The use of injected contrast agents in cadaveric computed tomography

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By

Dr Sarah Saunders BSc(Hons) MBChB PGCert

East Midlands Forensic Pathology Unit
University of Leicester
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Abstract

The use of multi-detector computed tomography and magnetic resonance imaging in autopsy practice is increasing, and there is an international push towards minimally invasive autopsy. A significant obstacle to replacing conventional autopsy with standard imaging is failure to yield detailed information concerning the coronary arteries. A previously established technique to outline arteries is the Swiss-developed ‘whole body angiography’ technique using a heart lung machine and up to 3 litres of contrast agent. This project concerns the novel development of a quicker and cheaper targeted cardiac post-mortem computed tomography angiography (PMCTA) method to allow higher throughput. This thesis introduces the current knowledge of PMCTA, presents the development of the novel method, including a patented task-specific device, and then studies the accuracy of PMCTA ‘cause of death’ against autopsy in 24 cases referred from HM coroners. Cause of death was recorded by three groups of reviewers using a ‘view scan and grant protocol’ of clinical history, external examination and post-mortem angiography findings. A further study was then performed related to obtaining informed consent by telephone from the next-of-kin for post-mortem imaging in 200 cases.

The data showed that using this protocol 82% of cases had a comparably worded cause of death to the autopsy. The ability of PMCTA to detect ischemic heart disease was assessed with a specificity of 88.9% and sensitivity of 100% (PPV = 92.31 %, NPV =100%). Recruiting for a 200 case study of PMCTA we achieved a 96% consent rate with considerable support from the next-of-kin.

These data suggest that a “View, scan and grant” protocol could be used to replace the routine autopsy in certain Corornial cases, leading to a larger 200 case study. The high consent rate helps dispel the notion that there is public objection to post-mortem research.
Original contribution to knowledge:

- A novel method in targeted post-mortem cardiac computed tomography angiography.
- The use of both positive and negative contrast agents (Urograftin® and air) to delineate the coronary arteries.
- A novel consent protocol for obtaining post-mortem research consent for adults from recently bereaved next of kin. A guide to practice and the demonstration of high consent rates (95%) if protocol followed.
- A novel design and prototype production for a task-specific medical device, ‘the Cadatheter’, for post-mortem cardiac angiography with a UK patent submitted and is pending for the device and the angiography method.
- A pilot study of 24 cases of targeted post-mortem cardiac angiography with comparison to subsequent conventional autopsies demonstrating an 86% correlation rate between post-mortem angiography and conventional autopsy.
- Introduction of the concept of a ‘View, Scan and Grant’ protocol and demonstration of how this could lead to a significant reduction in the coronial autopsy rate in the UK.
**Research output directly arising from this work:**

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“3-D body scans could spell end of autopsies-A hi-tech body scanner could eliminate the need to open up bodies on the autopsy table.”
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Chapter 1   Post-mortem computed tomography angiography: past, present and future.

The role of imaging has been long established in forensic practice as an adjunct to the conventional autopsy, especially the use of plain film (see Figure 1-1). Recently, with the development of multi-detector computed tomography (MDCT), there has been a large international push towards the development of the so-called ‘minimally invasive autopsy’. The failure of post-mortem imaging, to yield detailed information about the coronary arteries is an obstacle to gaining acceptance and confidence in ‘minimally invasive autopsies’. This is a significant deficiency of post-mortem computed tomography (PMCT) and post-mortem magnetic resonance imaging (PMMRI) compared to conventional autopsy. One possible way to overcome this is by the use of post-mortem CT angiography (PMCTA). This introductory chapter will discuss the past applications of PMCT and PMCTA, along with the current status of clinical cardiac PMCT and clinical angiography and how this is being translated into the post-mortem setting. The chapter will review the literature regarding PMCTA and the aims of this project.

Figure 1-1: A lateral plain film of the skull of a gunshot victim prior to autopsy showing the distribution of shot within the cranium and soft tissue.
1.1 Introduction

In England and Wales, Her Majesty’s (HM) Coroner investigates deaths of unknown cause or those in which an unnatural cause is suspected. In 2011 the proportion of all deaths reported to the coroner was 46% (222,371 deaths), of which 42% proceeded to autopsy (1). Approximately 90% of all autopsies undertaken in England and Wales are on the instruction of the coroner.

The prospect of an autopsy examination of a loved one may be upsetting for the next of kin of the decedent. There is a perception that the general public and certain religious faiths find the thought of their recently deceased loved one being subjected to an invasive autopsy distasteful (2). This perception is based on the public reaction to the organ retention scandals in Liverpool and Bristol, and the belief that the Islamic and Jewish faiths forbid autopsy. However, these perceptions may misrepresent actual public perceptions and faith beliefs, and reflect are more likely to reflect the personal opinions of the individual expressing them, especially from members of the medical profession (3-7). For example Hinduism ‘dislikes’ but does not forbid autopsy. Where as Islam and Judaism do not permit autopsy examination unless ordered by the coroner, but they are not absolutely against autopsy (8-10). It has been shown that knowing the faith of the decedent, or that there is family objection, may affect the coroner’s investigation (11)

Amongst pathologists undertaking autopsies, it is believed that a large number are being performed unnecessarily (12). Many doctors entering histopathology training do not aspire to undertake autopsies and many trainees are now choosing to opt out of autopsy training during their specialist training (12). A review of coroners’ services questioned the justification of such high numbers of autopsies (13) and a national audit criticised the number of poor and inadequate autopsy reports (14).
These perceptions have driven the medical profession and researchers, over the years, to seek an alternative to the invasive autopsy. This has included the use of ‘view and grant’ systems, needle biopsy, laparoscopic, endoscopic and toxicological autopsies (15-24).

However, despite the promotion and availability of these systems, the invasive autopsy remains the principle mode of examination of the dead. Currently, the future of autopsy remains unclear and there is a feeling that there needs to be a paradigm shift in the approach to death investigation (25-27).

Of the minimally invasive techniques available, post-mortem imaging has the greatest potential for investigation of deaths; specifically the imaging modalities of PMCT and PMMRI. This interest is reflected at government level with the Department of Health commissioning research to consider the role of imaging in both adult and child autopsy practice (28). The Ministry of Justice has also shown great interest in these developments and are in the process of issuing guidelines to coroners for the use of such imaging as an alternative to invasive autopsies (28,29).

The role of radiology within forensic autopsy practice is as old as the x-ray itself. It is considered an important and often essential adjunct to the forensic autopsy. Despite cross-sectional imaging becoming routine in clinical practice for whole-body assessment, traditional plain film radiography still tends to be the modality of choice amongst most forensic pathologists. Recently, the trend is moving towards a full-body PMCT scan before autopsy in countries such as Japan and Australia, but this is not yet the case in England and Wales.
CT scanning was first used as a form of a virtual autopsy in Israel in the 1990’s (30).

Since then, there has been a wealth of literature highlighting both PMCT and PMMRI as powerful adjuncts to post-mortem investigation, especially in blunt force trauma, stab wounds and ballistics injuries (see Figure 1-2)(25,27,31-50).

Internationally and at the East Midlands Forensic Pathology Unit (EMFPU). PMCT has been the favoured modality, for reasons outlined below. PMCT scans, where possible, are performed on all forensic cases referred to the unit i.e. cases where the death is suspicious and there is involvement from the police. The investigation and autopsy in these cases is considerably more detailed than for routine coronial autopsies, involving sampling of DNA, toxicology, photography, a much more detailed external examination and dissection and as well as full histological sampling.

Figure 1-2: 3-D Volume rendered reconstructed PMCT of a male road traffic victim involved in a head-on crash with a lorry. This image was acquired with the body in the body bag. The image shows in great detail the multiple fractures and debris from inside the vehicle.
Both PMCT and PMMRI have their strengths and weaknesses. CT is more widely available, less expensive and more radiographers are experienced in the modality. CT provides better spatial resolution and has a shorter image acquisition times than standard MRI clinical techniques. Total CT imaging times are generally less than 15 minutes compared to 60-75 minutes for whole-body MRI using standard protocols (51). Paediatric and ante-neonatal practices generally use PMMRI, as it is superior at defining soft tissues and delineating the types of pathology presenting in these cases (52,53). Some institutions currently using PMMRI are also performing a PMCT scan on the same case (51). The resource implications for doing this routinely are great and evidence to support this practice is currently scarce.

All digital imaging techniques have a great advantage over the traditional autopsy in that the information is easily stored and transmitted for review by other professionals. This provides a permanent record for future review or audit (the so-called ‘virtual exhumation’) (54). Data can be reconstructed into 3-D images for court purposes, which are deemed more acceptable to juries than autopsy photographs (55,56). A further benefit is that pre-autopsy scanning allows the pathologist to plan aspects of the autopsy procedure. For example, the need to tie off vessels to demonstrate an air embolism, or to identify the presence of potential hazards such as fragments of glass or metal (26,27,57)

There is a substantial body of literature demonstrating the advantages of PMCT in forensic cases; especially for trauma-related deaths, hangings, upper-airway obstruction, strangulation, haemorrhage from ruptured internal organs; as well as from the effects of penetrating projectiles and ballistic injuries (see Figure 1-3) (58-62). Complex fractures of the skull vault and facial bones are not normally detectable on routine autopsy
without extensive dissection, but are well demonstrated on PMCT thereby reducing the amount of dissection required (56,57,63).

Figure 1-3: 3-D Volume rendered reconstructed images of PMCT A) Axial image of the chest cavity with a knife penetrating the front of the chest and the left ventricle of the heart, with a large left-sided haemothorax. B) A penetrating injury to the left side of the skull with chisel, the depth and angle of penetration can easily be calculated.

PMCT has been shown to be a useful tool for the identification of bodies, especially in a mass fatality setting (64,65,65-68). It can be used to assist the identification of gender, stature, and ethnicity of an individual by allowing osteology measurements to be taken from reconstructed images, thus removing the laborious and destructive bone preparation normally required (67,69-76). Odontological assessment can also be undertaken from PMCT images (Figure 1-4) (56,69,73,77). Mobile CT scanners can be taken directly to temporary mortuaries sited at mass disasters to provide rapid information to the emergency services on the nature of the incident and aid in identification without removing the bodies from a body bag (64,78).
In recent years, a number of CT scanners have been placed in mortuaries in Europe, Australia and Japan for the sole purpose of imaging cadavers (27,79,80). The best example of such practice is at the Victoria Institute of Forensic Medicine (VIFM), Melbourne, Australia where over 80,000 cadaveric examinations have been performed since 2005, with an average of 3500 CT cases a year (81). PMCT has become an integral part of their autopsy process and has led to a change in the conduct of death investigation at the institute, although they still undertake invasive autopsies after the scan (80,82).

Despite the increased use of CT in autopsy practice there remains a lack of large-scale studies evaluating the diagnostic accuracy of post-mortem imaging when compared to full autopsy in the non-forensic setting. Published work at the point of starting this thesis in 2009 comparing autopsy and imaging comprised mostly of anecdotal reports or small case series (27,83-87). Within the United Kingdom (UK) several research groups are investigating the possible role of PMCT and MRI in both adult and paediatric autopsy practice with the consideration of the development of so-called “near-virtual”
or “minimally invasive autopsies” and many of these studies are now complete (32,52,53,88,89).

In terms of natural disease, PMCT is very sensitive when identifying haemorrhage, especially intracranial haemorrhage, ruptured aortic aneurysm (see Figure 1-5), haemopericardium and major organ trauma. Radiology can also identify air embolus and other abnormal gas collections, as well as infections such as pneumonia, perforation of organs and malignancy (38,39,42,49,89-95). However, the largest obstacle to the acceptance of minimally invasive autopsies is related to the inability of PMCT to provide sufficient assessment of the cardiovascular system to give an accurate the diagnosis of ischaemic heart disease as the cause of death (96,97).

Ischaemic heart disease is the most frequent cause of death found at coronial autopsy, and therefore, this weakness of imaging must be overcome before it can be considered as a viable replaced to traditional invasive of autopsy.

Figure 1-5: A coronial section and 3-D volume rendered CT of the chest and abdomen of an elderly male showing a large abdominal aortic aneurysm and widespread calcified atherosclerotic disease.
Several authors have suggested that the major limitations concerning cardiovascular pathology could be minimised by the introduction of post-mortem angiography (15,34,98,99).

1.2 Clinical Cardiac CT Angiography

Prior to considering the role of angiography in autopsy practice it is helpful to review recent developments in clinical cardiac imaging. Although clinical cardiac angiography relies on a functioning circulation, some of the recent advances in clinical imaging, especially MDCT, can be applied to autopsy practice. Thus, it is desirable for those using PMCT or PMMRI to develop close links with clinical practice, to allow cross fertilisation of expertise.

In clinical practice fluoroscopically assisted invasive coronary angiography is currently routine for assessing coronary artery stenosis and the degree of atherosclerotic disease. It has excellent spatial and temporal resolution providing diagnostic images (see Figure 1-6). It allows for percutaneous intervention simultaneously (e.g. insertion of stents to

Figure 1-6: A Fluoroscopic still (right anterior oblique view) of cardiac angiography in a living patient showing the course of the coronary vessels filled with angiographic die which demonstrate a patent lumen and patency of the coronary arteries. (G.N. Rutty, page 134, Figure 6.4.c With kind permission of Springer Science+Business Media).
relieve stenosis during the imaging procedure) and performance of pressure studies and more recently intravascular ultrasound. Intra vascular ultrasound (IVUS) and pressure studies may be considered the gold standard, but this is centre dependant. As with all invasive procedures there are risks of complications including arrhythmia, vascular dissection, bleeding and infection, although these are rare.

Non-invasive clinical assessment of coronary arteries is challenging, due to their small size and continuous motion during the cardiac cycle. Recent technological advances in MDCT, with quicker acquisition times and ECG cardiac gating, have overcome these factors, leading to it becoming a viable technique (96,100). Cardiac MDCT is fast emerging as a powerful diagnostic tool for the rapid assessment of acute chest pain and the assessment of coronary disease in chronic disease for planned intervention. It is being described by some as a ‘technological revolution’ (101,102).

Cardiac MDCT is now in routine day-to-day clinical practice due to its high sensitivity and specificity, along with a very high negative predictive value (91). This makes it a valuable modality in screening patients for coronary artery disease. Coronary artery assessment by MDCT is performed in two stages: Initially, images of the heart are obtained without intravenous contrast agent to assess the calcified atheromatous plaque burden, so-called ‘Calcium Scoring’ (98,99). The presence of calcium is invariably associated with coronary atherosclerosis, especially in its advanced stage (100). The amount of calcified plaque (which appears bright white on the scan (see Figure 1-8) can be quantified by semi-automated software and used for risk stratification of patients for future cardiac events; a high coronary calcium score, when adjusted for age and gender, is considered to be predictive of a high risk of coronary adverse events (100). However, this does not give any information regarding non-calcified plaques, coronary artery stenosis or patency of the lumen (91). It is accepted that the extent of the calcification
roughly relates to the amount of atherosclerosis, but not to the degree of coronary artery stenosis. To assess the patency of the coronary vasculature, intravenous contrast is administered for MDCT coronary angiography and scanning commences when the contrast bolus arrives at the coronary circulation (10-20 seconds after injection). Compared to conventional angiography, MDCT allows analysis of the vessel wall in addition to luminal quantification. Cardiac MDCT accurately defines the course of the coronary arteries (91,96,101,102).

This is particularly useful to demonstrate ‘malignant’ anatomy (when the vessel travels between the aorta and the pulmonary artery), which is a recognised cause of sudden cardiac death (103). It is also useful in assessment of complex congenital heart disease, cardiac masses, ventricular thrombi, and pericardial and aortic disease (101,104-108). The identification of such pathology is equally useful in autopsy practice.

Figure 1-7: A 3-D volume rendered reconstructed image of a PMCT coronary angiography showing the normal coronary arteries. (Source: East Midlands Forensic Pathology Unit)
Figure 1-9: Cardiac anatomy in a live patient during a standard clinical contrast enhanced MDCT: Software-generated images outlining the course of the left main stem, left anterior descending (A/B) and right (C) coronary artery.

1.3 Post-mortem Cardiac PMCT

One of the benefits of imaging cadavers is that concerns regarding radiation dose, artefacts caused by patient movement during the cardiac cycle and breathing are eliminated. Higher doses of radiation and repeat scanning to obtain optimal images are only limited by the scanner x-ray tube heat capacity. MDCT of the heart can easily be
performed on cadavers, but the inability of the technique to deliver circulating intravascular radiographic contrast means information on the vessel lumen and complete course of the vessels is lacking. During an autopsy, the coronary arteries are assessed by first removing the heart from the thorax, then making transverse cuts externally across the course of the coronary vessels and directly visualising the lumen (109-111). The nature and degree of occlusion by atheromatous plaques can then estimated, either by a subjective scale of mild-moderate-severe or by estimating the percentage of the lumen that is stenosed (109,111,112). Without the use of contrast within the vessels, to demonstrate the lumen patency, the same cannot be achieved with PMCT alone.

Currently, the failure to yield detailed information about the coronary vessels is a major deficiency of PMCT and PMMRI compared to conventional autopsy. It is often put forward as the principal reason why minimally invasive autopsies do not provide a realistic alternative to the invasive autopsy. One possible way to overcome this is by the use of PMCTA. A number of small studies have demonstrated the feasibility of PMCT angiography in animals and humans (98,113-117).

Post-mortem angiography has been shown to be useful in the investigation of stab, gunshot wounds, aneurysms and in locating vascular disruption in cases of natural pathology, surgery, and trauma such as non-accidental head injury (61,62,84,98,118-121). After successful filling of the coronary circulation in a cadaver followed by PMCT, multi-plane reformatting (MPR) and 3-D maximum intensity projections (MIPS) can be created using image analysis workstations, as in clinical practice. These packages allow detailed assessment of vessel course, luminal patency, plaque assessment and calcium scoring to be performed.
1.4 Casting and Contrast Agents for the Examination of the Coronary Vessels at Autopsy.

Casting and contrast examination of the coronary arteries and chambers of the heart, as part of the anatomical or autopsy dissection, can be traced back to Leonardo da Vinci who, circa 1500 AD, reported the first preparations of hollow anatomical structures. He produced wax casts of the chambers of the heart and the cerebral ventricles, the tissue being cleaned from around the casts using maggots. This method of maceration was later replaced by chemical means (122).

Post-mortem cardiac angiography was first reported in 1899, 3 years after the discovery of X-rays when Baumgarten injected radio-opaque material into the coronary arteries of an isolated human heart at autopsy (Figure 1-10)(98,122).

Following this, the use of different contrast agents for post-mortem angiography increased rapidly. The number of different methods and injected substances reached a peak in the first half of that century but only two of these older methods are still
currently being used; barium sulphate and silicone rubber. Study in 2007 demonstrated a novel casting method with a new red resin and hydrochloric acid that highlights that work still being undertaken in this area (123). In recent years, new types of contrast agents and methods have been tried for cardiac angiography: corpuscular skin preparations, oily liquids, water-soluble preparations and casts.

The first major group of agents and most commonly used, are the corpuscular preparations. These agents are made up of corpuscular radio-opaque material suspended in a solvent, often water. Historically, red lead oxide, bismuth chloride, barium sulphate or potassium iodide was used. Studies have shown the calibre of the vessel penetrated by the agent is dependent on the corpuscular particle size and the nature of the solvent. For example, fine particles of barium sulphate penetrate smaller vessels when suspended in water rather than gelatine (101). Upon injection, the agents are known to dislodge post-mortem clots, removing the artefacts formed by them. However, the agents can induce their own artefacts by the precipitation of corpuscular particles. The disadvantage with using water as a solvent is that a degree of extravasation occurs, leading to artefacts and difficulty with histological interpretation. Disadvantages of the other solvents, such as agar or gelatine, include poorer visualisation of the microcirculation due to reduced penetration of small vessels, and increased precipitation-induced artefacts.

