The work on which this thesis is based is my own independent work, except where acknowledged.

Nikil Patel

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Dedicated to the patients who took part in the study
Abstract

‘Causes of Brain Injury Associated with Cardiac Interventions’

Nikil Patel

Background & Objective

Brain injury after cardiac surgery is a serious concern for patients and their families. Thousands of air bubbles enter the cerebral circulation during cardiac surgery, but whether these are harmful to the brain and impact adversely on cognition remains subject of speculation.

The purpose of this study was to use MRI to characterise new and pre-existing cerebral ischaemic lesions in patients undergoing cardiac surgery, and to test whether the accumulation of new lesions adversely affects cognition. This study also draws upon recent advances in intra-operative bubble sizing to investigate whether high volumes of macro-bubbles have potential to result in new MRI lesions or increased risk of cognitive decline following surgery.

Methods

The burden of pre-existing versus new ischaemic lesions was quantified based on analysis of 3T MR images and compared with the results of cognitive testing. Intra-operative Doppler ultrasound recordings were used to estimate the number, volume and diameters of bubbles entering the middle cerebral artery during surgery for comparison with MRI and cognitive outcome.

Results

Post-operative lesions were identified in 31% of patients. Patients with pre-existing lesions were 10 times more likely to receive new lesions after surgery. Forty six percent of patients experienced postoperative cognitive decline, which was independent of whether new lesions were present. Intra-cardiac patients received over 16 times the total volume of air, 7 times as many macro-bubbles, 5 times as many emboli following aortic cross-clamp removal, and over twice as many emboli overall than CABG patients, but there were no significant differences in MRI or cognitive outcome.

Conclusions

New MRI lesions and high numbers of intra-operative macro-bubbles are common during cardiac surgery, but we found no evidence of any adverse effect on cognition.
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Conference and Meeting abstracts


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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>anterior cerebral artery</td>
</tr>
<tr>
<td>ADC</td>
<td>apparent diffusion coefficient</td>
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<tr>
<td>AS</td>
<td>aortic stenosis</td>
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<tr>
<td>AVR</td>
<td>aortic valve replacement/repair</td>
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<tr>
<td>AxC</td>
<td>aortic cross-clamp</td>
</tr>
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<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>CA</td>
<td>cerebral autoregulation</td>
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<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
</tr>
<tr>
<td>CBFv</td>
<td>cerebral blood flow velocity</td>
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<tr>
<td>CMRO₂</td>
<td>cerebral metabolic rate of oxygen</td>
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<td>CO₂</td>
<td>carbon dioxide</td>
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<tr>
<td>CPB</td>
<td>cardiopulmonary bypass</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>dB</td>
<td>decibels</td>
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<tr>
<td>DV</td>
<td>double and triple valve</td>
</tr>
<tr>
<td>DWI</td>
<td>diffusion weighted imaging</td>
</tr>
<tr>
<td>FFT</td>
<td>fast fourier transform</td>
</tr>
<tr>
<td>FLAIR</td>
<td>fluid attenuated inversion recovery</td>
</tr>
<tr>
<td>GP</td>
<td>grooved Pegboard</td>
</tr>
<tr>
<td>GRE</td>
<td>gradient echo sequences</td>
</tr>
<tr>
<td>HADS</td>
<td>hospital anxiety and depression scale</td>
</tr>
<tr>
<td>HCL</td>
<td>hypercholesterolemia</td>
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HCT          haematocrit
HTN          hypertension
ICA          internal carotid artery
IQR          inter quartile range
KPa          kilopascals
LLA          lenticulostriate artery
LVEF         left ventricle ejection fraction
MAP          mean arterial pressure
MCA          middle cerebral artery
MEBR         measured Embolus-to-blood ratio
MIDCAB       minimally invasive direct coronary artery bypass grafting
MHz          megahertz
MRA          magnetic resonance angiography
MRI          magnetic resonance imaging
MVR          mitral valve replacement/repair
NSE          neuron-specific enolase
O2           oxygen
Obvs.        observational study
OPCPB        off-pump cardiopulmonary bypass
PaCO2        partial pressure of carbon dioxide
PCA          posterior cerebral artery
PMEA         poly-2-methoxyethylacrylate
POCD         postoperative cognitive decline
PWI          perfusion weighted imaging
RCT          randomised controlled trial
SCA          superior cerebellar artery
SCOLP        speed and capacity of language processing test
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
</tr>
<tr>
<td>SE</td>
<td>spin echo</td>
</tr>
<tr>
<td>SMK</td>
<td>smoker</td>
</tr>
<tr>
<td>SWI</td>
<td>susceptibility weighted imaging</td>
</tr>
<tr>
<td>TAVI</td>
<td>transcather aortic valve implantation</td>
</tr>
<tr>
<td>TCD</td>
<td>transcranial Doppler</td>
</tr>
<tr>
<td>TE</td>
<td>echo time</td>
</tr>
<tr>
<td>Temp.</td>
<td>temperature</td>
</tr>
<tr>
<td>T₁</td>
<td>Time 1 (MRI)</td>
</tr>
<tr>
<td>T₂</td>
<td>Time 2 (MRI)</td>
</tr>
<tr>
<td>TI</td>
<td>inversion time</td>
</tr>
<tr>
<td>TMA</td>
<td>trail Making Test A</td>
</tr>
<tr>
<td>TMB</td>
<td>trail Making Test B</td>
</tr>
<tr>
<td>TOF</td>
<td>time of flight</td>
</tr>
<tr>
<td>TR</td>
<td>repetition time</td>
</tr>
<tr>
<td>TVR</td>
<td>tricuspid valve replacement/repair</td>
</tr>
<tr>
<td>WAIS-III</td>
<td>Wechsler Abbreviated Scale of Intelligence</td>
</tr>
<tr>
<td>WMS-III</td>
<td>Wechsler Memory Scale-Third Edition</td>
</tr>
<tr>
<td>$\text{Xe}_{133}$</td>
<td>Xenon$\text{Xe}_{133}$</td>
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Chapter 1

1 Brain injury during cardiac interventions part I: Pre- and peri-operative risk factors associated with cognitive decline

1.1 Introduction

Over the past 50 years, the question of whether ‘fixing the heart comes at a cost to the brain’ has been the subject of considerable research. With advances in anaesthesia, surgical technique, and post-operative care, cardiac surgery is now safer than ever before (Selnes et al., 2006). However, as more complex surgery is now being undertaken in older patients, the incidence of neurological complications following surgery, and potential impact on long term cognition has become a growing concern. It is therefore important to be able to quantify brain injuries and identify their causes.

The era of modern cardiac surgery began in the 1950s when cardiopulmonary bypass (CPB) machines were developed for bypassing the heart and lungs during surgery (GIBBON, 1954). Since then, the safety of cardiac surgery has improved year on year and hundreds of thousands of patients now undergo cardiac procedures worldwide. Despite advances in CPB technology and operative techniques, in recent years clinicians have become increasingly concerned about the potential effects of surgery on the brain. Patients are commonly reported to experience cognitive decline and new ischaemic lesions following surgery, which many researchers believe may accelerate long term neuropsychological dysfunction and vascular dementia. Although injuries are hypothesised to result from emboli entering the cerebral circulation during surgery, the role of emboli in causing cognitive decline is unclear. An embolus is the name given to any object that becomes free-floating in the bloodstream with potential to obstruct, or occlude, a blood vessel leading to ischaemia of the tissue. If periods of brain ischaemia are prolonged, it can eventually result in permanent tissue damage (infarction). In a cardiac surgery setting, emboli typically consist of air bubbles that enter the circulation from the bypass machine or open chambers of the heart, and dislodged pieces of...
atherosclerotic plaque released during application and removal of the aortic cross-clamp. Although cardiac surgeons use filters and de-airing procedures to try and reduce the number of emboli reaching the brain, none of these measures are completely effective at eliminating emboli from the cerebral circulation. This thesis focuses on the role of emboli in generating brain injury during cardiac surgery by identifying new brain injuries following surgery and comparing the timing and characteristics of intra-operative emboli with the results of magnetic resonance (MR) scans and neuropsychological testing.

1.2 Cardiac surgery procedures

1.2.1 Coronary Artery Bypass Graft (CABG)

One of the most common major surgical procedures carried out in the UK is coronary artery bypass grafting (CABG). CABG surgery aims to avoid cardiac ischaemia by bypassing diseased regions of the coronary arteries, to restore normal blood flow to the cardiac myocardium. During surgery, a piece of the saphenous vein, radial vein, or mammary artery is grafted to the coronary arteries to bypass regions that have been narrowed by atherosclerosis. In 2010/2011 alone, 16,408 CABG surgeries were performed in the UK (Society of Cardiothoracic Surgery, surgical statistics, 2013).

1.2.2 Valve replacement or repair

The second most common type of cardiac surgery after CABG involves replacement or repair of one or more heart valves. The heart contains four major valves; the tricuspid valve, pulmonary valve, mitral valve and the aortic valve. Over time, valves can become damaged or stenosed (aortic stenosis), or may leak and become inefficient (aortic regurgitation). The most common valve requiring treatment is the aortic valve, positioned at the outlet of the heart. Although in some cases the valve may be repaired, in the majority of operations the valve is completely replaced with a mechanical or biological (tissue) valve. Valve surgery is often performed in combination with CABG, sometimes referred to as combined surgery. According to the UK Society of
Cardiothoracic Surgery, around 5,000 aortic valve surgeries were performed from 2010-2011 (NHS direct website, 2012).

1.2.3 Cardiopulmonary bypass

CABG and valve procedures are both normally performed in conjunction with Cardiopulmonary Bypass. Recognition for the development of modern day cardiopulmonary bypass (CPB) is given to John Gibbon who developed the first functional heart-lung machine at the Mayo Clinic (USA) in the 1950s (GIBBON, 1954). Although early CPB machines were not safe for clinical use as they damaged red blood cells, Gibbon and other researchers gradually refined their methods and the first heart-lung bypass machine was trialled in humans in 1953. Today, CPB is commonly used to take the role of the heart and lungs for many hours during cardiac surgery. Despite advancements in CPB technology, key neurological complications were noted shortly after CPB came into widespread use (CAGUIN & CARTER, 1963; GILMAN, 1965). These complications ranged from; cognitive dysfunction, delirium and focal stroke, to coma and death. As injuries were thought by many clinicians to be associated with the use of CPB, the phenomenon of cognitive decline following cardiac surgery was commonly referred to as ‘pump-head’.

Over time, the demographic characteristics of patients undergoing cardiac surgery have shifted to include a higher proportion of elderly patients, undergoing increasingly complex procedures. The average age of cardiac surgery patients has increased from ~64 years in 2001 to ~67 years in 2010, fig. 1.1(a). The number of patients with neurological disease prior to surgery has nearly doubled from 1.4% in 2001 to ~2.8% in 2010, fig. 1.1(b). Cardiac surgery procedures have also become more complex, with the number of patients undergoing isolated CABG decreasing by almost 20% from 2001-2010, fig 1.1(c). Despite higher patient risk profiles, the mortality rate has fallen slightly from 4.0% in 2001/2002 to 3.1% in 2010/2011 (National Cardiac Surgery Audit, UCL, 2012), suggesting that the overall safety of cardiac surgery is improving.
Figure 1.1 In the decade from 2001 to 2011 (A) the mean age, and (B) the incidence of pre-existing neurological dysfunction of cardiac surgery patients both increased. (C) The proportion of patients undergoing isolated CABG decreased, reflecting an increase in the complexity of surgery. These data were taken from the National Office of Statistics, compendium of population health indicators, portal code P00680 (www.indicators.ic.nhs.uk, accessed on 20/01/2013).

1.3 Stroke and neurological complications following cardiac surgery

Neurological complications after cardiac surgery vary from mild/moderate neurocognitive impairment to fatal stroke. As the brain is one of the most complex organs of the human body, even small injuries have potential to lead to symptomatic loss of brain function, while, depending on location, larger lesions may remain asymptomatic.

The World Health Organisation (WHO) defines stroke as; “suddenly (within seconds) or at least rapidly (within hours), developing clinical signs of focal or global disturbance of cerebral functions, with symptoms lasting for 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin” (Report of the WHO task force on Stroke, 1989). If the symptoms and signs disappear within 24 hours the event is
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defined as Transient Ischaemic Attack (TIA). Symptoms and signs of stroke are caused by interrupted brain perfusion leading to tissue damage.

Previously, a large study investigating the incidence of stroke following cardiac surgery was conducted by Bucerius et al. (2003). Based on data from 16,184 cardiac surgery patients, the incidence of stroke was estimated to vary from 2 - 4% for CABG procedures rising to almost 10% for patients undergoing double or triple valve surgery, fig. 1.2.

![Figure 1.2](image)

Figure 1.2 The incidence of stroke is related to the type of surgical procedure. AV- aortic valve; CABG- coronary artery bypass grafting; COMB- combined procedures; DV- double and triple valve; MIDCAB - minimally invasive direct coronary artery bypass grafting; MV- mitral valve; OPCAB- off-pump coronary artery bypass grafting. Beating Heart - all patients undergoing beating heart surgery (Bucerius et al., 2003).

1.4 Post-operative cognitive decline

Routine clinical examination covers crucial neurological abnormalities such as; ataxia (disorders affecting co-ordination, balance and speech), visual defects, paresis (paralytic dementia) and hypoesthesia (decreased sensitivity to touch) (Brott et al., 1989). It also includes focal neuropsychological deficits such as; apraxia (motor dysfunction), dyscalculia (arithmetic disorder) and aphasia (communication disorder). However, more global cerebral dysfunction, such as neuropsychological decline, mood and memory disturbances, personality changes, and decline in psychomotor speed are commonly missed because they require more explicit examination using specialised neuropsychological tests (Murkin et al., 1995).
Post-operative cognitive decline (POCD) broadly refers to difficulties associated with memory and general information processing after surgery. At present POCD is not documented in the International Classification of Diseases and is not listed as a diagnosis. The term POCD is used in the literature to describe patients who experience decline in a range of neuropsychological domains such as speed and information processing, executive functioning, short-term and delayed memory. In the International Consensus Statement of Neurobehavioral Outcomes after Cardiac Surgery, POCD was defined as the following:

‘A spectrum of postoperative central nervous system dysfunction both acute and persistent, including subtle neurologic signs, neuropsychological impairment, stroke or brain death’ (Murkin et al., 1995).

According to the American Heart Association and American College of Cardiology, POCD can be divided into two categories. Type I is associated with major focal deficit, apathy or coma. Type II deficits are without detectable focal lesions but are nonetheless associated with diffuse symptoms in terms of confusion, memory loss, agitation and a decline in intellectual ability (Edmunds et al., 1996). Following cardiac surgery, between 2 and 8% of patients are thought to experience a type I deficit. Type II deficits (Wolman et al., 1999; Hogue et al., 1999) are estimated to affect 15-63% of patients, depending on the cognitive testing methods used (Mahanna et al., 1996; Barber et al., 2008). Throughout this thesis the term POCD is used to refer to type II POCD, identified using neuropsychological testing.

1.5 Neuropsychological outcome after cardiac surgery - Literature search

To investigate the incidence and causes of cognitive decline, a systematic literature search was performed drawing on papers from PubMed and EMBASE. All studies published in English between June 1967 and August 2013 and featuring adult human subjects were eligible for review.

Search terms were created by combining the following medical subject headings (MeSH terms):
#1: "Coronary Artery Bypass" OR "Coronary Artery Bypass, Off-Pump" OR "Valve Surgery" OR "Thoracic Surgery" OR "Cardiac Surgical Procedures"

AND

#2: "Cognitive Therapy" OR "Cognition Disorders" OR "Cognition" OR "Neuropsychology" OR "Neuropsychological Tests" OR "Mild Cognitive Impairment"

Abstracts involving both cardiac surgery and cognitive function (#1 AND #2) were independently reviewed by two investigators (N. Patel and E.M.L. Chung) and studies of adult cardiac surgery patients that assessed both pre- and postoperative cognitive function were identified for full manuscript review. Abstracts were excluded if they involved paediatric surgery, operations other than cardiac surgery, or no measurement of cognitive function. Case reports and studies of cardiac procedures such as, angioplasty, angiography, valvuloplasty and Transcatheter Aortic Valve Implantation (TAVI) were also excluded. Studies generating multiple publications from the same cohort were reported only once. Where there was disagreement between investigators the full text was reviewed. Additionally, the reference lists of selected articles were evaluated for any additional articles of interest. Articles short-listed for full manuscript review were summarised in an Excel spreadsheet listing the; study design (observational, RCT, etc.), number of patients, type(s) of surgery, outcome measures, and time point of neurocognitive assessment. Studies that included assessment of anxiety and depression were noted as mood is known to have an impact on cognitive test results.

