Protocol: Contrast enhanced CT angiography in post mortem imaging; a feasibility study

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Initial funding for 200 cases, but extended using departmental funds to achieve 200 successful angiograms.

Introduction:
The aim of this study is to consider a critical area of cadaveric scanning, often presented as why Post-mortem computed tomography (PMCT) scanning cannot replace the need for invasive autopsy in the majority of natural deaths, and thus is not a realistic alternative to the invasive autopsy. The concept is to introduce PMCT with targeted angiography techniques (PMCTA) to be able to diagnose coronary artery disease.

Objectives:
1. assess the diagnostic accuracy of PMCTA derived cause of death compared with autopsy and consensus of autopsy and PMCTA
2. assess potential reduction in the autopsy rate for HM Coroner cases
3. assess impact of introducing PMCTA on overall “cause of death” statistics.

Confidentiality and ethics:
- Local research ethics committee approval (04_Q2501_64).
- All participants were given a unique anonymisation code using the running EMFPU FP - - system. Starting with FPAA. Study manager to manage coding system. Trial team can access cadaver clinical information as necessary for purpose of review but all data to be stored under FP code.
Participants:
- Select study participants, including both natural and non-suspicious unnatural deaths, referred for invasive autopsy examination under the legal authority of Her Majesty’s (HM) Coroners from North and South.
- First suitable referral by fax machine on a chosen study day.
- Study days chosen based on staff availability and other on-going trials.
- Exclusion criteria were: age less than 18, known transmittable disease (e.g. tuberculosis, HIV or hepatitis C) and weight over 125kg.

Consent:
- Fully informed consent to be obtained from next-of-kin by telephone interview to undergo pre-autopsy CT scanning with cardiac angiography by a medical member of the East Midlands Forensic Pathology Unit (EMFPU) trained member of trial team of trial nurse if available. (See “Patient information sheet and Consent form document).
- The consenter will undertake the consenting in accordance with standard NHS and HTA consent guidelines.
- If the relative gives verbal consent, the consenter will complete the consent record form in accordance with the study guidelines. The original form will be stored in the site file.
- On notification of consent to the study coordinator, the EMFPU will organise for the scan to be undertaken prior to autopsy.
- If consent not obtained, this will be recorded.
- If time permits on the study day and consent has not been acquired then consider consenting the next HM Coroner referral for inclusion

Cadaver preparation:
This will be studied in the first 25 cases in order to perfect the system.

General principle:
In the mortuary, a medical member of the EMFPU will check the neck for pathology and particularly enlarged lymph nodes (tuberculosis). They will make an approximate 2cm incision to the lower aspect of the right / left side of the neck. This incision is used to locate the internal carotid artery under direct vision. This approach uses a traditional embalmers technique to gain access to this vessel for head and neck embalming and allows the incision to be hidden later as the autopsy will use an extended incision through this site to examine the neck contents. A catheter, guide wire or catheter sheath is inserted into the vessel and advanced to just above the aortic valve. A balloon catheter is advanced down the sheath / over the wire. The balloon is inflated above the level of the aortic valve to make a seal within the ascending aorta. The cadaver is taken to the imaging department and undergoes whole body CT examination. The site of the tip of the catheter sheath is checked at this stage and can be adjusted if necessary.

Final preparation:
Raise the body on a mortuary block placed under the middle of the shoulders, with the head turned to face right. The incision to expose of the left carotid artery should be just above the medial left clavicle head. Care should be taken during the dissection to avoid engorged veins especially in the area of the clavicle as blood loss may make arterial cannulation difficult. The mortuary block is then removed prior to catheter insertion; otherwise, the catheter is likely to proceed down the descending aorta. Aim the tip of the catheter towards the right axilla. It is possible to insert the catheter in the mortuary by ‘feel’ (haptic feedback). Any obstruction to catheter advancement between 5 and 10 cm is likely due to contact with the inferior wall of the arch of aorta and the catheter can be manipulated to advance into the ascending aorta. If no resistance is felt by 20 cm then it has likely advanced down the descending aorta and repositioning is required. When the catheter advances correctly down the ascending aorta, the catheter ‘bounces’ at about 10-15 cm on the leaflets of the aortic valve and can then be pulled back slightly. The balloon is then inflated above the ostia in the ascending aorta to prevent the flow of contrast up the ascending aorta.