The use of oily contrast agent preparations has been less frequently described. The most recent publications are by the Virtopsy® group and subsequent associated groups, who reported the use of diesel and paraffin oil for whole-body cadaveric angiography (98,113-116).
Oily liquids are also able to flush out post-mortem clots and yield high contrast images. The advantage with these agents is that they are retained in the vessels for a much longer time period without extravasation. This is beneficial if there is a significant delay between injection and imaging, or in bodies that have reached a more advanced stage of decomposition. The viscosity of the oil determines the calibre of vessel that can be penetrated. Low viscosity oils, such as diesel, can lead to excellent visualisation of the microcirculation. However, one study described a possible disadvantage in that the oil infiltrated the vessel walls potentially damaging it and dislodging lipid. This could alter the appearance of the atherosclerotic plaques (101).

Water-soluble preparations are used for clinical angiography. However, they are infrequently reported in post-mortem angiography. These agents rapidly diffuse through vessel walls \textit{in vivo}, can lead to extravasation and artefactual oedema, and therefore poorer image quality. Standard preparations are less radio-opaque than barium sulphate and do not flush out post-mortem clots, unlike other agents (98).

Casting involves the injection of a suitable material into the vascular system where it sets hard. The surrounding tissue is then removed to reveal a 3-D cast. Currently, a silicon rubber-lead oxide technique described by Yonas \textit{et al} (124) is the most practised method and allows visualisation of vessels less than 0.1 mm in diameter. The technique is so widely used in post-mortem angiography that a number of ready-made commercial products are available. Casting is excellent for single organ studies and the production of artefacts is minimal. The disadvantages are organ destruction and the impracticality of whole-body perfusion, making its application for minimally invasive autopsy unfeasible (101).
1.5 PMCT Angiography: The Practicalities

There are many different techniques described in the literature for post-mortem angiography. The main body of work has been performed on single organ systems such as the heart, brain, intestine, uterus, spinal column and the limbs. For the imaging of single organs (most commonly the heart), the organ is either injected in situ and then removed for imaging, or the organ is injected after removal. A number of techniques have been used to visualise the vasculature of single organs, including chemical fixation, or flushing out of post-mortem clots with saline before infusion with a contrast agent. No single technique appears to be the gold standard. A study in 1999 by Smith et al (125) described a technique in which the coronary arteries of an ‘ex vivo’ heart were injected with a mixture of Gastrografin® (an iodine containing contrast agent) and coloured dyes. This method allowed angiographic assessment of vasculature to be correlated with the histological findings. The coloured dye was easily identifiable in the histological preparations allowing assessment of perfusion of tissue by the vessel studied. Their method was fast and inexpensive, but never implemented on a wider scale.

Only a handful of whole-body post-mortem angiography studies have been reported in the literature to date (98,113-117,119,120,126-129). These were initially conducted on animal and human embryos, human foetuses and new-borns (113,130,131). The first report of PMCT angiographic imaging of a whole adult was published in 2005 by the Virtopsy® group (34). This method involved a discontinuous injection of contrast agent with the imaging performed at intervals. However, this method highlighted problems with tissue oedema as a result of the infused contrast medium that caused artefact in histological samples. In a bid to reduce this oedema, in a later study on an ex vivo porcine heart, the group increased the viscosity of the contrast media by dissolving the
contrast in polyethylene glycol (PEG)(132). This proved successful in reducing the tissue oedema. Following this, the group progressed to whole-body angiography on a human corpse using PEG. The contrast was injected under sustained pressure via a cannula in the left femoral artery. The body had to be turned a number of times to re-dissolve the cellular blood components, which had undergone sedimentation. This method produced good visualization of the arterial system with minimal oedema. However, the contrast agent distribution varied between organs and body regions. They theorised this was due to differences in the distribution of contrast agent within the capillary bed (117).

In 2008 the Virtopsy® group further modified the method by means of a two-step technique on a series of four human cadavers. Diesel oil was replaced by odourless paraffin oil, and a modified heart-lung machine was introduced. The first step was to perfuse the vascular system with an oily liquid using the heart-lung machine. This served to flush out post-mortem clots and any remaining blood. The second stage was to introduce an iodized contrast agent as a bolus injection prior to scanning. The method was applied to the upper and lower extremities to produce a full-body angiography. Scanning was conducted whilst the heart-lung pump was running. The study demonstrated the ability to image the entire vascular system and diagnose vascular abnormalities. One of their cases very clearly demonstrated a recent injection site used by a drug addict (116).

Their next paper was a comparative study looking at the differences between a water soluble contrast agent dissolved in PEG and a mixture of oily contrast and paraffin, 5 cases using each agent (98,113,114). The method used cannulation of the left femoral artery and vein. The cannulas were connected to a pressure-controlled modified heart-lung machine. A three-phase scan approach to imaging was performed (unenhanced,
arterial injection and venous injection). The study determined that for complete depiction of both coronary arteries, the body needed to be scanned in the prone position to achieve better filling of the more ventrally situated right coronary ostium. The study concluded that although both agents allowed whole-body angiography, the PEG agent was better for preventing extravasation at sites such as the pancreas and intestines. Due to its molecular size, PEG was also better for use in decomposed bodies where the vessel walls are more permeable. However, the oily based agent was better if there is to be a significant delay between the injection and imaging (114).

The scope of cardiac PMCTA is potentially wide, most importantly for determining the presence of coronary artery disease and thrombosis, delineating malignant coronary anatomy and congenital heart defects. In neonates, death is frequently associated with cardiac anomalies that are only apparent on angiography, even when the external appearance of the heart appears normal (46,133). Therefore, there is justification for performing angiography on all neonatal cases (125,134,135).

1.6 PMCT Angiography in England and Wales

Post-mortem angiography combined with detailed cardiac PMCT to assess coronary artery disease in adults could, in the future, establish a viable minimally invasive autopsy service for England and Wales. There will always be a requirement to undertake invasive autopsies on those cases where PMCT, with or without angiography, cannot provide sufficient cause of death such as sudden adult death syndrome.

Considering the history of post-mortem angiography, and despite the work undertaken in this area in recent times, the technique has not progressed outside research environments. There is no doubt that the images produced by whole-body angiography techniques using modified heart-lung machines and oily contrast agents are visually
spectacular, but they require specialist pumps, training, time and are costly (116,136,137). There is concern that such a technique is impractical for the high-volume throughput screening that would be required for routine autopsy practice in England and Wales (the number of cadavers examined per year will run into thousands). Such a high volume of work requires a technique for angiography that is quick, cost effective and possible within a clinical imaging environment. At the start of this thesis no such technique had been described in the medical literature.

1.7 Aims and Objectives:

The East Midlands Forensic Pathology Unit and University Hospitals of Leicester Radiology Department have proposed that, to make angiography a practical technique to investigate sudden unexpected death in the coronial setting in England and Wales, a targeted coronary angiography protocol is required. The aim of this thesis is therefore to develop the technique of targeted post-mortem CT coronary angiography.

The objectives are to establish:

- Is targeted PMCTA of the coronary arteries is possible?
- Is it practical to gain consent from the next of kin for this type of research?
- What is the best method for angiography? Can specific new equipment be developed to aid targeted coronary PMCTA?
- How does targeted coronary PMCTA compare to traditional autopsy?
- Could it ever really replace the conventional autopsy completely?

Chapter 1 reviews the past and present application of PMCT and PMCTA, with a focus on cardiac CT.

Chapter 2 details the development of the post-mortem angiography method.
Chapter 3 outlines the development of a task-specific catheter device.

Chapter 4 contains a pilot study of 24 cases to evaluate the diagnostic potential of PMCTA by directly comparing the findings with those of the conventional autopsy undertaken after the scan.

Chapter 5 details the development and experience of the protocol for gaining informed consent.

Chapter 6 summarises and contextualises the results.

1.8 Permissions:

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Chapter 2  Targeted post-mortem computed tomography cardiac angiography: proof of concept

2.1  Introduction

At the commencement of this thesis, no methodology of how to perform in-situ targeted post-mortem cardiac angiography had been published. Therefore, the method was developed from a mixture of clinical practice, in terms of the devices and imaging, and from embalming practice for the vascular access and contrast delivery. It was also necessary to determine the feasibility of the method before continuing to recruit to a large-scale comparative study of angiography in autopsy. The first suitable cases were used to establish the method and to perform an pilot study to learn lessons that would be required for the on-going studies. The learning curve for these cases was steep and the method was progressively altered on a case-by-case basis. This chapter will detail the developmental stages and define the final protocol taken forward for the larger comparative study at the EMFPU and University Hospitals Leicester Radiology Department. There were a number of issues that needed to be considered to enable the overall method to function e.g. case selection, catheter, cannulation and scan protocol, and these will be discussed in turn in this chapter.

2.1.1  Case Selection

Cases were selected for potential PMCTA from the first suitable coronial post-mortem request forms faxed to the Leicester Royal Infirmary mortuary on a particular day. Ethics permission to perform PMCT and catheter angiography, and to use the data for research and teaching, was obtained from the local ethics review board. In order to assess potential artefacts generated by the procedure, the cases selected needed to have
apparent normal neck and cardiac anatomy. Exclusion criteria during this stage included significant neck trauma e.g. hanging or previous cardiac surgery. Bodies weighing over 125 kg (19.5 stone) were also excluded due to manual handling considerations and the size of the CT gantry. Cases with a long post-mortem interval (i.e. greater than 72 hours since death) were excluded if possible, to try to minimise post-mortem artefacts e.g. gas collection.

The next of kin were contacted by the trial consenter or a forensic pathologist on the same day with the intention of scanning that evening and performing the autopsy on the next day. Informed consent was obtained by telephone, with information leaflets being sent to next of kin the next working day where requested (as per the consent protocol detailed in chapter 5).

2.1.2 Site and method of vascular access

The first major consideration was site selection for access to the vascular system in which to insert the device or catheter for delivering the contrast. In the UK, the most common technique for arterial embalming involves the injection of a blend of chemicals into the vascular system via a common carotid artery (typically the right). The bodily fluids are displaced and expelled via a jugular vein. Embalming solution is injected with a centrifugal pump. Occasionally, if circulation is poor, additional injection points are used (e.g. axillary, brachial or femoral arteries) (138).

For this study, a number of injection sites were considered, including the femoral, axillary and subclavian arteries. The common carotid artery was chosen due to its lack of branches, its size and because the incision over it could be incorporated into the routine autopsy incision, meaning no additional marks to the body would be seen after
reconstruction. It is also the vessel closest to the arch of the aorta allowing a shorter catheter to be selected (compared with femoral access catheters).

The method for raising the carotid artery was adapted from a standard embalming technique (138), and used standard mortuary equipment namely a scalpel, forceps, aneurysm hooks and twine.

Figure 2-1: A) Standard mortuary equipment used for cannulation: a male urinary Foley catheter with tip cut off, lengths of string, two aneurysm hooks, forceps, scalpel and radiographic guide wire. B) Incision site. C) The left common carotid artery is elevated by an aneurysm hook. D) The balloon catheter situated in the carotid artery.
Access to the carotid artery involved an oblique incision at the bottom of the neck, above the head of the clavicle to the lateral side of the neck (see Figure 2-1B). The subcutaneous tissue was blunt-dissected with an aneurysm hook. The soft tissue was divided downwards behind the left sternocleidomastoid muscle. The jugular vein and vagus nerve were dissected free and pulled laterally (a string sling was used to facilitate this). The soft tissue was further dissected inferiorly and medially until the carotid artery was located.

The carotid artery was dissected free of the soft tissue and elevated by means of an aneurysm hook. Once raised, a piece of string was passed under the artery and used to tie off the most superior aspect of the artery to act as an anchor. The artery was held in place during this process by threading the aneurysm hook underneath the artery (Figure 2-1C). A second piece of string was threaded under the artery and pulled inferiorly then loosely tied to act as a sling or a marker for the lower aspect of the artery. This second sling was useful to give traction on the vessel for repositioning. A transverse cut was made across the anterior wall of the artery.

The posterior wall was left intact, to prevent retraction of both ends of the artery; cannulation proved difficult if the artery retracted, especially if there was no string tether on the inferior aspect. The lower cut aspect of the carotid artery wall was held with toothed forceps, and a balloon catheter inserted (Figure 2-1D). The aim was to place the catheter tip in the ascending aorta, just above the aortic valve and adjacent to the coronary ostia, this was to allow the maximum amount of contrast into the coronary ostia. The balloon could then be inflated inside the ascending aorta above the ostia to prevent the flow of contrast down the descending
aorta. During the refinement of the method, both carotid arteries were cannulated to assess which offered the best placement.

2.1.3 Catheter Choice

Several different types of catheter used in interventional radiology and cardiology practice were trialled for suitability using ‘out of date’ stock. These included a variety of pigtail angiographic catheters, large balloon size catheters including an endovascular aneurysm repair (EVAR) balloon catheter and a Trans-Catheter Aortic Valve Implantation (TAVI) balloon catheter. These were initially chosen for their directional capability, as it was thought that this would be useful to navigate the aortic arch and ensure correct placement into the ascending aorta. However, using the directional capabilities was considered unnecessary for two reasons; firstly the catheter could be inserted with ease into the ascending aorta from a left-sided approach and secondly, if the catheter went into the descending aorta it was considered too difficult to perform image-guided catheter manipulations using CT fluoroscopy for staff not experienced in interventional radiology. The catheter was changed to a 14 Fr silicone-coated male urinary catheter (Bardia Foley Catheter, Bard, USA) used with standard guide wire (Cook, USA, fixed core wire guide: straight) after the first two cases. This catheter was chosen for its length, stiffness and inflatable balloon. The guide wire was used to determine the catheter position on PMCT and to facilitate introduction. The decision to trial a foley was made one evening after one of the angiographic catheter balloons had failed. So as not to lose the opportunity after consenting a patient the idea to try a simple urinary catheter as it had a balloon of an appropriate size was put forward as it could be obtained from the nearby emergency department.

Initially, the balloon of the catheter was inflated with 20 ml water, but this proved difficult for the pathologist to confidently identify its position in the aorta on the scout
CT scan (a preliminary low-resolution low-dose scan used to plan the full scan). It was later changed to 20 ml dilute water-soluble radiographic contrast (1 in 50 dilution of Urograffin®), which made it easier to determine the balloon’s position. The use of dilute contrast also removed the need for a guide wire to facilitate localisation, and consequently the guide wire was only used in cases where placement was difficult. Urograffin was chosen due to its routine use in the hospital and its relative cheapness.

2.1.4 Contrast medium choice
The literature relating to post-mortem angiography describes a number of different contrast agents being used; each with its own advantages and disadvantages (98) (as discussed in chapter 1). The Working Group on Post-mortem Angiography (TWGPAM) research group advocates the use of a lipid-based contrast agent called Angiofil® (Fumedica AG, Muri, Switzerland), which is essentially polyethylene glycol and iodized oil, in conjunction with the use of a pressure-controlled perfusion device called the ‘Virtangio’® machine (essentially a modified heart-lung bypass machine). This creates a whole-body ‘circulation’ (Fumedica AG, Muri, Switzerland) (99,116,139).
Our approach aimed to produce a quicker and simpler that could be used in any mortuary, be it permanent or temporary, using readily available materials and requiring minimal training. Therefore, instead of the oil-based contrast, we proposed using standard water-based iodinated contrast, as used routinely in clinical radiology, which was readily available.
Water-based contrast agents have been previously reported to cause tissue oedema leading to significant artefact generation on PMCT (98), therefore it was imperative to select a media that made minimal physiological impact on the extravascular space, as this could affect subsequent histological examinations. The literature states that extravasation artefacts appear to increase if there is a long delay e.g. few hours between
the injection of the contrast and the completion of the scan (98,99,114,116). Our protocol of scanning immediately after injection minimises the introduction of artefact due to contrast-induced tissue oedema. Urografin® 150 mg/ml water-soluble iodinated contrast was selected (Bayer Healthcare), as this is widely available and relatively inexpensive (approximately £20 per 500 ml bottle). A 1 in 10 dilution was used to be similar to the peak aortic concentration expected immediately after intravenous injection (140).

From our previous experience of post-mortem imaging on forensic autopsy cases, it was observed that the coronary vessels were often well delineated by air that had developed in the vascular spaces during the post-mortem period. This is a normal post-mortem artefact resulting from early decomposition (83,141-143). Carbon dioxide gas has also been used successfully as a negative contrast agent in clinical peripheral angiography. Therefore, the possibility of using air as a ‘negative’ contrast agent was proposed. This was thought to be potentially superior to ‘positive’ contrast agents due to better delineation of areas of calcification (both appear bright white on the PMCT scan and delineation can be difficult, whereas air is black providing excellent contrast). Foley catheters can only accept 60 ml bladder syringes, so all injected volumes were in 60 ml incremental amounts. A range of volumes and infusion rates of air and Urografin® were performed and evaluated.
Figure 2-2: A) Injection of contrast (air) by means of a 60 ml syringe. B) The body is rolled 90 degrees to the right lateral decubitus position and held in place with foam blocks and securing straps.

2.2 Scanning protocol

The PMCT scan was undertaken using a standard East Midlands Forensic Pathology Unit’s (EMFPU) post-mortem protocol using a Toshiba Aquilion 64 slice scanner (120 kVp, 300 mA and 64 x 0.5 mm slice thickness, matrix 512 x 512) reconstructed to either 1 or 2 mm thick slices. Cardiac images were then performed with a narrow field of view covering the heart and aortic arch with 0.5 mm slice reconstructions pre and post contrast injections. Scan time was recorded for the final 14 cases (after the initial learning curve). Times were recorded as whole scan time (from arrival to leaving the CT scan room) and were divided into two sections relating to the time to complete the standard PMCT scan and the extra time of the angiography (Table 2-1).

2.2.1 Positioning of the body

Each body was initially scanned within a labelled body-bag supine with the arms at either side. Bodies were scanned at variable post-mortem intervals (0-4 days) and in various states of rigor mortis. Access to the body for the angiography was through an
opening at the head of the body bag. A towel was placed over the face of the deceased to preserve dignity and to prevent distress to members of staff entering the CT scanning suite. In clinical practice, patients’ arms are positioned above the head to minimise the artefact produced by the arms, but to do this in the post-mortem setting would have meant taking fully opening the body bag and handling the body. This would have been problematic if rigor mortis was present, if there was fracturing or trauma to the limbs and upper torso or if the body was burnt. Since radiographers and porters are inexperienced in working with the deceased, the decision was made to leave the arms by the side to minimise the amount of handling required.

Previous studies have described incomplete filling of the vessels especially the right coronary artery, and used rotation of the body to assist contrast agent dispersal (99,116). We experimented with different body positions during injection. The positioning of the body was facilitated by foam blocks and Velcro® strapping (standard radiographic equipment). The body remained within the body bag at all times so there was minimal risk of contamination with body fluids.

2.3 Evaluation of angiography

The cardiac imaging was reported by two consultant radiologists; one a cardiac radiologist with two years experience of post-mortem imaging; the other a diagnostic and interventional radiologist with six years experience of post-mortem imaging. Image analysis was performed on workstations using multiplanar reconstructions (MPR) and 3-D analysis (Vitrea®, (Toshiba, Japan)). The optimum filling of the vessels by either air and/or a positive contrast medium was assessed subjectively on the ability to see the right coronary artery (RCA), posterior descending artery (PDA), left main stem (LMS), left anterior descending (LAD) and circumflex (Cx) arteries. For the first 14 cases, a
radiologist was present during the angiography to give ‘real time’ assessment. The first 17 cases were used to improve the protocol in terms of volumes and pressure of contrast injection. A more formal assessment of artery delineation was undertaken for the final 10 cases. After 24 cases in total, a final protocol was agreed in order to evaluate the use of PMCT coronary angiography in post-mortem investigation.