A total of 638 abstracts were systematically identified using our search criteria of which 426 papers were suitable for full review. Of these, 296 were observational studies and 130 were RCTs, fig 1.3.
Although over 420 original research articles were identified as having investigated cognitive decline following cardiac surgery, we found little consensus on the incidence, severity, and time course of symptoms. Differing methodologies used between studies made it difficult to directly compare study findings through systematic meta-analysis. Indeed, some studies suggest that cognitive decline following surgery is transient and that long-term decline in cognition is very similar to that in non-operative controls (Selnes et al., 2003). In a prospective study by Selnes et al. (2003) a group of 140 CABG patients were compared with 92 demographically similar patients with diagnosed coronary artery disease but no surgery. Both groups showed improved scores from baseline to 12 weeks with no statistically significant differences between the two groups.

1.6 Timing of assessment for postoperative cognitive decline

Most studies evaluating cognitive decline focus on changes in executive function, learning language, visual spatial skills, attention, and memory (Rudolph et al., 2010). However, neuropsychological tests vary considerably between studies and also appear
to depend on the timing of neurocognitive assessment. By narrowing the search to empirical research articles that studied postoperative neuropsychological assessment as a primary outcome, the number of publications was reduced to 109 articles. Thirty-three of these articles were excluded because the total percentage of patients who declined in cognitive tests was unclear. Four articles had published the same data twice and full-texts were unavailable for 6 articles. A total of 66 articles independently investigating 94 time-points are summarised in figure 1.4 and 1.5. This summarises the estimated percentage decline reported by previous researchers at discharge, 1 week, 2-8 weeks, 3 months, 6 months, 1 year and 3-5 years post-operatively.
Figure 1.4 Incidence of post-operative cognitive decline measured by previous researchers at (A) discharge and 1 week, (B) 2, 4, 6 and 8 weeks.
Figure 1.5 Incidence of post-operative cognitive decline measured by previous researchers at (A) 3 months and 6 months, (B) 1, 3, 4 and 5 years.
Grouping studies where assessments were performed at similar time points, and plotting the proportion of patients estimated to be affected by cognitive decline suggests that 40-60% of patients experience cognitive decline when tested within 2 weeks of surgery, falling to 30-40% after 8-10 weeks, recovering to 10-20% at 1 year, with proportion of patients experiencing cognitive decline increasing again at 3-5 years, fig 1.6.

Figure 1.6 Studies attempting to quantify neuropsychological decline at various time points. The weighted mean and standard deviation (number of patients and % decline) is plotted by combining data from a total of 15649 patients and 94 studies; Discharge (17 studies), 1-2 weeks (16 studies), 1 month (4 studies), 6 weeks (15 studies), 2-3 months (18 studies), 6 months (11 studies), 1 year (8 studies), 3-5 years (5 studies).

As can be seen from fig 1.6, large variations in the estimated incidence of postoperative cognitive decline are observed, even after grouping studies where tests were performed at similar time-points. Heterogeneity in assessment methods, patient demographics, and study design may be responsible for these variations.

In a previous study of 261 patients by Newman et al., 40% of patients were found to have cognitive decline 5 years after surgery. The authors also reported that patients who experienced early postoperative decline (~2-3 months) were more prone to experience further decline later in life (Newman et al., 2001). However, that study did not feature a control group, and the few studies that have compared cardiac surgery patients with
non-cardiac surgery controls possessing similar levels of cardiovascular disease suggest that cognition 3-5 years after surgery is similar to that of non-operative controls (Selnes et al., 2003). Most studies, including the study described in this thesis, do not include a control group.

### 1.7 Patient risk factors for post-operative cognitive decline

Factors thought to be associated with neuropsychological decline include years of education, advanced age, and pre-existing cognitive decline. A prospective longitudinal study investigating patient-related risk factors and the incidence of POCD in 1,064 patients following major non-cardiac surgery found that advanced age was the biggest single risk factor predicting the likelihood of POCD following surgery (Monk et al., 2008). The incidence of POCD is therefore likely to increase as the number of older patients grows (Robinson et al., 2012).

- Age (16 studies found evidence for an association with age and cognitive impairment)
- Pre-existing cognitive impairment (15 studies found evidence for an association with pre-existing cognitive impairment)
- Impaired cerebral autoregulation (2 studies found evidence for an association with impaired cerebral autoregulation)
- Pre-existing cardiovascular disease (10 studies found evidence for an association with cardiovascular disease or aortic stenosis)
- Cerebrovascular disease (9 studies found evidence for an association with pre-existing cerebrovascular disease)

Note that some studies investigated multiple factors.

### 1.8 Perioperative risk factors for cognitive decline

Studies investigating perioperative risk factors associated with cognitive decline suggest that there is no single causative factor. Potential mechanisms implicated in the pathogenesis of cognitive decline investigated in previous research include (RCTs):
• Cardiopulmonary bypass: 59 (19) studies
• Inflammation & systemic inflammatory responses: 28 (4) studies
• Blood temperature: 23 (10) studies
• Rate of re-warming: 4 (3) studies
• Embolisation: 27 (5) studies
• Neuroprotective agents: 16 (16) studies
• Blood pressure: 5 (3) studies
• Impaired cerebral perfusion during surgery: 4 (0) studies
• Haemodilution: 1 (1) studies
• Use of anaesthetics: 18 (0) studies

Figure 1.7 summarises the focus and conclusions of studies examining perioperative factors contributing to cognitive decline, weighted by the size of the study.

Figure 1.7 Studies examining perioperative factors contributing to cognitive decline. The bubble sizes represent the number of studies investigating each perioperative factor with the area shaded in red indicating the number of RCTs.
1.8.1 Anaesthesia

Sedative and anaesthetic agents with \(N\)-methyl-\(d\)-aspartate receptor antagonist and \(\gamma\)-aminobutyric acid mediated properties can temporarily change the neurotransmission of the brain by interacting at a cellular level to achieve deep sedation during surgery (Eckenhoff et al., 2004). Since it would be unethical to perform cardiac surgery without the use of anesthetic agents, the impact of anesthesia on cognition is difficult to study.

Fifteen studies have investigated whether choice of anaesthesia impact neurocognitive outcome after cardiac surgery. Of these, 8 were randomised controlled trials (RCTs), comparing 9 different types of anaesthetic agent. Studies showing an improvement, decline and no difference in postoperative outcome are summarised in table 1.1.

### Table 1.1 Studies comparing cognition after cardiac surgery following administration of different types of anaesthetic.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Type of anaesthesia/drug</th>
<th>Time of post-operative cognitive assessment</th>
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<tbody>
<tr>
<td><strong>Studies showing an improvement in post-operative outcome</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Dumas et al., 1999)</td>
<td>RCT</td>
<td>48</td>
<td>Fentanyl &amp; Early extubation</td>
<td>8 weeks</td>
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<tr>
<td>(Dowd et al., 2001)</td>
<td>RCT</td>
<td>78</td>
<td>Propofol &amp; lorazepam</td>
<td>6-12 months</td>
</tr>
<tr>
<td>(Bottio et al., 2007)</td>
<td>Observational</td>
<td>50</td>
<td>Epidural anaes.</td>
<td>6 months</td>
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<tr>
<td>(Delphin et al., 2007)</td>
<td>Observational</td>
<td>91</td>
<td>Sevoflurane &amp; isoflurane</td>
<td>2 hours and 1 day</td>
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<tr>
<td>(Kanbak et al., 2007)</td>
<td>RCT</td>
<td>40</td>
<td>Isoflurane, sevoflurane &amp; desflurane</td>
<td>3 and 6 days</td>
</tr>
<tr>
<td>(Hudetz et al., 2009)</td>
<td>Observational</td>
<td>78</td>
<td>Ketamine</td>
<td>1 week</td>
</tr>
<tr>
<td>(Schoen et al., 2011)</td>
<td>RCT</td>
<td>117</td>
<td>Sevoflurane &amp; propofol</td>
<td>2, 4 and 6 days</td>
</tr>
<tr>
<td><strong>Studies showing a decline in post-operative outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Kanbak et al., 2007)</td>
<td>RCT</td>
<td>40</td>
<td>Sevoflurane &amp; desflurane</td>
<td>3 and 6 days</td>
</tr>
<tr>
<td><strong>Studies showing no difference in test outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Kadoi et al., 2003)</td>
<td>RCT</td>
<td>180</td>
<td>Propofol and fentanyl</td>
<td>6 months</td>
</tr>
<tr>
<td>(Silbert et al., 2006)</td>
<td>Observational</td>
<td>300</td>
<td>Fentanyl</td>
<td>1 week, 3 months, 1 year</td>
</tr>
<tr>
<td>(Kadoi &amp; Goto, 2007)</td>
<td>Observational</td>
<td>109</td>
<td>Sevoflurane</td>
<td>6 months</td>
</tr>
</tbody>
</table>
This research suggests that choice of anaesthetic has potential to affect cognition, particularly when tests are performed soon after surgery. However, in the majority of larger studies, the choice of anaesthetic had no impact on cognitive outcome.

### 1.8.2 Blood pressure

A number of studies have investigated the association between low blood pressure during cardiac surgery and cognitive decline. Although normal blood pressure in conscious patients is approximately 120/80 mm Hg, it is common for the blood pressure to be much lower during surgery. As the brain has a lower metabolic demand during anaesthesia, this is not thought to adversely affect tissue perfusion; however, low blood pressure may impair embolus clearance and affect the efficiency of cerebral autoregulation. A total of 5 studies have used neuropsychological tests to investigate whether mean arterial blood pressure had any impact on postoperative cognitive outcome, table 1.2.

**Table 1.2** Studies investigating POCD associated with intra-operative blood pressure variation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Type of intervention</th>
<th>Time of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Gold et al., 1995)</td>
<td>RCT</td>
<td>248</td>
<td>High (80-100 mmHg) v low (50-60 mmHg) BP</td>
<td>6 months</td>
</tr>
<tr>
<td>(Siepe et al., 2011)</td>
<td>RCT</td>
<td>92</td>
<td>High (80-90 mmHg) v low (60-70 mm Hg) BP</td>
<td>2 days</td>
</tr>
<tr>
<td>(Gottesman et al., 2007)</td>
<td>Observational</td>
<td>15</td>
<td>Low MAP (50-70 mmHg)</td>
<td>3-5 days &amp; 1 month</td>
</tr>
<tr>
<td>(Newman et al., 1995)</td>
<td>Observational</td>
<td>237</td>
<td>Low MAP (50-60 mmHg)</td>
<td>Discharge</td>
</tr>
</tbody>
</table>

**Studies showing no difference in post-operative outcome**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Type of intervention</th>
<th>Time of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Charlson et al., 2007)</td>
<td>RCT</td>
<td>412</td>
<td>High MAP (57 -90 mmHg) v Custom (capped at 90 mm Hg)</td>
<td>6 months</td>
</tr>
</tbody>
</table>
In the study by Gold et al. (1995), a higher mean arterial pressure (80-110 mmHg) during CPB appeared to be associated with a lower stroke rate (2.4%) compared to a low mean arterial pressure between 45-60 mmHg (7.2%), \( p=0.026 \). However, at 6 months follow-up the proportion of patients with neuropsychological decline (11% and 12% respectively) were comparable (Gold et al., 1995). In another study, Siepe et al. (2011) showed greater proportion of patients with cognitive decline two days following CABG in patients with mean arterial pressure in the range 60-70 mmHg compared to 80-90 mmHg, however cerebral oxygen saturation was similar in both groups (Siepe et al., 2011). The largest RCT by Charlson et al. found no difference in cognition between a ‘custom’ group (average BP: 79 mmHg) and High BP group (average BP: 89 mmHg), however, the average difference in BP between groups was only 10 mmHg, which may not be a clinically significant difference (Charlson et al., 2007). Overall, studies appear to support the idea that maintenance of a sufficiently high mean arterial pressure during cardiac surgery is important for safeguarding perfusion to the brain.

1.8.3 Cerebral autoregulation

Some researchers have proposed that it is not mean arterial pressure (MAP) \textit{per se} that contributes to cognitive decline, but the capacity of the brain’s blood flow regulation mechanisms to respond appropriately to blood pressure variations and changes in oxygen saturation. A number of studies have investigated cerebral autoregulation (CA) in response to blood pressure changes during cardiac surgery and found that a significant proportion of patients struggle to autoregulate their cerebral blood supplies intra-operatively (Ono et al., 2012). However, only 4 studies have specifically investigated CA during cardiac surgery in conjunction with pre- and postoperative neuropsychological assessment (table. 1.3).
Table 1.3: Studies investigating cerebral autoregulation during cardiac surgery in conjunction with neurocognitive tests.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Cerebral autoregulation measures</th>
<th>Time of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Patel et al., 1993)</td>
<td>RCT</td>
<td>70</td>
<td>Xenon-133 isotope clearance, CMRO₂, (cerebral metabolic rate for oxygen) CERO₂ (cerebral extraction ratio for oxygen)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>(Patel et al., 1996)</td>
<td>RCT</td>
<td>70</td>
<td>CBF, CBFv and O₂ saturation were measured during 4 phases of surgery</td>
<td>6 weeks</td>
</tr>
<tr>
<td>(Govier et al., 1984)</td>
<td>Observational</td>
<td>67</td>
<td>Partial pressure of arterial carbon dioxide (PaCO₂), clearance of xenon 133</td>
<td>Discharge</td>
</tr>
<tr>
<td>(Newman et al., 1994)</td>
<td>Observational</td>
<td>215</td>
<td>Xenon-133 clearance, CMRO₂, cerebral AV difference (C[AV]O₂)</td>
<td>Discharge</td>
</tr>
</tbody>
</table>

All four studies determined pressure-flow and metabolic-flow cerebral autoregulation during cardiopulmonary bypass using the 133Xe clearance cerebral blood flow method. Two studies in table 1.3 by the same author (Patel et al.) support the theory that impaired cerebral autoregulation is associated with a decline in postoperative outcome at 6 weeks, whereas two studies showed no association. The largest study by Newman et al. investigated CA in 215 patients and concluded that neuropsychological dysfunction at discharge was not explained by impaired CA; however increased oxygen extraction (measured using a thermodilution pulmonary artery catheter) was observed to be associated with a decline in some cognitive tests. They interpreted this as suggesting that an imbalance in cerebral tissue oxygen supply may contribute to POCD (Newman et al., 1994). In a recent trial it has also been proposed that some anaesthetic agents suppress autoregulatory responses more than others (Tanaka et al., 2011). As far as we are aware, no studies have yet looked at the relationship between CA and POCD beyond 6 weeks.

1.8.4 Inflammatory responses

All types of surgery have the risk of developing systemic inflammation; however, in cardiac surgery using CPB the blood is exposed to foreign surfaces which have potential
to stimulate pro-inflammatory responses. Inflammation causes endothelial dysfunction, which can lead to leakage between the blood-brain barrier and tissue oedema (Abbott, 2000). It has been shown that cytokines (e.g. TNF-alpha, Interleukin-1 and Interleukin-6) have been linked to neuropathology (Terrando et al., 2011; Cibelli et al., 2010). These elementary changes are hypothesised to affect the brain regardless of microembolic load received during surgery (Reinsfelt et al., 2012; Reinsfelt et al., 2013) and potentially provide an explanation for early cognitive decline (Baufreton et al., 2005).

Bubble oxygenators require direct contact with the blood for gas exchange. One of the earliest advances in the development of CPB was replacement of the bubble oxygenator with the membrane oxygenator. Blauth et al. confirmed the emboli-handling characteristics of the superior membrane oxygenators in 34 patients and concluded that they generated significantly less emboli, as quantified by retinal fluorescein angiography (Blauth et al., 1990). Other investigators also noted that membrane oxygenators generated a reduced inflammatory response (Videm et al., 1989; Cavarocchi et al., 1986). As a result of these studies, the majority of the cardiac centres worldwide now use membrane oxygenators.