Use a standard 14Fr urinary catheter with a ≥30ml balloon size until Cadatheter is available. A guide wire may help stiffen the catheter in difficult cases. The balloon is inflated with dilute water-soluble radiographic contrast (1 in 50 dilution of Urografin®) to help ascertain the position of the balloon in the aorta on initial scans, and reposition if required (figure below).

Figure shows: (A) Basic mortuary equipment used for 'catherisation' prior to angiography; male urinary Foley catheter with tip cut off, lengths of string, two aneurysm hooks, forceps, scalpel and radiographic guide wire. (B) Suprascapular incision made on above the clavicle on the lateral side of the neck, based on a standard embalming technique. (C) Following blunt dissection of the soft tissue, the left carotid artery is elevated by means of an aneurysm hook prior to incision of the anterior arterial wall. (D) The modified Foley catheter is inserted into the carotid artery. Lengths of string are used to tie off the superior aspect of the artery and act as a marker for the inferior aspect.
Scan protocol:
See detailed instructions in CT scanner, if in doubt ring mortuary, pathologist or Claire for advice. Images archived to PACS under trial code.

Standard (native) PMCT scan

<table>
<thead>
<tr>
<th></th>
<th>Brain Angle C2</th>
<th>Head and Neck Straight to T2</th>
<th>Chest To include all ribs</th>
<th>Abdomen/Pelvis Above diaphragm to below symph pubis</th>
<th>Lower Limb Iliac crests to below feet</th>
</tr>
</thead>
<tbody>
<tr>
<td>kV</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>mA</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Rotation time</td>
<td>0.75</td>
<td>0.75</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Range</td>
<td>350</td>
<td>350</td>
<td>600</td>
<td>600</td>
<td>850</td>
</tr>
<tr>
<td>FOV</td>
<td>320 – M</td>
<td>320 – M</td>
<td>400 - L</td>
<td>400 - L</td>
<td>400 – L</td>
</tr>
<tr>
<td>Thickness</td>
<td>0.5 x 32</td>
<td>0.5 x 32</td>
<td>0.5 x 64</td>
<td>0.5 x 64</td>
<td>0.5 x 64</td>
</tr>
<tr>
<td>Recon thickness interval</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Pitch factor</td>
<td>0.656</td>
<td>0.656</td>
<td>0.828</td>
<td>0.828</td>
<td>0.641</td>
</tr>
<tr>
<td>Helical pitch</td>
<td>21.0</td>
<td>21.0</td>
<td>53</td>
<td>53</td>
<td>41</td>
</tr>
</tbody>
</table>

Notes:
Toshiba Aquilion 64 slice scanner.
The main reason for doing both an angled and straight tube for head scans is to avoid dental artefact across the posterior fossa.
Boost (metal artefact reduction) is on for all scans
Body is split into 2 areas to make smaller file sizes for image manipulation
2mm slice thickness in body to avoid data handling and data storage issues
Auto mA not used. Scans performed at higher mA than clinical scanning.
Large field of view used as body, arm and limb positioning can be difficult

Contrast angiography (pump injector)
Replace manual hand injections (using 60 mls bladder syringe) to use of pump injector, Medrad Stellant dual head pump injector system (Medrad UK Ltd, UK).

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NIHR Study Protocol Version 1.0
Use small FoV cardiac protocol with 0.5 mm reconstructions.
Air injection: Pump injector 300mls air at 6mls/sec, 43 second delay from start of injection to start of imaging. For hand injection 5 x 60 mls bladder syringe over 2 – 3 minutes.

Run 1: Supine
Run 2: Supine
Run 3: Right lateral decubitus position

Positive contrast medium (Urografin® 150 mg/ml, Bayer Healthcare) diluted 1:10 at 150mls at 3mls per second, 43 second delay from start of injection to start of imaging. For hand injection: 120 ml of positive contrast in 2 injections in approximately 40 seconds (20 seconds per syringe).
Run 4: right lateral decubitus position
Run 5: Supine

Autopsy:
- Autopsy performed as per standard UHL practice in LRI mortuary.
- The pathologists do not access PMCTA findings unless the trial team feels appropriate or they specifically ask.
- All pathologists undertake the autopsy following standard practice (Royal College of Pathologists generic and cause of death specific guidelines), with no trial specific instructions.
- Any further investigation, for example retrieving further background medical data or performing supplementary laboratory investigations, including toxicology and histology, was at their discretion.