2.4 Method development results for the first 24 cases

2.4.1 Cannulation

At the start of the pilot study, it was thought that the right side of the neck would be the most appropriate as it was the closest and most direct access to the aortic valve. The first few attempts centred on cannulating the right side of the neck but it soon became apparent that this side was problematic. Cannulation was subsequently attempted on the left side and this was found to be far easier with a greater degree of success. This was due to the angle of the left carotid artery opening into the arch of the aorta. With the right-sided cannulation, there were problems advancing the catheter out of the carotid artery. The catheter would often strike the inferior wall of the aortic arch and fail to advance or enter the descending aorta. Using the right carotid often required advancing the catheter around a 90° angle to reach the aortic valve and although this could be achieved by an interventional radiologist with directional guide wires and angled catheters using CT fluoroscopy, this is time consuming and considerably more problematic compared to the ease of cannulation on the left side (Figure 23).

Both sides of the neck were used in 7 cases, the right side only in 6 and the left side only in 11. In 5 out of 13 cases there was failed access to the ascending aorta using the right-sided approach, and 1 using the left sided approach. The left-sided approach therefore had a significantly higher success rate (chi-squared test p=0.02). The single
failure on the left side was due to inadvertent cannulation of the internal jugular vein, a mistake that was considered unlikely to be repeated. For the last 11 cases only the left side was accessed and a guide wire was used on only one occasion to assist placement of the catheter.

2.4.2 Catheter

One of the most important parts of the catheterisation was the balloon inflation in the ascending aorta to prevent the flow of contrast back down the descending aorta. Balloon inflation below 3 cm in diameter proved unsatisfactory for this task. The angiographic catheters had balloons that were too small in diameter or too long, causing them to inflate within the carotid artery and risking damage to the vessel. Due to the ease of access experienced from the left side (i.e. no directional manipulation required) we were able to change to a silicone coated 14 Fr Foley male urinary catheter to allow larger balloon inflation.

In order to be able to thread the catheter onto the guide wire, the rounded tip had to be cut off. Horizontal and oblique cuts were studied. It was found that the oblique cut, mimicking the bevel of a needle, was easier to insert into the cut vessel than the horizontal. The flexibility of the catheter, along with the length and inflatable capacity of the balloon were adequate. Latterly, the guide wire was used only for cases where it was difficult to advance the catheter alone (3/24 cases).

At the start, it was difficult to feel whether the catheter was positioned correctly and PMCT was relied upon to determine this. As more experience was gained, it became possible to ‘feel’ whether the catheter was in the correct position at the time of insertion in the mortuary. If the catheter contacted the inferior wall of the arch of aorta, a very clear obstruction to the advancement of the catheter was felt between 5-10 cm. The
catheter then had to be manipulated in order to insert it into the ascending aorta. This was done by pulling the vessel laterally and angling the catheter medially.

If it was possible to insert the entire length of the catheter, or advance >20 cm of the catheter without meeting any resistance, it was more likely that the catheter had entered the descending aorta and repositioning was required. Repositioning consisted of partially withdrawing the catheter then attempting to advance it at a different angle or completely withdrawing it and reinserting.

If the catheter went down the ascending aorta, it would contact the leaflets of the aortic valve, producing a sensation of a ‘bounce’ after advancing 10-15 cm. The process of learning this haptic feedback (‘to feel the bounce’) is a key stage in order to perform the technique independently. The catheter position was ultimately confirmed using the initial PMCTscan (Figure 1-3). If incorrect, repositioning would be attempted in the scanning suite, although this was not as easy as in the mortuary due to the exposure restrictions, lack of equipment, lack of space and body fluid issues. Generally if the catheter ‘felt’ in the correct position in the mortuary i.e. ‘the bounce’ was felt, then it would be positioned correctly, no specific data was kept of this however to qualify.

We only repositioned if the catheter was not within the ascending aorta. After learning to ‘feel the bounce’ of the catheter tip on the aortic valve we simply pulled back two centimetres and technique proved optimal for our contrast injections. The position of the balloon was determined by inflation with dilute Urografin® (1 in 50 ml). This enabled the balloon to be easily seen on the scout image. In certain cases the presence of the guidewire also assisted.

There was initially some concern regarding the catheter moving or falling out during transport from the mortuary to the scanning suite. Initially, the catheter and guide wire
were taped down (with adhesive tape) to the side of the neck, but it was found that this was an unnecessary measure. Even with significant handling of the body, and without taping, the catheter remained in place. There was some leakage of blood from the incision, so a towel was folded and wrapped around the neck to absorb any leakages during transportation and prevent excessive contamination of the inside of the body bag.

Figure 2-3: PMCT image showing the inflated balloon of the catheter sitting in the ascending aorta after being inserted into the left carotid artery.

2.4.3 Contrast injection

The bodies were scanned immediately after injecting the contrast agent (within 2 minutes). Throughout the 24 cases, no artefacts related to contrast extravasation were observed. The injection of Urografin® did not cause any damage to the vessels or organs detectable at autopsy, nor in subsequent histology. Other than the incision in the neck, the autopsy pathologists reported no signs internally that the angiography had taken place e.g. oedema or haemorrhage. One of the advantages of our targeted protocol is that relatively small amounts of contrast are injected directly into the coronary
circulation with minimal contamination of the rest of the body. This means that we did not anticipate any significant effect on toxicology, and this was subsequently demonstrated (144). No artefactual fat emboli were observed in histological lung sections examined as has been reported when using other oil-based contrast types (99).

For the first 5 cases, 60 ml manual injections of positive contrast at varying speeds from 5 to 20 seconds were trialled. It was found that slower manual injections with continued pressure were much better at circulating the contrast than fast, high-pressure injections, although the reason for this was not clear. This was an objective assessment made by looking at how far the contrast has gone into the vessels, if at all. After 5 test cases, larger volumes were administered giving better images. There was no significant improvement in positive contrast filling of the vessels over 120 ml. The final protocol was for manual injection of 120 ml of positive contrast via 2 injections taking approximately 40 seconds (20 seconds per syringe) (Table 2-1).

One of the disadvantages of Urografin® as a contrast agent is that it has the same opacity (whiteness) on PMCT as the calcification associated with atherosclerosis, making assessment of the coronary artery lumen difficult.

Positive contrast filling of the RCA and PDA was often incomplete but the vessels filled well when air was used. Air had the distinct advantage of demonstrating a patent lumen in the middle of a calcified plaque. With this in mind, a double contrast method was adopted; an initial injection of air followed by an injection of Urografin®. For the first few cases air, was injected in 60 ml increments until good filling was achieved (Figure 2-4). The final protocol was 300 ml of air via 5 manual injections using a standard 60 ml bladder syringe and gentle constant hand pressure over a period of 2 to 3 minutes with the body supine. The body was then turned and a further 300 ml of air
injected. The body was then rolled back to supine and 120 ml of positive contrast was injected.

Figure 2-4: A) Curved MPR, image showing normal left coronary system (arrow) delineated by contrast. B) Curved MPR showing normal RCA delineated with air. (C) Curved MPR image showing normal left (arrow) and right coronary artery segments (round head) delineated with positive contrast.
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<th>CT Time (mins)</th>
<th>Angio Time (mins)</th>
<th>PM interval (day)</th>
<th>Side Cannulated</th>
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<td>Uro</td>
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2.4.5 Body position

For the first 5 cases, the body was kept in the supine position throughout all stages of contrast injection. Injection of air in the supine position resulted in consistent filling of the RCA, but not the LMS and its branches. Conversely, positive contrast media filled the left-sided branches, but not the RCA (Figure 5A) due to gravity. Attempts to improve the filling involved the body being rolled into different positions. Inclining the body to 90° (to the right lateral decubitus position) was shown to improve filling of the RCA with positive contrast and also filling of the LMS, LAD and Cx with air. It was found to be unnecessary to roll the body into left lateral decubitus position as the filling of the RCA with air and contrast was sufficient with the supine body position, this was tried in one case and it did not show better filling than the lateral decubitus position but required significantly more handling.

![Image](image_url)

Figure 2-5: A) Preferential filling of RCA (round head) with air and LAD (arrow) with contrast. B) Luminal delineation of coronary artery in the presence of calcified plaque is inferior with positive contrast compared to air C) (Round head).

2.4.6 Pathology

Concerns were raised that injecting air or Urografin® might displace thrombi or open stenosed segments of coronary artery (Figure 5B) altering autopsy assessment. One case
showed a complete occlusion of the LAD on the initial pre-contrast scan and this remained with no alteration in the vessel following injection with both protocol volumes of contrast. At autopsy, the area of filling defect (suspected occlusion) was indeed shown to be an occlusive thrombus. The injection of protocol volumes of both contrasts did not appear to alter the thrombus. Although a single case, it perhaps negates the concern regarding thrombus displacement.

2.4.7 Timing

Considering the 24 cases, the average time for cannulation was 15 minutes (range 5-30 minutes) (Table 2-1). The longer time periods reflect the earlier cases and the initial learning curve for the technique. In later cases, when the operators were confident with the technique, the cannulation could be performed in less than 10 minutes with minimal blood spillage using standard mortuary equipment. Certain cases proved more problematic for cannulation; such as obese patients with short fat necks and cases with advanced rigor where the neck was flexed in an abnormal position, these cases took much longer (max 30 minutes).

For the final 14 cases, the complete scan time ranged from 39 to 90 minutes (mean 60 minutes). The standard post-mortem imaging time was 18 to 40 minutes (mean 28 minutes) and the angiography time was 15 to 55 minutes (mean 32 minutes). For the final 6 cases, the complete scan time improved to 39 to 63 minutes (mean 48 minutes)
2.4.8 Artefacts

Two cases in the series were found to have pacemakers in situ. This was not stated on the coroner’s history and was not apparent during the cannulation. The metal pacemaker, which was lying inline with the heart, caused ‘streaking’ (photon depletion artefact) which made complete evaluation impossible. In these two cases, the pacemakers had to be removed in the CT scanner, which was far from ideal. Best practice would have been to remove them at the time of cannulation in the mortuary, however, this information should have been provided on the history and the technician should have performed a check by palpating the torso.

Pacemaker removal in the CT scanner was difficult without the appropriate tools being readily available and caused considerable delay. As a result of the complications caused by these two cases, the protocol was adapted to include a pacemaker check and removal if present. During the course of the trial no other medical devices or implants were
identified on scan, so it was impossible to evaluate if other devices would cause interpretation problems.

2.5 Leicester protocol for PMCTA.

1. Case selection.
2. Informed consent obtained from next of kin.
3. Cannulation of left common carotid artery in the mortuary. Ensure no pacemaker present.
4. Transport body to CT scanner by porters.
5. Scout and catheter positioning scan, with repositioning of catheter if required.
6. Angiography:
   a. Ensure correct placement of catheter.
   b. Body supine: Inject 300 ml air, scan and evaluate.
   c. Body rolled into right lateral decubitus position: Inject 300 ml air, scan and evaluate.
   d. Body rolled back to supine: Inject 120 ml Urografin®, scan and evaluate.
7. Transport body back to mortuary in preparation for autopsy.
8. Images reported independently by Radiologist(s).

Table 2-2: The Leicester Protocol for targeted cardiac post-mortem angiography

2.6 Discussion

At the commencement of this project, there were no published methods for targeted angiography in the post-mortem setting, hence the reason for this body of work. During the early stages of the method it became apparent that another research group in Oxford were undertaking similar work and developing a method along the same lines. Just how similar was not apparent until after the Oxford method was published a few weeks after our own (145).
The Oxford research group published a series of 10 cases of targeted cardiac angiography. Their method also used the left side of the neck above the sternoclavicular joint for the site of vascular access. They used a similar device, namely a three-way urinary catheter (Teleflex medical, High Wycombe, UK). This catheter has a balloon volume of 30 ml (Figure 2-7).

![Figure 2-7: Image of a 3-way Teleflex urinary catheter used by the Oxford research group.](image)

They aimed to site the catheter balloon in the ascending aorta (145). The group also described the need to reposition the catheter on one occasion, when the catheter went down the descending aorta. This incorrect position was identified after the first native scan. They described the requirement for ‘slight repositioning’ in eight cases, following the native scan, in order to achieve optimal positioning of the catheter tip above the aortic valve (145).

The Oxford angiography protocol involved the injection of 100 ml - 200 ml of a water-based iodine contrast Omnipaque®(GE Healthcare AS, Oslo, Norway) (300 mg iodine/ml) diluted to 5% concentration with water, which gave excellent pictures with
no extravasation artefact (146). The body was rolled into the prone position during the angiography protocol. (We found that the prone position was no better than the decubitus position and harder to manoeuvre the body into. To turn the body prone on the narrow CT gantry table was difficult and required four people). Their scanning times were 27-54 minutes (median 41.5 minutes) (145). This is in keeping with our own timings.

For an independent research group to come up with a similar approach was reassuring. The notable difference was the effort the group went to minimise air gaining access to the circulation, whereas our method actually advocates its use. The Oxford Group used a 50 ml saline flush to eliminate air in the vessels prior to injecting contrast whilst rolling the body into the prone position. However, they do comment that when air was seen on one scan that ‘an air angiogram was adequate for evaluating coronary artery lesions’ (145).

Overall, the images obtained with our method of the double negative and positive contrast methods provided good quality images and allowed for detailed reporting of the cardiac CT scan in a similar way to clinical scans. As the method developed, much of the assessment was made on the air contrast alone as these images were very clear when all the vessels were inflated. However, the positive contrast added a further dimension to the assessment.

In cases where there was a degree of decomposition, there was air in the vessels prior to the angiography (a well-known post-mortem artefact) and the vessels seemed patent either side of a filling defect. With air-angiography alone, it was impossible to be sure if the defect was completely occlusive, but by also injecting positive contrast, we were able to unequivocally demonstrate absolute occlusion of the vessel by the lack of contrast passing beyond the occlusion.
Post-mortem clot within the coronary arteries is rarely encountered and was not seen in any of our cases nor the Oxford case series. The Oxford research group did report a post-mortem clot in the aorta and its occlusion of the coronary ostia preventing injection of the contrast. To resolve this issue they used a saline flush prior to contrast injections (145). Clot in the aorta was not an issue in our case series.

Both the Oxford research group’s methods and our own required no capital expense and cost less than £20 per case for the consumables (catheter and contrast medium). This is a strong advantage over the whole-body system, which is over £500 per case for consumables.

2.7 Method limitations

Initially, cases with coronary artery bypass grafting (CABG) were excluded. This was due to the need to refine the method on ‘normal’ anatomy. Traditionally, CABG surgery involved using the left internal mammary artery (LIMA) to anastomose to one of the coronary vessels. Injecting contrast into the aorta to access the coronary circulation from the ostia would not have been possible. This is, however, a theorised limitation to the method and a larger study should be conducted including post-CABG cases to investigate whether the PMCTA method could be utilised successfully. Saphenous vein bypass grafts are sutured at the level of the coronary ostia so CABG using these grafts should still be amenable to targeted angiography. It is hoped that this will also be investigated and proven in a larger study.

2.8 Summary

This chapter outlined the development of the key component areas of post-mortem angiography method and how the final protocol was reached. This method was
compared with the much published whole-body angiography method and the Oxford targeted cardiac method.
Chapter 3  Cadatheter design, development and patent application

This chapter details how a task-specific targeted cardiac post-mortem angiography device -the Cadatheter- was designed and developed. Evaluation of the first prototype is discussed. The process of patenting the Cadatheter is also presented.

3.1 Introduction

At the commencement of this body of work, there was no method for in-situ targeted post-mortem cardiac angiography described within the medical literature. The only literature that existed related to whole-body angiography techniques (see chapter 1). The whole-body methods were based on traditional embalming techniques using the femoral artery and vein, and mechanical pumps. This involved inserting tubes a few centimetres into the femoral vessels and pumping approximately 1.5 litres of contrast into the cadaver. For this project a simpler, quicker method was envisioned, so an approach that targeted the heart specifically was attempted. In order to attempt a targeted method, a specific delivery device would be required.

Clinical cardiac angiography was looked to for inspiration for the method and device design. In clinical practice the femoral or radial artery is catheterised and the catheter advanced towards the heart and positioned in the ascending aorta. Angiography catheters are therefore fairly long, typically 65-100 cm. This type of catheter was initially chosen for its directional capability, as it was thought that this would be useful to navigate the aortic arch and ensure correct placement into the ascending aorta. However, this was found to be unnecessary, as positioning was relatively straightforward when access was gained via the left carotid artery. The catheters proved
cumbersome to use, being overly long when cannulating the carotid in the cadavers (the
distance from the incised carotid and the aortic valve is 10-15 cm). The balloons in
these catheters were between 10-15 cm in length and ‘sausage-shaped’. This meant that
the balloon would be in position above the aortic valve but also still be within the lumen
of the carotid artery so inflation risked rupturing the artery, as these balloons could be
inflated to >5 cm in diameter. These catheters were also expensive (in the region of
hundreds of pounds depending on the model). Therefore, their use was abandoned and a
cheaper, simple and readily available alternative was sought.

Figure 3-1: Two urinary (Foley) catheters. The red is 16Fr diameter, the blue is 14Fr
diameter.

A 14 French (Fr) silicone-coated male urinary catheter (Bardia Foley Catheter, USA)
was selected. These are abundant in every hospital and cost less that £1 each. These
catheters are shorter than angiography catheters (40 cm as opposed to 100 -150 cm) and
have a smaller spherical balloon that achieved a good diameter (>5 cm) when fully inflated. The Foleys were easy to insert and manoeuvre into position, and could be cleaned and reused but were cheap enough to be single use.

Foley catheters have a rounded tip that meant a guidewire could not be threaded inside. This was important in the early stages for positioning. So the tip was cut obliquely to produce a shape similar to a needle bevel (Figure 3-2). This allowed a guidewire to be used but also allowed much easier insertion into the cut vessel than the rounded tip.

Figure 3-2: A) The rounded tip of the Foley catheter with side outlets, the balloon inflated to 20 cc. The rounded tip prevented threading of the guidewire. B) The tip of the Foley cut at an oblique angle allowing the guidewire to be threaded and to form a bevelled shape for easier insertion.

Foley catheters come with a 20 cc balloon as standard. The balloon could be overinflated to 70 cc before rupture occurred. The 20 cc filling produced a balloon diameter of 5 cm. This was adequate to hold the balloon in place but there was some back flow of contrast during the injection phase. A similar catheter design with a larger balloon diameter was not available on the market for human use. A veterinary catheter that has a 50 cc balloon was tried, however the diameter of the catheter (equivalent to a 16 F-18 F) was too large for cannulation on every case. Therefore, the team began to
consider designing a catheter specifically made for the post-mortem angiography method. A portmanteau word ‘Cadatheter’ was created from the words ‘cadaver’ and ‘catheter’ to describe the new device.

3.2 Components of the device

The first part of the design process was to draw on my experience from the angiography cases already performed and the use of the previous types of catheters. Many aspects of the Foley catheter worked well so the logical approach was to use the existing Foley as a base and modify and add desired features.

A sketch was prepared (Figure 3-3), by myself, and a list of the requested features was submitted to the designers.

Figure 3-3: First sketch of Cadatheter provided to the prototype manufacturers drawn up by the author.
1 & 2. A bevelled diagonal tip (like a hypodermic needle) with a minimal luminal diameter of 3 mm to allow threading of a guidewire.

3. Two side outlets, in addition to the hole at the tip, to allow more even distribution of contrast and encourage contrast flow into the coronary ostia.

4. Two radiopaque markers, above and below the balloon, to assist in locating the catheter on an MDCT scan.

5. An inflatable 50 cc balloon, giving an inflated diameter of at least 10 cm.

6. 1 cm gradation markings from the tip along the length of the catheter to determine how far catheter has been advanced.