Cardiopulmonary bypass components that come into contact with the blood can be coated with biocompatible materials such as; poly-2-methoxyethylacrylate, heparin, trillium, and synthetic proteins. These coatings aim to reduce inflammatory responses triggered during CPB. Heparin-coated circuits, in particular, have undergone considerable investigation in previous research. A total of 26 studies (including 7 RCTs) have used neuropsychological tests to investigate whether there is a strong association between inflammation and cognitive decline, table 1.4.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Marker for cerebral damage</th>
<th>Time of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies showing improved cognitive outcome when inhibiting complement activation via heparin-coated CPB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Fitch et al., 1999)</td>
<td>RCT</td>
<td>35</td>
<td>Inhibition of complement activation by specific antibody &amp; no antibody</td>
<td>Discharge</td>
</tr>
<tr>
<td>(Heyer et al., 2002)</td>
<td>RCT</td>
<td>99</td>
<td>Inhibition of complement activation by heparin-coated</td>
<td>5 days and 6 weeks</td>
</tr>
</tbody>
</table>
Pre- and peri-operative risk factors associated with cognitive decline

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>Risk Factor</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Baufreton et al., 2005)</td>
<td>RCT</td>
<td>30</td>
<td>Inhibition of complement activation by heparin-coated CPB</td>
<td>Discharge</td>
</tr>
<tr>
<td>(Skrabal et al., 2006)</td>
<td>RCT</td>
<td>39</td>
<td>(PMEA)-coated circuits and no-coated circuits</td>
<td>7-10 days</td>
</tr>
</tbody>
</table>

Studies showing a higher incidence of cognitive decline in the presence of high levels of biomarkers associated with inflammation

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>Biomarker(s)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Wimmer-Greinecker et al., 1998)</td>
<td>Observational</td>
<td>76</td>
<td>&gt;S-100 and NSE</td>
<td>5 days and 2 months</td>
</tr>
<tr>
<td>(Jonsson et al., 1999)</td>
<td>Observational</td>
<td>132</td>
<td>&gt;S-100</td>
<td>2 weeks and 2 months</td>
</tr>
<tr>
<td>(Kilminster et al., 1999)</td>
<td>Comparative study</td>
<td>130</td>
<td>&gt;S-100</td>
<td>6-8 weeks</td>
</tr>
<tr>
<td>(Rasmussen et al., 1999)</td>
<td>Observational</td>
<td>35</td>
<td>&gt;NSE</td>
<td>discharge and 3 months</td>
</tr>
<tr>
<td>(Derkach et al., 2000)</td>
<td>RCT</td>
<td>27</td>
<td>&gt;S-100 and NSE (deep and mild hypothermic)</td>
<td>6 months</td>
</tr>
<tr>
<td>(Diegeler et al., 2000)</td>
<td>RCT</td>
<td>40</td>
<td>&gt;S-100 (on- &amp; off pump)</td>
<td>1 week</td>
</tr>
<tr>
<td>(Georgiadis et al., 2000)</td>
<td>Observational</td>
<td>190</td>
<td>&gt;S-100</td>
<td>Discharge</td>
</tr>
<tr>
<td>(Lloyd et al., 2000)</td>
<td>RCT</td>
<td>125</td>
<td>&gt;S-100 (on- &amp; off pump)</td>
<td>3 months</td>
</tr>
<tr>
<td>(Basile et al., 2001)</td>
<td>Observational</td>
<td>16</td>
<td>&gt;S-100 and NSE</td>
<td>6 months</td>
</tr>
<tr>
<td>(Rasmussen et al., 2002)</td>
<td>Observational</td>
<td>15</td>
<td>&gt;NSE</td>
<td>discharge and 3 months</td>
</tr>
<tr>
<td>(Farsak et al., 2003)</td>
<td>Observational</td>
<td>50</td>
<td>&gt;S-100</td>
<td>discharge</td>
</tr>
<tr>
<td>(Mathew et al., 2003)</td>
<td>Observational</td>
<td>460</td>
<td>Reduced preoperative endotoxin immunity</td>
<td>6 weeks</td>
</tr>
<tr>
<td>(Jonsson et al., 2004)</td>
<td>Observational</td>
<td>56</td>
<td>&gt;S-100</td>
<td>6 months</td>
</tr>
<tr>
<td>(Kofke et al., 2004)</td>
<td>Observational</td>
<td>28</td>
<td>Apoepsilon4 allele, &gt;S-100</td>
<td>8 and 24hrs</td>
</tr>
<tr>
<td>(Snyder-Ramos et al., 2004)</td>
<td>Observational</td>
<td>64</td>
<td>&gt;S-100 and NSE</td>
<td>Throughout 7 days</td>
</tr>
<tr>
<td>(Kalman et al., 2006)</td>
<td>Observational</td>
<td>14</td>
<td>&gt;Cytokine interleukin-6</td>
<td>1 week and 6 months</td>
</tr>
<tr>
<td>(Ramlawi et al., 2006)</td>
<td>Observational</td>
<td>42</td>
<td>&gt;C-Reactive protein</td>
<td>6 hours and 4 days</td>
</tr>
<tr>
<td>(Lazibat et al., 2012)</td>
<td>Observational</td>
<td>62</td>
<td>&gt;S-100</td>
<td>2 days</td>
</tr>
<tr>
<td>(Bayram et al., 2013)</td>
<td>Comparative study</td>
<td>64</td>
<td>&gt;S-100</td>
<td>1 week</td>
</tr>
</tbody>
</table>

Studies showing no difference in post-operative cognitive outcome in the presence of high levels of biomarkers associated with inflammation

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>Biomarker(s)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Westaby et al., 2001)</td>
<td>Observational</td>
<td>1001</td>
<td>&gt;S-100 and NSE</td>
<td>5 days and 3 months</td>
</tr>
<tr>
<td>(Mathew et al., 2005)</td>
<td>Observational</td>
<td>440</td>
<td>Statin treatment</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>
All studies that have randomised patients to receive a heparin coated CPB system found neuropsychological outcome was better in patients receiving the heparin-coated circuit (Heyer et al., 2002; Baufreton et al., 2005; Fitch et al., 1999; Skrabal et al., 2006). In studies investigating inflammatory responses, a Consensus panel has concluded that ‘the use of surface-modified circuits might be effective at attenuating the systemic inflammatory response to CPB and improving outcome’ (Shann et al., 2006). Many markers associated with susceptibility to brain ischaemia such as, S-100beta and neuron-specific enolase (NSE) have been suggested to be associated with an increased risk of cognitive decline (Lazibat et al., 2012; Bayram et al., 2013; Westaby et al., 2001). Inflammation may also play an important role in our understanding of long-term cognitive function. Biomarkers for inflammation tend to be higher in patients with chronic cardiovascular disease (Bayram et al., 2013). Overall, the role of inflammation in the pathogenesis of cognitive decline appears to warrant further investigation (Carnevale et al., 2012).

### 1.8.5 Neuroprotective drugs

A number of neuroprotective agents have been investigated to assess whether these could be administered to help preserve neurocognitive function. The results of 17 studies investigating whether neuroprotective agents reduce the incidence of POCD are summarised in table 1.5.

**Table 1.5** RCTs investigating the efficacy of neuroprotection, or neuroprotective agents, in reducing cognitive decline after cardiac surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Type of neuroprotective drug</th>
<th>Time of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Grieco et al., 1996)</td>
<td>29</td>
<td>GM-100 (Ganglioside) or placebo</td>
<td>1 week and 6 months</td>
</tr>
<tr>
<td>(Arrowsmith et al., 1998)</td>
<td>171</td>
<td>Remacemide or placebo</td>
<td>2 months</td>
</tr>
</tbody>
</table>

NSE; neuron-specific enolase, PMEA; poly-2-methoxyethylacrylate
One of the most commonly used neuroprotective agents is Lidocaine, which featured in 4 of the 17 studies. Lidocaine is thought to inhibit inflammatory responses during cardiac surgery by modulation of inflammatory mediators, reduction in cerebral metabolism, and deceleration of ischaemic ion fluxes (Mitchell & Gorman, 2002). Two studies showed improved outcome with the use of the drug (Svensson et al., 2001; Wang et al., 2002), while two studies showed no difference (Mitchell et al., 2009; Mathew et al., 2009). Currently, no trials have demonstrated a reproducible clinically significant benefit conferred by the use of any particular neuroprotective drug.
1.8.6 Hypothermia and rewarming

The patient’s temperature during cardiac surgery has long been thought to play a role in neurological outcome. Several studies have focused their trials on whether reducing the metabolic demand of the brain through hypothermia is neuroprotective. Based on our literature search, 41 studies investigating the effects of temperature were identified. Seventeen studies were excluded from the final result due to lack of clarity in neuropsychological assessments and outcomes. Results from a total of 19 studies investigating the effect of temperature on pre- and post-operative neuropsychological tests are summarised in table 1.6.

Some studies suggest that hypothermia is more effective than normothermia in protecting the brain during surgery, however, other studies report no obvious difference between ‘mild hypothermia’ and ‘normothermia’ in terms of neuropsychological performance at discharge (49% and 45% respectively) and at 3 months (4% and 8% respectively) (Boodhwani et al., 2007).

Table 1.6 Studies investigating POCD associated with temperature during cardiac surgery.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Mean temperature (Celsius)</th>
<th>Time of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies showing a better post-operative cognitive outcome in favour of normothermia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Grimm et al., 2000)</td>
<td>RCT</td>
<td>144</td>
<td>1. Normothermia: 37°C 2. Hypothermia: 32°C</td>
<td>1 week and 4 months</td>
</tr>
<tr>
<td><strong>Studies showing an improvement in post-operative cognitive outcome in favour of hypothermia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Nathan et al., 1995)</td>
<td>Observational</td>
<td>30</td>
<td>Maintain ≤ 34°C</td>
<td>1 week</td>
</tr>
<tr>
<td>(Grocott et al., 2002)</td>
<td>Observational</td>
<td>300</td>
<td>Post-op hypothermia only</td>
<td>6 weeks</td>
</tr>
<tr>
<td>(Kadoi et al., 2004)</td>
<td>RCT</td>
<td>60</td>
<td>1. Normothermia: 37°C 2. Hypothermia: 32°C</td>
<td>1 month</td>
</tr>
<tr>
<td>(Boodhwani et al., 2006)</td>
<td>RCT</td>
<td>448</td>
<td>1. Normothermia: 37°C 2. Hypothermia: 34°C</td>
<td>1 week</td>
</tr>
<tr>
<td>(Hiraoka et al., 2012)</td>
<td>Observational</td>
<td>11</td>
<td>Hypothermia: 20-22°C</td>
<td>3 weeks and 6 months</td>
</tr>
<tr>
<td><strong>Studies showing no difference in post-operative outcome regarding temperature</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(McLean et al., 1994)</td>
<td>RCT</td>
<td>155</td>
<td>1. Hyperthermia: &gt;34°C 2. Hypothermia: &lt;28°C</td>
<td>5 days and 3 months</td>
</tr>
</tbody>
</table>
Some researchers have proposed that the brain could be susceptible to insult during rewarming from hypothermia, particularly if cerebral autoregulation mechanisms are unable to compensate for a sudden increase in metabolic activity associated with changes in temperature. Six studies have been conducted to examine the effect of rewarming rate on POCD, and all of these have shown a benefit in post-operative outcome associated with slower rewarming (table 1.7).
Chapter 1

Table 1.7 Studies investigating POCD associated with the rate of re-warming during cardiac surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>No. of patients</th>
<th>Mean temperature (Celsius)</th>
<th>Time of assessment</th>
</tr>
</thead>
</table>
| (Mora et al., 1996)    | RCT          | 138             | 1. Rewarm 1-2°C (per increase)  
2. Rewarm 3-5°C (per increase) | 1-3 days, 7-10 days & 1 month |
| (Nathan et al., 2001)  | Observational | 294             | 1. Rewarm to 34°C (1°C per increase)  
2. Rewarm to 37°C (3°C per increase) | 1 week and 3 months |
| (Grigore et al., 2002) | Observational | 100             | 1. Rewarm to 32°C (max within 3 mins)  
2. Rewarm to 37°C (max within 3 mins) | 6 weeks |
| (Kawahara et al., 2003)| RCT          | 100             | 1. Rewarm 1-2°C (per increase)  
2. Rewarm 4-5°C (per increase) | 1 month |
| (Nathan et al., 2007)  | RCT          | 223             | 1. Rewarm to 34°C (1°C per increase)  
2. Rewarm to 37°C (3°C per increase) | 1 week |
| (Sahu et al., 2009)    | RCT          | 80              | 1. Rewarm 1-3°C (per increase)  
2. Rewarm 3-5°C (per increase) | 5 days |

1.9 Summary

Interpreting the risk factors associated with postoperative cognitive decline, it seems that efforts to protect the brain during surgery are intrinsically linked with the need to control the progression of cardiovascular disease, especially in older patients. It is possible that patients may be exceeding a ‘threshold’ of pre-existing vulnerability where the brain’s ability to compensate for injuries or inflammation during surgery are absent. In summary, the literature examining underlying risk factors, and perioperative risk factors associated with the pathogenesis of cognitive decline suggests that there is no single factor responsible for postoperative cognitive decline or single intervention capable of protecting the brain during surgery. Overall, the pathogenesis of cognitive decline following surgery still remains unclear.
Chapter 2

2 Brain injury during cardiac surgery part II: Impact of new MRI lesions and embolic events on cognitive decline

2.1 New MRI lesions; Magnetic Resonance Imaging of the brain

Magnetic resonance imaging (MRI) of the brain provides an alternative method of identifying and quantifying brain injury after cardiac surgery (Ebinger et al., 2010; Merino et al., 2013). A range of imaging pulse sequences can be used, including diffusion weighted imaging (DWI) (Crisostomo et al., 2003) and FLuid Attenuated Inversion Recovery (FLAIR) (Ebinger et al., 2010).

The majority of previous studies have used DWI as their imaging modality. An advantage of using DWI is that preoperative assessment is unnecessary as DWI identifies acute ischaemic injury as bright lesions. DWI lesions typically appear within 2-3 hours of onset and are thought to resolve within 2-3 weeks (Crisostomo et al., 2003). A disadvantage of using DWI is that patients need to be scanned very soon after surgery (<48 hours), which is not always possible, and that acute DWI lesions may not reflect clinically significant long-term injuries. New ischaemic brain lesions can also be detected using FLAIR imaging, and once developed are usually permanent. Therefore, in assessing FLAIR images for the presence of new lesions it is important that a preoperative scan is carried out in order to be able to distinguish new lesions from old.

Acute ischaemic changes are visible using DWI MRI in 15-61% of patients following cardiac surgery (Gerriets et al., 2010; Messe et al., 2014) and new chronic ischaemic lesions are found in approximately 13% of patients using FLAIR (Lund et al., 2005). Lesions are typically multiple, small, and spherical, whose radiographic appearance is strongly suggestive of embolisation (Restrepo et al., 2002; Bendszus et al., 2002; Knipp et al., 2005). To the best of our knowledge, no studies have attempted to quantify the accumulation of new ischaemic injuries against a backdrop of chronic pre-existing cerebrovascular disease.
2.2 MRI lesions after cardiac surgery - Literature search

A number of studies have investigated whether there is an association between postoperative MRI brain lesions and cognitive decline after cardiac surgery.

To investigate the incidence of MRI lesions and cognitive decline a systematic literature search, drawing on papers from PubMed and EMBASE was performed. All studies published in English between June 1967 and August 2013 and featuring adult human subjects were eligible for review.

Search terms were created by combining the following medical subject headings (MeSH terms):

#1: "Coronary Artery Bypass" OR "Coronary Artery Bypass, Off-Pump" OR "Valve Surgery" OR "Thoracic Surgery" OR "Cardiac Surgical Procedures"

AND

#2: "Cognitive Therapy" OR "Cognition Disorders" OR "Cognition" OR "Neuropsychology" OR "Neuropsychological Tests" OR "Mild Cognitive Impairment"

AND

#3: "Brain Infarcts" OR "Cerebral Infarction" OR "Ischaemic lesions" OR "Lacunes"

Abstracts involving cardiac surgery, cognitive function and MRI outcome (#1 AND #2 AND #3) were independently reviewed by two investigators (N. Patel and E.M.L. Chung) and studies of adult cardiac surgery patients that assessed both pre- and post-operative assessments were identified for full manuscript review. Abstracts were excluded if they involved paediatric surgery, operations other than cardiac surgery, or no measurement of cognitive function. Case reports and studies of cardiac procedures such as angioplasty, angiography, valvuloplasty and Transcatheter Aortic Valve Implantation (TAVI) were also excluded. Studies generating multiple publications from the same cohort were reported only once. Where there was disagreement among investigators the full text was reviewed. Additionally, the reference lists of selected
articles were evaluated for any additional articles of interest. Articles short-listed for full manuscript review were summarised in an Excel spreadsheet listing the: study design (observational, RCT, etc.), number of patients, type(s) of surgery, outcome measures, and time point of neurocognitive assessment.

A total of 33 articles were extracted for full text review, and a total of 19 articles were included in our final summary of results, table 2.1. Studies were excluded if patients did not complete a battery of pre- and post-operative neuropsychological tests. Of these, 2 studies observed no MR changes in their patients and 6 studies concluded that postoperative MRI changes were significantly associated with cognitive decline. Eleven studies found no evidence of an association between new lesions and cognitive decline but these studies were mostly small and focussed on acute changes observed using DWI MRI.

