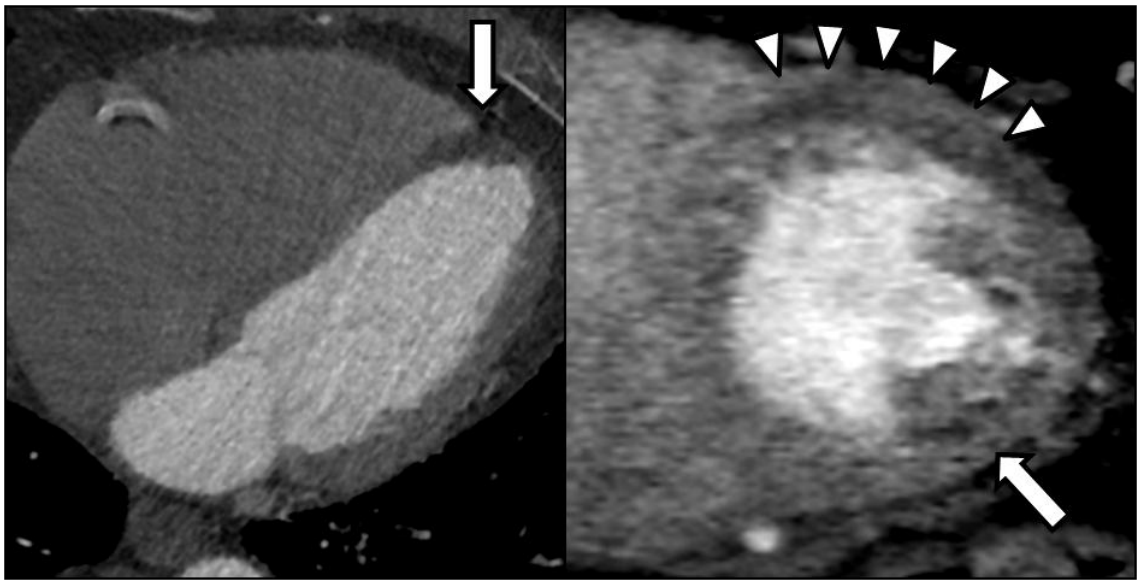

Figure 21.2
CT Perfusion Patient 1 – CT. Left – rest image demonstrating hypoperfusion at the apical septum. Right – cross-section through the basal left ventricle comparable to the rMPI images in Figure X.1 demonstrating anterior (arrowheads) and posterior (arrow) perfusion defects. The anterior defect is unusual as it appears larger than the rMPI defect and does not follow a precisely subendocardial distribution, suggesting that it may partially be artefact.

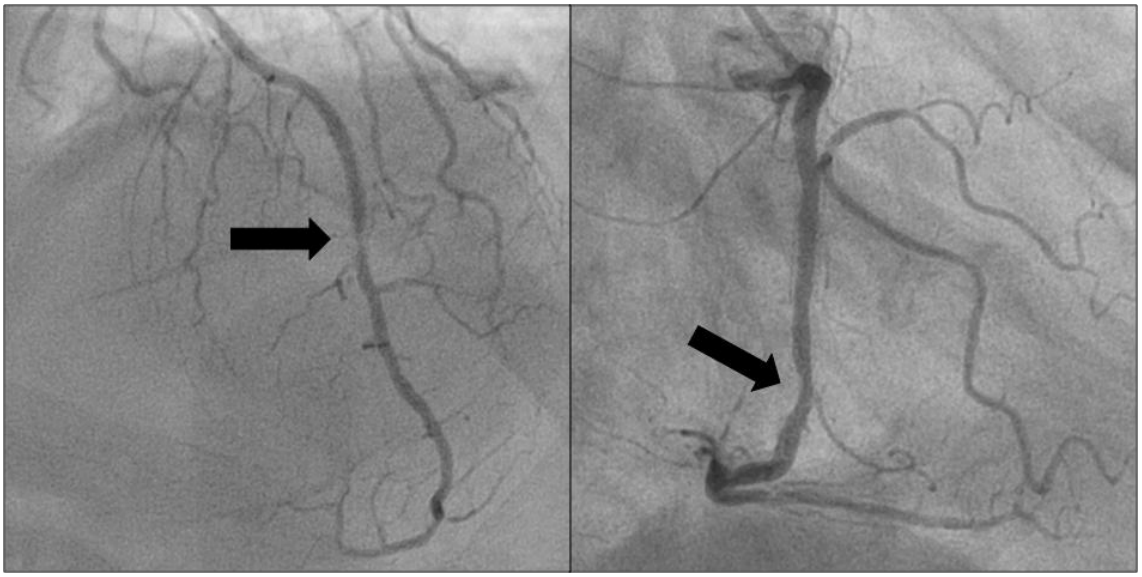

Figure 21.3
CT Perfusion Patient 1 – invasive angiogram. The left anterior descending artery (left) and right coronary artery (right) lesions are indicated.

Patient 2

Gender	Male
Age	74 years
Body mass index	30 kg/m^2
Previous medical history	Peripheral vascular disease, hypertension, former smoker
Total dose ($CTDI_{vol}$/DLP)	30 mGy / 424 mGy·cm
rMPI diagnosis	Moderately severe, fully reversible anteroseptal perfusion defect
Perfusion CT findings	Anteroseptal perfusion defect with severe proximal LAD stenosis
Onward management	Patient underwent PCI to the LAD
Comments	The rMPI and CT results appeared to show good concordance

Table 21
CT Perfusion Patient 2 – Summary.

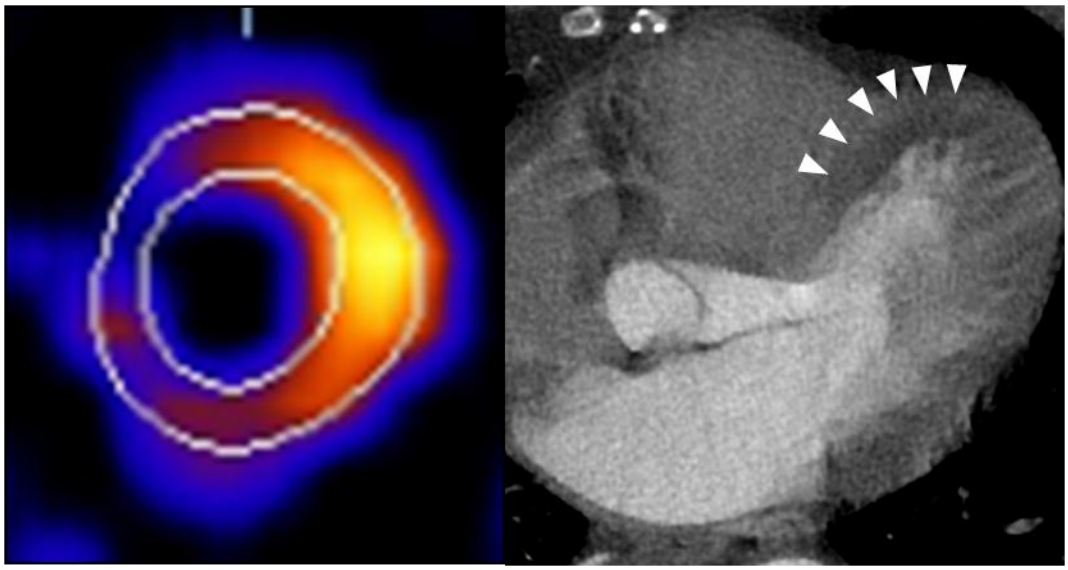

Figure 22.1
CT Perfusion Patient 2 – Perfusion. rMPI (left) and CT (right) images demonstrating clear anteroseptal hypoperfusion.

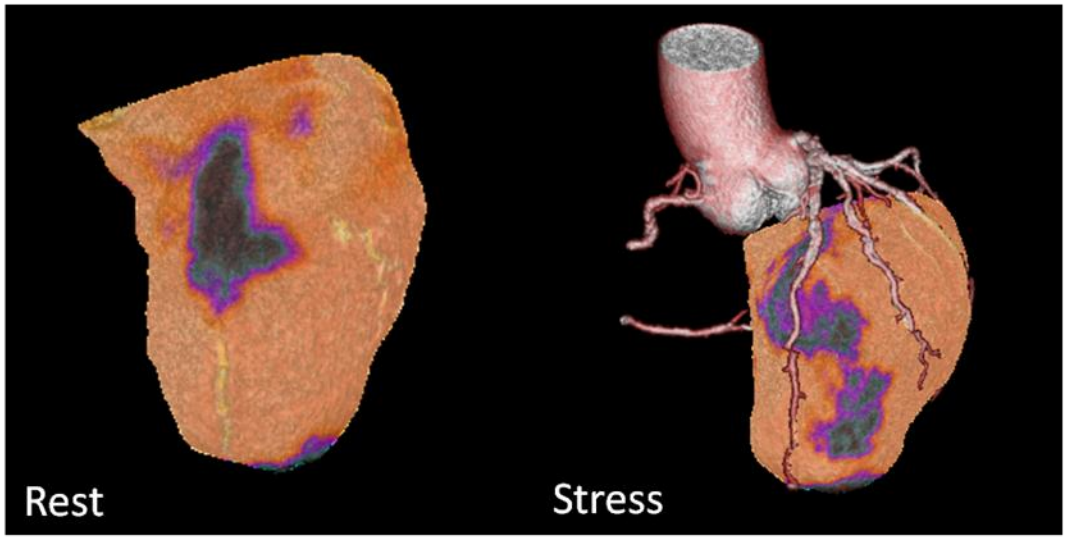

Figure 22.2
CT Perfusion Patient 2 – Iodine map. Rest and stress perfusion images reconstructed using iodine mapping. This demonstrates an apparent, relatively small perfusion in the basal anterior region with extension at stress, corresponding to the perfusion defect seen visually and by rMPI. The coronary arteries can be layered over the myocardial mapping.