7. A movable valve/diaphragm that slides up and down the length the catheter. The valve is cone shaped and is inserted into the vessel and the vessel wall tied with a ‘purse-string’ suture to prevent leakage of contrast.

8. A 3-way tap with standard medical screw-fit attachment, to control input into the catheter and to allow attachment of standard medical syringes and tubing.

9. Reversible inflation valve to inflate the balloon (similar to a standard Foley valve).

10. The catheter should be 40 cm in length and the diameter of the catheter should be similar to a 12-14 F Foley.

11. The catheter should be made of silicone rubber of a similar firmness and flexibility as the Foley catheter to allow ease of cannulation and positioning.

12. The catheter should be a non-sterile, multi-use device to reduce costs (but could be single use in high-risk cases or for faith related cases (e.g. Jewish people).
13. There should be adult and paediatric versions of the device. The device should also be modifiable for veterinary use.

3.3 Decision to patent device

After the initial design stage and researching what other types of balloon catheter were commercially available, it became clear that there was nothing similar to our proposed design. There were certainly no devices specifically for post-mortem cardiac angiography on the market. Therefore, due to the uniqueness of the device, it was decided that a patent application would be submitted.

‘A patent is a form of intellectual property. It consists of a set of exclusive rights granted by a sovereign state to an inventor or their assignee for a limited period of time in exchange for the public disclosure of an invention’ (147).

A patent protects new inventions and covers how things work, what they do, how they do it, what they are made of and how they are made. It gives the owner the right to prevent others from making, using, importing or selling the invention without permission.

To obtain a patent, an invention must:

- be new.
- have an inventive step that is not obvious to someone with knowledge and experience in the subject.
- be capable of being made or used in some kind of industry.
Figure 3-4: 3-D graphic of the prototype from the initial sketch
• not be: a scientific or mathematical discovery, theory or method, a literary, dramatic, musical or artistic work, a way of performing a mental act, playing a game or doing business, the presentation of information, some computer programs, an animal or plant variety, a method of medical treatment or diagnosis, against public policy or morality.

The origins of patents for invention are obscure and no single country can claim to have been the first in the field with a patent system. However, Britain does have the longest continuous patent tradition in the world. It originated in the 15th century, when the Crown started making specific grants of privilege to manufacturers and traders.

Open letters marked with the King's Great Seal called 'Letters Patent', signified such grants. Henry VI granted the earliest known English patent for invention to Flemish-born John of Utynam in 1449. The patent gave John a 20-year monopoly for a method of making stained glass, required for the windows of Eton College, which had not been previously known in England (147).

3.4 Benefits of patent protection

A patent gives the inventor the right to stop others from copying, manufacturing, selling and importing your invention without permission. The existence of a patent may be enough on its own to stop others from trying to exploit such an invention. If it does not, it gives the inventor the right to take legal action and claim damages.

The patent also allows the inventor to:

• sell the invention and all the intellectual property (IP) rights.
• license the invention to someone else but retain all the IP rights.
• discuss the invention with others in order to set up a business based around the
invention.

The patent is published in the public domain after 18 months by the Intellectual Property Office in the UK.

A patent application was made for the method of targeted cardiac post-mortem angiography with air and radiographic contrast as well as the Cadatheter device by the author and the project supervisors. The patent was filed by Murgitroyd and Company, European Patent and Trade Mark Attorneys with a priority date of 18th Feb 2011 (148).

3.5 Cadatheter prototype

After a period of 8 months, the product device company sent the first prototype of the Cadatheter. The prototype included all the required specifications.

Figure 3-5: The first prototype produced.
Figure 3-6: Close-up elements of the Cadatheter. A) The 3-way tap with universal attachments. B) The 1 cm graduations along the length of the Cadatheter C) The 50 cc balloon with radiopaque markers either side.

3.6 Trialling the prototype and future development

The unexpected delays in the prototype production meant that the initial stage of the project (first 24 cases) had been completed before the prototype arrived. So it was not used to collect the data within this thesis. However, the device was trialled in a number of extra cases.

The initial prototype worked well for the most part. The length was similar to the original Foley and worked well. The prototype was more rigid, which made it easier to position than the Foley. The two radiopaque markers either side of the balloon were an excellent addition which made determining the position of the catheter easier on the MDCT scan and meant the balloon could be inflated using saline rather than dilute contrast. The 1 cm gradations were also helpful to determine how far the catheter had been advanced. The 3-way tap was beneficial in limiting backflow and allowing attachment of any size syringes, this meant we could stop using the 60 ml bladder syringes, as they were the only syringes that could be attached to the standard Foleys.
The increased size of the balloon greatly reduced the back flow of the contrast. However, the material the balloon was made from was very friable and ruptured after every use when inflated to the full 50 cc. This was far from satisfactory. The rupturing seemed to occur during deflation of the balloon. Fluoroscopic angiography was undertaken of this process and it was determined that one of the radiopaque marker rings was cutting the balloon. This marker will be moved in the next prototype to prevent this problem.

The movable valve was less successful than anticipated. Securing the valve with a purse-string suture was difficult and there was still a degree of back flow. This was no worse or better than using the standard Foley catheter. This valve may be removed or modified for future designs.

These issues were fed back to the design team and at the time of writing, further prototypes are in production. It is hoped the Cadatheter design will continue to be refined as the larger study progresses.

3.7 Summary

This chapter outlined the design requirements for a task-specific targeted post-mortem cardiac angiography that was developed for this study. The design and method was subsequently patented and made into a prototype. A brief overview of the patent process and evaluation of the first prototype were described. The next chapter presents the data for the first cases to undergo the angiography.
Chapter 4  Targeted Cardiac Post-mortem Computed Tomography

Angiography; results from 24 cases.

This chapter will look at the results of the pilot study of 24 cases that underwent PMCTA. This pilot study formed part of a larger study later undertaken at the end of this body of work to evaluate if PMCTA autopsy could be used as an acceptable alternative to the conventional autopsy in the Coronial system of England and Wales.

4.1 Introduction

The aim of this study was to evaluate the diagnostic accuracy of PMCTA and the potential of the technique for the investigation of the cause of death in cases undergoing coronial autopsy. The objectives were firstly to compare findings on PMCTA against the findings of the autopsy, to evaluate the sensitivity and specificity of the technique to identify the presence of ischemic heart disease. The second objective was to evaluate the utility for PMCTA in predicting the cause of death and to assess whether a proposed “view, scan and grant” protocol using PMCTA could provide a cause of death sufficient for death certification, which would be acceptable to a coroner as a replacement for a routine autopsy.

4.2 Method

4.2.1 Population

Cases were selected for potential PMCTA, by a forensic pathologist, from the coronial autopsy request forms faxed to the Leicester Royal Infirmary mortuary between April 2010- December 2010. Ethics permission to perform PMCT and catheter angiography, and to use the data for research and teaching, was obtained from the local ethics review
board. Exclusion criteria during this stage included significant neck trauma e.g. hanging, previous complex cardiac surgery such as bypass grafting (for the same reason) and bodies weighing over 125 kg, due to manual handling considerations and the size of the CT scanner gantry. The exclusion criteria were to ensure the method was assessed on individuals with ‘normal’ neck and cardiac anatomy to allow any artefacts generated by the procedure to be identified.

Informed consent was obtained from the decedents’ next of kin, via the telephone by the trial consenter on the day prior to the autopsy (as per the consent protocol detailed in chapter 5). Information leaflets were sent the next working day if requested.

4.2.2 PMCT Angiography

The angiography was performed using the protocol specified in chapter 2.

4.2.3 PMCT image reporting

Two consultant radiologists reported the imaging in consensus, blind to the autopsy findings. One was a cardiac radiologist with two years experience of post-mortem imaging, the other a cross-sectional and interventional radiologist with six years experience of post-mortem imaging. Image analysis was performed on workstations using multi-planar reconstructions (MPR) and 3-D analysis (Vitrea®, (Toshiba, Japan) and OsiriX v4.0 64-bit software (Pixmeo, Switzerland). The optimum filling of the vessels by air and positive contrast medium was assessed subjectively on the ability to see the right coronary artery (RCA), posterior descending artery (PDA), left main stem (LMS), left anterior descending (LAD) and circumflex (Cx) arteries.
4.2.4 Autopsy

The autopsies were undertaken following the Royal College of Pathologists Guidelines for autopsy practice in England and Wales (149) with the pathologist blind to the PMCT findings. The coronary vessels were examined by sectioning the coronary arteries at 3-5 mm intervals, as is standard practice (109,111). The pathologists were asked to evaluate the degree of stenosis (in %) of each of the coronary vessels at the proximal, mid and distal aspects and record this figure. Additional laboratory investigations, such as histology or toxicology, were undertaken as required, and where permissible, under current coroner’s legislation (150,151). At the start of the project, the prospect of histology of the coronary arteries being undertaken on every case was considered. However, it was decided by the study group that it added too much complexity at this early stage and should be a focus later in the larger 200-case study once the method had been developed. No histology was taken for this pilot study.

4.2.5 Review of findings

The autopsy and PMCTA reports were collated by the study co-ordinator and anonymised. Two anonymous reports were produced for each case; a complete report and one with the circumstances of death, medical history, and external examination only (internal findings, comments and cause of death (COD) removed). When all the cases had been collated, consensus meetings were held between the two radiologists and an impartial forensic pathologist (FP) (who had not undertaken the autopsies), to review all reports and imaging. This consensus group was felt to have all the skills necessary to evaluate the images and post-mortem finding and issue an appropriate COD. The radiologist felt that they did not have enough experience in determining COD. The findings of each case were considered for the quality of coronary artery imaging and any differences between the PMCTA and autopsy findings recorded. This data was used
to calculate the sensitivity and specificity of the technique and provide the first set of results.

The data was then provided to a histopathologist and a forensic pathologist in addition to the consensus group. All three groups were asked to propose a COD blind to the autopsy findings by considering the clinical history, external examination, the PMCTA report and any laboratory results from each case. This data was then tabulated. Discrepancies were considered on the basis of potential clinical or medico-legal outcome. Possible reasons for discrepancies were considered at a subsequent meeting between the radiologists and pathologists.

4.2.6 View, scan and grant

If PMCTA is to replace the autopsy in the future it is envisaged that a “view, scan and grant” system will be the way to implement this change. This would involve a review of the circumstances of death, medical history, an external examination by a pathologist (to document matters related to identification, injuries and natural disease), and to take toxicology samples if necessary (as dictated by the history). PMCTA would be performed and the scan reviewed. If a definitive cause of death was apparent from the imaging, then a COD would be proffered, and reported to the coroner. If the coroner is satisfied that the COD is ‘on the balance of probability’ then an autopsy would not be performed. If the COD is not apparent then the case would proceed to autopsy (as per the current coronial system). The implementation of such a protocol could result in a reduction in the overall number of autopsies undertaken. For the cases that did proceed to autopsy, the pathologists would be provided with a pre-autopsy PMCT report as an adjunct to the post-mortem examination. This pre-autopsy report would facilitate targeted or limited autopsies e.g. not opening the head if no pathology was seen.
In an attempt to mimic this process, a paper ‘view scan and grant’ assessment was undertaken for the 24 cases. Three different independent assessments were made as to whether the PMCTA could be used as a replacement to the internal examination to provide a COD. Assessments were made by a histopathologist, a forensic pathologist and a consensus group (made up of the two radiologists and a different forensic pathologist). They were asked to provide a COD based on the circumstances of death, the external examination findings and the PMCTA report, along with any additional laboratory tests. They were asked to give comments if there was uncertainty. The CODs provided were compared to the autopsy report. The assessors were asked to make their decisions based ‘on a balance of probabilities’; the burden of proof required for the Coronial courts in England and Wales.

4.3 Results for objective 1

Twenty-four cases were consented for this pilot study, of which 21 were considered to be of sufficient diagnostic quality. Three cases were excluded from the analysis, at the consensus review stage, due to incomplete PMCTA. The three cases occurred early in the series and were due to difficulties experienced by the operators during the development of the cannulation procedure; passing the catheter into the descending, rather than ascending thoracic aorta. These errors were identified on the initial native scan, but attempts to rectify the problem had been unsuccessful. These cases proceeded to autopsy as would have been the protocol if the ‘view, scan and grant’ system were in operation.

The first part of the study was to assess the accuracy of the technique for identifying ischemic heart disease.

The sensitivity and specificity for the identification of ischemic heart disease on PMCTA is given in
Table 4-1. The specificity (ability to detect normal) of PMCTA was 88.9%. The sensitivity (ability to detect abnormal) was 100%. The positive predictive value (PPV) was 92.31%, and the negative predictive value (NPV) was 100%.

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Table 4-1: Calculation of sensitivity and specificity of PMCTA to detect the presence of ischemic heart disease when autopsy findings are taken as the gold standard.

4.4 Discussion for objective 1

The first objective was to compare findings on PMCTA against the findings of the autopsy, to evaluate the sensitivity and specificity of the technique to identify the presence of ischemic heart disease. From the first 24 cases we were able to demonstrate that targeted cardiac PMCT angiography can provide detailed imaging of the cardiovascular system of sufficient quality to allow cause of death to be proffered.
When compared directly to the autopsy, the PMCTA method showed a high specificity (88.9%) and sensitivity (100%). The specificity would have also been 100% had it not been for one case. The positive predictive value (PPV) was 92.3%, and the negative predictive value (NPV) was 100%. These suggest a great future potential for the method. It is hoped that this similar results are replicated in the larger trial.

One of the greatest potential strengths of our PMCTA method is its ability to confidently rule out ischemic heart disease, thus allowing greater confidence to be attributed to the clinical history and toxicology in determining the cause of death.

In one case the ischemic heart disease was reported as the cause of death by the consensus group, the histopathologist and the forensic pathologist. The post mortem detected a pulmonary embolism and gave this at the cause of death, this is an ‘under call’ by the non-autopsy groups. Without contrast agents in the pulmonary arteries, the diagnosis of pulmonary embolism (PE) is practically impossible, unless there was sufficient time to develop a wedge-shaped pulmonary infarction, but this usually takes days. Acute pulmonary thromboembolus has been demonstrated to not be recognised with arterial angiography, and therefore would only be diagnosed by autopsy or the use of combined venous angiography. There is a risk that death due to acute PE, if not recognised, could be incorrectly attributed using PMCTA if significant other pathology, such as coronary artery disease, is present. In our small series we did not have any ‘over calls’ so it is difficult to speculate on what such pathologies these might be, this is discussed further below in the general discussion and the final chapter.

4.5 Results for Objective 2

The second objective was to evaluate the utility for PMCTA in predicting the cause of death and to assess whether a proposed “view, scan and grant” protocol using PMCTA
could provide a cause of death sufficient for death certification, which would be acceptable to a coroner as a replacement for a routine autopsy.

For the purpose of this study, the invasive autopsy was taken as the “Gold standard”. Thus the COD provided at autopsy was accepted as being correct for all 21 cases.

In 14 / 21 cases the Autopsy and PMCT findings were in complete agreement. The cases with differing opinions will now be discussed and summarised in Table 4-3.

In Case 15, the final COD at autopsy was given as bronchopneumonia. The PMCTA suggested ischaemic heart disease as the COD due to extensive calcification. No histology or macroscopic photographs were taken in this case to evidence the pathologist’s decision. This is a limitation of this study bore out by the coroners rules prohibiting routine collection of histology. it would have be ideal to have the histological confirmation of the pneumonia in order to prove a true over call. In the absence of this data the pathologist’s diagnosis has to be taken as correct. In Case 14, the COD at autopsy was given as ‘1a ruptured abdominal aortic aneurysm secondary to atheroma’ with a description of 1 litre of blood in the left retroperitoneal space. The PMCT showed that the collection of blood was within the left pleural cavity and clearly demonstrated that the point of rupture was at the descending thoracic aorta (Figure 4-1). This case highlighted a clear inaccuracy in the autopsy to determine the location of the bleed and therefore giving a slight difference in the wording of the COD, but ultimately the nature and mechanism of the death are the same. As this was a natural COD there were no medico-legal consequences to alter the coroner’s verdict.
There were other omissions from the autopsy reports identified in this series, the presence of a coronary artery stent, a small primary pulmonary tumour and a primary bladder tumour. The reasons for the omissions were not investigated due to the analysis of the PMCT occurring after the autopsy. The omissions could have been due to the pathology being missed at autopsy, or simply dismissed from the report as incidental findings. The significance of the omissions are debatable. In terms of accuracy of recording every finding present then they are important. In terms of whether the findings had a bearing on the cause of death and therefore relevant to the coroner then the findings could be argues to be insignificant.

The findings from this series of cases confirmed that PMCTA, with the correct placement of the catheter and the use of both positive and negative contrast, can illustrate the origin and the course of the left and right coronary arteries (21/21) (Figure 4-2), filling defects due to atheroma (with or without calcification) (14/21) and thrombotic occlusions are demonstrated by the technique (1/21).
Figure 4-2: Multiplanar reconstructions (MPR) demonstrating the origin and course of the coronary arteries with positive (A,B) and negative contrast (C,D)

4.5.1 View, scan and grant protocol.

Table 4-2 details the COD given in the autopsy report and by each assessor. Table 4-3 gives a breakdown of the cases where there was a discrepancy between the CODs and the reasons for the differences. A COD was given based on the ‘view, scan and grant report’ in 21/21 of cases (100%) by the consensus team, 20/21 (95%) by the histopathologist and 16/21 (76%) by the forensic pathologist. Where a cause of death was given, it showed a discrepancy with the autopsy report in 3/21 (14%) of cases by the consensus team, 2/20 (10%) by the histopathologist and 2/16 (13%) by the forensic pathologist.
For Case 6, the histopathologist and the consensus group agreed with the autopsy findings and gave the COD as ischaemic heart disease. Both assessors acknowledged the subdural haemorrhage (SDH) but disregarded its role in death, as did the autopsy. The forensic pathologist, without access to the images, considered the PMCT report to express uncertainty about the significance of the acute-on-chronic subdural haemorrhage. This uncertainty regarding the wording of the report lead to the FP placing more emphasis on the SDH as a cause of death than if the report had stated it was a definitive old chronic SDH. At the consensus group review, this difference in interpretation was attributed to specific wording used by radiologists in their report, who could have made it clearer that the SDH was small with no mass effect, cerebral oedema or midline shift. This problem could be eliminated in the future by joint reporting of the pathologists and the radiologists, or by the pathologists conferring with the reporting radiologist when they feel there is uncertainty in the report. This was not possible during this trial.

All assessors gave an incorrect COD with Case 7. This was a case of pulmonary thromboembolus (PE), which was missed by PMCTA, although the forensic pathologist did consider this diagnosis in her comments based on the history alone, but advised progression to autopsy.

In case 15, PMCT correctly showed chronic lymphocytic lymphoma and ischaemic heart disease (IHD) but did not mention bronchopneumonia, the COD given by the autopsy pathologist. All the three assessment teams favoured IHD over the pneumonia as the COD due to the presence of severe coronary artery disease and bilateral pleural effusions. Thus, although this is reported as a PMCT error, it was felt that a different pathologist might have interpreted the autopsy differently.
Case 9 led all assessors to suggest peritonitis but a different site of rupture was identified on PMCTA from autopsy leading the assessors to favour a different wording to the COD. In fact, on review of the PMCT it was felt that the images favoured the correct diagnosis of ruptured colonic diverticulum. Although different, these three cases correctly gave a natural COD and therefore would be unlikely to lead to any medico-legal repercussions.

The forensic pathologist expressed further uncertainty/different COD with a further three cases although, the level of certainty in Case 6 would have been improved if the radiology report had been more specific as to why it considered the subdural haematoma insignificant. This would have caused the forensic pathologist discrepancy figure to change to 1/16 (6%).