**Table 2.1** Studies investigating POCD associated with the postoperative MRI lesions (obsv.: observational)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Type of surgery (n)</th>
<th>MRI scan (Field Strenght)</th>
<th>Incidence of new lesions (%) (time of post-op scan)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies concluding that new ischaemic lesions are associated with neuropsychological impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Toner et al., 1994)</td>
<td>RCT</td>
<td>CABG (n= 15)</td>
<td>T2-weighted spin-echo (0.5T)</td>
<td>26 (1 week)</td>
</tr>
<tr>
<td>(Goto et al., 2001)</td>
<td>Obsv.</td>
<td>CABG (n= 421)</td>
<td>DWI (1.5T)</td>
<td>50 (1 week)</td>
</tr>
<tr>
<td>(Restrepo et al., 2002)</td>
<td>Obsv.</td>
<td>CABG (n= 13)</td>
<td>DWI (1.5T)</td>
<td>31 (5 days)</td>
</tr>
<tr>
<td>(Barber et al., 2008)</td>
<td>Obsv.</td>
<td>Valve (n= 30) Combined (n= 6)</td>
<td>DWI (1.5T)</td>
<td>43 (5 days)</td>
</tr>
<tr>
<td>(Schwarz et al., 2011)</td>
<td>Obsv.</td>
<td>CABG (n= 47)</td>
<td>DWI (1.5T)</td>
<td>18 (3 days)</td>
</tr>
<tr>
<td>(Ito et al., 2012)</td>
<td>Obsv.</td>
<td>CABG (n= 449)</td>
<td>T1- and T2-weighted scans</td>
<td>49 (unclear)</td>
</tr>
</tbody>
</table>
### Studies showing no association between new ischaemic lesions and neuropsychological impairment

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>MRI Protocol</th>
<th>Timepoint</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Sylivris et al., 1998)</td>
<td>Obsv. CABG (n= 28)</td>
<td>T1- and T2-weighted scans (1.5T)</td>
<td>18 (1 week)</td>
<td>‘There was no relationship between MR changes and neuropsychological deficit.’</td>
</tr>
<tr>
<td>(Vanninen et al., 1998)</td>
<td>Obsv. CABG (n= 38)</td>
<td>T2-weighted (1.5T)</td>
<td>21 (8 days)</td>
<td>‘MRI lesions did not correlate with neuropsychological deficit.’</td>
</tr>
<tr>
<td>(Bendszus et al., 2002)</td>
<td>Obsv. CABG (n= 35)</td>
<td>DWI (1.5T)</td>
<td>26 (3-5 days)</td>
<td>‘There was no significant association between the presence of a new lesion and neuropsychological deficit.’</td>
</tr>
<tr>
<td>(Knipp et al., 2004)</td>
<td>Obsv. CABG (n= 29)</td>
<td>DWI (1.5T)</td>
<td>45 (3 months)</td>
<td>‘No statistical correlation between the presence of new brain lesions on MRI and neuropsychological deficit.’</td>
</tr>
<tr>
<td>(Knipp et al., 2005)</td>
<td>Obsv. Valve (n= 30)</td>
<td>DWI (1.5T)</td>
<td>47 (5 days)</td>
<td>‘There was no significant association between the presence of new lesions and neuropsychological deficit at 5 days or 4 months.’</td>
</tr>
<tr>
<td>(Lund et al., 2005)</td>
<td>RCT CABG (n= 120)</td>
<td>FLAIR (1.5T)</td>
<td>13 (3 months)</td>
<td>‘There was no significant correlation between the presence of a new lesion and neuropsychological deficit.’</td>
</tr>
<tr>
<td>(Cook et al., 2007)</td>
<td>Obsv. Cardiac surgery (n= 50)</td>
<td>DWI (1.5T)</td>
<td>32 (5 days)</td>
<td>‘There does not appear to be any relationship between early or persistent cognitive change and new MRI lesions.’</td>
</tr>
<tr>
<td>(Gottesman et al., 2007)</td>
<td>Obsv. CABG (n= 13)</td>
<td>DWI (1.5T)</td>
<td>46 (3-5 days)</td>
<td>‘The relationship between DWI and early cognitive dysfunction is unclear.’</td>
</tr>
<tr>
<td>(Knipp et al., 2008)</td>
<td>Obsv. CABG (n= 20)</td>
<td>DWI (1.5T)</td>
<td>51 (discharge)</td>
<td>‘An association of early or late cognitive changes to new ischemic brain lesions on DWI was not found in this cohort.’</td>
</tr>
<tr>
<td>(Gerriets et al., 2010)</td>
<td>RCT CABG Embol-X (n= 43) Dynamic bubble trap (n= 50)</td>
<td>DWI (1.5T)</td>
<td>15 (3 days)</td>
<td>‘The number of new lesions did not correlate with early or late POCD.’</td>
</tr>
<tr>
<td>(Mirow et al., 2011)</td>
<td>RCT CABG (n= 63)</td>
<td>DWI (1.5T)</td>
<td>20 (discharge)</td>
<td>‘The number of new lesions did not correlate with postoperative neurological complications.’</td>
</tr>
</tbody>
</table>

### Studies showing no new neuropsychological deficit or MRI abnormalities

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>MRI Protocol</th>
<th>Timepoint</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Eifert et al., 2003)</td>
<td>RCT CABG (n= 17)</td>
<td>Valve (n= 4) Combined (n= 12)</td>
<td>0 (5 days)</td>
<td>‘No patients developed neuropsychological deficit or MR abnormalities.’</td>
</tr>
<tr>
<td>(Agarwal et al., 2010)</td>
<td>Obsv. CABG (n= 11)</td>
<td>Valve (n= 8)</td>
<td>FLAIR (1.5T)</td>
<td>0 (4-6 weeks)</td>
</tr>
</tbody>
</table>
Prior to the advent of DWI, T$_2$-weighted imaging was used to detect new postoperative lesions (Toner et al., 1994). In a study by Toner et al., 4 out of 15 patients with new MRI abnormalities were all found to have significant neuropsychological deficits. Toner et al. concluded that these preliminary data suggest a link between structural brain changes and cerebral function after CABG (Toner et al., 1993). More recent studies have used DWI to detect acute cerebral injury. These suggest that acute cerebral injury is common and often more extensive than clinical symptoms would suggest (Wityk et al., 2001).

The earliest DWI study by Goto et al. reported new ischaemic lesions in 50% of patients after CABG surgery and concluded that lesions seen immediately after cardiac surgery correlated to cognitive decline (Goto et al., 2001). Another study investigating cognitive decline in relation to DWI lesions immediately after surgery concluded that postoperative lesions were of embolic origin and unrelated to any neurological symptoms or decline in neurocognitive performance (Bendszus et al., 2002). Subsequent trials have confirmed the proportion of patients receiving new ischaemic lesions ranges from 31% (Restrepo et al., 2002) to 51% (Knipp et al., 2008) after CABG surgery and 32% (Stolz et al., 2004) to 47% (Knipp et al., 2005) for valve surgery. In both CABG and valve surgery, the pattern of new lesions is found to be consistent with an embolic pathogenesis (Cook et al., 2007). Atheromatous disease of the aorta may be an important factor in predicting the risk of new MRI lesions. A study of 110 patients by Djaiani et al. observed new DWI lesions in 60% of patients who suffered from moderate atherosclerosis in the aorta and the aortic arch, in comparison to 0% of patients with no atherosclerotic disease (Djaiani et al., 2004). It has been shown in various studies that factors linked to the risk of receiving new ischaemic lesions include the patient’s age (Djaiani et al., 2004; Stolz et al., 2004), presence of pre-existing lesions or pre-existing white-matter disease (Bendszus et al., 2002; Stolz et al., 2004; Lund et al., 2005), and the presence of atheroma burden (Djaiani et al., 2004).

### 2.3 Clinical significance of new MRI lesions

Although high proportions of patients experience new lesions after cardiac surgery, the majority of lesions are clinically silent and do not appear to generate any noticeable neuropsychological impairment. Lesion location is crucial in determining the likelihood of generating clinical symptoms (Sudo et al., 2004). Previous studies suggest that only
7% of patients with symptomatic ischaemic lesions peri-operatively showed subsequent neurocognitive impairment once their symptoms had resolved (Kang et al., 2003).

### 2.4 Embolus detection using transcranial Doppler (TCD)

In a cardiac surgery setting, TCD can be used to measure cerebral blood flow velocity (CBFv) and detect embolic material entering the cerebral circulation. TCD studies suggest that the number of emboli experienced during surgery varies widely between patients. Factors such as length of procedure, type of surgery, and number of surgical and perfusionist interventions are all closely linked with the number and timing of embolic counts. Previous studies have demonstrated that emboli mainly occur during aortic cannulation, removal of the aortic cross clamp, initiation of CPB, during cardiac ejection, and at the end of CPB (van der Linden & Casimir-Ahn, 1991; Barbut et al., 1994; Hartman et al., 1996; Barbut et al., 1996). Potential sources of emboli during surgery are summarised in figure 2.1.
Figure 2.1 Schematic diagram of a cardiopulmonary bypass circuit. Atherosclerotic debris can be dislodged from diseased arteries during surgery. Air bubbles can also be introduced into the circulation via, trapped air in the chambers of the heart, leakage of air into the venous cannula, the cardiotomy reservoir, the venous reservoir, air bubbles generated by the pump and air introduced by injection of drugs or blood sampling. Note that all emboli entering through the arterial line usually pass through a ~40 μm line filter.

A. Application of the aortic cross-clamp - solid emboli
B. Atherosclerotic debris dislodged from diseased arteries during cannulation – solid emboli
C. Air bubbles introduced into the circulation via the cardiopulmonary bypass circuit
D. Leakage of air into the venous cannula – gaseous emboli
E. The cardiotomy suction/reservoir - gaseous emboli & lipid microparticles
F. The venous reservoir - gaseous emboli
G. Air bubbles generated by the pump – gaseous emboli
H. Perfusionist and anaesthetist interventions – gaseous emboli
I. Air introduced by injection of drugs or blood sampling – gaseous emboli
J. Release of trapped air in the chambers of the heart – gaseous emboli
2.4.1 Clamping

Clamp applications when constructing the coronary artery bypass graft are known to be a common source of cerebral emboli (Boivie et al., 2003). In a prospective RCT of 46 patients, Hammon et al. showed that the use of a partial occluding (side-biting) clamp was linked with a higher rate of neuropsychological decline 6 months after CABG. In contrast, the use of a single cross-clamping technique was found to significantly \( (p=0.005) \) reduce the proportion of patients experiencing cognitive decline from 57% to 33% (Hammon et al., 2006). Hammon et al. therefore recommend avoiding the use of partial occluding clamps during CABG whenever possible. The use of a proximal aorta coronary anastomosis device (called ‘stitch-less’), which eliminates the need for aortic cross-clamp application, has also been shown to reduce cerebral emboli (Calafiore et al., 2001). Another study by Barbut et al. used TCD to detect embolic signals in 20 patients undergoing CABG surgery. Thirty-four percent of embolic signals were reported to be associated with removal of the aortic cross-clamp, and another 24% with removal of aortic partial occlusion clamps (Barbut et al., 1994). This suggests that over half of emboli detected during surgery were associated with the release of clamps. Emboli detected following the removal of clamps are more likely to be clinically significant than emboli during other stages of surgery, as these have potential to contain pieces of aortic atheroma which pass direct to the brain without being captured by the 40 µm arterial line filter.

2.4.2 Cannulation and aortic arch atheroma

The choice of site for aortic cannulation is also thought to influence the numbers of cerebral emboli (Mullges et al., 2001). A study by Borger et al. (1999) involving 34 patients undergoing CABG surgery showed that cannulation of the distal aorta was associated with fewer cerebral emboli. The authors concluded that arch cannulation, is associated with lower peak aortic flow velocities than conventional short, right-angled, cannulas (Borger et al., 1999). A decrease in flow velocity, and positioning of the cannula tip below the left subclavian artery, is thought to result in decreased embolisation from the atherosclerotic artery wall. Several studies (Karalis et al., 1991; Toyoda et al., 1992; Katz et al., 1992; Stern et al., 1999) have investigated the relationship between aortic atheroma and perioperative stroke. A study by Katz et al...
(1992), demonstrated that patients with aortic arch atheroma had a significantly higher incidence of perioperative stroke (15%) compared to patients without significant disease (2%) (Katz et al., 1992). One of the patients studied by Katz et al. experienced perioperative stroke after cannulation through an aortic arch plaque. Stern et al (1999) investigated the outcome of 268 patients, all of whom had been identified by transesophageal echocardiography (TOE) as possessing significant (>5 mm) aortic arch atheroma, and found that perioperative stroke occurred in 11.6% of patients (Stern et al., 1999).

2.4.3 Number of perfusionist interventions

Perfusionist events have also been linked to the number of embolic signals detected using TCD. Studies by Taylor et al. and Lynch et al. demonstrated that cerebral emboli were more likely to be detected during sampling of blood or injection of drugs due to the introduction of small air bubbles to the CPB circuit (Taylor et al., 1999). The number and timing of embolic signals detected by TCD during cardiac surgery is found to be closely linked to the timing of perfusionist and surgical interventions. Taylor et al. used TCD to monitor 18 CABG patients and found that perfusionist and surgical interventions both generated a significant rise in embolisation compared to baseline figures (Taylor et al., 1999), table 2.2.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Number of emboli / minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline embolisation</td>
<td>0.4 ± 0.5</td>
</tr>
<tr>
<td>Surgical Interventions</td>
<td>1.5 ± 1.5</td>
</tr>
<tr>
<td>Blood sampling</td>
<td>4.5 ± 5.8</td>
</tr>
<tr>
<td>Drug administration</td>
<td>10.2 ± 5.0</td>
</tr>
</tbody>
</table>

A study by Borger et al. demonstrated that patients experiencing high numbers of perfusionist events had a worse postoperative neuropsychological outcome (Borger et
In a small study by Lynch et al., 34 patients were monitored during cardiac surgery and it was found that patients receiving more than 10 perfusionist interventions had a greater decline in neuropsychological outcome than the patients who received 10 or fewer interventions (Lynch & Riley, 2008). However, the number of perfusionist interventions may also reflect the complexity of the surgery and is therefore unlikely to be casual.

### 2.4.4 The cardiopulmonary bypass (CPB) machine

Development of the CPB circuit was critical to the development of modern cardiac surgery techniques. Although, neuropsychological dysfunction, was first noted early after the use of CPB, and has since long been suspected a cause of neuropsychological impairment (sometimes referred to as ‘pump-head’), the literature suggests no difference in ‘on-pump’ and ‘off-pump’ cognitive decline. Several key components of the CPB circuit and surgical procedures have also been independently investigated, such as CPB filters, coating of the CPB circuit, cell saver and cardiotomy suction, cannulation, clamping and de-airing process during weaning off bypass. However, none of the modifications introduced so far appear to confer significant cognitive benefit.

There are a number of methods the perfusionist can use to minimise introduction of bubbles to the circuit during surgery. For example, Rodriguez et al. showed that by removing air from the venous line before starting CPB, the number of emboli is clearly reduced (Rodriguez et al., 2006). A study by Pugsley et al, which involved 100 patients undergoing CABG surgery, demonstrated the efficacy of arterial line filtration and showed that filtration was associated with an improved score in postoperative neuropsychological test performance. More patients were found to have neuropsychological deficits in the group without the arterial line filter at both 8 days ($p<0.05$) and 8 weeks ($p<0.03$) after surgery (Pugsley et al., 1994). There are several parts of the CPB machine that are potential sources of small air bubbles. Clinical trials suggest that membrane oxygenators produce less emboli than bubble oxygenators (HELMSWORTH et al., 1963; Deverall et al., 1988). Studies have also shown that avoiding CPB during cardiac surgery reduces the number of emboli (Novitzky & Boswell, 2000; Watters et al., 2000). In a study by Lund et al, which compared embolic counts detected using TCD in 60 patients randomised to either off-pump or on-pump
CABG surgery, researchers found a statistically significant reduction in the number of emboli that patients received during ‘off pump’ surgery compared to the ‘on pump’ procedure (Lund et al., 2003). An increased number of emboli entering the cerebral circulation were found by Patel et al (1996) to be a strong indicator for poorer neuropsychological outcome following arterial blood gas management during CPB.

The two types of pump used during CPB are roller pumps and centrifugal pumps. Roller pumps have the advantage of administering pulsatile flow. A previous study by Scott et al. randomised 103 patients to receive either roller or centrifugal pumps during CABG surgery (Scott et al., 2002). The investigators found a lower incidence of neuropsychological dysfunction with the centrifugal device (33%) over the roller pump (51%) on the fifth day postoperatively, but this was not statistically significant ($p=0.08$).

In a larger retrospective study, 4000 patients undergoing CABG and/or valve surgery were studied over a 5 year period. The investigators found a lower rate of coma and postoperative stroke for the patients who were operated with the centrifugal pump (Parolari et al., 2000). Unfortunately, this larger study did not include detailed neurocognitive testing. At present, it is unclear whether the type of pump used has any impact on cognition.