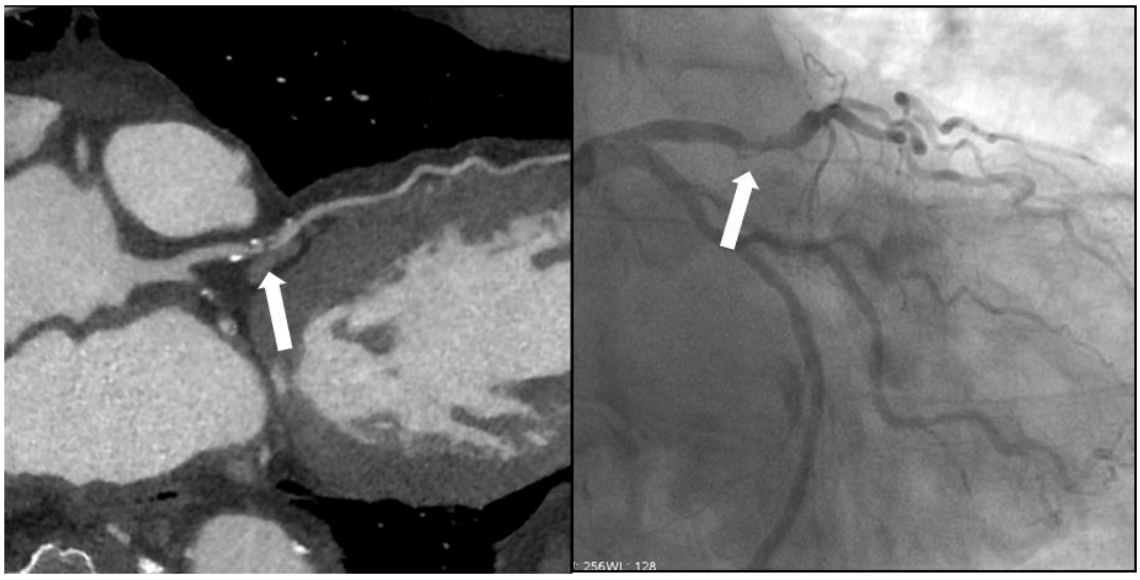

Figure 22.3
CT Perfusion Patient 2 – Angiography. CT coronary angiography (left) from the 'rest' perfusion acquisition and invasive coronary angiography (right) demonstrating the proximal LAD stenosis responsible for the perfusion defect.

Patient 3

Gender	Male
Age	65 years
Body mass index	26 kg/m^2
Previous medical history	Nil. Intermediate pre-test probability of coronary artery disease.
Total dose ($CTDI_{vol}$/DLP)	32 mGy / 344 mGy·cm
rMPI diagnosis	Mild, mid-basal anterior wall reversible perfusion defect. Fixed abnormality in the posterior territory suggestive of artefact.
Perfusion CT findings	No perfusion defects identified. Coronary artery atheroma in the LAD but no significant coronary obstruction.
Onward management	This patient underwent a CT coronary angiogram on clinical grounds which confirmed the absence of coronary obstruction and was therefore managed medically.
Comments	This case suggests highlights the benefits of simultaneous perfusion and angiography using CT

Table 22
CT Perfusion Patient 3 Summary.

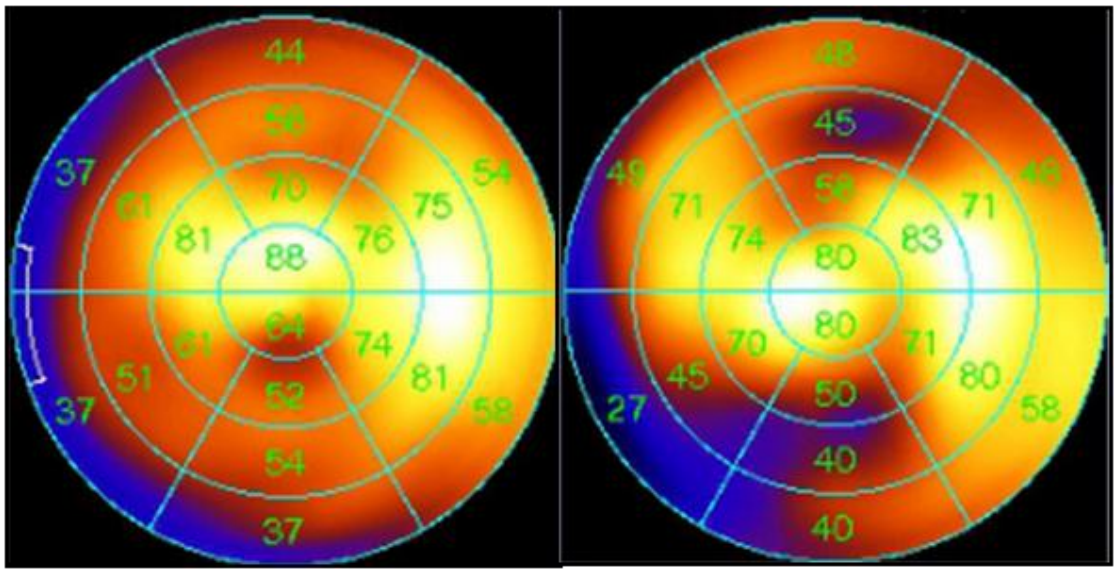

Figure 23.1
CT Perfusion Patient 3 – rMPI. Rest (left) and stress (right) 'bullseye' reconstructions of left ventricular perfusion. This demonstrates an apparent perfusion defect anteriorly, with a posterior abnormality which was felt to be an artefact.

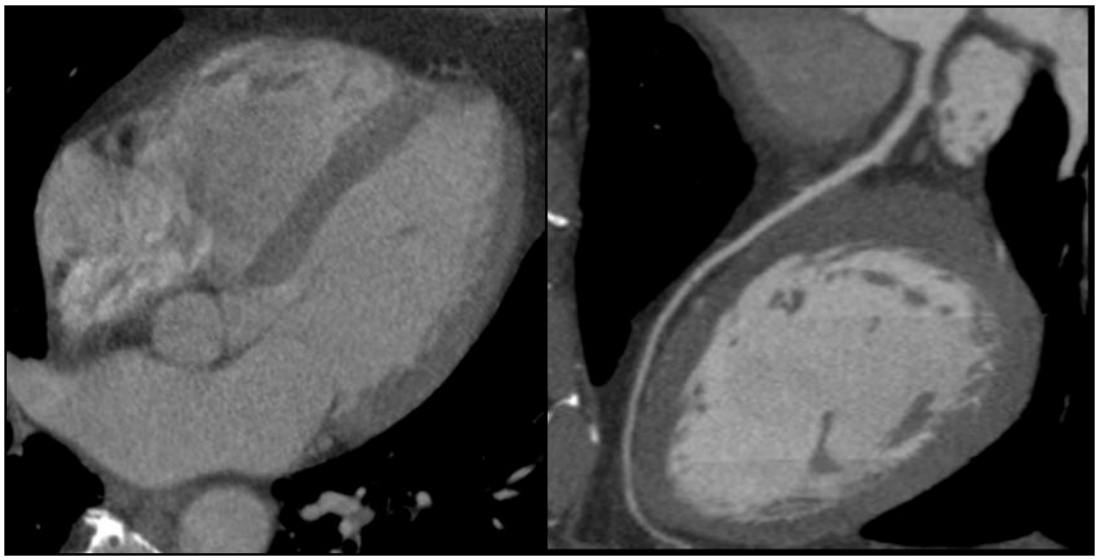

Figure 23.2
CT Perfusion Patient 3 – CT. No obvious perfusion defect could be identified on the CT stress study (left) and the LAD appeared completely unobstructed (right) suggesting that the rMPI result was a false-positive.

Patient 4

Gender	Female
Age	61 years
Body mass index	24 kg/m^2
Previous medical history	Type 1 diabetic with increasing angina, undergoing pre-operative evaluation prior to pancreatic islet cell transplant
Total dose ($CTDI_{vol}$/DLP)	27 mGy / 273 mGy·cm
rMPI diagnosis	Limited severity, fully reversible perfusion defect involving the entire inferior wall
Perfusion CT findings	Extensive perfusion defect in the LAD territory. Subtotally occluded RCA with likely collateral filling from the LAD.
Onward management	The patient underwent correlative angiography (see below) and then coronary artery bypass grafting to the LAD and RCA.
Comments	The inferior wall perfusion defect was not obvious on the CT images. However, there was significant LAD territory perfusion deficit. Furthermore, the subtotally occluded RCA was evident, with LAD collateralisation, such that it was possible to explain the inferior perfusion defect on rMPI as a consequence of the LAD stenosis.

Table 23
CT Perfusion Patient 4 Summary.

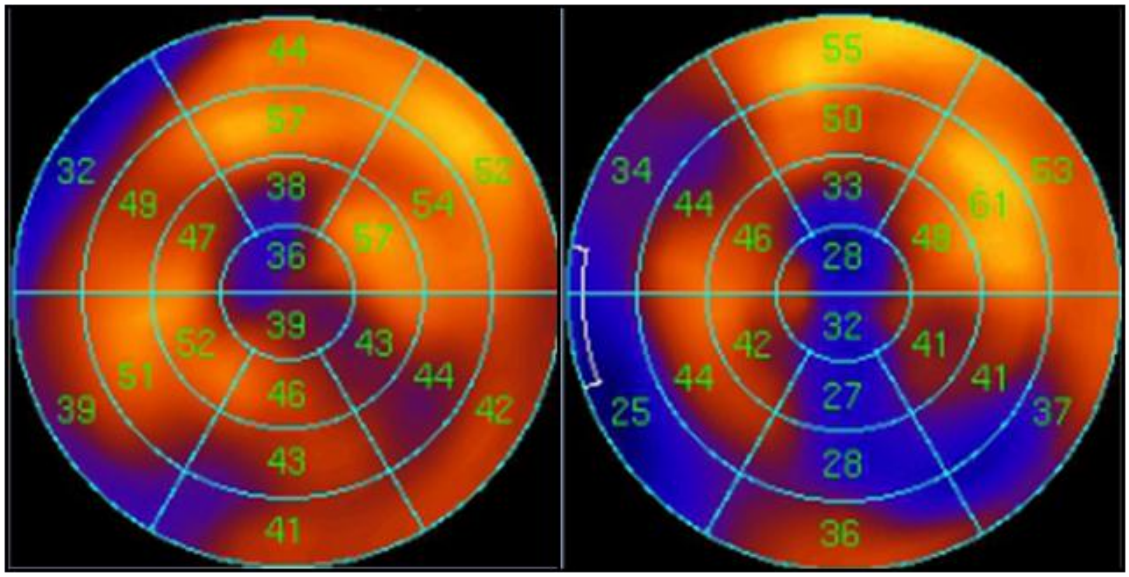

Figure 24.1
CT Perfusion Patient 4 – rMPI. There is a large perfusion defect encompassing most of the inferior wall.

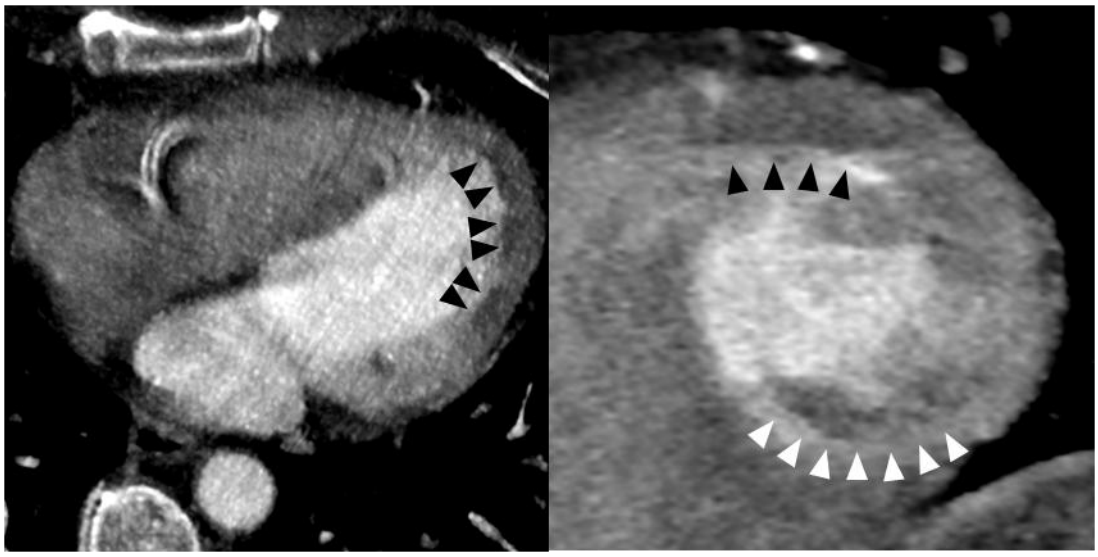

Figure 24.2
CT Perfusion Patient 4 – CT. There are extensive regions of subendocardial hypoenhancement in the anterior (black arrowheads) and inferior (white arrowheads) on this stress perfusion acquisition, not evident on the rest study (left – axial four chamber slice, right – left ventricular short axis view). Note the step artefact due to heart rate variation in the right hand image.