4.5.2 PMCT versus autopsy

The final part of the assessment considered the differences in pathologies reported by PMCT compared to invasive autopsy. Although the external surface of the body can by produced by 3-D PMCT reconstruction (16,35) it cannot, at present, be produced in sufficient detail for diagnostic purposes and thus a detailed external examination by a pathologist is required in all cases, and this is unlikely to change in the near future.

Toxicology was undertaken in all of the trauma cases and 4 of the non-trauma cases and assisted in providing the COD in 2 cases. A histological examination was undertaken in 4 cases. This supported the macroscopic observations at autopsy but did not provide a new diagnosis or alter the COD in any case.

In the case of PMCT it became apparent at the consensus reviews that some findings recorded at autopsy e.g. uncomplicated renal cysts and diverticulosis were not reported by the radiologists. The reason given for this was that these are common findings in the
study population and would not always be reported in clinical radiological practice unless causing a clinically significant pathological process. Omissions from the autopsy reports (for example failure to record pleural fluid collections or pleural plaques, both of which could have clinical and medico-legal consequences) could have been attributed to bodies being eviscerated by anatomical pathology technologists (morticians) rather than the pathologists. The presence of a coronary artery stent, a small primary pulmonary tumour and a primary bladder tumour were also not reported within the autopsy reports.

Road traffic collisions (RTC) were included in the series to assess the PMCT angiography findings against the cardiac findings at autopsy rather than to undertake a detailed assessment of the findings of trauma PMCT verses autopsy. In all RTC cases the same COD was reached by use of PMCT with angiography.
<table>
<thead>
<tr>
<th>Case</th>
<th>Cause of death (COD) from autopsy</th>
<th>Consensus group’s COD</th>
<th>Histopathologist's COD</th>
<th>Forensic pathologist’s COD</th>
</tr>
</thead>
</table>
| 1    | 1a Coronary thrombosis  
1b Coronary atherosclerosis | Sudden cardiac death due to thrombosis of right coronary artery | Ischaemic heart disease | Refer for autopsy |
| 2    | 1a Alcoholic ketoacidosis | Alcoholic ketoacidosis | Alcoholic ketoacidosis | Alcoholic ketoacidosis |
| 3    | 1a Ischaemic heart disease  
2 Diabetes mellitus and chronic renal disease | Ischemic heart disease | Ischaemic heart disease | Coronary artery disease |
| 4    | 1a Ischaemic heart disease  
1b Coronary artery disease  
2 Chronic renal failure | Ischaemic heart disease due to coronary artery disease contributed to by chronic renal disease | Ischaemic and hypertensive heart disease | Coronary artery disease |
| 5    | 1a Ischaemic heart disease  
1b Coronary artery disease | Cardiovascular cause of death – ischaemic heart disease and coronary artery disease seen on PMCT | Ischaemic heart disease | Cardiac arrhythmia due to atrial fibrillation or myocardial fibrosis. |
| 6    | 1a Ischaemic heart disease | Ischaemic heart disease | Ischaemic heart disease | REBLEED OF PREVIOUS SUBDURAL HAEMORRHAGE |
| 7    | 1a Pulmonary embolism  
1b Deep vein thrombosis  
2 Primary caecal adenocarcinoma | CARDIOVASCULAR CAUSE OF DEATH - SEVERE CORONARY ARTERY DISEASE | ISCHAEMIC HEART DISEASE | Refer for autopsy.  
- raised the possibility of PE as COD |
| 8    | 1a Acute myocardial infarct  
1b Coronary artery thrombosis  
1c Coronary artery atherosclerosis | Cardiovascular cause of death – severe coronary artery disease | Ischaemic heart disease | 1a Ischaemic heart disease  
1b Coronary artery atherosclerosis |
<table>
<thead>
<tr>
<th></th>
<th>Description</th>
<th>Cause</th>
<th>Refer For Autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>1a Perforated diverticulitis</td>
<td>PERITONITIS SECONDARY TO PERFORATED DUODENUM</td>
<td>Refer for autopsy</td>
</tr>
<tr>
<td>10</td>
<td>1a Sudden unexpected death in alcohol misuse</td>
<td>Sudden unexpected death in alcohol misuse</td>
<td>Refer for autopsy</td>
</tr>
<tr>
<td>11</td>
<td>1a Acute myocardial infarct</td>
<td>Cardiovascular cause of death - severe coronary artery disease</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td></td>
<td>1b Coronary artery thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1c Coronary artery atherosclerosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1a Ischaemic heart disease</td>
<td>Ischaemic heart disease</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>13</td>
<td>1a Ischaemic heart disease</td>
<td>Ischaemic heart disease</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td>14</td>
<td>1a Ruptured abdominal aortic aneurysm</td>
<td>RUPTURED DESCENDING THORACIC AORTIC ANEURYSM</td>
<td>1a HAEMOTHORAX</td>
</tr>
<tr>
<td></td>
<td>1b Atheroma</td>
<td></td>
<td>1b RUPTURED AORTIC ANEURYSM</td>
</tr>
<tr>
<td></td>
<td>2 Hypertensive heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1a Bronchopneumonia</td>
<td>ACUTE HEART FAILURE DUE TO CORONARY ARTERY DISEASE CONTRIBUTED BY CHRONIC LYMPHOPROLIFERATIVE DISEASE</td>
<td>1a ACUTE LEFT VENTRICULAR FAILURE</td>
</tr>
<tr>
<td></td>
<td>1b Chronic lymphocytic lymphoma</td>
<td></td>
<td>1b ISCHAEMIC HEART DISEASE</td>
</tr>
<tr>
<td></td>
<td>2 Ischaemic heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>1a Acute myocardial infarct</td>
<td>Cardiovascular cause of death - severe coronary artery disease</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td></td>
<td>1b Coronary artery atheroma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>1a Myocardial ischemia</td>
<td>Cardiorespiratory death in presence of left ventricular hypertrophy</td>
<td>Ischaemic heart disease</td>
</tr>
<tr>
<td></td>
<td>1b Left ventricular hypertrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 Pulmonary fibrosis consistent with asbestosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4-2: List of all cases showing the official autopsy report COD, and the COD given from the ‘view, scan and grant report’ (using external examination findings, the PMCT report along with any additional laboratory tests) by the consensus group (CG), histopathologists (HP) and forensic pathologist (FP). Discrepancies are highlighted in bold capitals.

<table>
<thead>
<tr>
<th></th>
<th>Case Description</th>
<th>COD from Autopsy Report</th>
<th>COD from View, Scan and Grant Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>1a Multiple injuries</td>
<td>Multiple injuries</td>
<td>Multiple injuries</td>
</tr>
<tr>
<td>19</td>
<td>1a Crush asphyxia during a road traffic incident</td>
<td>Severe chest trauma</td>
<td>Severe chest injury</td>
</tr>
<tr>
<td></td>
<td></td>
<td>during a road traffic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>incident</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>1a Multiple injuries sustained in a road traffic</td>
<td>Multiple injuries</td>
<td>Multiple injuries</td>
</tr>
<tr>
<td></td>
<td>collision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>1a Multiple injuries</td>
<td>Multiple injuries</td>
<td>Multiple injuries</td>
</tr>
<tr>
<td>Case</td>
<td>Autopsy based cause of death</td>
<td>Reason the review pathologist or consensus team felt unable to provide a cause of death</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-----------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| 1    | 1a  Coronary thrombosis  
1b  Coronary atherosclerosis | Due to body decomposition the FP requested a toxicology report. As none was available she did not issue a COD. The HP and CG felt sufficient pathology was seen on PMCT despite post-mortem changes to offer a COD. |
| 6    | 1a  Ischaemic heart disease | A thin acute-on-chronic subdural haematoma was seen on PMCT and at autopsy. The CG considered this insignificant due to absence of cerebral swelling or mass effect. The FP felt that the clinical history was insufficient to confidently give a COD and requested a neuropathology examination. The HP favoured ischaemic heart disease but also thought an autopsy was required. |
| 7    | 1a  Pulmonary embolism  
1b  Deep vein thrombosis  
2  Primary caecal adenocarcinoma | The PMCT did not identify the pulmonary thromboembolus (PE) but did show significant coronary vascular disease. The HP and CG therefore gave coronary vascular disease as the COD. The FP raised the potential for a PE and so did not provide a cause of death |
| 9    | 1a  Perforated diverticulitis | The PMCT identified perforated bowel but suggested a ruptured duodenum rather than diverticulum as described in the autopsy report. Both the HP and FP felt that there was insufficient certainty in the PMCT report to provide a cause of death. |
| 10   | 1a  Sudden unexpected death in alcohol misuse | Both the CG and the FP were thought the clinical history raised the possibility of an epilepsy related death and requested neuropathology. The CG however decided to provide a cause but the FP decided not to provide one. |
| 15   | 1a  Bronchopneumonia  
1b  Chronic lymphocytic lymphoma  
2  Ischaemic heart disease | Despite the autopsy report giving bronchopneumonia as the COD, on review the CG and both review pathologists felt that the PMCT showed features of cardiac failure due to ischaemic coronary artery disease as the COD. They felt that although the PMCT showed lymphoproliferative disease that this was not the primary COD. |
| 17   | 1a  Myocardial ischemia  
1b  Left ventricular hypertrophy  
2  Pulmonary fibrosis (asbestosis) | The FP felt that there was insufficient information in the PMCT report to differentiate between a cardiac and respiratory death. As there was a history of asbestos exposure they were unprepared to provide a cause of death without an internal examination. |

Table 4-3: Details of cases that caused difficulty for the ‘view, scan and grant’ report for the consensus group (CG), histopathologist (HP) and forensic pathologist (FP). COD = cause of death
In the other methods of targeted and whole-body PMCTA described in the literature, significant attempts were made to avoid the injection of air. We found air to be an ideal initial contrast medium that improved the imaging of vessels with severe calcification or stents, due to the stark black against white effect. With the sole use of positive contrast, there can be a lack of clear differentiation between the contrast and calcifications within the vessel wall. For this reason, the combination of both negative and positive contrast was thought to be a superior method in our trial. The use of negative contrast alone in most cases could have adequately provided sufficient information for coronary artery assessment. However, in some cases such as bodies in advanced state of the decomposition where there is a significant volume of gas already in the coronary vasculature, positive contrast is also required. Our method is currently the only post-mortem method to use air, and air in combination with a positive contrast.

With curved multi-planar reconstruction (cMPR) software, the images of the coronary vessel can be manipulated to show a ‘fly though’ view, allowing a transverse measurement of luminal diameter and quantification of luminal diameter. Autopsy practice involves slicing the vessels every 2-5 mm, which may actually miss a stenosis or small thrombus, as was the process in this study (109,111). Extensive calcification of coronary arteries causes sectioning of the vessels to become difficult and the lumen can be crushed and distorted. Estimating luminal diameter becomes inaccurate and the distance between the sections increases, thus increasing the risk of missing thrombi or stenosis (146).

Although it has been suggested that this technique can actually dislodge thrombi, thrombi have been demonstrated using PMCTA both in later experience by our unit and
using the TWGPAM whole-body PMCTA technique (152). Removal and retention of the whole artery for decalcification prior to sectioning would be the ideal. However, under the current coronial system due to time constraints, cost, and tissue retention issues this is untenable.

Even in less diseased vessels, the reliability and accuracy of the degree of stenosis of estimated by pathologists is dubious. It has been reported that pathologists can only accurately assign stenosis when it is less than 30% or greater than 70% (153). One study showed that pathologists classified stenosis as “severe” when the actual stenosis was between 40-90%, this might have been due to the variation in eccentric and concentric occlusion (153).

Cardiac CT allows computer-assisted estimation of luminal area and diameters to be recorded in a more reliable and reproducible way, along the entire length of the vessel. The computer packages identify the area of the most severe stenosis from the vessel (96,106,107). This can be correlated directly with cardiac CT performed in life, provided the patient had already undergone the procedure. This could be especially beneficial in the follow up of cardiology and cardiac surgery patients and help to further research.

One of the early concerns with injecting contrast under pressure into the coronary vessels was that the contrast might dislodge thrombi and therefore alter the autopsy findings. However, our study did not show this. Despite the injection of contrast, thrombotic occlusions were still found at autopsy, indicating that the angiography did not significantly alter such pathology (case 11), although, this cannot be completely excluded.
Figure 4-3: MPR images showing varying degrees of coronary artery disease. A) Calcified plaque in Cx artery with no significant luminal occlusion. B) Moderate to severe filling defect of the RCA is seen secondary to mixed plaque disease. C) Image demonstrating a filling artefact of the ostium of the RCA. D) Image showing occluded coronary artery due to a recent thrombus. (E&F) Images demonstrating varying degrees of luminal disease due to calcified plaque disease.

A recent whole-body angiography study by Palmiere et al (154) using constant low-pressure contrast infusion with the Virtangio® machine reported the removal or displacement of post-mortem clots within the coronary arteries but not thrombi (154). Their study of 150 cases underwent PMCTA using the standard TWGPAM method (136), with subsequent autopsy and histological examinations of the coronary arteries. They correlated complete arterial luminal filling defects with acute coronary thrombosis.
by histological examination. They were also able to correlate varying degrees of coronary calcification and incomplete arterial luminal filling with histology to demonstrate coronary artery atherosclerosis (152).

One additional benefit of angiography is the presence and patency of coronary artery stents can be visualised. This can be difficult to achieve in the autopsy setting as the metal stents require cutting longitudinally, preventing luminal diameter assessment. The data from our series shows this is best undertaken using air as the contrast medium. A positive contrast medium can obscure the lumen of a metal stent due to both appearing with a similar brightness on the PMCT.

PMCT also has the ability diagnose other cardiac pathologies such as cardiac masses, valvular calcification and vegetations, pericardial fibrosis, arterial and ventricular septal defects, and ventricular wall abnormalities such as hypertrophy, aneurysm, fibrosis and fatty infiltration (Figure 4-4). However, only ventricular dilatation and fibrosis was seen in our small series.

One observation from this study was the difference in how radiologists and pathologists examine and report the heart. Cardiac radiologists follow very strict defined guidelines (155) for the reporting of cardiac PMCTA scans as opposed to autopsy reporting which varies greatly, depending on the individual histopathologist and the clinical situation, despite guidelines. The difference in reporting standards was not anticipated at the start of the study. The reporting of both was to be standardised for the subsequent larger study.
Figure 4-4: Short axis (A) and four chamber (B) views of two different left ventricles demonstrating mural thinning (A) and calcification (B) in keeping with fibrosis secondary to previous infarction.

In live patient scans, cardiac radiologists give an assessment of the coronary artery at the proximal, mid and distal segments of every coronary artery, whereas pathologists tend to vary greatly in their practice. Some just give an estimation of the worst area of stenosis for each artery, or fail to stipulate the location of the stenosis along the vessel.

After due consideration, the group of pathologists adopted the radiologists approach to cardiac reporting to ensure a uniform approach and enable correlation between clinical and autopsy findings. The pathologists were asked to give an estimation of stenosis of three segments of each artery and document their findings on a pro forma in addition to their report.

A 2003 UK-wide audit (13) and the 2006 The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report (14) highlighted a large number of autopsies where the standard of the report was either poor or inadequate; as many as 1
in 4. Although autopsy reports can be audited against the Royal College of Pathologists guidelines (156), the adequacy of the procedure cannot. In Scotland, medico-legal autopsies requested by the Procurator fiscal are undertaken by two pathologists present at the same time, who individually report their findings (157). This method has never been adopted in England and Wales. Post-mortem imaging provides a detailed permanent record which can be used for audit purposes or review – the so-called “virtual exhumation” (54).

The cases of alcoholic ketoacidosis and drug misuse were diagnosed correctly by the assessment teams using PMCTA. This was achieved by PMCT illustrating no other natural disease that could account for death, the presence of a fatty liver and the interpretation of the alcohol/drug/ketone levels within the toxicology report. This illustrates that toxicological causes of death can be diagnosed correctly using this system especially with the method demonstrating high sensitivity to exclude the presence of ischemic heart disease. In a case with a clinical history pointing towards a toxicological cause of death (e.g. drug paraphernalia at the scene or alcoholic binge), a normal external examination and CT scan which excludes trauma and ischemic heart disease, with the addition of a positive toxicology report (e.g. with fatal range) will allow the pathologist to feel confident to attribute the cause of death without an autopsy.

In this series, targeted cardiac PMCTA along with a detailed external examination and toxicology, if required, could replace the need for an autopsy in at least 66% of routine coronial cases. In our data, the main source of error appeared to be when a PMCT occult diagnosis, such as pulmonary emboli, occurred in the presence of other life-threatening pathology such as severe coronary artery disease.
Considering the proposed ‘view, scan and grant protocol’ in our pilot study, the cases with a confident COD would have had been triaged to ‘no autopsy’, if the coroner was satisfied. From this series there would have been four discrepancies in cause of death, three minor and one major if the protocol was followed as specified.

In three of these cases the error was considered of little medico-legal relevance for the purpose of the coroners’ court. The major discrepancy was a case of acute pulmonary thromboembolus (PE) (which is not recognised with arterial angiography) and therefore would only be diagnosed by autopsy or possibly the use of pulmonary angiography (158). The minor discrepancies could be acceptable to the coroner, and perhaps even the major discrepancy, as a natural cause of death, provided there were no other parties involved or the death was not related to a medical procedure. If the family and authorities have no concerns the coroner may accept the ‘natural death’ being given as IHD instead of PE correctly. This needs to be investigated and the opinion the coroners of England and Wales assessed to see if they would consider the protocol in their daily practice.

In addition to excluding the presence of ischemic heart disease PMCT can also be used as a negative predictive test for neuropathological disease; for example to demonstrate the absence of gross intracranial pathology and avoid opening the head at autopsy. Further data is required, however, to ensure pathologies such as encephalitis or primary neuropathological disorders would not be missed by such an approach. These types of pathologies are not always macroscopically visible at autopsy and require neuropathology (86,159). There could be a case for brain only limited autopsy using this method to allow neuropathology.
If PMCTA is introduced as an alternative to the traditional autopsy, there will still be a number of cases that require invasive autopsy if no COD is identified, or there is ambiguity in the radiology report. Skill in catheter placement, local anatomical vascular variations, neck shape, intra-thoracic trauma and local vascular bleeding all affect the use of the system. Training is required to enable a high success rate, including both catheter placement and immediate image assessment (required for catheter placement and to ensure adequate imaging of the coronary arteries). This requires knowledge of human anatomy, autopsy/embalming procedures and a basic level of understanding of clinical cardiac angiography image assessment. Some cases will also not be suitable for the site of insertion, for example severe neck trauma.

The data from this pilot study shows that the strength of this PMCTA technique in its day–to-day application in autopsy practice is to allow confident excluding of the presence of ischemic heart disease in a number of scenarios with a cause of death strongly suggested by clinical history, e.g. toxicology related death and multiple trauma resulting from road traffic collisions. Also, to confidently identify the presence of severe ischemic heart disease in scenarios with clinical histories strongly suggestive of IHD as the COD e.g. elderly patients with known chronic IHD who die in the community, thus preventing unnecessary autopsies. This last scenario would see a significant reduction in total autopsy numbers.

4.7 Limitations of this study

This small pilot study of 24 completed cases suggests that targeted cardiac PMCTA is possible in most autopsy cases and a cause of death can be given in two thirds of cases (or greater) of unexplained sudden death. The design of the pilot study is limited by the
low numbers, but this is still one of the largest studies of targeted post-mortem angiography with autopsy comparison to be described.

This pilot study demonstrates the feasibility of the method and forms a solid grounding for a much larger study. The National Institute for Health Research (NIRH) have funded a larger 200-case study undertaken at the East Midlands Forensic Pathology Unit in conjunction with University Hospitals of Leicester and this pilot study will form part of that study. It is hoped that this study will collect sufficient data to identify those cases of natural and unnatural causes of death where an external examination, PMCT can, on a “balance of probabilities”, provide a COD acceptable to HM coroner without the need for an invasive autopsy in a significant number of cases.