The autopsy report is created independent to the study and communicated to the HM Coroner in the standard way.

The study manager uses the autopsy report to create anonymised trial specific reports
1. a full report
2. a reduced report for PMCTA reporting
   A: excluding the internal examination findings
   B: including external examination details
   C: including additional medical history.
   D: including Toxicology and biochemistry if radiologist requests
   E: including histology information
   If easily be accessed by CT guided biopsy
and requested by radiologist

Image Analysis:
Images archived to:
1. UHL PACS Agfa Impax 6-5 workstation © Agfa HealthCare Corp. USA.
2. UoL Imaging Apple Mac Pro workstation using OsiriX v4-0 64-bit software (Pixmeo, Switzerland).
Images interpreted by BM with VR or MP when available, with HM Coroners’ history. Then increased information obtained with external examination, more medical Hx if available and previous imaging / tests if required. Toxicology / Histology requested if considered warranted (as above)

BM groups all information together and drafts final trial report. All cases then reviewed by BM and GNR for pathology assistance in defining cause of death and significance of findings. Final PMCTA report created.

Data recorded

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Age</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of death</td>
<td>Clearly traumatic with no obvious natural factors e.g. RTC, gunshot, hanging</td>
<td>Natural or not clearly traumatic</td>
</tr>
<tr>
<td>Intervals</td>
<td>Time of death plus certainty, accurate, within a day, unknown</td>
<td>Time of scan</td>
</tr>
<tr>
<td>Angiography</td>
<td>Good</td>
<td>Poor – why?</td>
</tr>
<tr>
<td>Further requested tests</td>
<td>Toxicology – why Before or after PMCT reading</td>
<td>Histology possible by PMCT control – Why Before or after PMCT reading</td>
</tr>
<tr>
<td>Triage</td>
<td>Pre-PMCT reading due to type of death i.e. needs autopsy for legal reasons not scientific</td>
<td>Post-PMCT reading due to low confidence</td>
</tr>
<tr>
<td>Too much information</td>
<td>Record if unrequested toxicology / histology information obtained</td>
<td></td>
</tr>
<tr>
<td>Findings</td>
<td>Summary of findings</td>
<td>Cause of death if possible* or state unknown</td>
</tr>
</tbody>
</table>

Unblinding:
Anonymised final autopsy report accessed. Data recorded

<table>
<thead>
<tr>
<th>Pathologist (kept anonymized except for counting)</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Further tests performed</td>
<td>Toxicology – why</td>
</tr>
<tr>
<td>Findings</td>
<td>Summary of findings</td>
</tr>
</tbody>
</table>

The two reports are evaluated to create a new “gold standard” based on the autopsy findings, autopsy cause of death unless there are clear contradictory PMCT findings.

Examples
1. PMCTA shows a clear and incontrovertible finding, such as fracture or major haemorrhage.
2. Autopsy findings in agreement with PMCTA, but autopsy conclusions shown to be not “on the balance of probabilities” based on change in relative significance of autopsy findings due to PMCTA.
3. Pre-mortem investigations discovered in PMCT investigation, not appreciated in the autopsy report, clearly contradict findings.
4. CoD constructed incorrectly, based on the autopsy findings (audit of autopsy report in isolation).

Data from unblinding

<table>
<thead>
<tr>
<th>Cause of death Discrepancy</th>
<th>Autopsy</th>
<th>PMCT</th>
<th>Gold standard (GS)</th>
<th>GS changed: Major, Minor, Trivial, No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Findings error</td>
<td>Autopsy: Major / Minor / No - Specify</td>
<td>PMCT: Major / Minor / No - Specify</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Major:
- Significant Trauma relevant to CoD,
- Wrong organ system or very different mechanism,
- Missing any significant potentially fatal finding, even if not the CoD

Minor:
- CoD related to wrong organ system on balance of probabilities BUT with no discrepancy in findings,
- Both tests report significant heart and lung disease, but ascribe CoD differently,
- Same organ system with linked but different cause,
- Significant trauma not directly relevant to CoD, Failure to find a second condition that may have contributed to death

Not discrepant:
- Order of CoD reversed,
- Minor differences in detail,
- Two diagnoses instead of one if there are no discrepancy in findings,
- Failure to mention a chronic condition in part 2 that is clear in the medical record,
- Failure to mention common incidental pathology e.g. Age related changes, simple renal cysts, enlarged prostate gland, and uncomplicated diverticulosis.