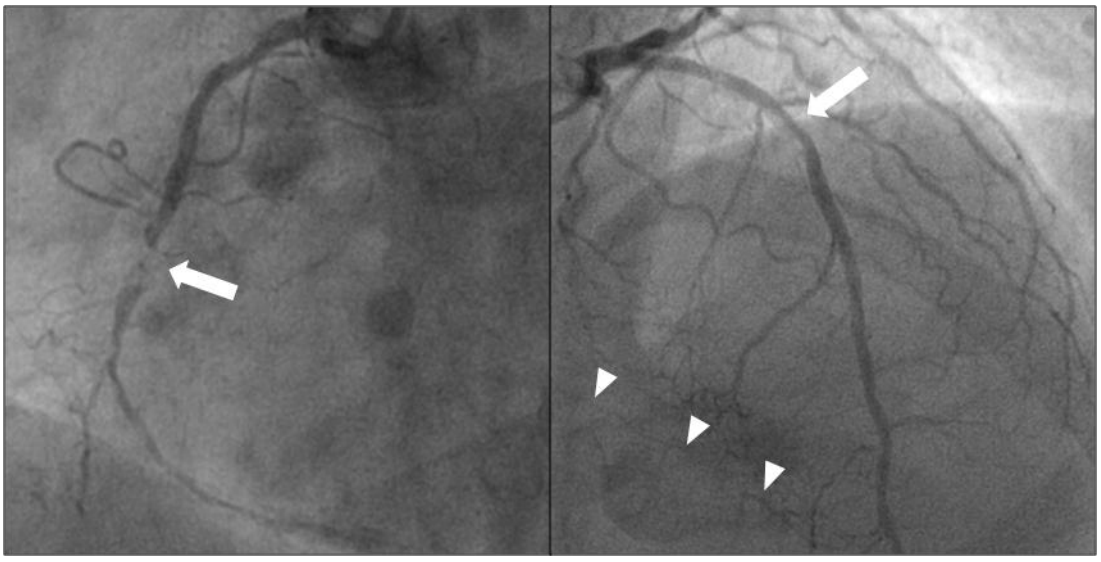

Figure 24.3
CT Perfusion Patient 4 – Invasive angiogram. There is a short length of occlusion in the mid RCA (left, arrow) and a moderate stenosis in the mid LAD (right, arrow), with collateral filling from LAD to RCA (arrowheads), consistent with the CT findings.

Patient 5

Gender	Male
Age	64 years
Body mass index	31 kg/m^2
Previous medical history	Previous coronary artery bypass grafts to LAD and RCA
Total dose ($CTDI_{vol}$/DLP)	60 mGy / 733 mGy·cm
rMPI diagnosis	Mild, fully reversible, apical inferoseptal perfusion defect, with a more significant basal to inferobasal fixed defect
Perfusion CT findings	Possible apical posteriolateral perfusion defect and clear inferobasal hypoperfusion or scar
Onward management	The patient underwent invasive angiography and the grafts were felt to be satisfactory. The patient was therefore managed medically
Comments	The inferobasal segment appears has the appearances of myocardial scar due to previous infarction on CT. There is an apparent posterolateral perfusion defect on the CT which does not fully correspond to the reversible defect on rMPI and it is unclear which of these is inaccurate.

Table 24
CT Perfusion Patient 5 Summary.

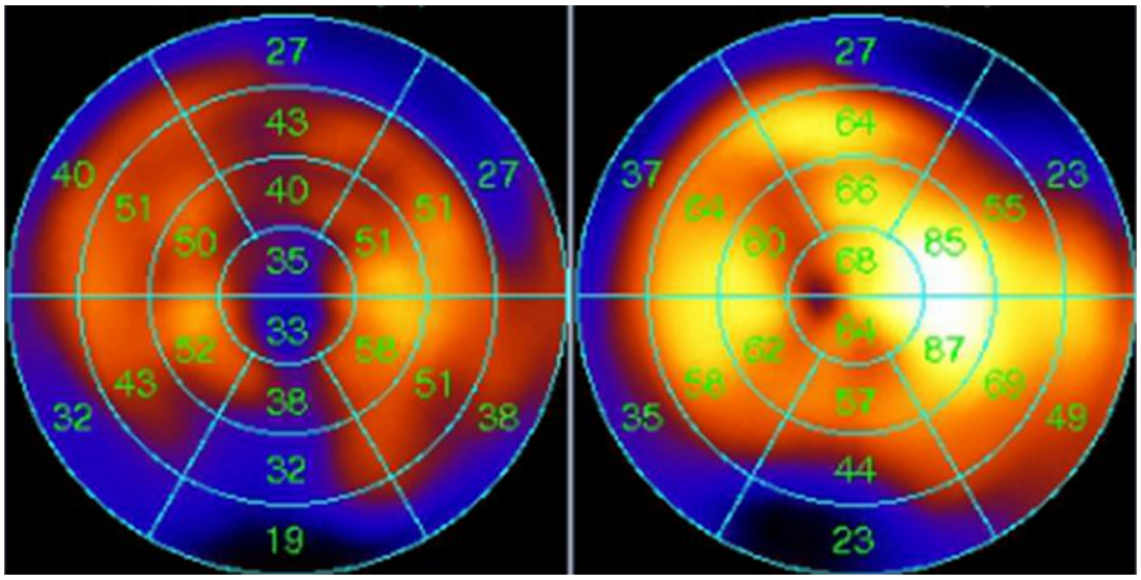

Figure 25.1
CT Perfusion Patient 5 – rMPI. Stress (left) and rest (right) images demonstrating a large inferobasal perfusion defect which is evidence on both, suggesting irreversibility, with reversibility evident more apically.

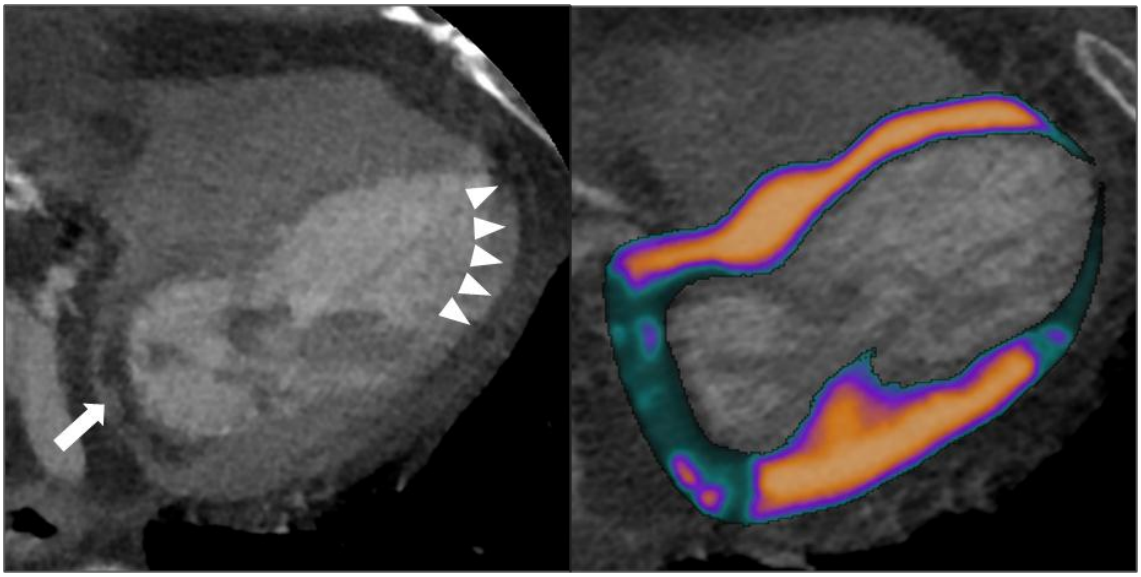

Figure 25.2

CT Perfusion Patient 5 – CT. The fixed hypoenhancement in the inferobasal segment (left, arrow) is consistent with fibro-fatty infiltration which occurs following myocardial infarction. There also appears to be a perfusion defect in the lateral wall towards the apex, which extents posteriorly. The image on the right is a myocardial iodine mask, which can help to visualise perfusion defects.

Patient 6

Gender	Female
Age	81 years
Body mass index	22 kg/m^2
Previous medical history	Previous PCI to LAD
Total dose ($CTDI_{vol}$/DLP)	33 mGy / 288 mGy·cm
rMPI diagnosis	Distal-mid anterior to anterolateral, moderately large, fully reversible perfusion defect.
Perfusion CT findings	Clear, corresponding perfusion defect. Suboptimal coronary artery imaging.
Comments	Patient underwent PCI to a severe Cx stenosis (see below).

Table 25
CT Perfusion Patient 6 Summary.