4.8 Summary

This chapter presented the data from 24 cases undergoing targeted cardiac post-mortem computed tomography angiography. This pilot study aimed to evaluate if targeted cardiac PMCTA could provide sufficient cardiac information to assist in deriving a cause of death (COD) without the necessity to undertake an invasive autopsy. The data showed a cause of death could be proffered for 76-100% (reviewer dependent) of cases. Where a cause of death was offered, between 10-14% were discrepant with that of the autopsy report. This suggests that, even allowing for a reduced comparable rate with a larger data set, it can be predicted that in the future a “view, scan and grant” protocol could be used to replace a significant number of non-forensic, medico-legal autopsies.

This next chapter will look at the consent protocol developed to gain consent for the post-mortem research for the study.
Chapter 5  Consent ing the recently bereaved for post-mortem research
- our experience of 207 adult cases.

This chapter looks at the issue of obtaining consent from the recently bereaved for autopsy-related research. It will discuss the feasibility and acceptability of a prospective telephone consenting model for post-mortem imaging in HM coroners’ cases as part of the PMCTA study at the EMFPU. The study looks at trends in consenting rates between next of kin members. Thematic analysis is applied to the comments and questions provided by the next of kin during the consenting process, along with the given reasons for giving and refusing consent.

5.1  Introduction

The autopsy has undisputed value, not only for the investigation of who, where, when and how the deceased came by their death, but also for audit, medical education, quality control and informing public health decisions. However, the hospital autopsy rate has steadily fallen during recent decades by as much as 80% (5,157). This has led to a decline in autopsy-based research in the United Kingdom (UK).

There has recently been wide public debate and controversy relating to organ retention and autopsy practice arising from cases such as Bristol and Alderhey (5). However, when the families involved in the organ retention scandals were questioned, the common theme was that they had no objection to the autopsy, or to the tissue being retained for research. Their distress and anger was caused by not being informed and the lack of formal consent being taken from them for such purposes (5).
Another proposed factor for the decline in autopsy research was due to the perception of medical professionals; clinicians anticipated a negative reaction from families and were therefore reluctant to discuss the possibility of an autopsy with families and seek consent (5). Some believed that contacting the newly bereaved to gain research consent was unethical (160). Changes to the coroner’s rules and introduction of the Human Tissue Act 2004 added further complexities to autopsy research; this made it harder to take, store and use tissue for research (160).

The majority of autopsies performed in England and Wales are undertaken on the legal authority of HM coroner. HM coroner does not require consent from the next of kin for the specific purpose of investigation of the cause of death. This includes the retention of tissue or other biological samples if they are required for the investigation of the deceased’s identification and/or the cause of death.

The Coroners’ Act, however, does not provide permission for the use of tissue or CT data in research where the intention from the outset is to collect said data or samples for research purposes (161). This may only be performed with the consent of the relatives or, in the absence of relatives, appropriate legal authority under standard governance arrangements using Good Clinical Practice guidelines.

Obtaining research consent from a newly bereaved next of kin remains a difficult and sensitive area. Whilst there is a significant body of literature outlining prospective consenting for tissue retention and imaging for research relating to paediatric cases (162-164), there is a paucity of peer-reviewed literature relating to prospective consent acquisition from the next of kin for post-mortem research related to adult death.

As part of the National Institute for Health Research funded study to evaluate the efficacy of PMCTA performed by the EMFPU, next of kin were approached to obtain
consent for their relative to be included in the study in order to recruit 200 ‘consented’
cases. Thematic analysis of the reasons for consenting, or refusing to enter the deceased
into the research study was performed. The aim was to demonstrate that prospective
consenting for HM coroners’ cases for autopsy research is feasible in adults, and can be
done ethically and in the limited time available by consenting the next of kin over the
telephone prior to autopsy. A simple protocol was developed, based on telephone
consenting methods that had been shown to be effective in previous studies, particularly
in consenting for paediatric post-mortems (160,162,165,166).

5.2 Method
In all cases, a doctor (myself) or a nurse specialist (JA) gained informed consent from
the next of kin for their relatives to be included in the study, including PMCT, PMCTA,
tissue and biological fluid retention. The PMCTA scans were performed in an NHS
hospital scanner outside standard clinical hours when the scanner was not normally in
use. The PMCTA caused no delay to the autopsy, as the scans were performed the
evening before the scheduled autopsy date. This was considered important to the
consenting process, as delays could impact on funeral arrangements, thereby creating a
reason for the next of kin to refuse consent.

5.2.1 Recruitment
Recruitment for this study was from September 2010 to May 2012. The step-by-step
method for obtaining consent is outlined below. All types of non-suspicious, non-
homicide adult deaths including decomposed cases and non-suspicious trauma deaths
were included in the study with the exception of the first 24 cases, which excluded
significant neck trauma and previous complex cardiac surgery. The only exclusion
criteria for cases 25-200 were that the body needed to be below 125kg (this is to permit
the body entering the CT scanner gantry). Consenting continued until 200 cases had
been recruited. The coroner’s officers, when initially speaking to the family, would pre-
warn the relatives that they might receive a phone call from the EMFPU concerning
potential entry into a clinical trial. If no objections were expressed at this point, the
coroners officers would add the contact details of the next of kin on the bottom of the
faxed request form. Faxes are the normal communication method between coroners offices, the mortuary and pathologists. Thus, this followed normal working practice.
The next of kin were contacted by telephone on the day of the coroners autopsy request
between the hours of 11.00-15.00 hours by the trial consenter (a specialist nurse
practitioner) or one of the study forensic pathologists. The 15.00 hours cut-off time was
instigated in order to allow sufficient time to find radiographer cover, arrange porters
and to perform the angiography before the 17.00 hours slot in the CT scanner. This
resulted in a narrow window of time for consenting. The consenter would try the phone
number provided by the coroners officers, if there was no answer during the first hour,
then the decision to try another case was made. All consenters had undergone ‘consent’
and ‘Good Clinical Practice’ training and had significant experience in talking to the
relatives of the recently deceased. The study protocol used order of precedence for next
of kin as defined in the Human Tissue Act (148). The consenters followed an outline
script template (see below).

If consent was declined, the next of kin was reassured that that their wishes would be
adhered to. If consent was granted, the consenter completed a consent acquisition sheet
noting which aspects of the trial the relatives had consented to for example PMCTA,
use of images for teaching and training, histology sampling etc.

The relationship of the next of kin to the deceased who provided consent was
documented. During the consent process, any questions or comments raised by the next
of kin were recorded verbatim. No additional formulated questions were asked about reasons for giving or refusing consent, but these were recorded if volunteered during the conversation. Commonly asked questions were also recorded. The religious denomination of the next of kin or the deceased was not specifically asked or recorded unless it was stated as a reason for or against the consent being given. Both consenters kept a logbook and recorded the comments and questions verbatim. The consenters also kept a reflective journal of challenging or upsetting cases.

**Script Template**

1) General introductions
2) Confirm identify of the next of kin and ask if convenient to speak to them
3) Express condolences, sympathetic listening if next of kin wished to talk about matters surrounding the death
4) Explain post-mortem examination is scheduled to take place and clarify that the next of kin understand why this is being undertaken (i.e. Coronial law)
5) Explain University’s current research into minimally invasive autopsies and need for trial
6) Explain nature and stages of the trial, advised that no delay to the post-mortem or release of the body will occur
7) Obtain oral consent to enter trial, and for each stage (if applicable):
   a. Whole-body PMCT scan
   b. Targeted angiography (if required)
   c. Use of anonymised images for teaching and research
8) If permission is not granted, express thanks and re-assure their wishes will be honoured
9) If consent granted to all, or parts of trial, ask if next of kin would like an information sent to them in the post the next working day
10) Ask if they have any further questions regarding the trial or the post-mortem
11) If questions are raised regarding general bereavement issues outside of the trial then contact with the coroners office was advised
12) Consent form signed by the consenter documenting whom consent was obtained from, the data and what was consented to.

Figure 5-1: Script Template
One dilemma that was often faced, when calling the number provided by the coroner’s office, was when no answer was received. The consenters often made multiple attempts before the end of the day (15.00 cut off). The question was raised as to whether messages could be left. But, it was felt that such messages might cause anxiety and further distress to the next of kin, or that they might ring later or the next day with a view to giving consent to find that the opportunity had passed, again causing guilt or disappointment.

On rare occasions, it became very evident to the consenters that the next of kin was extremely distressed, or in such a condition of shock, that capacity to consent might be questionable or that to continue would cause increased distress. In these cases (6) the consenters chose to abandon the consent process and say they were just ringing to confirm that the autopsy would be going ahead as planned. As consent was not attempted, details were not taken and the case discounted from the trial results (these were not included in the 207 case number).

The responses were then analysed using phenomenological approach. This is a recognised qualitative research methodology (167,168). Phenomenology is concerned with the study of experience from the perspective of the individual, “bracketing” taken-for-granted assumptions and usual ways of perceiving. The aim was to record all of the contrasting opinions and individual perceptions rather than to present the most commonly held opinions. The comments underwent a themed content analysis. Themes were identified by collating similar comments.
5.3 Results

Between September 2010 and May 2012, 207 next of kin were contacted, from two HM coroners’ jurisdictions, and consented for the PMCTA research. Full consent was obtained from 200 of the 207 cases (96.6%). The median age at death was 66.4 years (range 18 to 96), including 130 males and 70 females. The interval time between death and the autopsy was 1 to 7 days.

The average duration of the telephone conversation was 30 minutes (range 10 to 90 minutes). The relationship of the next of kin to the deceased is showing in Table 5-1. Although refusal was more common from the son there is no statistically significant trend (p=0.2).

In 10 cases (5.7%) the next of kin requested more time to speak to other family members before giving consent, and subsequently called the consenter back to give consent. In seven cases consent was declined. No objection to being contacted by telephone was stated by any next of kin.

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Total number</th>
<th>Consent refused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Son</td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td>Wife</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Daughter</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>Husband</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Brother</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Sister</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Nephew</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Niece</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Cousin</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Daughter in law</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Aunt</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Executor</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Granddaughter</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Grandson</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Table 5-1: Relationship of the consenting next of kin to the deceased.
Seven metathemes were identified as the reasons for giving consent for research, see Table 5-2. Five metathemes were identified as reasons for refusal to give consent to enter their relative into the trial see Table 5-3.

<table>
<thead>
<tr>
<th>Number</th>
<th>Reason given</th>
</tr>
</thead>
<tbody>
<tr>
<td>92</td>
<td>No specific reason given</td>
</tr>
<tr>
<td>32</td>
<td>The deceased would have wanted to contribute to research</td>
</tr>
<tr>
<td>29</td>
<td>The deceased was on the organ donor register and would have wanted to give their life</td>
</tr>
<tr>
<td>22</td>
<td>Feels like less of a waste of their life</td>
</tr>
<tr>
<td>12</td>
<td>Felt like the death of their relative was benefiting people in the future</td>
</tr>
<tr>
<td>9</td>
<td>Believed more information about the cause of death might be found</td>
</tr>
<tr>
<td>3</td>
<td>Felt research is important</td>
</tr>
</tbody>
</table>

Table 5-2 Metathemes for consenting: Reasons given by next of kin for agreeing to participate in research (there may be more than 1 reason per case).

<table>
<thead>
<tr>
<th>Number</th>
<th>Reasons for declining of consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Objection to autopsy procedure in general</td>
</tr>
<tr>
<td>2</td>
<td>Want to limit the amount of unnecessary intervention to the body</td>
</tr>
<tr>
<td>2</td>
<td>Religious objection- especially Muslim families</td>
</tr>
<tr>
<td>2</td>
<td>Concern regarding disfigurement of the body</td>
</tr>
<tr>
<td>2</td>
<td>Wanting to discuss with more family members before consenting</td>
</tr>
</tbody>
</table>

Table 5-3 Metathemes for declining: Reasons for declining of consent (there may be more than 1 reason per case)

The seven cases where consent was declined are summarised below:

1. 89-year female: multiple co-morbidities and long history of ischemic heart disease. She died in a nursing home, but as her family doctor was away and unable to sign the death certificate, her death was referred to HM coroner who requested an autopsy. Her son, himself a doctor, gave permission for a PMCT scan but declined any invasive procedure, as he did not wish for additional
disturbance to his mother’s body. Subsequently a medical certificate of cause of death was released without autopsy.

2. 20-year male: a passenger in a road traffic collision. His mother was very distressed and refused permission for a scan to be performed. She also strongly objected to the autopsy being undertaken. The mother did not understand why the autopsy was being done when the cause of death was evident.

3. 54-year male: from a large Spanish family. The next of the kin spoke limited English and the consent process was translated through a cousin. The family wanted to discuss the consent as a whole but could not do so until the next day. The cousin did not feel he could give consent on that day without the knowledge of the whole family.

4. 73-year female: death from natural causes. The deceased was from a Muslim family who were trying to get the autopsy stopped; they stated it was against their religion and they wanted to bury her immediately. They believed the autopsy was delaying the burial.

5. 37-year male: suicide. The family members were unhappy with the autopsy, due to their religious beliefs (Muslim), and therefore were not happy to give consent to anything involving post-mortem handling of the body.

6. 70-year female: death from natural causes. She was from a large West Indian family and the daughter of the deceased wanted to wait until the next day when relatives would have arrived from the West Indies. On realising that consent was necessary that day she said she felt she had to decline.

7. 85-year lady: death from natural causes. The son was upset about the autopsy as he felt it was inappropriate when she had been ill for so long. He was unhappy to give consent to any post-mortem intervention.
Had the consent window not have been so tight the families in 5 and 7 were likely to have returned with a consent following checking with the other family members, therefore increasing the consent rates.

Commonly asked questions during the consenting are given in Table 5-4. Generally, the next of kin seemed familiar with the concept of a CT scan, either through personal experience or seeing it on television, and had very few questions about the CT scan procedure. The majority of the questions were related either to the angiography procedure or to the autopsy itself. A number of questions were asked in relation to finding out the results of the autopsy, or to issues relating to the funeral and body release process. These were answered where possible, but if they were of a specific nature they were directed back to the coroner’s officer e.g. final date for death certificate.

<table>
<thead>
<tr>
<th>Commonly asked questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Would the procedure delay the autopsy or funeral?</td>
</tr>
<tr>
<td>Would the body be disfigured by the autopsy or angiography technique?</td>
</tr>
<tr>
<td>Would there be any additional cost?</td>
</tr>
<tr>
<td>Would the deceased be identifiable in the images/publications?</td>
</tr>
<tr>
<td>Would any tissue be retained due the procedure?</td>
</tr>
<tr>
<td>Would other people be watching?</td>
</tr>
<tr>
<td>Can the body be viewed after the procedure?</td>
</tr>
</tbody>
</table>

Table 5-4 Metathemes questions asked: Commonly asked questions during consent procedure.

One of the recurring metathemes was whether the PMCT scan procedure or the angiography would lead to increased disfigurement of the body, and whether it would still be possible to view the deceased after the procedure. It was explained that the
PMCT scan left no visible marks, and that although the angiography technique was undertaken through a 5 cm incision just above the left collarbone, the incision would be incorporated into the standard autopsy incision.

One family consented to the angiography and to the use of the data in research but declined to have the PMCT images used for publication for fear of identification of their father. This was despite reassurance that the images are not identifiable.

Sixteen individuals during the consenting process asked if it was possible to perform just the PMCT scan and not the autopsy. They expressed a preference for a ‘minimally invasive autopsy’ rather than conventional autopsy. The awareness of the general public for minimally invasive autopsy is increasing and a recent study showed that there was widespread support for a PMCT scan as an alternative to autopsy (>80%) (169). It was explained that this would not be possible as the autopsy was being performed at the coroner’s request in this instance, but that the aim of the trial was to assess whether PMCT scans alone in the future could be used instead of autopsy.

5.4 Discussion

It has been suggested that consenting by telephone is intrusive compared to obtaining written consent by post (162). However, due to the logistics and time constraints of this study, it was deemed to be the only option. Telephone consenting has been shown to be effective in previous studies. We based our own method on one successfully used in two other autopsy studies (160,162). Our application of this method proved very successful. Contrary to popular belief, we found that rather than being upset or angry at such an approach, the newly bereaved next of kin commonly viewed the process positively. No objection to being contacted by telephone was stated by any next of kin.
The perception of the medical profession that the general public is averse to giving consent for autopsy research appears to differ from the actual feelings of the next of kin, especially when approached in a sensitive and informed manner. It has been shown that using specifically trained staff to obtain consent for hospital autopsy investigation improves acceptance (170).

One of the strongest trends to emerge from the next of kin responses in our study was that giving consent was in some way honouring the wishes and beliefs of the deceased. Many of the next of kin stated, without prompting, that the deceased had been an organ donor or had previously expressed a wish to contribute to medical research and they felt that giving consent was very much in keeping with what the deceased would have wanted.

This was especially true of the relatives of younger people who had died from traumatic injuries. They frequently expressed sadness at not being able to donate their next of kin’s organs due to the circumstances of death and felt that by participating in the research, their death was ‘not a waste’ and ‘some good would come of their death’. Some expressed their wish to help develop a technique that would be of benefit to families in a similar circumstance in the future. For others it seemed to be a purely altruistic decision to give consent.

The majority of individuals appreciated being able to talk about their relative/next of kin, their death and about the autopsy procedure and the death registration procedure in more depth to a member of the medical profession. Bereavement counselling was not specifically offered, but the consenter was able to spend time listening to the next of kin, and the phone call gave the next of kin an opportunity to ask questions that had come to mind after speaking to the coroners’ officers.
There have been several studies in the area of informed consent for research using tissue taken during coronial autopsies. Millar et al. showed that if approached appropriately, the next of kin are willing to consent to an autopsy that is extended to include retrieval of tissue or organs for research purposes, during forensic autopsies. They found that 96% of those who were approached gave consent, with 17% agreeing to whole brain donations (160,171). Our findings are consistent with similar trials conducted on neonatal and paediatric cases (52,162,172,173).

These studies showed that post-mortem research is highly valued by the parents and they were keen to make a contribution to research out of altruism, and to feel that their child’s life was not wasted. It has even been suggested that consenting may be beneficial in the grieving process (162).

Thayyil et al. found that 96.8% parents of children who had died from sudden unexpected childhood death agreed to MRI scan to be undertaken after death in addition to autopsy. The reasons stated were to gain as much information about the death as possible and to help other parents in a similar situation in the future. Millar et al. concluded that ‘the perception that the public is unwilling to give consent to research in many cases is unjustified, with unwillingness often resulting from lack of information and consultation’. Indeed, most families were of the opinion that all parents should be offered the opportunity to donate for research (160). Our work supports this observation.

This high consenting rate has been reflected in some recent adult studies; one consenting for hospital autopsy in lymphoma patients achieved an 89% consent rate, (5) another sought consent from relatives to retain post-mortem blood, lymph node and liver tissue and obtained 66% consent rate (165). This result compares to the 98%
consent rate for the use of surplus tissue for research among surgical patients from the same hospital trust (174).

Ideally, the consenters should have an excellent understanding of what was involved in a routine autopsy, as well as the trial procedures, the death registration process and role of the coroners and their officers. The consenters underwent one week of specific training observing a number of routine coronial post-mortems including the reconstruction, and the angiography and CT scanning procedure. The consenters also spent time at the coroners’ office to gain greater understanding of the death registration process. The consenter observed three telephone consenting procedures prior to starting their own.