Venous reservoirs are generally classified as ‘open’ or ‘closed’ depending on whether the reservoir is open to air. So far, no clinical studies have studied a difference in cerebral embolisation and neurocognitive outcome between the two types of reservoir. In an *in vivo* study, Mitchell et al. used an *ex vivo* model to show that operating the CPB circuit with low volumes in open reservoirs was associated with a higher risk of air embolisation (Mitchell et al., 1997). In 2006, open venous reservoirs were used in over 80% of cardiac surgery centres (Baker & Willcox, 2006).

The introduction of arterial line filters was another important development in reducing cerebral embolic injury during CPB. Loop et al. in 1976 used ultrasonic insonation of the arterial line proximal and distal to a 20 µm woven nylon mesh arterial filter and showed a 90% reduction in observed emboli with the use of the filter (Loop et al., 1976). One of the earliest studies which monitored the middle cerebral artery (MCA) using transcranial Doppler during cardiac surgery was by Padayachee et al. The investigators demonstrated that arterial line filters resulted in a significant reduction of emboli detected (Padayachee et al., 1988). After a number of years, subsequent studies
with similar results led a consensus group to recommend arterial line filters during the application of CPB (Shann et al., 2006).

The dynamic bubble trap directs gaseous microbubbles to the middle of the CPB tubing flow to aid with removal of bubbles. The efficacy of the bubble trap was demonstrated in a randomised controlled trial (RCT) by Schoenburg et al and resulted in a 70% reduction of gaseous microemboli detected in the MCA for patients undergoing CABG (Schoenburg et al., 2003).

Cardiotomy suction is an effective tool for recycling shed blood and reducing the levels of blood loss during CPB. However, drained blood that has been suctioned from the operative field through cardiotomy suction has been shown to contain high levels of lipid microparticles and other cellular debris arising from the sternotomy incision (Kincaid et al., 2000). These lipid microparticles can be found in the cerebral vasculature after cardiac surgery using laser microprobe mass spectrometry (Challa et al., 1998). Liu et al. were one of the first groups of investigators to demonstrate a link between cardiotomy suction and the number of emboli in the CPB circuit measured by a Coulter counter (Liu et al., 1992).

The use of blood salvage devices to process the blood before returning it to the venous reservoir may reduce the number of particulate emboli. Two prospective randomised double-blinded clinical trials have investigated the effects of blood processing through the cell saver system, as opposed to cardiotomy suction, on cognitive outcome following cardiac surgery. The first RCT included 264 patients undergoing CABG and/or valve surgery. This failed to show any positive benefit of using a cell saver on POCD (Boodhwani et al., 2007). Ruben et al. randomised 268 patients and concluded that there was no difference in the number of observed cerebral emboli or the incidence of neuropsychological dysfunction between the two groups (Rubens et al., 2007). In contrast, a further trial performed by Djaiani et al. randomised 226 patients and found a lower risk of neuropsychological impairment 6 weeks after surgery in the cell saver group (6% versus 15%, \( p=0.04 \)), however, there was no difference in the number of cerebral emboli and their findings of a reduction in the incidence of cognitive decline were of borderline statistical significance (Djaiani et al., 2007). Reduction of both platelet and coagulation factors due to the washing process is an undesirable side effect of processing the cardiotomy blood and both studies showed an increase in bleeding and
requirement for blood transfusion. To date, it is unclear whether the potential benefits of recycling the blood outweigh the disadvantages.

2.5 Neuropsychological outcomes for off-pump and on-pump CPB

Given that neuropsychological impairment is often thought to be associated with the use of CPB, an off-pump surgery technique was developed (Murkin et al., 1999). A systematic review and meta-analysis performed by Marasco et al. in 2008 included eight trials incorporating 892 patients in total, and found no significant difference between neuropsychological outcomes when comparing patients undergoing off- and on-pump CABG surgery (Marasco et al., 2008). Since then, an additional 8 RCTs comparing off- and on-pump CABG have been conducted (Hernandez et al., 2007; Yin et al., 2007; Jensen et al., 2008; Tully et al., 2008; Sousa Uva et al., 2010; Kozora et al., 2010; Lamy et al., 2013; Shroyer et al., 2009). Kozora et al. investigated neuropsychological outcome up to a year after surgery in 1,156 patients randomised to either off- or on-pump CABG. The study concluded that neither on- nor off-pump surgery adversely impacts long-term neurocognitive function (Kozora et al., 2010). One of the largest of these studies was by Shroyer et al. 2009, who investigated neuropsychological outcome in 2203 patients randomly assigned to either on- or off-pump surgery. Neuropsychological outcomes were similar in both groups 1 year postoperatively (Shroyer et al., 2009). Another RCT by Motallebzadeh et al. investigated neurocognitive outcome on 212 patients randomly assigned to either off- or on-pump surgery concluded that off-pump surgery was linked to a better cognitive outcome at discharge but there was no significant difference at 6 weeks or 6 months (Motallebzadeh et al., 2007). Whilst the neuropsychological outcomes may differ slightly at hospital discharge, these RCTs have found no difference in neuropsychological outcomes between off-pump and on-pump CABG surgery with a postoperative follow-up of up to 6 months to 1 year. The only study to investigate neuropsychological impairment over 2 years postoperatively found no differences between the on- and off-pump groups in CABG surgery at 5 years (van Dijk et al., 2007).
Seventeen RCTs (Van Dijk et al reported 3 times, counted as one) assessing neurocognitive outcome after on- and off-pump cardiac surgery are summarised in table 2.3.

**Table 2.3** Randomised controlled trials investigating POCD associated with on- and off-pump cardiac surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Total no. patients (on-pump/off-pump)</th>
<th>Outcome measures (postoperative testing)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies favouring the off-pump procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Diegeler et al., 2000)</td>
<td>40 (20/20)</td>
<td>TCD (embolic load)</td>
<td>‘POCD seems to be strongly associated to CPB and the occurrence of emboli’.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cognitive tests (1 week)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>S-100β serum levels</td>
<td></td>
</tr>
<tr>
<td>(Zamvar et al., 2002)</td>
<td>60 (30/30)</td>
<td>Neuropsychological tests (1 week/10weeks)</td>
<td>‘Off-pump surgery resulted in less neurocognitive impairment than on-pump surgery’.</td>
</tr>
<tr>
<td>(Motallebzadeh et al., 2007)</td>
<td>212 (104/108)</td>
<td>TCD (embolic load)</td>
<td>‘At discharge, neurocognitive function is better after off-pump surgery, possibly as a result of the lower embolic load. However, the difference in neurocognitive function does not persist at 6 weeks and 6 months.’</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuropsychological tests (discharge/6 weeks/6 months)</td>
<td></td>
</tr>
<tr>
<td>(Puskas et al., 2011)</td>
<td>87 (44/43)</td>
<td>Neuropsychological tests (mean of 7.5 years) MRI-FLAIR</td>
<td>‘After a mean of 7.5 years of follow-up, patients undergoing off-pump surgery performed marginally better than on-pump technique in several cognitive domains; these differences were small and of uncertain clinical importance. Early MRI showed no significant differences in acute cerebral infarctions between the off-pump and on-pump groups.’</td>
</tr>
<tr>
<td><strong>Studies showing no difference in POCD outcome after on- or off-pump surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Van Dijk et al., 2002)</td>
<td>281 (139/142)</td>
<td>Cognitive tests (3months/1year)</td>
<td>‘No statistically significant differences were observed between the on-pump and off-pump groups in quality of life, stroke rate, or mortality at 3 and 1 year’.</td>
</tr>
<tr>
<td>(Keizer et al., 2003)</td>
<td>81 (36/45)</td>
<td>Cognitive tests &amp; questionnaire (1year)</td>
<td>‘Irrespective of the type of surgical technique (on-pump v off-pump), POCD does not result in substantial impairment 1 year after cardiac surgery’.</td>
</tr>
<tr>
<td>(van Dijk et al., 2004)</td>
<td>281 (139/142)</td>
<td>Cognitive tests (4 days/3months)</td>
<td>‘Early cognitive decline is not significantly influenced by the use of CPB.’</td>
</tr>
<tr>
<td>(Kobayashi et al., 2005)</td>
<td>(167) 81/86</td>
<td>S-100β serum levels</td>
<td>‘Off-pump technique was as safe as the on-pump technique.’</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cognitive tests (2 months weeks)</td>
<td></td>
</tr>
<tr>
<td>(Lund et al., 2005)</td>
<td>106 (52/54)</td>
<td>Neuropsychological tests (3 months/1year)</td>
<td>‘Long-term cognitive function and magnetic resonance imaging evidence of brain injury were similar after off-pump and on-pump surgery.’</td>
</tr>
</tbody>
</table>
The majority of studies found no evidence to support the hypothesis that use of CPB was associated with worse cognitive outcome, fig 2.2. In the few studies favouring off-pump surgery, sample sizes were small (i.e. the studies were more likely to be underpowered, or differences were either short-term or marginal).
Figure 2.2 Majority of the RCTs showed no evidence that CPB was associated with cognitive decline. Only 4 RCTs (299 patients) favoured off-pump compared to 13 RCTs (4748 patients) showing no difference.

2.6 Cardiac de-airing and weaning from bypass

Large numbers of bubbles are observed by TCD during de-airing of the heart and resumption of cardiac contractions due to the release of air that becomes entrained in the cardiac chambers during surgery. Although several mechanical de-airing techniques can be employed, such as use of the Trendelenburg position, aspiration, and gentle squeezing of the heart, none of these methods is completely effective at eliminating emboli. A further method of reducing air emboli during cardiac surgery is by flooding the operative area with carbon dioxide (CO₂). CO₂ is heavier than air, and therefore sinks to the bottom of the chest cavity. By surrounding the wound with CO₂ rather than air, any bubbles introduced to the circulation consist of fast dissolving CO₂ which is highly soluble and dissolves easily into the bloodstream. A study by Svenarud et al. randomised 20 patients undergoing valve surgery to flooding of the operative area with CO₂ and found a 78% reduction in the number of emboli (Svenarud et al., 2004). Another similar study by Martens et al. randomised 80 patients to CO₂ field flooding and found ‘auditory-evoked potentials’ (small electrical voltage potentials originating
from the brain recorded from the scalp in response to an auditory stimulus) were improved in the CO$_2$ group compared to the control group. However, Martens et al. failed to show any significant differences in neuropsychological outcome between the CO$_2$ group and controls (Martens et al., 2008). A multicentre RCT by Chaudhuri et al. compared neurocognitive outcomes 6 weeks postoperatively in 125 patients undergoing open chamber cardiac surgery who were assigned to CO$_2$ insufflation or placebo (control group). The investigators concluded that CO$_2$ insufflation did not improve cognitive outcome (Chaudhuri & Marasco, 2011).

2.7 Link between number of emboli detected on TCD and the risk of perioperative stroke

Several observational studies have investigated potential links between the number of emboli detected during surgery and stroke risk (Salazar et al., 2001; McKhann et al., 2002; Ritzl et al., 2004; Lynch & Riley, 2008). The main difficulty of using ‘stroke’ as an end-point/outcome is that the event rate is low, which means studies are generally underpowered. A study by Lynch et al. (2008) comparing the total number of emboli during surgery with the incidence of stroke in 82 CABG patients found that 4 suffered a stroke. Interestingly, the number of emboli recorded in these 4 stroke patients was almost 3 times higher than the average number of emboli detected in the remaining 78 ‘stroke free’ patients. The same study found that patients experiencing greater numbers of emboli also tended to have longer hospital stays. Patients who experienced more than 500 embolic signals spent over 6 times longer in hospital compared to patients with less than 100 embolic signals (table 2.4) (Lynch & Riley, 2008). Again, an explanation for this association may be that high numbers of emboli are associated with more difficult cases in patients with extensive atherosclerosis disease. The longer surgery times and complexity of the procedure have potential to result in both longer hospital stays and more emboli, but the two are not necessarily causally related.
Table 2.4 Higher numbers of embolic signals are associated with longer hospital stay (Lynch & Riley, 2008).

<table>
<thead>
<tr>
<th>Number of emboli</th>
<th>Number of patients</th>
<th>Number of days in hospital ($p = 0.0007$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100</td>
<td>40</td>
<td>8.6</td>
</tr>
<tr>
<td>100-300</td>
<td>23</td>
<td>13.5</td>
</tr>
<tr>
<td>300-500</td>
<td>16</td>
<td>16.3</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>6</td>
<td>55.8</td>
</tr>
</tbody>
</table>

2.8 Emboli and cognitive decline - Literature search

A number of studies have investigated whether there is an association between intraoperative emboli and cognitive decline after cardiac surgery.

To investigate this question, a systematic literature search drawing on papers from PubMed and EMBASE was performed. All studies published in English between June 1967 and August 2013 and featuring adult human subjects were eligible for review.

Search terms were created by combining the following medical subject headings (MeSH terms):

#1: "Coronary Artery Bypass" OR "Coronary Artery Bypass, Off-Pump" OR "Valve Surgery" OR "Thoracic Surgery" OR "Cardiac Surgical Procedures"

AND

#2: "Cognitive Therapy" OR "Cognition Disorders" OR "Cognition" OR "Neuropsychology" OR "Neuropsychological Tests" OR "Mild Cognitive Impairment"

AND

#3: "Emboli" OR "Transcranial Doppler" OR "Doppler ultrasound" OR "Embolism" OR "Intracranial embolism" OR "Microemboli"
Abstracts involving cardiac surgery, cognitive function and intraoperative emboli (#1 AND #2 AND #3) were independently reviewed by two investigators (N. Patel and E.M.L. Chung) and studies of adult cardiac surgery patients that assessed both pre- and post-operative assessments were identified for full manuscript review. Abstracts were excluded if they involved paediatric surgery, operations other than cardiac surgery, or no measurement of cognitive function. Case reports and studies of cardiac procedures such as, angioplasty, angiography, valvuloplasty and Transcatheter Aortic Valve Implantation (TAVI) were also excluded. Studies generating multiple publications from the same cohort were reported only once. Where there was disagreement among investigators the full text was reviewed. Additionally, the reference lists of selected articles were evaluated for any additional articles of interest. Articles short-listed for full manuscript review were summarised in an Excel spreadsheet listing the; the study design (observational, RCT, etc.), number of patients, type(s) of surgery, outcome measures, and time point of neurocognitive assessment.