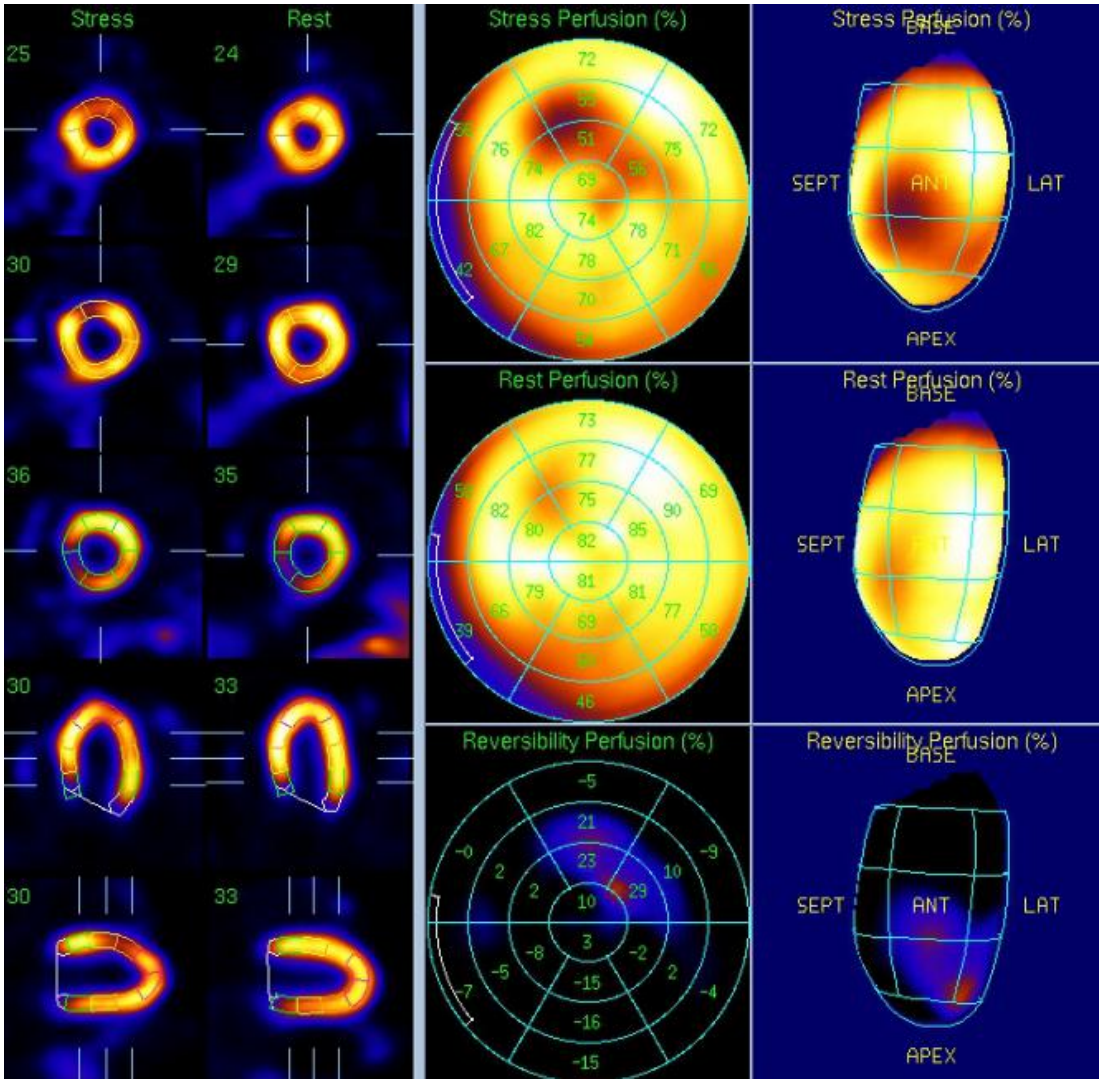

Figure 26.1
CT Perfusion Patient 6 – rMPI. Montage of rMPI images demonstrating a reversible anteriolateral perfusion defect.

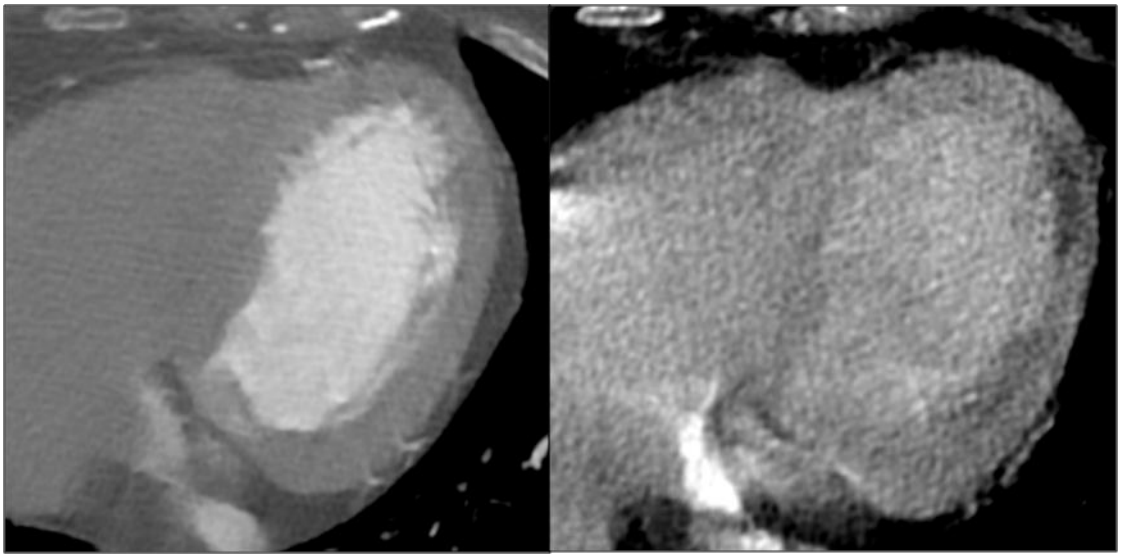

Figure 26.2
CT Perfusion Patient 6 – CT. Rest (left) and stress (right) images demonstrating a reversible anterolateral perfusion defect.

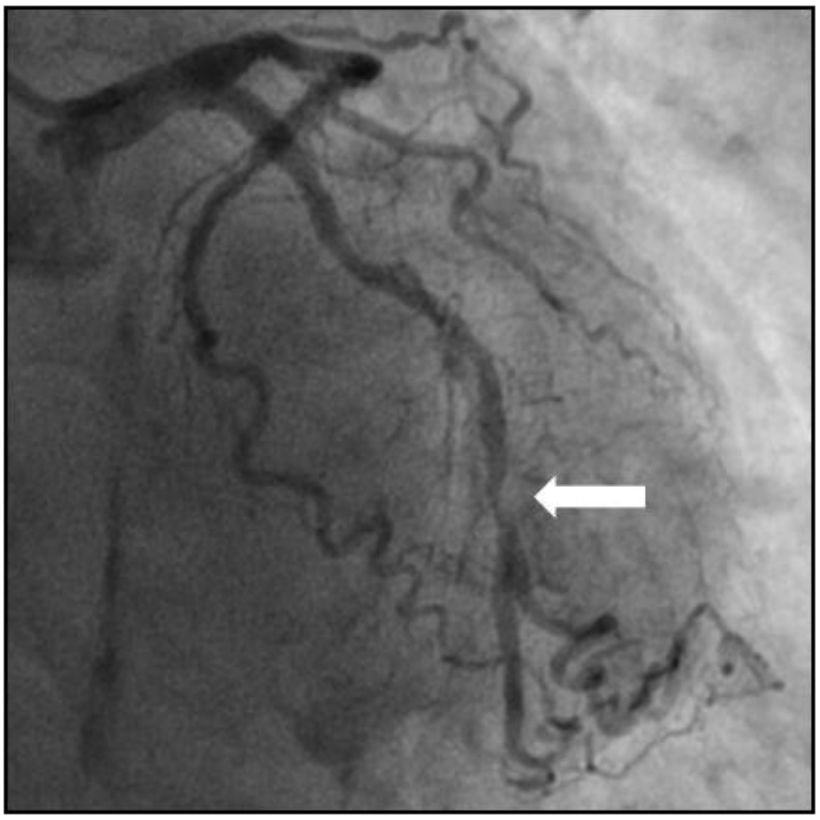

Figure 26.3
CT Perfusion Patient 6 – Invasive angiogram. The culprit lesion is a severe stenosis in the mid Cx which supplies an unusually anterior portion of the left ventricle due to a small calibre LAD.

Patient 7

Gender	Male
Age	67 years
Body mass index	30 kg/m^2
Previous medical history	Known angina but no previous coronary imaging. Type 2 diabetes mellitus
Total dose ($CTDI_{vol}$/DLP)	35 mGy / 401 mGy·cm
rMPI diagnosis	Mild, inferoseptal, inferior, and inferolateral perfusion defects. These are mainly reversible in the inferior and inferolateral territory but may represent scarring in the inferoseptal segment.
Perfusion CT findings	No perfusion defect identified. Moderate LAD stenosis.
Onward management	The patient underwent angiography demonstrating an unobstructed right coronary artery. The LAD had a moderate stenosis in the proximal course, consistent with the CT findings, which was stented on the basis of the patient's symptoms.
Comments	The functional significance of the LAD stenosis is again uncertain – it was not identified on either the CT or the rMPI and was stented due to the patient having a convincing history of ischaemic-sounding pain.

Table 26
CT Perfusion Patient 7 Summary.

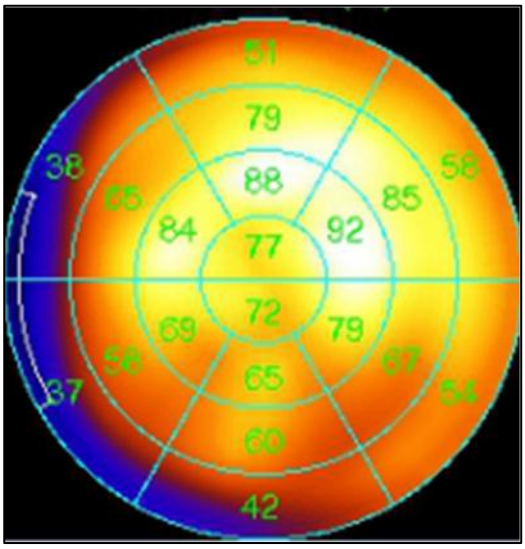

Figure 27.1
CT Perfusion Patient 7 – rMPI. Perfusion 'bullseye' demonstrating apparent basal inferior and inferoseptal perfusion defects (dark blue).

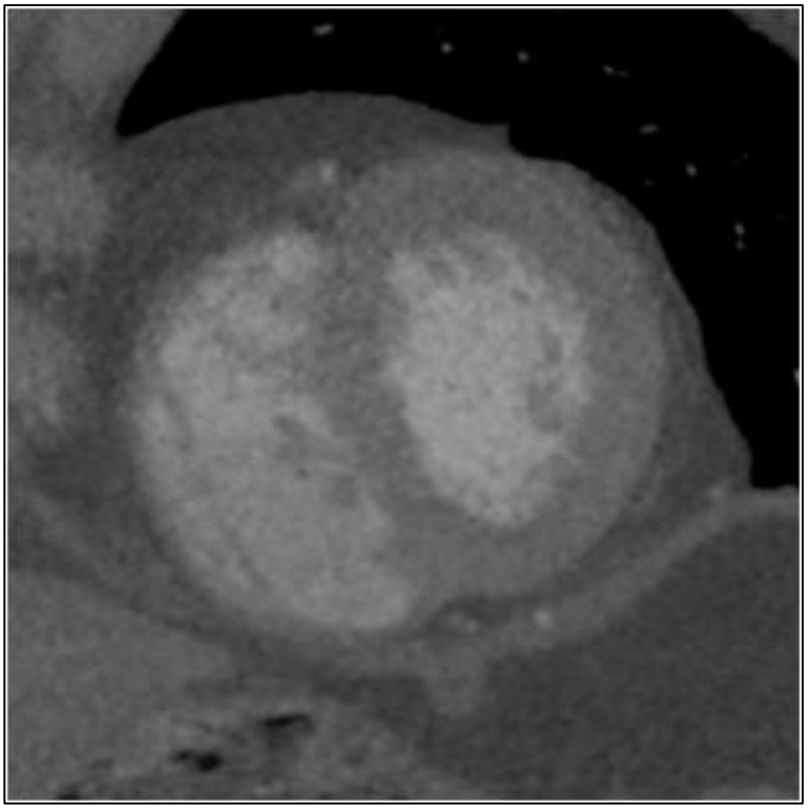

Figure 27.2
CT Perfusion Patient 7 – CT. CT demonstrating apparently normal perfusion of the left ventricle at the basal level.