The process of taking the consent and obtaining the background information is relatively straightforward and any allied health professional could be trained. The process is akin to that of breaking bad news and can be emotionally demanding. Consent needs to be taken in a quiet environment where distractions are minimal. Sufficient time should be made available for the consultation. The consenter should have all the patient details and the coroner’s history available at the time of the phone call. The consenter should confirm the next of kin’s understanding of the procedure and take step-by-step consent for each stage. Opportunity for the next of kin to ask questions should be given and a contact number left should they wish to change their mind or ask further questions.

The personality of the consenter is of critical importance; a significant degree of empathy and emotional resilience is required to deal with the emotional nature of some of the more challenging encounters. Some experience of bereavement counselling is helpful. In our trial, the consenters were a specialist nurse practitioner and a doctor;
both very experienced in breaking bad news and dealing with bereaved families. Despite this, the very personal nature of speaking to a very recently bereaved next of kin in an emotionally raw state was at times very difficult and occasionally upsetting for the consenter. Many of the conversations involved family members re-telling the last few hours of the decedents life, some of which were traumatic, some very personal and intimate. The consenters felt very touched by some of the emotional stories relayed to them. As with other fields of medicine and nursing, where professionals deal with emotionally challenging situations, it was necessary at times for the consenters to debrief to each other about the particularly difficult cases.

5.5 Summary

This chapter concludes that prospective next of kin consenting by telephone is feasible for autopsy research participation in HM Coroners’ cases. We proposed a simple protocol with a script to be followed by the consenter. The data from this study should give encouragement to clinicians and researchers that consent for autopsy research, and indeed hospital autopsy, is possible if an appropriately trained person approaches the next of kin sensitively. Although this can be a difficult task for the consenter, the process can be beneficial for the next of kin.
Chapter 6  Summary of project and a look to the future

The prospect of an autopsy may be upsetting for the next of kin. There remains a perceived public objection to autopsies in the UK, attributed in part to the organ retention scandals in Liverpool and Bristol. As a result, there is increasing demand for an alternative to the conventional invasive autopsy. Even amongst pathologists it is believed that a large number of potentially unnecessary autopsies are being performed. Many junior doctors entering histopathology training do not wish to undertake autopsies, and are choosing to opt out of autopsy training entirely during their specialist training. The future of autopsy practice remains unclear and there is an impetus to change the current approach to death investigation.

With the increasing use and availability of multi-detector computed tomography (PMCT) in autopsy practice, there has been an international push towards the development of the so-called ‘minimally invasive autopsy’. One of the major obstacles to the implementation of this so far has been the failure of post-mortem imaging to provide sufficiently detailed information about the coronary arteries. This is due to the lack of radiographic contrast in the vessel lumen as a result of the absence of a physiological circulation. In England and Wales most autopsies are carried out in routine coronial practice, of those the most common cause of death in these cases is ischaemic heart disease, therefore overcoming this deficit in PMCT is paramount. One proposed method for overcoming this is PMCTA, where contrast is injected or pumped into the coronary circulation, mimicking cardiac CT in living patients. The emergence and history of PMCT and PMCTA was described in chapter 1.
This aim of this research project was to develop a method for delivering radiographic contrast into a cadaver so that the coronary arteries could be visualised and the degree of ischemic heart disease assessed. The method needed to be simple, quick, cost effective and practical on a day-to-day basis in the current coronial autopsy system. This research project formed the basis for a larger NIHR funded trial at the EMFPU and University Hospitals of Leicester involving 200 cases undergoing PMCTA followed by routine autopsy. This thesis concentrated on developing the method (chapter 2), device (chapter 3), a pilot study of 24 initial cases (chapter 4) and the consent protocol (chapter 5).

The early stages of the project focused on developing the method of targeted cardiac PMCTA. At the commencement of the project there were only a handful of papers describing PMCTA; mainly whole-body angiography with modified heart-lung bypass pumps to create an artificial circulation or ex-vivo studies of single organs. There was no method for in-situ targeted cardiac PMCTA described in the literature.

A novel method of targeted cardiac PMCTA using a modified Foley catheter was developed as part of this project (chapter 2). This two-stage protocol, which introduced air followed by a positive contrast, is the first and only method described in the literature to date. The method was published as a ‘proof of concept’ paper (175).

During the course of the project it became clear that a task-specific device would enhance the technique by allowing easier cannulation and identification of the catheter on scan. So, based on the experience of the first 24 cases a novel design for a post-mortem targeted cardiac angiography device was created and a prototype commissioned by a design company (chapter 3). The initial prototype has been made and is currently being studied. The device appears to be very promising, however, there
are a number of further modifications to be made which are being addressed at the time of writing this thesis. The design of the catheter, called the ‘Cadatheter’, and the targeted angiography method was granted a patent on 23/8/2012 (148).

Informed consent was required from the decedent’s next of kin for this pilot study and the future larger study. There were limited guidelines, protocols and few published examples of how best to go about obtaining prospective consent, especially in our short time frame between the autopsy being requested and carried out.

A protocol for prospective telephone consenting was modified from a published protocol used for prospective autopsy research on children and neonates at Great Ormond Street (chapter 5) (162,176). A total of 207 designated next of kin were approached for consent, of those 200 granted consent (95%). This high level was very surprising and challenges the perception that the general public are strongly opposed to autopsy or post-mortem research. This data gives a great boost to autopsy research and should encourage other researchers and ethics committees to consider more autopsy-based research, as it is currently overlooked. This study shows that prospective consenting of HM coroners’ cases for autopsy research is feasible in adults and can ethically be taken over the telephone by appropriately trained staff.

Pilot study of the first 24 cases aimed to evaluate if targeted PMCTA could provide sufficient information, especially relating to the coronary arteries, to assist in deriving a cause of death without the necessity to undertake a full invasive autopsy (chapter 4). A cause of death was given in 76% of cases and where given it showed a discrepancy with the autopsy report in 10% of cases.

It is foreseen by some that PMCT will replace the need to undertake full invasive autopsies in the majority of routine ‘non-suspicious’ coronial cases. It is possible that in
the future the so-called ‘view, scan and grant’ protocol could become standard practice (see chapter 4 for protocol).

The ‘view, scan and grant’ protocol is very similar to the ‘Preliminary Examination protocol’ currently being undertaken at the Victorian Institute of Forensic Medicine (VIFM) in Melbourne, Australia. In 2005 the institute installed a CT scanner in the mortuary. Since that time, all bodies admitted have undergone a full body PMCT scan. At this institute the PMCT does not replace the autopsy but it assists the pathologist in determining a cause and manner of death, mechanism of injury and documentation of injuries for presentation as evidence in court.

Recent changes in the Victorian Coroner’s Act allowed the creation of a ‘preliminary examination’. This entails a) visual identification of the body, b) review of medical history and circumstances of death, c) taking of body fluids for toxicology, d) forensic imaging – PMCT and photography, e) taking of surface swabs, f) fingerprinting of the body (177). All the information is then review by a duty pathologist and they formulate a judgement as to whether the death was natural and provide the coroner with a recommendation as to the necessity for an autopsy to be undertaken. The coroner then makes a decision as to whether the autopsy should proceed, usually in consultation with the deceased’s next of kin. The coroner and pathologist conduct daily meetings to discuss the preliminary findings relating to all admissions during the previous day.

Forensic pathologists who have undergone training by a forensic radiologist read the PMCT scans. A forensic radiologist is available to review scans where there is uncertainty about any of the pathology. There is an on-going teaching program for consultants and registrars of forensic pathology (177).
Subsequent to the adoption of the preliminary examination at the VIFM in 2009, analysis of autopsy rates showed a reduction to 47% of admission from an average of 62% over the previous 5 years. The authors note that PMCT is not entirely responsible for this decline but that formalisation of the preliminary examination has encouraged pathologists to use PMCT as part of their formulation and advice to the coroner (177).

In 2012 the VIFM institute released data from 318 consecutive cases over a period of a month that underwent the preliminary examination process. Of the 318 cases examined, 124 were accidents, suicides or homicides, and reported with no ascertained causes of death. The remaining 194 were deemed ‘natural’ causes of death. The authors reported approximately half of the cases triaged as ‘accidental deaths’; a complete autopsy was deemed unnecessary following PMCT. In cases triaged as ‘suicide related death’ only 31% underwent an autopsy. Of 138 cases that were triaged as ‘natural death’ on admission and had a PMCT, a definitive cause of death was given in only 8 cases (6%). These included intracranial haemorrhage, haemopericardiums and ruptured aortic aneurysms. Overall, the process was advocated as effective in developing closer interactions with the pathologists and the coroners and for reducing the numbers of unnecessary autopsies. In cases that proceeded to autopsy, the PMCT served as a useful adjunct (82).

Our pilot study suggests that such a protocol augmented by using PMCTA could see a significant reduction in the number of routine coronial autopsies. The study suggests a reduction of up to 80% might be possible, although the small pilot study size is noted. If the scanned cases were to proceed to autopsy, the scan would still be of use to the autopsy pathologist, for planning the examination (e.g. demonstrating cardiac air embolism) and avoiding disfiguring dissections of fractures in the pelvis and the face.
6.1 PMCT Vs Autopsy

Before implementation of such a protocol, the comparability of PMCTA to autopsy has to be validated. In the past year there have been a number of studies comparing PMCT or PMCT/PMMRI to autopsy significantly increasing the evidence base of forensic imaging. The largest of these studies was undertaken in Japan and looked at 339 consecutive cases (178). The authors reported that PMCT alone could provide the COD in only 7% of cases. These were usually trauma and cardiac rupture. A suggestive COD could be given in 56% but further information was required, such as toxicology results. These cases included subarachnoid haemorrhage and pericardial haematoma. The COD could not be given in 38%. The authors appeared sceptical about PMCT being used as a replacement for autopsy. They do however advocate the use of PMCT for screening and suggest that PMCTA could improve enhance the autopsy process (178).

A group from Hamburg, Germany (179) reported a prospective study of 47 intensive care patients. Of the 196 clinical diagnoses known before death, 173 (88%) were identified on PMCT alone, and 183 (93%) by autopsy alone. 14 new major and 88 new minor diagnoses were identified by combined PMCT and Autopsy. PMCT missed cardiovascular events (9/72) and cancer (12/30). Autopsy missed 13 fractures and 2 pneumothroaces. The authors commented that PMCT, despite its limitations in cardiovascular diagnosis, might serve as a substitute for autopsy, especially with respect to education and confirmation of clinical diagnosis (179).

A second German group (180) analysed a prospective mixed cohort of 29 cases, both hospital and community deaths, that underwent PMCT and autopsy. The study found the combined diagnostic accuracy of PMCT with autopsy to be 133% compared to autopsy alone. In 66% of the cases the PMCT matched the autopsy diagnosis. Coronary
thrombosis and myocardial infarction were not observed on PMCT, but associated pathologies e.g. coronary calcification, pleural effusions and pulmonary oedema were reported. The authors comment that PMCT complements autopsy and the combination of both methods enhances the diagnostic accuracy of the autopsy report (180).

Leth et al undertook a study of 67 road traffic fatalities in Denmark (181). The PMCT scans were reported by a clinical radiologist with no previous post-mortem imaging experience, and a forensic pathologist with 5 years experience in PMCT. Together, a total of 994 injuries were reported. The radiologist reported more injuries than the pathologist, especially in the skeletal system (14% compared with 2% of the injuries), but the pathologist reported more organ injuries (26% compared with 12%). The study also states that CT was superior to autopsy in detecting abnormal air collections. But, that autopsy was superior in the detection of organ injuries and aortic ruptures. The authors therefore recommend that both PMCT and autopsy be undertaken in traffic fatalities and that a radiologist reports the scan as well as the pathologist (181).

Daly et al (182) presented a series of 21 cases of fatal accidental blunt force trauma that underwent PMCT and autopsy. They reported a concordance of in 86% and 76% of skeletal and soft tissue injuries respectively. PMCT detected an additional 37 skeletal and 31 soft tissue injuries not identified at autopsy. Autopsy detected 8 skeletal and 22 soft tissue injuries were not detected by PMCT. PMCT was more sensitive for skeletal and head and neck injuries, and showed an overall greater sensitivity than autopsy but this did not reach statistical significance (p=0.083). The authors commented that at that time they felt PMCT would be unlikely to completely replace the autopsy, but that it could be used as a triage tool or enhance a limited autopsy sufficiently to meet legal requirements (182).
Smekal et al (183) undertook a prospective study of 31 patients who had received cardiopulmonary resuscitation. PMCT and autopsy together revealed rib fractures in 22 patients. In 8 patients, CT revealed more rib fractures than autopsy; and in 12 patients, autopsy revealed more rib fractures than PMCT. A total of 260 pathological findings were noted by PMCT and 244 by autopsy. There was a strong concordance between the two methods in finding rib fractures but not sternal fractures, for which autopsy was more sensitive. These results support the concept of CT as a valuable adjunct to autopsy in detecting rib fractures from cardiopulmonary resuscitation but not as a replacement (183).

The overwhelming evidence from the key comparison papers of the past two years, indeed that past 10 years, is that PMCT is a great adjunct and in cases of trauma and head and neck injuries, it is far superior to traditional autopsy. PMCT alone still has deficits in determining pulmonary and cardiac deaths in particular but the addition of PMMRI to PMCT has been proposed as a solution to closing such diagnostic deficits. PMMRI is thought to show a change in attenuation of the myocardium that correlates with decreased perfusion, and therefore possible myocardial infarction.

An Oxford and Manchester research group published the results of their comparison study of PMCT and PMMRI with autopsy, a series of 182 cases in 2012. Their findings show a rate of major discrepancies between the COD identified by radiology and autopsy of 32% for CT, 43% for MRI, and 30% for consensus radiology (CT and MRI) reports; the rate for CT was 10% lower that for MRI. For cases in which radiologists gave a definite COD, the major discrepancy rate between radiology and autopsy COD was 16% for CT, 21% for MRI and 16% for consensus report (145). They reported that CT provided the visualisation of coronary artery calcifications that were not apparent with MRI. They concluded that the COD derived from post-mortem imaging have
reliability similar to that of death certificates, but only when radiologists are confident about their diagnosis. They suggest that radiologically confident causes of death could be acceptable for medico-legal purposes (145). This was the first large-scale study to be published that compares PMCT/PMMRI with conventional autopsy. The majority of publications comparing PMCT/PMMRI or minimally invasive post-mortem examination techniques (such as needle biopsy) have been on small series of cases. We hope the NIHR funded 200-case PMCTA study that is currently undergoing data analysis at the EMFPU will be the next and biggest trial of its kind published.

6.2 PMCTA vs Autopsy

Besides the work in this thesis, there are still relatively few papers on PMCTA in the literature and even less comparing PMCTA directly to autopsy. To date there have been only two studies published on this topic.

Roberts et al (146) in Oxford published a 10 case series of targeted cardiac PMCTA (see chapter 2 for method outline) that showed a good correlation with the subsequent autopsy and is the only other targeted cardiac method in the literature. Of particularly interest was the 80% correlation between the degree of coronary artery stenosis and calcification reported on PMCTA. This allowed a confident cause of death to be given. There was a single discrepancy in their series, the PMCTA reported a short segment stenosis and with the clinical history of chest pain immediately prior to death, the COD was reported by the radiologists as ischemic heart disease. However, the stenosis was not seen at autopsy, and the pathologist gave the COD as asthma and hypertensive heart disease. The authors commented that it was likely that the pathologist missed focal stenosis. This highlights one of the great benefits of PMCTA in that the whole length of the vessel can be examined, both transversely and longitudinally, rather than 2-5 mm segments during autopsy (146). One interesting observation with this study is that the
definitive diagnosis is surprisingly low given that the COD is often clear before either
PMCT or autopsy has occurred based on pre-test probabilities (184).

Data, such as ours and from the studies above report additional pathologies being
identified on PMCT, this raises questions about the accuracy of autopsies.

Michaud et al (185) reported a series of 23 cases that underwent pump-assisted whole-
body PMCTA (post-mortem angiography working group (TWGPAM) method). The
PMCTA showed calcification of the coronary arteries in 78% of the cases, most of
which were not detailed at autopsy. Of the 14 cases of coronary thrombosis detected at
autopsy, 11 were seen on the PMCTA as filling defects, and the remaining 3 showed
partial perfusion. The authors report that PMCTA is a ‘reasonable tool’ to view the
coronary arteries, rule out significant stenosis and target sampling for histology (185).

One of the advantages of whole-body angiography is the improved quality and
precision of diagnoses especially in cases with injuries involving the vascular system
(38,119-121,186-189).

Palmiere et al (154) showed that data from the ante-mortem and post-mortem
radiological examinations were similar, but that the PMCTA surprisingly showed a
higher sensitivity for detecting the haemorrhage source than the ante-mortem
investigations and the autopsy. This is surprising and thought to be due to the contrast
in a living person being only briefly observed at the bleeding site before being pumped
past the site. In addition, higher radiation dosages and thinner slices are used to produce
better images, as radiation is not an issue. In fact, the location of the fatal haemorrhage
points were identified in eight out of nine cases using PMCTA, but only three through
conventional autopsy. Their conclusion was that PMCTA determines the arterial and/or
venous lesions associated with cases of acute fatal haemorrhages with higher sensitivity than autopsy (154).

A more recent observation by O’Donnell et al reported an incidental finding determined on whole-body angiography (44). PMCTA revealed a dense hepatic ‘parenchogram’ containing multiple large filling defects indicative of metastases, which were confirmed on histological diagnosis. The histology confirmed the presence of metastatic adenocarcinoma with a typical pattern, but also that the background liver showed marked centrilobular sinusoidal expansion which was attributed to the angiography. Their case demonstrates that PMCTA can be used to improve post-mortem detection of hepatic mass lesions such as metastases (44).

The most recent comparison published was from the TWGPAM group and sought to highlight the advantages and inconveniences of PMCTA versus conventional autopsy. Their conclusion was that PMCTA demonstrates higher sensitivity for identifying skeletal and vascular lesions but vascular occlusions due to post-mortem blood clots could be falsely assumed to be true vascular lesions.

PMCTA was stated to be better at fracture detection and pinpointing the exact site of bleeding. However, autopsy gives information on organ morphology and definitive assessment of vascular occlusion. In order to correctly interpret the findings and clearly define the indications for PMCTA the authors state that the differences in the techniques and the respective advantages and disadvantages must be understood (190). Its advantages and disadvantages depend largely on the context within which it is used e.g. natural versus unnatural death; PMCTA being a great tool for trauma-related deaths, but with the possibility for misdiagnosis in natural deaths especially related to pulmonary or cardiac disease without subsequent autopsy. The results and
recommendations from this paper are in keeping with the conclusion of the other PMCTA comparison papers of the past year.

Even with the addition of PMCTA to forensic imaging, there will always be a number of conditions that are not diagnosable such as drowning, asphyxiation, asthma, anaphylaxis, hypothermia, strangulation, burns and cervical cord injuries without bony injury (191). Indeed in death due to drowning, asphyxia, asthmas, anaphylaxis and even strangulation there may be no signs at autopsy. In such cases, a pathologist or coroner might rely on the circumstances of death in conjunction with the absence of significant pathologies to give the COD based on the ‘balance of probability’. This is common practice in England and Wales. Therefore, it should be possible for coroners to accept the same standard of proof for COD given by imaging modalities.