A total of 29 articles were extracted for full text review, and a total of 19 studies have investigated whether neuropsychological impairment is related to the number of emboli entering the MCA territories during surgery, table 2.5. Of these, 9 studies observed the incidence of emboli to be significantly associated with cognitive decline. However, the majority of studies had <50 patients and are likely to be underpowered. Nine studies found no evidence of an association between intraoperative emboli and cognitive decline. One study was excluded from further review because of limited information on TCD use and application. The remaining 18 studies are summarised in table 2.5.
Table 2.5 Studies investigating the relationship between POCD and embolic load (obsv: observational)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Type of surgery (n)</th>
<th>Embolus detection criteria</th>
<th>Median/Mean number of emboli (range)</th>
<th>Comment (postoperative testing)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies showing a positive association between embolic load and subsequent neuropsychological impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Clark et al., 1995)</td>
<td>Obsv.</td>
<td>CABG (n= 120)</td>
<td>All emboli detected &gt;40 dB</td>
<td>Mean: 22 (0-251)</td>
<td>Patients with the highest number of emboli had the highest incidence of POCD (5-10 days).</td>
</tr>
<tr>
<td>(Braekken et al., 1998)</td>
<td>Obsv.</td>
<td>CABG (n= 14)</td>
<td>All emboli detected &gt;3 dB</td>
<td>Mean: CABG: 1155 (151-3074) Valve: 2083 (251-451)</td>
<td>A positive association between emboli and POCD was seen in the valve group but not in the CABG group (2 months)</td>
</tr>
<tr>
<td>(Sylivris et al., 1998)</td>
<td>Obsv.</td>
<td>CABG (n= 41)</td>
<td>All emboli detected &gt;3 dB</td>
<td>Mean: 1,038 ± 4,164 (not stated)</td>
<td>Embolic load during surgery was associated with early POCD. Additionally, patients who showed evidence of strokes during CABG had a higher embolic load during the pre-incision phase than those without cerebral infarction (1 week).</td>
</tr>
<tr>
<td>(Fearn et al., 2001)</td>
<td>Obsv.</td>
<td>CABG (n= 70)</td>
<td>All emboli detected &gt;8 dB</td>
<td>Median: 225 (not stated)</td>
<td>The number of emboli is linked to the cause of memory deficits. Cerebral hypoperfusion impaired subsequent attention in postoperative tests (1 week, 2 &amp; 6 months).</td>
</tr>
<tr>
<td>(Whitaker et al., 2004)</td>
<td>RCT</td>
<td>CABG (n= 192)</td>
<td>Not clear</td>
<td>Median: 67 (5-846)</td>
<td>A lower number of emboli showed a strong trend towards improving cognitive performance (6-8 weeks).</td>
</tr>
<tr>
<td>(Abu-Omar et al., 2006)</td>
<td>Obsv.</td>
<td>CABG (n= 15)</td>
<td>An additional reference probe to reject artefacts</td>
<td>Median: 254 (116-397)</td>
<td>Patients undergoing the use of CPB surgery have a significant relative reduction in prefrontal activation, which correlates with intraoperative cerebral embolic load (4 weeks).</td>
</tr>
<tr>
<td>(Bokeria et al., 2007)</td>
<td>Obsv.</td>
<td>CABG (n= 26)</td>
<td>All emboli detected &gt;7 dB</td>
<td>Unclear</td>
<td>Embolic load induces specific cognitive impairment in accordance to the brain region to which they are delivered.</td>
</tr>
<tr>
<td>(Gerriets et al., 2010)</td>
<td>RCT</td>
<td>CABG (n= 91)</td>
<td>Embolic signals defined by detection within 120 secs after event markers</td>
<td>Median: 154 (30-2572)</td>
<td>Embolisation contributes to neuropsychological decline, which is measurable 3 months post-operatively (3 months).</td>
</tr>
<tr>
<td><strong>Studies showing no association between embolic load and neuropsychological impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Thiel et al., 1997)</td>
<td>Obsv.</td>
<td>CABG (n= 10)</td>
<td>Full text unavailable</td>
<td>-</td>
<td>Results showed moderate deterioration of neurocognitive function after surgery for both</td>
</tr>
</tbody>
</table>
Given that neuropsychological impairment is often thought to be associated with intraoperative embolisation, correlations between cerebral emboli with postoperative neuropsychological complications have been shown in a number of studies. Based on the results of this literature search, 9 studies have reported that cerebral emboli do contribute to impaired neurocognitive outcome post-surgery and 9 studies reported no correlation. A study conducted by Bokeriia et al. looked at the effects of asymmetric cerebral embolic load of cognitive function using TCD. He examined the cognitive outcome of 30 patients who underwent open heart surgery with completed pre- and postoperative neuropsychological assessments (Bokeriia et al., 2007). He concluded
that a significant embolic load during cardiac surgery induced specific cognitive impairments in accordance to the region of the brain they are delivered. Another study by Gerriets et al. investigated embolic load and neurocognitive outcome and concluded that microembolisation contributes to neuropsychological decline measurable at 3 months postoperatively, however this was only of borderline significance ($p=0.049$) (Gerriets et al., 2010). Many studies have also reported no correlation between embolic load and postoperative neurocognitive dysfunction. A study by Liu et al. measured the embolic load in 59 CABG patients with pre- and postoperative neuropsychological tests. The authors concluded that neither emboli nor the duration of CPB was independently associated with neurocognitive dysfunction at 1 week and 6 months (Liu et al., 2009). Another study investigating emboli in 50 CABG with cognitive testing at 1 week and 6 months postoperatively failed to show any correlation between emboli and cognitive decline. It is important to note that the majority of detected emboli do not produce immediate symptoms. Previous studies using intra-aortic filtration and atheroma avoidance techniques suggest that these have potential to reduce the risk of both perioperative stroke and neuropsychological decline.

Overall, there were an equal number of studies reporting a correlation and no correlation between embolic load and cognitive decline, fig 2.3 (9 studies in both groups). However, 2 studies reporting a correlation between emboli and cognitive decline was only of borderline significance (Braekken et al., 1998) ($p=0.03$), (Gerriets et al., 2010) ($p=0.049$).
Figure 2.3 Equal number of studies supporting both no association and favouring a link between emboli and cognitive decline. Total number of patients was higher in the studies showing an association (617 patients) compared to studies showing no association (434 patients).

2.9 Overview of literature

Based on previous research, our reading of the literature suggests that we can expect to observe a 1-4% incidence of peri-operative stroke, 0-63% incidence of neurocognitive decline (at 6 weeks), and new MRI lesions on FLAIR in approximately 13% of patients. If new MRI lesions arise from potential solid emboli, then we could expect to see a correlation between new lesions and pre-existing atheroma, pre-existing lesions, and solid emboli detected using TCD (e.g. following removal of the aortic cross-clamp).

Neuropsychological function is a soft outcome measure and has proved challenging to quantify post-operatively. Although neuropsychological tests theoretically provide a highly sensitive means of quantifying changes in cognition, differences in test batteries, timing of assessment and criteria for defining neuropsychological decline generate considerable heterogeneity in the data, which limits our ability to compare the results of different studies. To better understand the incidence, causes, and time course of POCD we performed a systematic literature review incorporating over 426 articles.

Depending on the timing of the neurocognitive tests and the definition used for determining decline, the reported incidence of neurocognitive decline after cardiac
surgery varied extensively. The outcome suggests that 50-70% of patients experience cognitive decline when tested within one week of surgery, falling to 30-50% after 8-10 weeks, recovering to 10-20% at 1 year, and then declines again at 3-5 years. Currently, there is no widely accepted clinical definition of cognitive decline; therefore, it is possible that arbitrary definitions of decline have resulted in an overestimation of the incidence of decline. At present, there is no evidence to suggest that the long-term incidence of cognitive decline differs from that of non-operative controls. Estimating long-term cognitive decline can be difficult, as normal ageing and dementia interfere with studies with older populations.

Interpreting patient risk factors associated with POCD, it seems that efforts to protect the brain during surgery are intrinsically linked with the need to control long-term progression of cardiovascular disease, especially in older patients. Although cognitive decline is common in all ages, the incidence of long-term neurological deficit is consistently higher in older patients who have higher level co-morbidities, regardless of whether they undergo cardiac surgical interventions.

Further research is required to develop a more dynamic and nuanced picture of interactions between underlying pre- and peri-operative risk factors. It is apparent that studies investigating isolated peri-operative factors are insufficient to explain complex interactions between temperature, cerebral autoregulation, oxygen saturation and brain metabolism. To date, isolated interventions and neuroprotective drugs aimed at improving cognitive outcome have proved largely ineffective. Literature examining underlying and perioperative risk factors associated with the pathogenesis of cognitive decline suggests that there is no single causative factor responsible for POCD. It seems likely that the causes are multi-factorial, due to emboli, impaired perfusion, chronic cardiovascular disease, and inflammatory responses. As the majority of studies show no correlation between new lesions on MRI and neurocognitive decline (table 2.1) it seems that clinically silent cerebral infarcts tend not to impair cognitive functions as assessed through neurocognitive testing.
2.10 Study aims

At present, it is difficult to predict which patients will experience stroke or neurocognitive decline as a consequence of cardiac surgery. A major hypothesised cause of brain injury within the literature is from showering the brain with solid and gaseous emboli which become lodged in the cerebral arteries supplying brain tissue. The overarching aim of this thesis was to investigate the causes of brain injury during cardiac surgery by relating measurements of intra-operative emboli obtained using transcranial Doppler ultrasound to MRI and neuropsychological outcome. The current study focuses particularly on the role of large bubbles in generating new lesions on MRI and/or deficits of POCD and utilises a novel algorithm for sizing bubbles entering the MCA territory, which allows us to estimate the volume of air and the likely impact of bubbles on cerebral blood flow. Doppler data were analysed to estimate the sizes of bubbles and volume of air entering the cerebral vasculature during cardiac surgery. The potential impact of air emboli on brain tissue perfusion was then estimated using virtual patient Monte Carlo simulations.

Specific clinical questions addressed in the following chapters of this thesis include:

1. Do the presence, total number, and/or volume of new postoperative FLAIR MRI lesions adversely impact cognition?
2. Does increased embolic load during heart surgery result in a higher incidence of new MRI lesions and/or greater decline in neuropsychological performance?
3. Does size and composition of emboli impact MRI or neuropsychological outcome?

This research was conducted as part of a British Heart Foundation study investigating brain injury following cardiac surgery. The main aim of our study was to investigate the proposed link between large gaseous emboli, cognitive decline, and new lesions on MRI, and to try to quantify the impact of emboli on cerebral blood flow.

**Chapter 3** provides technical details describing our embolus detection, MRI and cognitive testing methods, statistical analysis, and simulation techniques.

**Chapter 4** outlines the clinical study protocol, patient time-line, and methods for recording and analysing patient data.
**Chapter 5** reports the incidence of POCD and new MR lesions 6-8 weeks following surgery and tests the hypothesis that new MRI lesions are associated with a decline in cognition.

**Chapter 6** presents our embolus detection and bubbles sizing results, alongside the results of Monte-Carlo simulations, to test whether the prevalence, size, or timing of emboli influences MRI or neurocognitive outcome.

**Chapter 7** reflects on the key findings of this dissertation.

**Chapter 8** concludes the main findings and purposes future work.
Chapter 3

3 Anatomy and Techniques

This study involved three main types of investigative technique: detection of cerebral ischaemic lesions using Magnetic Resonance Imaging (MRI) (sections 3.2 & 3.3), cognitive assessment (section 3.4), and detection of blood-flow and emboli moving through the Middle Cerebral Artery (MCA) using transcranial Doppler (TCD) ultrasound (section 3.5). This chapter briefly describes the anatomy of the cerebral arteries and provides a detailed description of MRI and neuropsychological tests used as part of our study to assess patient outcome. The final part of this chapter outlines the software and data analysis methods used to record and analyse embolic signals using transcranial Doppler ultrasound.

3.1 Basic anatomy of the cerebral vasculature

The brain is one of the most highly perfused organs in the body and the anatomy of the major cerebral arteries supplying blood to the brain is described in various textbooks (Lasjaunias, P, Brugge, K.G, 2006; Saladin, 2014). The brain receives blood from the heart via four main arteries; the left and right common carotid arteries and the left and right vertebral arteries. Each common carotid artery divides into internal and external carotid arteries. The internal carotid arteries principally supply the cerebrum, whereas the left and right vertebral arteries join to form the basilar artery which supplies blood to the brain stem and cerebellum. At the base of the brain, the two internal carotid arteries and the basilar artery are linked via communicating arteries to form a ring-like structure known as the ‘Circle of Willis’ (fig 3.1).
The Circle of Willis gives rise to three main arteries supplying the brain, the Anterior Cerebral Artery (ACA), Middle Cerebral Artery (MCA) and Posterior Cerebral Artery (PCA). These branch into smaller arteries and arterioles that run along the surface of the brain, eventually penetrating the tissue to supply blood to the regions of the cerebral cortex. A schematic diagram of the cerebral arteries and associated perfusion territories is provided in figure 3.2 (David & Moore, 2008).
**Figure 3.2** A schematic of the cerebral arteries, labelled by their abbreviations and illustrating the general regions of the brain which they supply with blood, *(David & Moore, 2008)*.
3.2 Imaging of the brain using MRI

3.2.1 Introduction to the basic principles of MRI

The Noble Prize in 1952 was awarded to Felix Bloch and Edward Purcell for their early research into nuclear magnetic resonance (NMR) phenomena. In 1971, Raymond Damadian discovered that healthy tissue and tumours exhibited differing NMR relaxation times, which encouraged scientists to consider harnessing MR for the detection of disease. In 1975, Richard Ernst proposed using phase and frequency encoding for Magnetic Resonance Imaging (MRI), which now forms the basis of modern MRI techniques (Rocchi et al., 2015). Magnetic resonance imaging (MRI) is increasingly used for the identification of ischaemic lesions and is useful for detecting changes occurring in brain tissue following acute cerebral ischaemia.

MR images are generated by the detection of signals from protons contained mainly in tissue water and fat. Protons possess a magnetic moment that causes them to align with an externally applied magnetic field. MRI uses a sequence of radiofrequency electromagnetic pulses to align the magnetic moment of the protons. The moments then generate a decaying oscillating magnetic field before they relax back to their disordered equilibrium level. It is this oscillating magnetic field that is detected as a voltage induced in a receiver coil and which can be converted into images showing the distribution of protons (proton density). The relaxation rate of the excited tissue depends on tissue composition, and is characterised by the relaxation time constants, $T_1$ and $T_2$ (McRobbie, 2007). The contrast in the image results from different intensities of the emitted signals, which in turn result from different concentrations of protons and different $T_1$ and $T_2$ values in the various tissues of the body.

Interest in MRI as a technique for quantification of cerebral ischaemia lies in its capacity to detect early ischaemic lesions with high sensitivity, enabling researchers to identify their size and location. Typical MRI pulse sequences include: Diffusion-Weighted Imaging (DWI), Gradient-Recalled Echo (GRE), $T_2$-weighted, FLuid-Attenuated Inversion Recovery (FLAIR), and Perfusion-Weighted Imaging (PWI). MRI is capable of identifying hypo-perfused tissue that is at risk of infarction, as well as additional features of cerebrovascular pathology such as acute or chronic haemorrhage (McRobbie, 2007). Magnetic resonance angiography (MRA) can also be used to
investigate the anatomy of the Circle of Willis. In the next few sections, I describe each of the types of MRI scan performed as part of our study protocol and provide example scans from patient data.

### 3.2.2 Types of MR scan: $T_1$ and $T_2$ weighted images

$T_1$ weighting refers to a set of standard scans that show differences in the spin-lattice relaxation time of various tissues within the body. $T_1$ weighted images can be acquired using either spin-echo or gradient-echo sequences. $T_1$ weighted contrast can be increased with application of an inversion recovery RF pulse. Gradient-echo based $T_1$ weighted sequences can be acquired very rapidly because of the ability to use short inter-pulse repetition times (TR). In some applications, for example in oncology, $T_1$ weighted sequences are often collected before and after infusion of a $T_1$ shortening MRI contrast agent. In the brain, $T_1$ weighted scans provide acceptable contrast between grey and white matter and work well for differentiating fat from water, with water appearing darker and fat appearing brighter (McRobbie, 2007). Conversely, in a $T_2$ weighted scan, fat appears darker, while water appears lighter (fig. 3.3).
Figure 3.3 Brain MRI showing $T_1$ and $T_2$ weighted scans. Images A and C are $T_1$ weighted images; B and D are $T_2$ weighted images [http://physiology-physics.blogspot.co.uk/2010/07/relaxation-in-nuclear-microcosm.html, accessed on 15/04/2013]. Fluid appears dark on $T_1$-weighted images, but bright on $T_2$-weighted.

3.2.3 FLAIR Imaging

Fluid Attenuated Inversion Recovery (FLAIR) is an inversion recovery pulse sequence which uses a combination of $T_1$ and $T_2$ relaxation sequences to null the signal contributed by fluids. This can be used in brain imaging to suppress the appearance of cerebral spinal fluid and enhance visualisation of periventricular lesions. By carefully choosing the inversion time, $TI$ (the time between the inversion and excitation pulses), the signal from any particular tissue can be suppressed. By including an additional Radio Frequency (RF) pulse, and manipulation of magnetic field gradients, a $T_2$ weighted sequence can be converted to a FLAIR sequence in which free water appears dark, but damaged tissue remains bright (fig 3.4). This sequence is currently one of the most sensitive ways to evaluate new ischaemic lesions (McRobbie, 2007).
Figure 3.4 MRI FLAIR image showing a lacunar infarct in the right territory of the middle cerebral artery (patient 13).

### 3.2.4 Susceptibility weighted Imaging

Susceptibility weighted imaging (SWI), creates contrast in the image in a different way from traditional spin density, $T_1$, or $T_2$ imaging. SWI uses a fully flow-compensated gradient echo (GRE) scan to acquire images. This method exploits differences in magnetic susceptibility between tissues and uses the phase image to detect these differences. Magnitude and phase data are combined to produce an enhanced contrast magnitude image which is sensitive to venous blood and haemorrhage. The imaging of venous blood with SWI is sensitive to blood oxygen level and is occasionally still referred to as BOLD. Due to its sensitivity to venous blood, SWI is commonly used to investigate traumatic brain injuries and for high resolution brain venography (fig 3.5) (Lingegowda et al., 2012).
Figure 3.5 Example SWI scans: (a) shows cortical veins draining into enlarged transmedullary veins (black arrows), which are difficult to see on the contrast-enhanced T1-weighted axial image (b) [http://www.neurology.org/content/71/5/382/F1.expansion.html, accessed on 15/04/2013].

3.2.5 Diffusion-weighted Imaging

Diffusion weighted imaging (DWI) is useful for the diagnosis of acute ischaemic stroke and is the only brain imaging method demonstrated to reliably show ischaemic injury within the first minutes to hours after stroke onset (fig 3.6). Ischaemia-induced membrane dysfunction and cytotoxic oedema restrict the diffusion of water and lead to a decrease in the ‘apparent diffusion coefficient’ (ADC). The ADC provides a physiological measure of the rate of water movement through brain parenchyma (Warach et al., 1992). The sensitivity of DWI for detection of acute ischaemia ranges from 73% (3 hours after the event) to 92% (>12 hours after the event). By contrast, the sensitivity of computed tomography (CT) at these times was 12% and 16%, respectively. The specificity of DWI MRI for stroke detection was 92% (at 3 hours) and 97% (>12 hours) (Chalela et al., 2007). The sensitivity of DWI MRI was also higher than that of either CT (39-75%) or FLAIR (46%) (Lansberg et al., 2000).