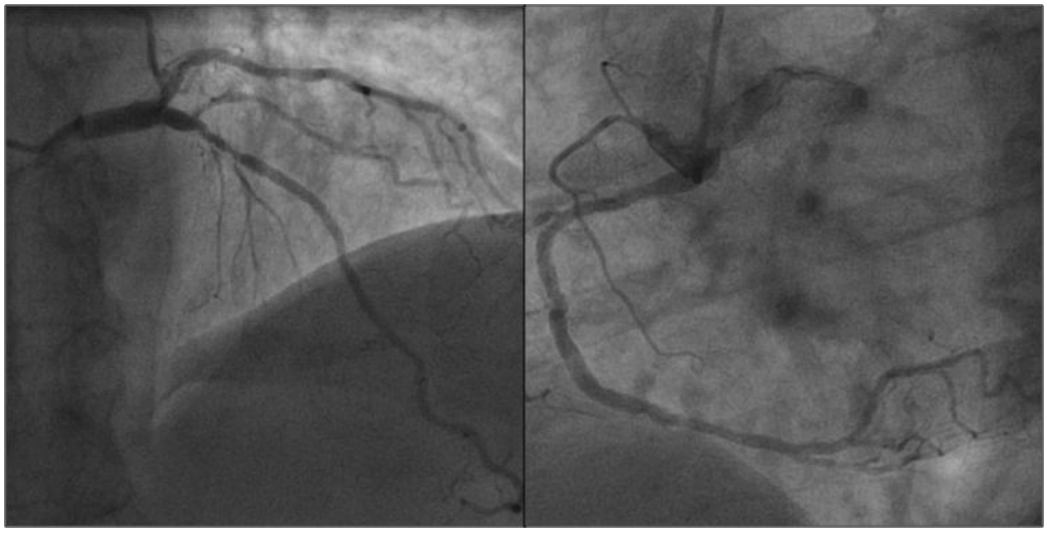

Figure 27.3
CT Perfusion Patient 7 – Invasive angiogram. Left (left image) and right (right image) coronary arteries demonstrating grossly normal calibre other than in the proximal LAD where a moderate stenosis is present.

8.3 Discussion

This exploratory study of the usefulness of single source, dual energy CT for the assessment of perfusion has demonstrated the potential of CT to accurately assess myocardial blood flow during stress and at rest. It has identified 63% of the perfusion deficits seen at rMPI, but those which have been 'missed' appear to be false positives, based on angiographic correlation. Furthermore, CT seems to have identified two perfusion defects which were missed by rMPI. This suggests that this approach with CT might be able to offer superior accuracy over rMPI. This has also been identified with previous studies comparing CT with rMPI, which note the improved spatial resolution of CT which may identify perfusion defects missed by the nuclear medicine technique.[230]

When compared to the angiographic testing strategy, CT correctly identified eight perfusion defects for which revascularisation was undertaken. The single false positive and two false negatives were all determined based on visual estimation of coronary stenosis rather than pressure wire study, which is a fallible strategy.[117]

There are some apparent disadvantages to this CT perfusion algorithm, not least being the significant radiation dose. At a time when radiation doses from cardiac CT are falling markedly[19,34] the CT perfusion protocol used here resulted in a far greater dose. The selected scanner protocols used in this study (Table 9, Chapter 3) represent the highest tube settings available and this may be able to be reduced – further evaluation of the technique examining signal to noise ratios in a larger, clinical population will be required. Furthermore, the current protocol uses the same scan

acquisition parameters for both stress and rest images, to ensure optimal comparability. It is important to maintain the spatial resolution for the coronary imaging that slice thickness is maintained at 0.625 mm but for myocardial imaging this is not required. Indeed, optimal myocardial images require increased slice thickness and greater image smoothing than coronary imaging.[230] It is therefore likely that, at least for the stress acquisition, the slice thickness can be increased which will in turn reduce the radiation dose.

The radiation dose also limits some of the data which can be obtained during a CT perfusion examination. The generation of functional information about left ventricular performance was routinely gathered when multiple phases of the cardiac cycle were always collected, with retrospective gating, and the accuracy of this data has ensured that quantifying ventricular function remains an appropriate use of cardiac CT.[99] However, the radiation exposure from this method is considered to be high, particularly in comparison to modern, prospective (or high-pitch retrospective) gating and this relegates CT to a second-line investigation for this indication. This means that whereas cardiac MRI is able to evaluate a combination of both myocardial blood flow and regional wall motion abnormality when assessing transcoronary perfusion, CT is generally limited to the former. Regional wall motion abnormalities can be identified using CT, with so-called 'dynamic' perfusion protocols, but at the expense of considerably high radiation exposure.[234] It is perhaps worth noting that there is some disagreement about whether single, static images can correctly be referred to as 'perfusion' images.[235]

In addition to the above problems, some difficulties with the scanning process itself were identified. The image analysis was significantly hampered by the failure of the software to accurately delineate the myocardium (Figure 28). Particularly on stress imaging, the insufficient temporal resolution resulted in motion blur which impaired the accurate identification of the myocardial border and prevented the creation of a left ventricular perfusion map. This meant that image analysis had to be performed visually – given that the major purported advantage of dual energy CT is its improved iodine detection, this is clearly a major limitation. The hope going forward would be for improved software capability, to compensate for such artefact, or improved temporal resolution such that image quality would not be affected. Of course, the latter may also facilitate the improvement of coronary image quality, such that perfusion studies are not needed as a technique for improving diagnosis in the difficult-to-image patient.

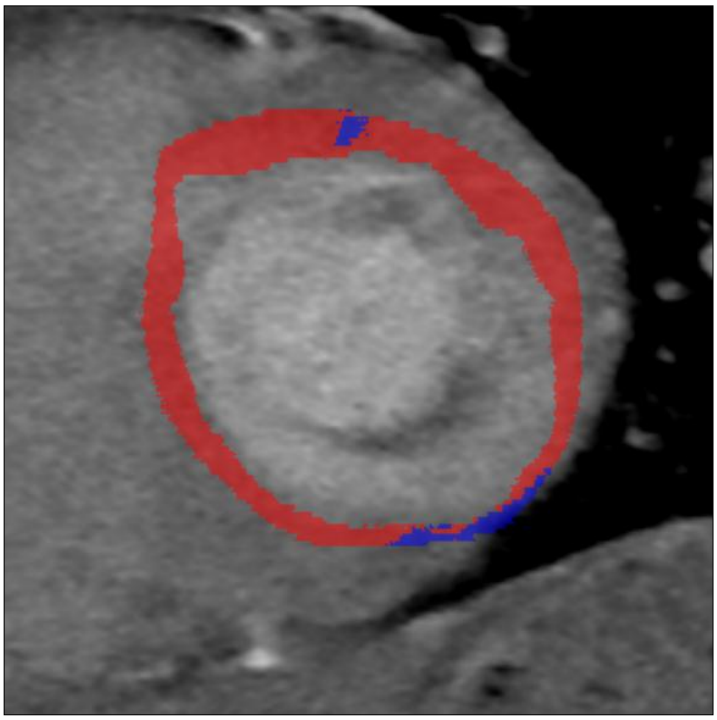

Figure 28
Myocardial border detection. This image demonstrates the limited ability of the post processing software to accurately delineate the myocardial border. The myocardial overlay (red and blue) does not conform to the myocardial borders.

One further concern, beyond the technical ability of the scanner technology, is the ability of CT to identify defects in myocardial iodination at rest, which can only be identified on the stress study with rMPI. This may be due to the vasodilatory effects of iodinated contrast, acting as a pharmacological stressor and eliciting coronary steal, or the differences in distribution kinetics between radionuclide tracer and CT contrast.[235] One recent study found that 45% of reversible perfusion defects were misclassified as fixed due to this phenomenon.[236] This cannot be overcome by technological adjustments and the implications will need to be considered prior to adoption of this investigative process into routine clinical practice.

The major limitation of this study is the small sample size. While it has been useful to evaluate the relative ease and initial usefulness of the technique, the sample size is too

small (and the number of apparently false positive rMPI studies is too high) to be able to draw firm conclusions as to its accuracy. As mentioned previously, this is in part due to a diminishing pool of patients with the increase in stress MRI being conducted at our institution, along with recent evidence suggesting that cardiac MRI may be superior to rMPI.[232] A study comparing this CT perfusion technique against what might now be considered as the current, non-invasive, gold standard of stress MRI is currently underway at our institution.

Future studies may also consider exploiting the other potential benefits of dual energy CT imaging. The use of virtual monochromatic datasets may improve tissue characterisation, particularly at lower kVp energies, and might therefore help lower density, hypoperfused regions to become more conspicuous. In this study there were no true positive perfusion abnormalities which were not detected by CT.