6.3 Myocardial ischemia and infarction.

In clinical practice, the significance of luminal narrowing on CT can be questionable, especially in the presence of severe coronary artery calcification. A patient may suffer with significant symptoms and suffer sudden death even with a minor degree of stenosis. Conversely, patients may die of other pathology (e.g. trauma or hanging) and be found to have significant stenoses at autopsy. Like invasive angiography, PMCTA is a morphological imaging technique and cannot demonstrate the functional relevance of stenoses. Demonstration of coronary artery stenosis alone on PMCTA does not prove coronary artery disease as the cause of death ‘beyond reasonable doubt’, but can be used to establish ‘a balance of probability’ in the absence of other lethal pathology. This is the same premise as with autopsy findings. It is not currently possible to definitively image an acute myocardial infarct with PMCT but historical fibrosis resulting in localised ventricular wall thinning or aneurysm, and mural calcification can be seen as well as wall rupture due to infarction (33).
In their trial of 10 cases, Roberts et al noted a localised absence of ‘myocardial blush’ of contrast medium in 4 of the cases undergoing angiography. They attributed this to an absence of the normal capillary leakage of water-soluble contrast medium into the myocardial interstitium, and suggested that this may be useful in identifying segments of non-perfused myocardium (146).

Conversely, Michaud et al (185), using oily contrast agent not expected to leak out of the vessels, described localised enhancement of the myocardium (≥100 Hounsfield units) in the five cases of series of 23 whole-body angiography cases, which correlated with areas of infarction. They theorised this could be an indirect sign of myocardial infarction due to abnormal leak. Subsequent experience suggests that left ventricular hypertrophy may be the major cause of ventricular wall enhancement using oily medical.

The Palmiere et al 2012 study reported pathological enhancements of the myocardium during the PMCTA in some of the cases showing coronary luminal filling defects. Such findings suggested the presence of myocardial lesions due to infarction (152), although it was possible that the enhancements were due to post-mortem artifacts. Unfortunately they did not correlate the enhancements with the histological findings in this study, but they report they are currently undertaking this work.

This is one area where a PMMRI might actually be superior as it has excellent resolution of soft tissues and extravasation of contrast appears to be associated with areas of recent infarction (192,193).

The Virtopsy® group have recently concentrated on PMMRI imaging. They analysed a series of 30 cases to ascertain whether PMMRI could detect the early changes of myocardial infarction. They used the presence of chemical shift artefact (CSA), which
is an MR misregistration artefact occurring at the interface between fat and water due to their differing resonance frequencies. The result is the characteristic appearance of light and dark bands on opposite sides of a structure. The Virtopsy® group proposed that this should only be seen in patent coronary vessels. In their series of 30 cases they conclude that the presence of CSA suggests the absence of significant stenosis and that the occurrence of paired dark bands indicated coronary artery disease, with a high specificity. However, they also reported that the sensitivity of CSA is low, meaning that the absence of CSA does not suggest the presence of a stenosis. Their final conclusion was that cardiac PMMRI should be used in combination with PMCT to improve the ability of minimally invasive autopsy to detect cardiac related deaths (194).

The group also presented 4 adult cases that underwent PMMRI with angiography. The method was similar to the TWGPAM group in terms of cannulating the femoral vessels and using an iodinated contrast medium diluted in polyethylene glycol injected with a mechanical pump. The authors demonstrated feasibility of the technique and claimed equal technical quality to PMCTA, but they do acknowledge that MRI is slower and more expensive (195). In fact, the authors struggled to make a valid reason why MRI should be done instead of, or alongside PMCTA and merely presented it as another radiological tool for post-mortem investigations.

MRI has been shown to be significant better at evaluating the central nervous system and the musculoskeletal system (145,196-198). It is also superior at detecting abnormalities within soft tissues. However, it is less sensitive than CT in the detection of lung pathology, pneumothorax, pneumoperitoneum and coronary artery calcification (198). The undisputed disadvantage of MRI in any form is the extended time, complexity and cost. A number of other groups are still working on PMMRI worldwide
(32,86,193,196,197,199,200), so the “is PMCT better than PMMRI” question is far from resolved.

6.4 PMCT and PMCTA limitations

The inability of PMCT to detect embolism is a major defect with the current protocol and an area that needs significant research development.

Without contrast agents in the pulmonary arteries, the diagnosis of pulmonary embolism (PE) is practically impossible, unless there was sufficient time to develop a wedge-shaped pulmonary infarction, but this usually takes days.

Acute pulmonary thromboembolus has been demonstrated to not be recognised with arterial angiography, and therefore would only be diagnosed by autopsy or the use of combined venous angiography. There is a risk that death due to acute PE, if not recognised, could be incorrectly attributed if significant other pathology, such as coronary artery disease, is present. Sudden adult death syndrome or sudden death due to epilepsy would present with normal PMCT and angiography, in which case as no pathological cause of death could be identified then one would proceed to autopsy examination.

Secondary signs of pulmonary hypertension, like right-sided heart dilation are detectable by PMCT, but not specific (50,142). Pulmonary abnormalities are extremely common in post-mortem imaging, but often the abnormalities appear non-specific and can be attenuated by post-mortem hypostasis and pulmonary oedema that occurs as a result of resuscitation (50,179). Diagnoses of these pathologies are more accurate on CT than MR, just as with living patients. But, as in the living, determining pneumonia from cardiac failure is difficult (50,198). One possible way to remove this limitation is with whole-body angiography that fills the pulmonary artery, however it is still currently
difficult to differentiate post-mortem clot from true thrombus at the present time (44,145,201). This may, with future research, be resolved. Germenott et al have suggested that pulmonary ventilation may improve the detection of thrombosis and pulmonary imaging in general (201).

Another limitation of post-mortem imaging is that it does not include microscopic examination of tissues and organs. Percutaneous biopsies have been proposed as a means of improving the minimally invasive autopsy (18,26,136,202,203). A number of studies have shown that this significantly increases the detection of diagnostic findings not detectable on PMCT or PMMRI (26,198).

In a 2005 meta-analysis of histology indicated it gives clinically unexpected autopsy findings in 20% of cases, of which 5% are regarded as major (204). In a 2006 audit of 638 adult forensic cases, histology was considered contributory (providing, altering or confirming a COD) in 53% of cases. The use of histology provided the COD in 49 (24%) of the 203 cases not given a COD after the completion of the macroscopic examination. The majority of the discrepancies involved the heart or the lungs. As a result, the author suggested that routine histological examination would continue in their institution, even when there was a macroscopically apparent cause of death (205).

The taking of histology, even in the form of biopsies, adds substantially to the time and cost of the procedure. Therefore, selective biopsy might be adopted e.g. to obtain tissue from a tumour to type it or of the lung to determine whether oedema or infection is present.

A microscopic diagnosis is required for disease processes such as myocarditis, ion channelopathies or cardiomyopathy, and this will probably always be the case (109). Even though abnormal heart morphology suggesting a primary muscle disease has to be
identified on PMCT (33,51,193,206). PMCT, with or without angiography, will not be able to replace the autopsy in all cases, this is especially true in sudden adult death syndrome in young adults (109,207-209).

The external surface of the body can be scanned and mapped by 3-D PMCT reconstruction with specialist equipment (as demonstrated by the Virtopsy® group (16,122), however, it cannot be produced in sufficient detail for diagnostic purposes and thus, a detailed external examination by a pathologist is still required. It is felt that this will always be the case with minimally invasive autopsies as the external examination is a complex skill and signs of trauma and natural disease can be subtle (210).

6.5 Forensic radiology reporting.

There are currently no national standards for reporting PMCT scans, and no body of clinical radiologists specialising in autopsy imaging (54). Forensic imaging is emerging as a new field of radiology, and in the UK there are only a few radiologists who have the confidence and expertise to report the scans. There are even fewer pathologists who are confident or experienced to report. This raises the question that if post-mortem imaging is going to be implemented, who is best to report the scan. There is some debate as to who is best to interpret post-mortem MDCT scans. Is it best to train pathologists in radiology or to train radiologists in pathology? One option is to create a completely new sub-speciality of forensic radiology – the ‘necro-radiologist’ (83). Such a speciality would be best suited to radiologists with experience in trauma and an interest in forensics, and would lead to a thorough understanding of post-mortem anatomy and decomposition (181).

It is often not appreciated that there are many differences between PMCT images those on the living (54,83,142,143,198,211). The differences between clinical and post-
mortem scans are numerous, such as the artefactual effects of lividity, the sedimentation of blood, intravascular clot formation and alteration in the shape of organs and large vessels due to a lack of a circulation. Bodies in rigor mortis, severely charred or in the advanced stages of decomposition are often not in optimal scanning positions and are difficult to manoeuvre, e.g. prone, fetal or pugilistic poses (142,211).

The artefacts caused by decomposition and putrefaction are particularly problematic. Lividity can alter the density of organs; in particular the venous sinus in the brain and this can be mistaken for thrombosis or haemorrhage (54). Post-mortem gas formation causes significant artefact, and the untrained radiologist can make incorrect diagnoses if this is not fully understood or appreciated (142,211,212). Air in unusual sites can also simulate fractures (54). At the present time, the origins and distribution patterns of post-mortem gas formation are still not fully understood and are subject of on-going research, particularly in relation to the contribution of trauma and resuscitation. In addition, there are a number of processes that are not seen in the living but are well known to the pathologist, such as heat haematomas, fractures in burnt bodies and the facial distortion seen with advancing decomposition that would be unfamiliar to a radiologist (83).

With the increasing use of PMCT and PMMRI, is it likely that radiologists will find themselves under increasing pressure to assess complex cases. Radiologists with limited exposure to post-mortem PMCT are at risk of misinterpreting findings if they apply the rules of clinical radiological analysis, even when they have experience of the forensic interpretation of plain radiographs. Most radiologists in clinical practice prefer reporting contrast enhanced scans due to better discrimination of normal and pathological tissues.
Ultimately, the individual who produces a written radiological report must understand the relevant legislation, be prepared to provide verbal expert evidence to a court and endure the demands of a legal system that tightly test the validity and interpretation of presented facts in a rigorous manner. Some radiologists are reluctant to take on such responsibilities in addition to their normal workload.

One possibility would be for pathologists to be trained in forensic radiology and to report the preliminary scan with a secondary review by a radiologist (similar to X-rays taken in the emergency department on living patients). This is the system employed in the VIFM and the EMFPU where the forensic pathologists undergo training by radiologist. If PMCT is to become the mainstay in autopsy practice, then forensic radiology may be integrated into pathology or radiology training and may even result in its own certification or diploma.

Another consideration is who will perform the angiography and PMCTA. For this project, the pathologists performed the angiography and radiographers, with additional training, undertook the scanning. However, since this pilot study a forensic technician has been employed. This person has previous experience in embalming and was specifically trained to undertake the method.

In Switzerland (TWGPAM group), radiographers have been trained to perform the complete whole-body angiography process including toxicology sampling and biopsy sampling of tissue. This has created a new role of a ‘forensic radiographer’ (213). In the future, the roles of radiographers may extend to performing PMCTA routinely in Europe. It is also possible for anatomical pathology technologists to perform the angiography and the scanning undertaken by radiographers.
6.6 Cost and future implementation.

A detailed review regarding the logistics, implementation, workflow and cost of a PMCT service are beyond the scope of this thesis. The Department of Health has very recently brought out a national report entitled ‘Can Cross-Sectional Imaging as an Adjunct and/or Alternative to the Invasive Autopsy be Implemented within the NHS?’ (28). The report was compiled by the NHS Implementation Sub-Group of the Department of Health’s Post-mortem, Forensic and Disaster Imaging Group (PMFDI). The group in their report called on the NHS to adopt post-mortem cross-sectional imaging for as an adjunct to, and under the right circumstances, a replacement for autopsies.

The report recommends the NHS introduce a national cross-sectional autopsy imaging service provided by 30 mortuary-based imaging centres in England. These 30 bases would form part of a single, integrated service involving radiology and pathology services, attracting a single fee no matter what investigations are required to ascertain the cause of death. This would be supported by transparent costs for each professional group delivering the service. A national teaching and training programme for all professionals involved in the service was suggested: funded and developed with sub-speciality recognition for all professions involved in the delivery of the service. Further funded research to produce an evidence base to expand the types of death amenable to the use of non-invasive imaging was recommended. The group envisages that the service would be delivered primarily by the Department of Health in collaboration with the Ministry of Justice and local authorities.

The report suggests the service should make use of alternative techniques, including PMCT and PMMRI for carrying out non-invasive autopsies and suggests that ‘PMCTA could provide a minimally invasive radiological adjunct and, in the right circumstances
as alternative for the investigation of natural and unnatural deaths’ (28). The Department of Health and Ministry of Justice are now considering the recommendations before making a decision on whether to implement the service.

The implementation of such a service has also been considered by The Royal Colleges of Radiologists and Pathologists in their document “RCR/RCPath practice guidance on medico-legal post-mortem imaging in adults.” (29). This joint collegiate document provides general guidance and current standards of practice for those involved in this area of work.

To establish the new service described in these documents there will be a requirement for capital investment and the cost of the autopsy service would increase by the addition of imaging. A full assessment of the cost of such a service has not been fully recognised. The report acknowledges that there are important religious, cultural and humanitarian benefits offered by non-invasive autopsies and it is recognised that there is no longer the need to undertake invasive autopsy examinations in certain types of death. The current demand by the general public for a non-invasive autopsy service is expected to grow.

The tendency to include imaging technique in post-mortem investigation will continue to increase in the future. There is no doubt that the cost of acquiring the radiological equipment is costly, but more and more forensic centres are gaining access to their own scanners or those in nearby hospitals (154). It is felt that this trend will lead to an increase in the use of PMCTA as its potential for increased PMCT sensitivity is recognised. With the introduction of standardised protocols and increased experience, the entire examination could be performed within 1 hour, thus allowing the technique to be easily integrated into the daily standard post-mortem investigation. The sensitivity
and the higher incidence of accurately locating bleeding sources may also be of great use in forensic autopsy practice. However, a shift in the acceptance of PMCT and PMCTA images in the courts as evidence would be required. This is beginning to happen both in the UK and Europe (214,215).

Also of importance is that the permanent digital images that result from post-mortem imaging are of considerable advantage. Post-mortem images are outside the scope of the Human Tissue Act therefore, unlike tissue samples and organs, these images can be kept for audit and diagnostic review (permitting so-called ‘virtual exhumation’), even after the coroner’s authority has ended and with no legal requirement for consent. MPR and 3-D reconstructions may also be very useful to demonstrate pathology to lay people, such as juries, in a manner that is understandable and also less upsetting than real life photographs (54).

6.7 Limitations of this research and suggestions for future research.

There is no doubt that the small case number limits the pilot study of the comparative data and we await the results of the larger study. However, the project demonstrates that a simple, cost-effective method of delivering contrast into the coronary circulation of a cadaver is possible. And, that the introduction of such contrasts, be they positive or negative, allow better imaging and assessment of the vessel wall and lumen.

This project showed good correlation between autopsy and PMCTA, which is in keeping with the other major studies published. The specificity of PMCTA was 88.9%. The sensitivity was 100%. The positive predictive value (PPV) was 92.31 %, and the negative predictive value (NPV) was 100%.

Larger studies are required to increase this evidence base. Our group will be presenting a study of 200 cases of targeted PMCTA with autopsy control, planned for later this
year and next year the TWGPAM group intend to publish data from a 500-case multicentre/multinational study of whole-body PMCTA with autopsy control.

The pilot study would have been enhanced by histological correlation of both of the coronary vessels and of the myocardium. There still is, despite all the recent work, a definitive understanding of how the PMCTA appearances and luminal diameters correlate to the autopsy assessment although our group have subsequently published a small study showing good correlations of targeted PMCTA coronary angiography and histology (216). Correlation measurements of ventricular diameters and wall thickness are also needed. It is imperative that in the future the extravasation of contrast or absence of it in the myocardium is correlated with histology to ascertain if myocardial infarction can be identified. This work is currently being undertaken by the EMFPU and the TWGPAM group (185).

The work in this thesis has gone forward to form the basis of the 200-case study at EMPFU and University Hospitals of Leicester. There is no doubt that the method has undergone refinement during this process (217), so too the design of the Cadatheter. The results, both in terms of method development and correlation data, are much anticipated. The series will be the largest published to date (218).

In terms of the consent process, one of the limitations was a lack of additional demographic information such as religion of the deceased or the next of kin. But due to the sensitive timing of the consenting encounter this data might be difficult to collate. One possible suggestion for future research is to re-interview the next of kin a period of time after the death to follow up on the feelings of the relatives, and request additional information as to reasons for giving consent and gain feedback on how the consenting process may be improved.
A final key aspect to the implementation of such a service would be to assess, on a large scale, the acceptability of the method to members of the public, the police and HM coroners. This research would build on the work of Rutty et al and Jeffery et al who have so far shown an overwhelmingly positive response to the concept of a “minimally invasive autopsy” (2,219).

It is very much hoped that the work in this thesis will act as a springboard for further PMCT, PMCTA and autopsy research in general.

6.8 Summary

Significant, funded research is still needed in this area and groups from around the world are working towards proving the validity and limitations of the minimally invasive autopsy e.g. the determination of pulmonary embolism and acute myocardial infarction.

Here at the EMFPU and University Hospitals of Leicester the results of the 200-case PMCTA comparison study are currently being analysed and it is anticipated that this work will be published in the next year. The EMFPU are now associated with a number of institutions worldwide forming a post-mortem angiography working group (TWGPAM) whose common goal is to produce a standardised protocol and publish high quality research validating the use of PMCTA.

There is no doubt that PMCTA is a topic that is gaining momentum and is likely to precipitate a paradigm shift in autopsy practice over the next 10 years. The inclusion of PMCT, with or without angiography, to autopsy will likely become the gold standard for forensic autopsy practice, perhaps a new standard of excellence. It is hoped that the research and publications generated from this thesis will be part of the evidence that precipitates that paradigm shift. A better coronial autopsy service could be achieved by
the commissioning of fewer autopsies, with emphasis on those cases in which the cause of death cannot be arrived at in any other way. These autopsies would be carried out by pathologists with specialist expertise and interest (220).

With the number of pathologists wanting to do coronial autopsies reducing, we could see pathologists undertaking training in cadaveric radiology alongside traditional histopathology, or perhaps a new breed of ‘necro-radiologists’ will emerge and take over the practice.

Thirty years ago surgeons would take a patient to theatre without so much as an x-ray; today few surgeons would undertake a major operation without a CT or MRI scan and the opinion of a radiologist. Will our future colleagues in thirty years think themselves foolish to undertake an autopsy without post-mortem CT or MRI, or will they look back with wonder on why we did the autopsy at all… A space to be watched…
References


(14) National Confidential Enquiry into Patient Outcome and Death. The Coroner's Autopsy: Do we deserve better? 2006; Available at:


(39) Brook OR, Hirshenbaum A, Talor E, Engel A. Arterial air emboli on computed tomography (CT) autopsy. Injury 2012 9; 43(9):1556-1561.


(54) Morgan B. Initiating a post-mortem computed tomography service: the radiologist’s perspective. Diagnostic Histopathology 2010 12; 16(12):556-559.


(65) O’Donnell C, Lino M, Mansharan K, Leditscke J, Woodford N. Contribution of postmortem multidetector CT scanning to identification of the deceased in a mass


(82) Bedford Paul. Routine CT scan combined with preliminary examination as a new method in determining the need for autopsy. Forensic Science, Medicine, and Pathology 2012 Dec 01(4):390-394.


(96) Roberts WT, Bax JJ, Davies LC. Cardiac CT and CT coronary angiography: technology and application. Heart 2008 June; 94(6):781-792.


(103) Jappar IA, Chua T, Htoo MMA, Cheah FK, Allen JC, Tan SY. Diagnosis of anomalous origin and course of coronary arteries using non-contrast cardiac CT scan and detection features. Journal of Cardiovascular Computed Tomography 2012 0; 6(5):335-345.


(186) Kominato Y, Fujikura T, Hata Y, Matsui K, Takizawa H. A case of postoperative hemorrhage after a hysterectomy in which a bleeding point of the left uterine artery was identified by postmortem angiography. Legal Medicine 2004; 6(3):187-189.


(198) Traill Z. The role of computed tomography and magnetic resonance imaging in the investigation of natural death. Diagnostic Histopathology 2010; 16(12):560-564.