It is interesting to note that acute ischaemic lesions on DWI are dynamic: information from clinical trials and case series shows that DWI lesions initially grow with time and that the initial diffusion lesion volume tends to correlate well with final infarct volume and neurological and functional outcomes (Schwamm et al., 1998). Stroke patients with multiple DWI lesions or large artery disease are more likely to experience additional
new lesions than stroke patients with single lesions on DWI (Kang et al., 2003). This 'stroke-prone' state continues for up to 90 days, with the greatest risk occurring during the first month after the initial stroke (Kang et al., 2004).

Differing lesion patterns are associated with specific stroke sub-types. Single cortico-subcortical lesions, multiple lesions in the anterior and posterior circulation, and multiple lesions in cerebral territories are thought to be associated with cardiac embolism (Baird et al., 2000). Multiple lesions in the unilateral anterior circulation, and small scattered lesions in one vascular territory, particularly in a watershed distribution, are usually related to large artery atherosclerosis (Chaves et al., 2000).

![Figure 3.6 DWI: ischaemic infarct in the right middle cerebral artery identified using DWI imaging](http://www.neurology.org/content/74/24/1946/F2.expansion.html, accessed on 15/04/2013)

### 3.2.6 Time of flight MR angiography

Time-of-flight (TOF) MR angiography is based on the phenomenon of flow-related enhancement of spins entering into an imaging slice. As spins entering the image slice are unsaturated, these spins give a stronger signal than surrounding stationary spins.
With 2D TOF MRA, multiple thin imaging slices are acquired with a flow compensated gradient-echo sequence. These images can be combined using a reconstruction technique, such as maximum intensity projection (MIP) mapping, to obtain an image of the vessels in an analogous fashion as in conventional angiography (fig 3.7). With 3D TOF MRA, a number of images are obtained simultaneously by phase encoding in the slice select direction. An angiographic appearance can be generated using a MIP, as is done with 2D TOF. Several 3D TOF volumes can also be combined to visualise longer segments of vessels. 3D TOF angiography allows greater spatial resolution in the slice-select direction than 2D TOF MRA; however, with thick volumes and slow flowing blood, loss of signal can be seen with the 3D TOF method (Carr, 2012).

![Figure 3.7 An example of a 3-D time-of-flight MR-angiography scan of patient 13.](image)

Figure 3.7 An example of a 3-D time-of-flight MR-angiography scan of patient 13.
3.3 ‘In house’ MRI registration and subtraction software

In the current study pre- and post-operative MRI FLAIR images were registered and subtracted to aid in the detection of new lesions. This was performed using ‘in house software’ written by Dr Mark Horsfield. Registration involves creation of an average ‘template’ formed from both images. This ‘reference image’ is then kept fixed whilst the pre- and post-surgery source images are spatially transformed by translation and rotation until differences between the two images are minimised. Below is a schematic representation of the translation and transformation of the images (fig. 3.8).

![Figure 3.8 Registration is performed by allowing (a) translation, and (b) rotation, of the image.](image)

The ‘goodness of fit’ of the source to the reference image is quantified by defining a cost function to describe differences between one image and another. Registration was optimised using a ‘normalised cross-correlation’ method with a fixed reference image and translation and rotation of the source image in the x, y- and z- planes (6 degrees of freedom in total). Once the two images are aligned and matched within this common geometrical template they can be compared by digital subtraction to identify new lesions. Figure 3.9 shows example data from one of our patients, displayed using Dr Horsfield's software.
Figure 3.9 Example data subtraction analysis performed using in-house software for patient 76. (A) subtraction scan of the pre- and post-operative scan, (B) pre-operative scan, (C) post-operative scan.

The two images on the right hand side show 'before' and 'after' data, and the larger image on the left shows a 'difference' image following optimised registration and digital subtraction. In the difference image it becomes easier to identify new lesions, which show up as bright intensity regions. As similarities between before and after images are 'cancelled out', it also becomes easier to distinguish new lesions from pre-existing features such as old infarcts or small vessel disease.

3.3.1 Delineation of the number and volume of new and pre-existing lesions

To distinguish chronic lesions from acute ischaemic changes, the MR-FLAIR images were presented to a qualified neuroradiologist who was blinded to the results of neuropsychological assessments. Chronic ischaemic changes were then characterised through registration and subtraction of pre- and post-operative FLAIR images (fig. 3.10).
Images were analysed for the location and volume of pre-existing and new lesions, which were quantified using a semi-automated contouring technique (fig 3.11).

After selecting all lesions using the semi-automated contouring technique, the software outputs a report summarising the total number and volume of the lesions. Lesion volumes are reported in mm$^3$. In order to visualise the lesion distribution, post-operative FLAIR images were registered to a standard MRI brain atlas (Mazziotta et al., 2001),
and lesions from all patients were segmented and displayed using the atlas as reference for the 3-D display.

3.4 Neuropsychological Assessment

Cognitive changes can be assessed by asking patients to complete a battery of neurocognitive tests. By comparing the results of cognitive tests conducted before and after surgery it becomes possible to determine whether patients have experienced a significant decline in function following surgery. Each test assesses different aspects of visual, verbal and co-coordinative functions of the human brain.

3.4.1 Pre- and post-operative neuropsychological tests

To examine the possible neuropsychological effects of cardiac surgery, all participants completed a battery of well-established neuropsychological assessments, lasting approximately 1.5 hours. Tests were conducted at the patient’s bedside if necessary. These compromised the WASI test (which measures verbal and performance IQ via Block Design, Pattern Matrices, and Similarities and Vocabulary tests), parts A and B of the Trail-Making test (which measures attention), the WMS-III digit span task (which measures verbal and visual memory), the SCOLP test (measures the speed of information and language processing) and the Grooved Pegboard test (measuring attention and psychomotor speed). Cognitive domains corresponding to each neuropsychological test are listed in table 3.1.
Table 3.1 Neuropsychological domains tested and associated tasks.

<table>
<thead>
<tr>
<th>Domains/tests</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention and psychomotor</td>
<td>Connecting numbers on a test sheet</td>
</tr>
<tr>
<td>Trail making test A</td>
<td>Inserting identical pegs into grooves in a parallel order</td>
</tr>
<tr>
<td>Grooved pegboard</td>
<td></td>
</tr>
<tr>
<td>Executive functioning</td>
<td>Connecting number/letters alternately</td>
</tr>
<tr>
<td>Trail making test B</td>
<td>Connecting patterns by identifying missing shapes</td>
</tr>
<tr>
<td>WASI matrix reasoning</td>
<td></td>
</tr>
<tr>
<td>Visual memory</td>
<td>Recalling the family members and situations after 35 mins</td>
</tr>
<tr>
<td>WMS-III pictorial memory (family pictures)</td>
<td>Recalling a short story</td>
</tr>
<tr>
<td>Short-term learning</td>
<td>Recalling the story after 35 mins</td>
</tr>
<tr>
<td>WMS-III pictorial memory delayed learning</td>
<td></td>
</tr>
<tr>
<td>Verbal memory</td>
<td></td>
</tr>
<tr>
<td>WMS-III short-term learning</td>
<td></td>
</tr>
<tr>
<td>Verbal intelligence</td>
<td></td>
</tr>
<tr>
<td>SCOPA speed of comprehension</td>
<td>Stating true or false for as many sentences possible within 2 mins</td>
</tr>
<tr>
<td>WMS-III delayed learning</td>
<td></td>
</tr>
<tr>
<td>Information processing</td>
<td></td>
</tr>
<tr>
<td>SCOPA spot-the-word</td>
<td>Identifying the correct and incorrect word</td>
</tr>
<tr>
<td>WASI vocabulary and similarities exercise</td>
<td>Defining the word and the connection between the 2 words</td>
</tr>
<tr>
<td>Visual Constructive functions</td>
<td>Assembling square blocks to construct different designs</td>
</tr>
<tr>
<td>WASI block design</td>
<td></td>
</tr>
</tbody>
</table>

3.4.2 Standardisation and normative data for the neuropsychological tests

The statistical performance of a person’s test score on a norm-referenced scale (raw scores) is of little significance by itself. A meaningful interpretation of the baseline test scores is obtained through comparison of the distribution of scores from a group of individuals of similar age, sex, and education level. All neuropsychological tests used in this study were standardised tests that were accompanied by normative data obtained from a large sample population to characterise the normal range of values expected.

For meaningful interpretation of test scores, the standardisation procedure takes into account two important factors:

1. **Size of the standardisation sample**: the sample should be large enough to reduce the impact of individual variations in intelligence and personality.
2. *Representativeness of the sample*: the standardisation sample should be representative of the population for whom the test is intended.

3.4.3 The Wechsler Memory Scale-Third Edition Abbreviated (WMS-III) [Harcourt Assessment Company, London, UK].

*WMS-III* is a fast reliable, survey of auditory and visual memory abilities (fig 3.12), which is designed to provide clinicians with an estimate of general memory functioning when extended memory testing is not indicated or is not feasible.

The test is sensitive to memory impairments associated with a variety of clinical conditions including dementia, neurological, and neuropsychiatric conditions. The battery may be used as part of a standard psychological or neuropsychological evaluation. The WMS®-III was designed to monitor changes in memory performance through statistical analysis of serial assessments. This contains 4 subtests measuring auditory and visual, immediate, and delayed memory. This test is usually administered within 20-25 minutes.
The standardisation sample for WMS-III is presented within the manual (Lo et al., 2012) and is based on a national standardisation sample representative of a population of U.S. adults.

**Age:** For the WMS-III abbreviated standardisation sample, 1,250 adults were tested, aged 16-89 years. The sample was divided into 13 age bands: 16-17, 18-19, 20-24, 25-29, 30-34, 35-44, 45-55, 55-64, 65-69, 70-74, 75-79, 80-84, and 85-89. One-hundred participants were included in each age group, except the two oldest groups, which comprised of 75 participants each.

**Sex:** The sample consisted of an equal number of male and female participants in each group between ages 16-64. The older groups included more women than men, in proportions consistent with census data.

**Race/ethnicity:** For each group in the sample, the proportion of whites, African Americans, Hispanics, and other ethnic groups were based on the racial/ethnic
proportions of individuals within each age band in the U.S. population according to 1995 Census data.

**Education:** The samples were stratified according to the following 5 education levels based on the number of school years completed; ≤8 years, 9-11 years, 12 years, 13-15 years, ≥16 years.

### 3.4.4 Trail making exercise (Parts A and B) [GL Assessment, London, UK]

The first part of this test, Trails A, requires the subject to rapidly sequence numbers from 1 through to 25 (fig 3.13a). The second part, Trails B (fig 3.13b), is a more difficult cognitive flexibility task requiring the subject to sequence from 1 to 13 while switching between numbers and letters (i.e., 1-A-2-B, etc.). Scoring of trail-making tests A and B are reported as the number of seconds required to complete the task. Higher scores indicate greater impairment. Performance varies with age and education, and thus normative standards are used to classify patient performance. If a patient has not completed both parts after 5 minutes, it is unnecessary to continue the test. Parts A & B need to be completed together and in the correct order for test administration to be valid.

![Figure 3.13 Trail making part A, Trail making part B](image-url)
Normative data for the Trail Making Test was obtained from a trial published by N. Tombaugh in 2004 (Tombaugh, 2004). The sample was taken from community-dwelling individuals living in Canada.

**Age:** A total of 911 individuals were included in the sample, aged between 18-89 years. The norms were stratified for both age (11 groups) and education (2 levels). This article presents the most recent set of normative data for determining impaired performance in individuals of varying age and level of education.

**Sex:** The male to female ratio for this sample was 408 males to 503 females.

**Education:** The samples were stratified into two education levels based on the number of years of school completed; 0-12 and 12+ years.

### 3.4.5 The Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) [Pearson Assessment, London, UK]

The *WASI* test gives an estimate of general intellectual ability based on 4 subtests, ‘Vocabulary’ (42 total items that require the subject to orally define 37 words presented both orally and visually), ‘Matrix Reasoning’ (35 incomplete grid patterns that require the participant to select the correct response from five possible choices), ‘Similarities’ (26 pairs of words which require the patient to give a word similar to the 2 words given), and ‘Block making’ (where the patient has to rearrange blocks to imitate an image) (fig 3.14). *WASI* provides a quick estimate of an individual's level of intellectual functioning, with higher scores indicating greater intellectual ability. This test can usually be administered within 20-25 minutes.
Normative data for the WASI test is presented in a manual accompanying the test (Harman-Smith et al., 2013) and is based on a national sample of the English-speaking U.S. population.

**Age:** A total of 2,245 participants were included in the standardisation sample of which 1,145 were adults aged 6-89 years. The standardisation sample was divided into 23 age groups spanning from 6-89 years, of which 12 groups were adult: 17-19, 20-24, 25-29, 30-34, 35-44, 35-44, 45-54, 55-64, 65-69, 70-74, 75-79, 80-84 and 85-89. One hundred participants were included in each group, except for the 75-79, and 80-84 age groups with 85 adults, and the 85-89 group with 75 adults.

**Sex:** The sample consisted of an equal number of male and female participants in each group from 6-64 years of age. The 3 oldest groups included more women than men, in proportions consistent with census data.
Race/ethnicity: For each group in the sample, the proportion of whites, African Americans, Hispanics, and other ethnic groups were based on the racial/ethnic proportions of individuals within each age band in the U.S. population according to 1997 Census data.

Education: The samples were stratified based on the number of school years completed; ≤8 years, 9-11 years, 12 years, 13-15 years, ≥16 years.

3.4.6 Grooved pegboard test. [Benefitsnow, Petersfield, UK]

This test is used to identify a decline in fine motor function, hand-eye coordination and sensory motor integration. The aim of the test is to orientate 25 identical pegs into the holes in the pegboard (fig 3.15). This process is repeated for both the dominant and non-dominant hand. The investigator records how long it takes to complete the task with both the left and right hand, and notes are made of any pegs that have been dropped. The total time (in seconds), plus the amount of drops, totalled with number of pegs correctly placed, gives the patient’s overall score. A higher score in the post-operative test compared to the pre-operative test would indicate a decline in performance.
Normative data for the Grooved Pegboard Test was obtained from the manual (KLOVE, 1963). This sample was based on participants in the city of Waterloo, Canada.

**Age:** A total of 153 individuals aged between 9 and 89 years were included in the standardisation sample. Age ranges were divided into 12 groups: 9, 10, 11, 12, 13, 14, 15-19, 20-29, 30-39, 40-49, 50-59 and 60+.

**Sex:** Of the 153 participants, 47 were male, 39 right handed and 8 left handed. Of the 106 females, 97 were right handed and 9 were left handed.

**Education:** The sample was not stratified to level of education.

### 3.4.7 The Hospital Anxiety and Depression scale (HADS) [GL Assessment, London, UK]

This test is considered a reliable self-rating scale for assessing anxiety and depression in both hospital and community settings. The HADS score is not used to assess cognition, but to adjust for anxiety and/or depression as a confounding factor. The test comprises
of a brief one page questionnaire, with 14 questions; seven questions for anxiety and seven for depression, which can normally be answered within 2 – 5 minutes (fig 3.16).

![Figure 3.16 Hospital Anxiety and Depression Scale](image)

Scores are classified as ‘normal’, ‘mild’, ‘moderate’ and ‘severe’ (table 3.2).

**Table 3.2 Interpretation of the HADS score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-7</td>
<td>Normal</td>
</tr>
<tr>
<td>8-10</td>
<td>Mild</td>
</tr>
<tr>
<td>11-14</td>
<td>Moderate</td>
</tr>
<tr>
<td>15-21</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Validation has previously been performed through comparison with the four-point psychiatric rating scale for anxiety and depression for 100 medical outpatients (Zigmond & Snaith, 1983). Further validation has also been reported in psychiatric patients (Bramley et al., 1988) and in a heterogeneous group of patients with physical illness (Aylard et al., 1987).
3.5 Ultrasound embolus detection

3.5.1 Transcranial Doppler ultrasound embolus detection

Transcranial Doppler (TCD) was developed by Aaslid et al. in 1982 and uses 1-2.5
MHz ultrasound to measure cerebral blood flow velocity (CBFv). TCD is an important
tool for measuring CBFv (Bishop et al., 1986), evaluating cerebral autoregulation
(Aaslid et al., 1991), and the detection of emboli (Ringelstein et al., 1990; Mackinnon et
al., 2004). It is also important in the diagnosis of haemorrhage, stenosis and other
problems related to CBF (Vora et al., 1999; Markus, 2000).