9. Infarction and scar with cardiac CT

9.1 Introduction

Case 5 in the previous chapter demonstrates the relative ease with which fibrofatty replacement of the myocardium, occurring following myocardial infarction, can be observed.[237,238] This is facilitated by the tissue differentiation between relatively dense myocardium, particularly when it contains iodine, and low density fat. Following infarction, fatty replacement of the myocardium initially within fibrous scar[237,239] eventually leads to significant lipomatous metaplasia.[240] Although this is a relatively late feature, not described within the first 6 months following infarction,[237] it can ultimately be extensive and is evident in severely diseased hearts excised from patients receiving transplants.[239,241] On CT, fat in infarcted myocardium is usually, although not exclusively, subendocardially distributed[105] in a curvilinear pattern, within a coronary artery territory[240,242] (Figure 29). Transmural extension does not seem to occur.[243] It is easily visualised, even on non-enhanced images undertaken for calcium scoring,[244] and extremely common, with the prevalence of post-MI LV fat as high as 96% in some studies.[245] The frequency of infarct-related LV fat on CMR is reportedly lower, at around 68% – histological studies suggest the true prevalence to be somewhere in between.[239]

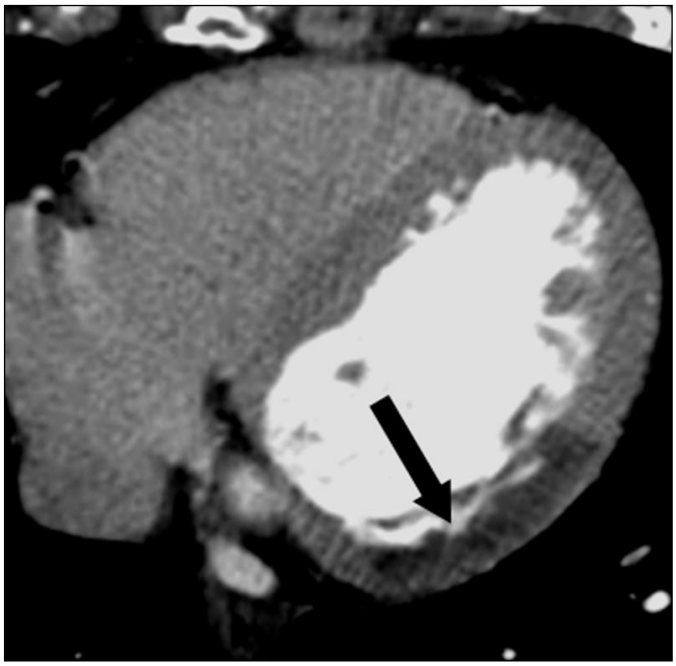

Figure 29
A large, focal, fibrofatty lesion seen in C due to a circumflex territory infarction (black arrow)

The prevalence, and relative ease of detection, of fibrofatty infiltration makes the identification of post-infarction scar an appealing objective for the identification of coronary artery disease, particularly if the coronary arteries themselves prove difficult to image, and the identification of previous infarction at CT has been explored.[246] Due to the previously described manner in which fibrofatty replacement occurs, it would also be necessary to identify scar prior to the development of low density lesions. The gold standard for the identification of myocardial scar is cardiac magnetic resonance imaging (MRI).[52] This exploits the difference in the way healthy and pathological myocytes process gadolinium, (altered clearance and volume of distribution)[247] to which cardiac MRI is highly sensitive. The operator is able to suppress or 'null' normal myocardium by setting a particular inversion time, such that healthy myocardium does not return a signal to the detector and thus appears black.

Regions of myocardium containing gadolinium display different magnetic properties and are therefore seen as bright white.[248]

The purported improvement in iodine characterisation with dual energy CT[225] offers the possibility of improved identification of myocardial segments containing iodine against otherwise normal segments. This may allow improved detection of 'delayed enhancement' of the myocardium with CT, a concept which has been provisionally explored by a number of studies. These have generally been investigations in animal models,[249–251] or as part of a stress perfusion protocol,[230] where the combined accuracy of both stress perfusion and delayed enhancement has been used to identify coronary artery disease with comparators being invasive angiography or rMPI,[230,252] rather than as a direct test of the ability to identify delayed enhancement compared to cardiac MRI.

This study therefore aimed to evaluate, for the first time in humans, the feasibility of single source, dual energy CT to identify delayed myocardial enhancement, in comparison to cardiac MRI.

9.2 The study

Materials and methods

The study was performed in a prospective fashion, with prior approval by a committee of the UK National Research Ethics Service. It was registered as part of a larger clinical trial of the applications of single source, dual energy cardiac CT (NCT 01816750). All participants gave informed, written consent. All patients with an MRI scan

demonstrating myocardial late gadolinium enhancement, having been imaged on standard clinical grounds between March 2013 and May 2014, were screened against the study criteria.

The exclusion criteria were patients under 50 years old, body mass index >30kg/m^2, allergy to iodinated contrast media, estimated glomerular filtration rate <30ml/min, or pregnancy. Patients requiring urgent revascularisation before CT scanning could take place were also excluded.

Cardiac MRI imaging protocol

All patients underwent cardiac MRI assessment on a 1.5 Tesla system (Achieva 1.5 d-stream conversion, Philips Medical Systems, Best, Netherlands) using dedicated cardiac phased array receiver coils for signal reception. Patients were weighed and an intravenous cannula was inserted. The standard cardiac MRI protocol included initial scout images in the axial, sagittal and coronal plains, followed by 2, 3 and 4-chamber cine images, and 4-chamber and left ventricular short axis cine volume stacks. The patients were then administered intravenous gadolinium (0.2 mmol/kg gadobutrolum, Gadovist, Bayer-Schering Pharma, Germany). Ten minutes after the injection of gadolinium, myocardial nulling was be assessed via a look-locker sequence. Individually optimised times (200-350 msec) determined from the look-locker sequence were then used to acquire inversion recovery gradient-echo 2 and 3-D images in the ventricular short axis and ventricular horizontal long axis, as well as a single vertical long axis. A 2D FFE multi-slice short axis inversion recovery sequence (TR/TE = 6/2.7; reconstructed

voxel-size 1 × 1 × 8 mm acquisition; SENSE-factor = 1.2; TI = 240 – 340 ms) was employed.

CT imaging protocol

Patients were weighed and measured and a body mass index (BMI) calculated, and an intravenous cannula was inserted. All patients underwent a prospectively gated, unenhanced scan (100 kV, 80 mA) with 2.5 mm slices, for calcium scoring and to assess for hypodense myocardium. Following this they underwent CTCA, performed using a single source, dual energy scanner (Discovery CT750 HD, GE Healthcare, Milwaukee, WI). Iodinated contrast (Optiray 350, Covidien, MA, USA) was administered as a 100 ml, multiphase bolus at an initial rate of 6.5 ml/s, followed by a 50 ml saline flush and the scan was triggered manually upon opacification of the ascending aorta, with a seven second scan delay. The scan was conducted using prospective ECG gating, without additional tube-on time, irrespective of heart rate. The following parameters were used: slice acquisition 64 × 0.625 mm, z-axis coverage 40 mm with an increment of 35 mm, gantry rotation time 350 ms, 80 – 140 kV fast switching tube voltage, with tube current according the manufacturer-specified settings (see Table 9, Chapter 3).

Immediately following the scan a further 50 ml iodinated contrast was administered as an intravenous bolus over one minute, using a hand injection. Ten minutes after this the patient underwent a delayed enhancement scan using the same settings. The images were reconstructed using a 50% blend of iterative reconstruction.

Image interpretation

The image sets from both examinations were anonymised and transferred to remote workstations for interpretation. They were assessed by expert readers in each modality, each with more than 5 years experience, blinded to the results of the other test. All image sets were analysed using the American Heart Association 17-segment myocardial model.[253]

Statistics

Statistical analysis was performed using SPSS Statistics 21 (IBM Corp., New York). The distribution of data was assessed graphically and parametric or non-parametric tests selected accordingly. Continuous variables were assessed with an unmatched t-test or independent samples Kruskal-Wallace test. Test accuracy was estimated using descriptive statistics.

Results

Twenty patients were recruited to the study although two withdrew prior to completing the full image protocol. Therefore eighteen patients were included in the analysis, comprising 16 with prior myocardial infarction and two with hypertrophic cardiomyopathy. There were no adverse events.

The baseline demographics of the study participants were as follows: median age 66.5 years (interquartile range 56 – 72 years), body mass index 28 kg/m^2 (IQR 25 – 29 kg/m^2), and 94% were male (n = 17). The median $CTDI_{vol}$ was 33.15 mGy (IQR 28.9 – 36.8 mGy) and the median dose length product was 418 mGy·cm (IQR 365 – 420 mGy·cm).

In total, 306 myocardial segments were analysed. Eighty four segments (27%) displayed late gadolinium enhancement at cardiac MRI. With CT, 60 segments (71%) containing late enhancement were correctly identified (true positive) and 216 (98%) were correctly classified as normal (true negative). There were 5 false positive and 25 false negative segments. The overall accuracy of CT to identify delayed enhancement compared to cardiac MRI was therefore: sensitivity 0.71 (95% confidence interval 0.59 – 0.80), specificity 0.98 (0.95 – 0.99), positive predictive value 0.92 (0.83 – 0.97) and negative predictive value 0.90 (0.85 – 0.93).

9.3 Discussion

This study suggests that, using a single source, dual energy technique, CT may offer good performance for the detection of myocardial scar with late iodine enhancement. This feature was identified with both focal (Figure 30) and coronary territory (Figure 31) scar. The specificity is particularly impressive at 0.98, which is notable as the usual limitation of CT with coronary artery disease. Also of note, the false positive readings all occur in segments directly adjacent to true positives, suggesting that these may be due to differences in reader assignment of myocardial territory, rather than entirely spurious anomalies.

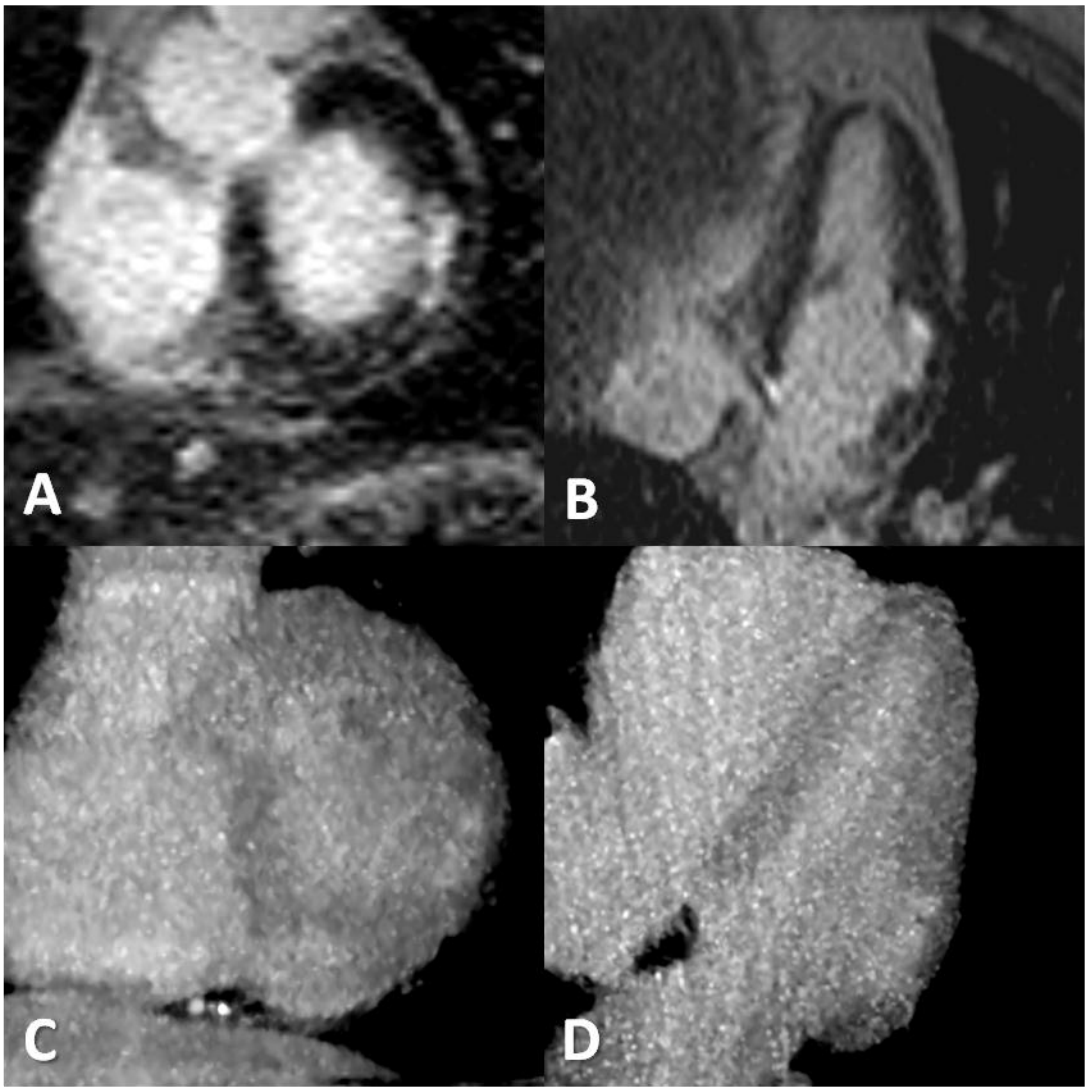

Figure 30
Focal late contrast enhancement. Cardiac MRI images in the short axis (A) and 4 chamber (B) views and corresponding CT images, also in the short axis (C) and 4 chamber (D) views, demonstrating focal enhancement in the basal lateral wall.

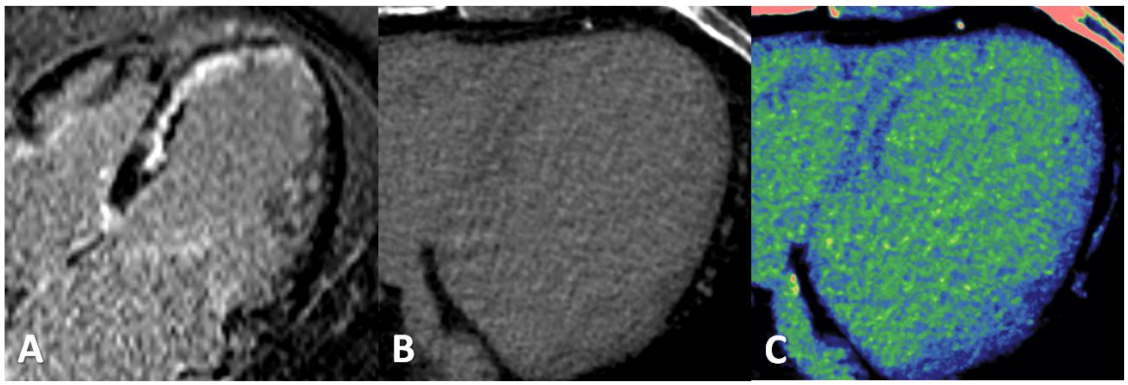

Figure 31
Late iodine enhancement. Cardiac MRI image (A) demonstrating late gadolinium enhancement in the left anterior descending artery territory. While this scar is visible in the low keV image (B) the use of a myocardial iodine overlay (C) accentuates the abnormality further.

This finding has since been repeated by another group using a dual source, dual energy scanner in patients with only ischaemic scar.[254,255] One group has also achieved similar results using conventional 64-multidetector row CT technology rather than dual energy, with a sensitivity of just 53% but a specificity of 98%.[256] Although not directly comparable, these additional results would support the prospect of CT being able to offer delayed iodine enhancement imaging, with dual energy scanners potentially improving on the performance of conventional technology.

CT scanners are narrower and generally have a wider bore than MRI scanners, which may improve patient tolerance. CT scanning is also much faster with a typical acquisition complete in a under a second, whereas MRI scanning takes tens of minutes. Furthermore, CT is able to combine delayed iodine enhancement imaging with the identification of fibro-fatty replacement, perfusion and delineation of the coronary anatomy in a single test (Figure 32). Finally, patients with pacemakers and other metallic implants can undergo CT without special devices or precautions being required, which is particularly relevant as patients with myocardial scar may well require complex cardiac devices, such as implantable defibrillators or cardiac resynchronisation therapy.

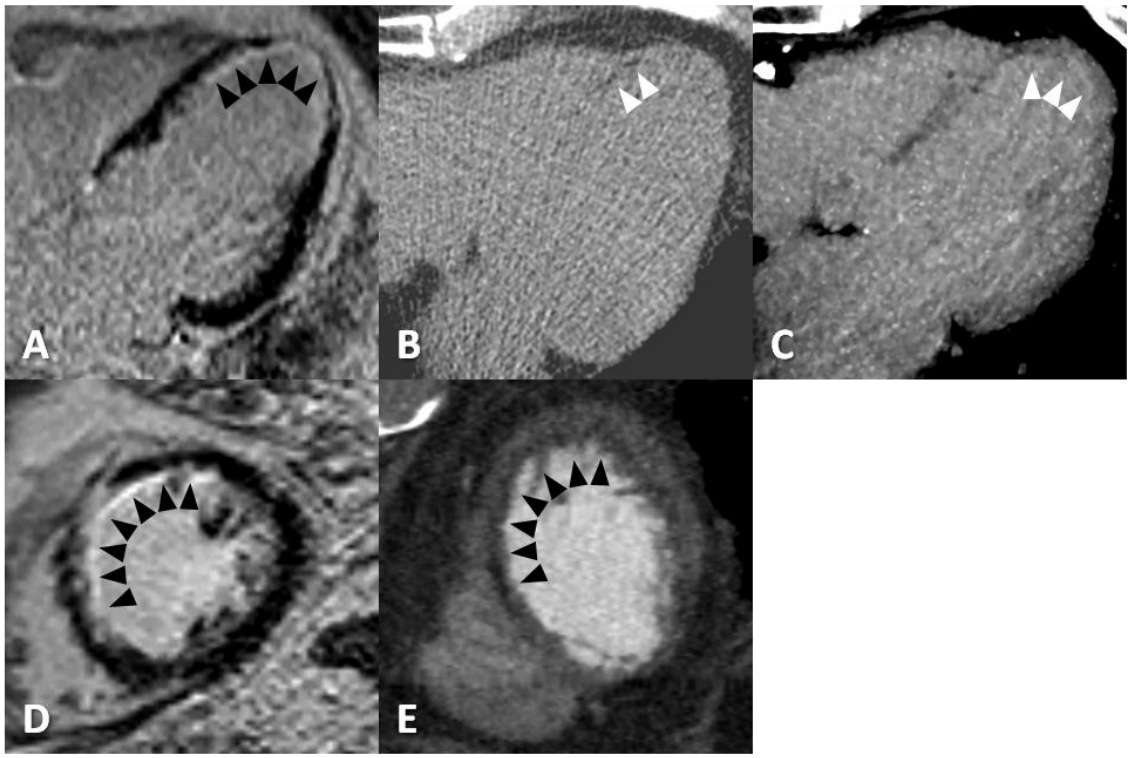

Figure 32
Various contrast phases in a left anterior descending artery territory scar. A – cardiac MRI 4 chamber view demonstrating late gadolinium enhancement in the LAD territory. B – unenhanced CT image demonstrating small areas of low density material consistent with fibro-fatty replacement of the myocardium following infarction. This territory is smaller than in image A suggesting that only part of the scar has undergone replacement. The remainder is seen in C – with late iodine enhancement at the left ventricular apex. D demonstrates late gadolinium enhancement in a short axis view. Note the corresponding, dark, hypoperfused region during the contrast phase of the CT scan (E).

One limitation of CT is the static nature of the imaging. As previously discussed the use of multi-phase cycles is costly in terms of radiation exposure. This limits imaging to the primary identification of delayed enhancement. At least for ischaemic scar, the presence of regional wall motion abnormality may also be useful to help identify pathological myocardium, but this was not available in this study.

As with the perfusion imaging in chapter 8, one major difficulty is the current inability of the workstation software to accurately delineate the myocardium. It appears that the algorithm uses the high density blood pool within the left ventricle from which to

identify the myocardial border and the absence of contrast limits prohibits this (Figure 33). Further improvement in performance may be achieved if myocardial masks were readily available to display iodine patterns.

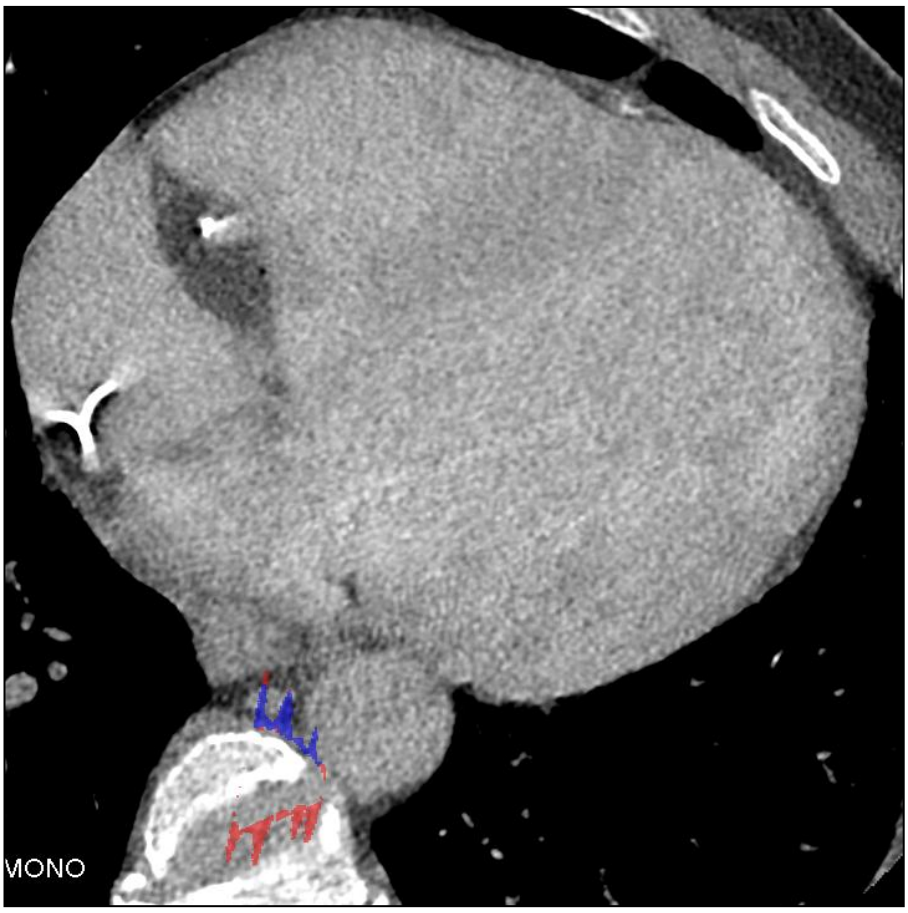

Figure 33
The absence of a defined intra-ventricular blood pool of high (contrast) density prohibits the identification of the myocardial border. Instead the software appears to have selected the densest structure, in this case the spinal vertebra.

One further consideration is the optimal timing of delayed enhancement images. Time is needed for the iodine to egress from healthy tissue, and to be taken up by diseased tissue,[251] but also to allow a reduction in iodine in the blood pool. Therefore, further

delay before the non-contrast acquisition may allow the myocardium, and any enhancement thereof, to be more conspicuous.[250]

This study was conducted in a small number of patients to ensure its feasibility. It is tolerated well and there appears to be reasonable accuracy with the technique. Before widespread clinical introduction further study will be required, in unselected, all-comer populations to determine a more precise accuracy and further evaluate the limitations of CT for this application.

Section 5 – Discussion

The opportunities to improve the investigation of the difficult-to-image patient comprise a diverse range of approaches and this thesis therefore explores a number of novel contributions to the knowledge base. The examination of calcified vessels is crucial to modern CT practice; firstly for improving the positive predictive value in patients with a high coronary calcium burden. This is important not only because it may reduce the need for downstream, invasive testing, improving the patient experience and potentially reducing costs, but also because coronary calcium is one of the few variables which cannot be predicted or ameliorated prior to a patient's attendance for a scan. This has a further implication, in that CT has been considered as inappropriate in patients deemed as being at high pre-test risk of coronary artery disease, partly because of the associated risk of calcified coronary arteries. Hence, removing coronary calcification as a barrier to successful CT coronary angiography would bring the opportunities of non-invasive coronary imaging to patients at higher risk, particularly in the United Kingdom where this is currently limited to those at low clinical risk (10 – 20% pre-test likelihood).[82]

The studies outlined here exploring calcified coronary disease are not directly comparable but, superficially at least, high definition imaging seems to offer much a greater improvement in image quality than dual energy, calcium subtraction techniques. Further research will be needed in a larger, diverse population and incorporating multiple sites, but HD scanning appears to offer a highly accurate solution to this major imaging limitation. There is a curious dichotomy in the NICE Diagnostics Guidance 3, whereby CT is recommended for patients at low pre-test probability and also those with known coronary disease who have previously

undergone revascularisation[98] and HD CT certainly appears capable of dealing with the latter. The rationale for limiting CT to the lower risk groups is predominantly the association with high calcium levels resulting in imaging difficulties, which might be removed with the introduction of HD scanning.

The positive predictive value of CT in this context must of course be considered, influenced as it is by the pre-test likelihood. The use of CT for higher risk patients also has important implications for the risk-benefit ratio of this investigative modality. The risks of radiation exposure, discussed in Chapter 1.3, are a necessary consideration for referring clinicians and CT operators but the relative risk of ionising radiation is less if the likelihood of identifying a serious pathology, with implications for mortality and morbidity, is higher.

Even without new generation technology, progress might be made in improving image quality in the face of calcified coronary arteries. While the findings need examining *in vivo*, it seems that careful consideration of the reconstruction methods used may help to improve the accuracy of imaging of high density structures. This might include stents as well as calcified atheromatous lesions. The benefits of novel methods of image reconstruction extend not only to this challenging patient group, but to all patients undergoing cardiac CT who may benefit from significant reductions in radiation exposure as a consequence. These methods exist in all CT systems and the variability in image quality and, crucially also, diagnostic accuracy which has been demonstrated should lead all those who use CT to question the methods being utilised to answer each clinical question.

The use of simple interventions to reduce the difficulty with which patients are imaged is an appealing one. The use of a more aggressive beta-blocker strategy is another relatively simple amendment which may improve imaging quality with important implications for radiation exposure. The use of intravenous beta-blockers minimises the impact on the clinical work flow, although referring clinicians might also be encouraged to prescribe oral agents for the days leading up to the scan.

The combination of aggressive beta-blocker use and further simple adjustments in acquisition methodology also facilitates the imaging of patients with atrial fibrillation. The association of AF with coronary ischaemia makes the ability to successfully image patients with this arrhythmia of real clinical importance. Again, the findings presented here suggest that this is readily achievable with conventional 64-MDCT technology.

The other, emerging applications of cardiac CT of perfusion and delayed enhancement imaging also show promise. While these may be useful as surrogate markers of coronary artery disease and its sequelae in patients who are difficult to image, they may also have applications of their own. Not all patients are suitable for cardiac MRI, due to claustrophobia or the presence of metallic foreign bodies or implants, for example, and an alternative imaging modality would be beneficial here. Furthermore, there is the suggestion that the combined CT perfusion and angiography might even be superior to rMPI, which has been established for many years.

If imaging can be improved in patients conventionally considered to be challenging then a range of additional potential uses for CT emerge. There is growing interest in assessing the functional significance of a coronary stenosis using fractional flow reserve estimations; applying principles of computational fluid dynamics to the CT images to infer functional significance. In addition, the identification of 'vulnerable' plaque, which is at high risk of rupture leading to acute coronary occlusion, is currently a key research topic across a number of imaging modalities, including with CT. Both of these techniques require excellent CT image quality, which becomes more likely if the challenges of imaging are diminished.

These novel applications neglect the strength of CT for the assessment of coronary artery disease (CAD). If obstructive CAD can be confidently excluded across all patient groups, this would permit the consideration of CT as a genuine alternative to invasive angiography. There is already evidence that decision making about onward management is the same regardless of whether the patient was imaged with invasive angiography or high quality CT scanning[257]. Moreover, clear differences in mortality have been demonstrated between patients with non-obstructive coronary atheroma and patients with completely normal coronary arteries,[258] which can be a challenging distinction in the face of reduced image quality.

Limitations

There are a number of limitations to the evidence presented here. Most of these have been considered in each chapter, as relevant, but there are some key, overarching themes.

The studies have been performed in a single centre with considerable expertise in, and experience of, cardiac CT and the expert readers were highly experienced. Most evidence in cardiac CT has been developed from similar environments and this limits the wider clinical applicability of the findings.[7] Furthermore, the sample sizes are very small in a number of the studies. This makes the drawing of firm conclusions about the benefits of the technologies challenging and potentially dangerous.

Finally, the benefits of dual energy CT over conventional technology need to be explored. While it appears that these techniques are useful, particularly for myocardial evaluation, there are some theoretical benefits to dual energy scanning, including differentiation of low contrast tissue densities and the reduction of artefacts, which have not been thoroughly explored. With the small sample sizes the populations contain insufficient examples of these phenomena to ensure that they are overcome by dual energy techniques.

Future developments

Incredibly, some commentators believe that CT has reached the limits of technological developments and will never be able to truly compete with angiography as a coronary diagnostic modality.[259] In reality, in some ways the findings from the studies presented here are already out of date. Technology is moving on at an incredible pace and it seems we are entering a revolutionary phase in the development of cardiac CT. With the increasing availability of wide detector scanners, which provide whole-heart coverage, allowing acquisition of the entire cardiac volume, the ‘slice war’, with

manufacturers competing to deliver scanners with ever more detector rows, may be reaching its limit. This by no means suggests that the development of CT technology has peaked otherwise. Increasing miniaturisation (Figure 34), improved spatial, temporal and contrast resolution, the use of dual-energy and progressive reconstruction methods are all driving CT forward.

Figure 34
Detectors in 'new-generation' and 'next-generation' CT scanners. On the left is the detector module from a modern scanner (in the region of 25 cm length), evaluated in the NICE review of 'new-generation' technology[98] *and on the right is the equivalent component in the newest scanner to market (3 – 4 cm length).*

The latest wide detector, cardiac-capable scanner to reach the market claims a temporal resolution of 0.14 seconds, approaching that of fluoroscopy, with high-definition scanning to achieve a spatial resolution of 18 line pairs per centimetre. Such developments make the prospect of single-heartbeat imaging, irrespective of heart rate or breath-hold, in patients with coronary calcification or stents, and with modern iterative reconstruction brings sub-milliSievert scanning into the routine, with

radiation doses well below that of fluoroscopy and even competing with plain film x-ray.[166] If artefact and concern about radiation doses reduce this significantly then it also offers the possibility of using CT in other ways, with longer, perhaps multi-cycle acquisition, or to facilitate cardiac procedures in the same way that fluoroscopy facilitates percutaneous coronary intervention and CT already permits precise biopsy of stationary structures. Dynamic, whole cycle perfusion studies at peak stress could be conducted to identify perfusion defects and wall motion abnormality, with simultaneous coronary delineation. As far as coronary imaging is concerned it may well be, in the very near future, that no patient will be 'difficult-to-image' at all.

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Appendix 1

Information film available at: tinyurl.com/derrifordheartct

Cardiac CT Scan

Patient Information Sheet

It has been requested by your doctor that you have a CT scan of your heart. This is a scan which can assess your heart and the arteries that supply it, to help your doctor make a diagnosis of your symptoms. The scan uses x-rays to take pictures of your heart.

1. Why am I having this scan?
Based on your symptoms, your doctor has decided to investigate your heart and the blood vessels that supply it.

2. Do I need to take any medication for the scan?
No - you do not need to take any medication before the scan.
You should continue to take all the routine medication your doctor has prescribed.

If you have diabetes and take Metformin you should stop taking this medication on the day of the scan. You will be advised after your scan when you can restart your Metformin.

3. Can I eat and drink normally before the scan?
Yes you can – in fact we advise you to be well hydrated (drink lots of water) before the scan. Please try and avoid coffee, tea and chocolate on the day of the scan as these increase your heart rate, which will result in a poorer quality scan.

4. Do I need to tell the staff what tablets I take?
Yes – it is very important to tell the doctor or staff in the department what medication you take, before you have the scan. It is often useful to bring your repeat prescription on the day of the scan.

5. Will I be given any medications during the scan?
In order to get a good quality scan, your heart rate needs to be slow. Some people may have a slightly faster heart rate than others. If your heart rate is slightly fast a doctor will give you an injection to slow it down (a beta blocker). This is standard practice and there is nothing to worry about. The drug will slow your heart rate gently; it does not have major side effects. It acts for about 20 minutes.

6. Does the doctor need to know any other information about me before giving the drug?
Yes – the doctor will check if you take any medication or have any allergies. It is important to say if you have any allergies, if you have taken Beta blockers before and if you had any problems with them. You should also mention if you suffer from asthma.

7. What happens during the scan?
You will be given a dye (contrast) through a small needle (venflon) in your arm. This helps to show arteries in your heart better. It may produce a hot flush and a feeling that you are passing water. This only lasts for a short time and symptoms pass quickly.

You will be asked to hold your breath for approximately 20 seconds during the scan. It is important that you are able to hold your breath, as this will affect the quality of the scan. You could practice holding your breath at home so you are familiar with this when asked to do so during your scan.

If you cannot hold your breath please tell the staff in the scanner who will be able to help you.

8. How long will the scan take?
The actual scan will only take a minute or two but preparing you for the scan might take a little longer. We also ask you to wait in the department for 20 minutes after your scan to monitor you. You should estimate to spend an hour in the department.

You can normally drive home but we advise you to try and arrange for someone to pick you up.

If you have any concerns or need further information about your scan please contact the department on
01752 437182

You can now see a short film about having a heart CT scan at Derriford. Please visit our YouTube page by typing this address into your internet browser:

tinyurl.com/derrifordheartct

If you are unable to access the internet and would like to borrow a DVD, please contact us on the number above.