3.5.2 Basic principles of Transcranial Doppler

Any sound wave with a frequency above that of the human hearing (approximately 20
KHz) is termed ultrasound. Sound waves behave in a similar way to light waves in the
sense that energy is absorbed as the wave passes through a propagating media, and
undergoes refraction, reflection and scattering at interfaces between media with
differing acoustic impedances. The detection of reflected sound waves forms the basis
of ultrasound imaging (Diagnostic Ultrasound: Physics and equipment, Hoskins et al,
2010).

Transcranial Doppler (TCD) ultrasound provides a method of estimating the velocities
of scatterers moving through the arteries by harnessing a phenomenon called the
Doppler effect. This was first described theoretically by Christian Doppler in 1842, and
describes the change in the apparent frequency, or wavelength, of a wave caused by the
relative motion of the source of the wave and an observer. For instance, if a wave
source (sound emitter) is moving towards an observer, the frequency of the wave will
appear higher than if the source was stationary (fig. 3.17).
Doppler ultrasound was first applied to the measurement of blood flow in the cerebral circulation by Rune Aaslid in 1982 (Aaslid et al., 1982). Transcranial Doppler applications make use of a technique called pulse-wave Doppler to sample velocity information from a specific sample depth. In this technique, pulses of ultrasound are emitted at regular intervals (the pulse repetition frequency) by a stationary transducer, which is angled so that the sample volume coincides with the position of the target vessel. If the scatterers are moving, the frequency of the scattered ultrasound returning to the transducer will be slightly shifted compared to that of the emitted ultrasound due to the Doppler effect. The difference between the transmitted and received frequencies \( (f_t - f_r) \) is known as the Doppler shift \( (f_D) \), and is related to the velocity of the scatterer via equation 3.1.

\[
f_D = f_t - f_r = 2f_t \frac{v \cos \theta}{c}
\]

Equation 3.1

In this equation, \( v \) is the velocity of the scatterer (e.g. an embolus or red blood cell), \( \theta \) is the angle between the ultrasound beam and the direction of the motion of the scatterer (also known as the Doppler angle), and \( c \) is the propagating velocity of ultrasound through the tissue (1540 m/s) (Hoskins, 1994). A typical TCD transducer emits

**Figure 3.17** The Doppler effect describes the change in frequency observed when there is relative motion between the source and an observer. [http://www.einstein-online.info/spotlights/Doppler, accessed on 16/04/2013]
ultrasound with a central frequency of 2 MHz. Motion of the blood generates a Doppler shift of the order of 100-1000 Hz, which is in the range of normal human hearing. The Doppler shift will either be positive or negative depending on the Doppler angle between the direction of motion and the ultrasound probe. If the Doppler angle is known, then measurements of the Doppler shift can be used to calculate the velocity of the scatterer based on equation 3.1. In TCD applications, the Doppler angle is not usually known and a 0° Doppler angle is often assumed so that the y-axis can be displayed as a velocity rather than a frequency. In practice, the audio signal is made up of contributions of Doppler shift frequencies from an ensemble of scatterers. Most commercial ultrasound machines display this information visually by Fourier transformation of the audio signal as a Doppler frequency spectrum. A typical recording of MCA blood flow using TCD can be seen in fig 3.18. The top panel shows the Doppler spectrogram with velocity along the y-axis and time along the x-axis. The intensity colour scale of the sonogram indicates the backscattered power contributed by scatterers moving at each velocity. The bottom panel shows ‘power M-mode’ data where the y-axis indicates depth from the transducer in mm. Forward/reverse flows are coded red/blue with the intensity of the signal indicating backscatter signal intensity.

Figure 3.18 MCA Doppler spectrogram
3.5.3 Using TCD to measure cerebral blood flow

TCD measurements of the MCA provide a means of monitoring fluctuations in cerebral blood flow velocity and detecting emboli in real time during surgery. To obtain a TCD signal through the skull, a low frequency of ultrasound (~ 2 MHz) is used and the TCD probe must be positioned over the temporal bone window where the skull is relatively thin, fig 3.19. TCD signals can be obtained in around 90% of individuals (Sarkar et al., 2007).

![Image of TCD probe](image.png)

**Figure 3.19** (A) headset is used to hold the TCD probe in position. (B) The beam is orientated through the temporal bone window towards the MCA.

Transmission of ultrasound is aided by using aqueous ultrasound gel. Typically, the probe is directed antero-superiorally from the temporal bone window using an initial sample depth of 50 mm. Minor adjustments can be made to angle the probe and increase or decrease the depth of insonation until a clear MCA signal is obtained.

There are various criteria for identification of the MCA in TCD monitoring, but the most important is that the blood flow in the MCA is towards the probe and persists over a wide range of sample depths, typically 30-60 mm. Although the MCA has potential to be confused with the PCA, which also generates flow towards the probe, the PCA signal is usually obtained at deeper sample depths (60-80 mm) with the probe angled downwards and slightly posteriorly.
TCD is a convenient method for monitoring the cerebral circulation; however, a thick temporal bone window precludes monitoring in some patients, and it is often difficult to locate the position of the MCA. The use of M-mode colour Doppler can help in identifying whether there is a window and locating the MCA. M-mode displays the Doppler signal as a function of depth, coloured red or blue depending on the direction of flow. M-mode facilitates rapid window location and alignment of the ultrasound beam, and makes it possible to view multiple vessels at different depths simultaneously (Moehring & Klepper, 1994).

### 3.5.4 Monitoring emboli using TCD

In addition to monitoring blood flow within the MCA, TCD can also be used to detect emboli (Ackerstaff et al., 2004). As emboli travel swiftly through the ultrasound sample volume with a specific velocity give rise to a transient ‘snap, chirp or moan’ sound in the Doppler audio signal. The embolus appears in the Doppler spectrogram as a transient increase in backscatter intensity located at a discrete velocity within the blood flow profile. A typical Doppler sonogram illustrating the differing appearances of emboli and artefacts is shown in fig 3.20.

![Figure 3.20](image)

**Figure 3.20** Doppler spectrogram showing the typical appearances of emboli and artefacts in the Doppler spectrum and Doppler M-mode display. This image is taken from a surgical recording of a patient recruited to our study.
3.5.5 Embolus detection criteria

Differences in criteria used for the identification of embolic signals previously led to formation of a consensus committee who recommended criteria for the identification of embolic signals. The Consensus Committee proposed that investigators should specify; the ultrasound frequency, gain settings, dynamic range and identification criteria for classifying microembolic signals. The Consensus Group recommended that; ‘microembolic signals can be identified as a short duration (<0.01-0.03 s), unidirectional intensity increase’ (Ringelstein et al., 1998).

Experts in the field of ultrasound discussed the limitations and problems involved with embolus detection and developed guidelines for its proper use in clinical practice and scientific investigations. Key parameters the authors suggested investigators report include: (1) ultrasound device, (2) transducer size and type, (3) insonated artery, (4) insonation depth, (5) algorithms for signal intensity measurements, (6) scale settings, (7) detection threshold, (8) sample volume, (9) transmitted ultrasound frequency and (10) recording time.

Emboli can be detected in numerous settings, such as in patients with atrial fibrillation (AF), acute stroke, decompression sickness, severe cardiac atheroma, and patients with mechanical heart valves (Grosset et al., 1994). High numbers of cerebral emboli are also detected during cardiac surgery, catheter ablation as a treatment for AF, and during carotid surgery (Dagirmanjian et al., 2000). During cardiac surgery, emboli are detected in virtually all patients regardless of the type of procedure or whether cardiopulmonary bypass (CPB) was used.

3.5.6 Embolic signal analysis

In the current study, Doppler signals were analysed using ‘in house’ software developed in MATLAB (The MathWorks Inc., Natick, MA) by Dr Caroline Banahan and Mr Clément Rousseau. The raw audio data from the Doppler recording was converted to bin files using the DWL QLS 2.10.3 software. Individual bin files are read into the ‘in house’ software (shown in fig 3.21) to analyse embolic signals.
Figure 3.21 The ‘in house’ Doppler MATLAB GUI used to detect and analyse embolic signals. (A) detected current peak; (B) image of the current stage of the Doppler sonogram; (C) Time of detected peak during the surgery; (D) Frequency modulation index; (E) Decision to record as an embolus or discard as an artefact; (F) Navigation throughout the file to select a certain stage of the surgery; (G) Signal properties of the peak detected; (H) Adjustable functions to improve signal output (e.g. manually re-selecting the background, or the start and end points of the peak detected, along with the timing information of the current file).

Embolic signals were identified as peaks within the recording if they generated backscattered intensities >7 decibels (dB) above the average background intensity. An image of our ‘in house’ software in MATLAB showing an example embolic signal is shown in fig 3.22. Based on inspection of the sonogram and audio signal by a trained expert, signals were either accepted as emboli, or rejected as artefacts, based on internationally agreed consensus criteria (Ringelstein et al., 1998).
Figure 3.22 ‘In house’ MATLAB software showing an embolic signal recorded during surgery. 
(A) Windows used to calculate the background value. (B) Window used to calculate the 
backscatter from the emboli. (C) During embolic showers, there is an option to retain the same 
background estimate for subsequent peaks by ticking the ‘Keep Bkg’ box.

The backscattered embolic signal intensities of accepted signals were then estimated 
relative to the scattering from the blood as a Measured Embolus-to-Blood Ratio (MEBR) in dB. To estimate MEBR, the intensities of the two background windows 
either side of the embolic signal are integrated and normalised with respect to time to 
estimate the mean scattering from blood flow. The Peak MEBR in dB is then calculated 
by taking the ratio of the maximum intensity of the embolic signal in blood ($I_{E+B}$) and 
average intensity of the background blood signal ($I_B$) using equation 3.2:

$$MEBR = 10 \log_{10} \left[ \frac{I_{E+B}}{I_B} \right] \text{dB} \quad \text{Equation 3.2}$$
During embolic showers (fig 3.23a) (>5 emboli/sec), it became difficult to confidently select a background signal on either side of the embolus. In this case, a background signal was selected prior to the shower and used in subsequent MEBR estimates. In the case of dense 'curtains' of emboli (fig 3.23b), it becomes impossible to distinguish individual emboli. In this case, only the duration of the curtain can be recorded.

**Figure 3.23** (A) Embolic shower, (B) curtain of emboli where it becomes impossible to distinguish between individual embolic signals.

### 3.5.7 Estimating bubble size and volume

Bubble sizes were estimated using an algorithm developed by Banahan et al. (Banahan et al., 2012) based on a theoretical model describing backscattered ultrasound from a spherical embolus moving through a blood-filled vessel (Moehring & Klepper, 1994). Conversion of MEBR values from gaseous emboli to bubble diameters is illustrated in fig 3.24. In tests, 91% of 10,000 randomly generated simulated emboli were correctly
sized to within 10% of their true value (Banahan et al., 2012). In general, embolic signals with MEBR >30.5 dB can be assumed to be gaseous, whereas weaker embolic signals could be attributable to either solid emboli or gas bubbles.

Figure 3.24 Measured Embolus-to-Blood ratio (MEBR) values for air emboli with diameters ranging from 1 μm to 2.5 mm using the model described in Moehring et al., 1994, assuming an average middle cerebral artery (MCA) diameter of 2.5 mm.

3.5.8 Estimating MCA diameters for accuracy of bubble sizing

Since uncertainty in MCA diameter can modify volume estimates by up to a factor of 3 for small bubbles, to improve the accuracy of our bubble sizing, patient specific measurements of MCA diameter were obtained for all patients by 3D reconstruction of the circle of Willis using time-of-flight magnetic resonance (MR) angiography (Magnetom Skyra, Siemens Medical, Erlangen, Germany). This analysis was carried out by Mr David Marshall who is a PhD student in the Department of Cardiovascular Sciences. The Vascular Modelling Toolkit (Antiga et al., 2008) was used for analysis. Images were segmented using level sets at a constant threshold for all patients. Mean
diameter was calculated by averaging 5 cross sections separated by distances equal to the vessel radius, starting at two vessel radii from the internal carotid artery bifurcation (fig 3.25). Sections on poorly resolved areas were discarded. Diameter error was estimated based on the standard deviation of measurements of the vessel area.

Figure 3.25 3D reconstruction of the circle of Willis of patient 47 with labelled MCA measurements used to estimate average diameters for both the left and right MCA.

3.5.9 Output of the bubble sizing algorithm and estimating volume of air

Each analysed bin file (fig 3.26a) outputs a text file containing the time a peak was detected, along with its signal properties. Signal properties are given a value of 0 if the signal was discarded as an artefact (fig 3.26b). Doppler recordings can be replayed during the analysis to help identify whether a signal is an embolus or an artefact. The user needs to manually note any periods of signal loss and the start and end of embolic curtains. Once all the bin files have been analysed, text files were collated into a single text file containing embolus data only (fig 3.26c). This text file was then used as an input for the bubble sizing algorithm.
Figure 3.26 (A) the corresponding bin files for a patient’s Doppler recording; (B) the output text file for individual bin files outlining signal properties for each recorded embolic signal. A ‘0’ is given to peaks that had been discarded. (C) All text files combined for all the bin files into a final text file only containing embolus data.

The collated text file is imported into the ‘in house’ sizing software algorithm (described below) along with haematocrit data taken from the perfusionist notes (time and percentage), start and end time of cardiopulmonary bypass, MCA diameters, and Doppler sample volume (fig. 3.27a). There is an option to only size emboli with Peak MEBR values greater than 30.5 dB (corresponding to gas bubbles ~18 µm), to facilitate simulations estimating the impact of bubbles on perfusion. The output of this text file was then stored in a separate folder for further analysis using Monte-Carlo simulations (as described in section 3.6). The full text file output with the tick box ‘unchecked’ was used as the output for the full embolic signal data analysis (fig. 3.27b). This process was repeated for all patients through detailed analysis of both the left and right MCA Doppler recordings.
Figure 3.27 (A) option for the ‘in house’ sizing software; (B) text file output from the sizing software giving (from columns left to right) the time, bubble diameter, diameter error and volume of individual emboli which is reformatted in excel for the next stage.

The text file output from the sizing software (fig 3.27b) was reformatted in excel to give the time of each embolic signal, Peak EBR (dB), left or right sided recording, stage of surgery, embolus diameter (mm), error in the diameter estimate (mm), and the calculated volume (ml) for each embolus, which is then saved as a ‘master text file’ (fig. 3.28a). Bubble diameters were then converted to volume of air \( V \) by assuming a spherical bubble with bubble radius \( r \):

\[
V = \frac{4}{3}\pi r^3
\]

Equation 3.3

Conversion of bubble diameters to volume of air via equation 3.3 was used to estimate the total volume of air entering the MCA territories for each patient. The master file was then run through a final script in MATLAB to output the following data for each procedure/patient (fig. 3.28b):

1. The total number of emboli per side
2. Total estimated volume of air per side
3. Total number of emboli per side for each stage of the surgery (1-4)
   i. Stage 1: start of recording to aortic cross-clamp on
ii. Stage 2: 1 minute following aortic cross-clamp on
iii. Stage 3: 1 minute following aortic cross-clamp off
iv. Stage 4: Aortic cross-clamp off to end of recording.

4. Number of emboli < 40 microns
5. Number of emboli 40-99 microns
6. Number of emboli 100-999 microns
7. Number of emboli ≥ 1 mm

Figure 3.28 (A), the ‘master text file’ containing all the embolus data for both the left and right MCA recordings; (B) a final script in MATLAB that summarises the results of embolic signal analysis and bubble sizing for each patient.
3.6 Monte-Carlo simulations

Timing and sizing information (outlined in section 3.5.6) for the bubbles were used to model the accumulation and clearance of air bubbles within the vasculature during the surgery, using patient specific Monte-Carlo simulations featuring gaseous emboli which become lodged within a bifurcating arterial tree (Chung et al., 2007; Hague et al., 2013).

Previous simulations using theoretical emboli predict that solid emboli are responsible for focal persistent injuries, while fast clearing gas emboli produce diffuse transient blockages similar to global hypoperfusion. The model simulates the fundamental interactions between emboli and the geometry of the arterial tree. This model is based on a bifurcating fractal tree comprising over a million branches ranging between 1 mm and 12 microns in diameter. In this study, the model was adapted by Dr Jim Hague at the Open University for use with gaseous emboli to predict the duration of vascular occlusion and percentage of affected vasculature (fig 3.29). This provides a novel means of investigating the role of gaseous emboli in producing neurological injury. Further details of this Monte-Carlo simulation are described in previous publications (Chung et al., 2007; Hague & Chung, 2009; Hague et al., 2013).

Figure 3.29 ‘virtual patient’ computer simulations can be used to predict the impact of emboli on cerebral blood flow for comparison with patient outcome.
3.6.1 Model algorithm

The algorithm starts by calculating flows, pressures and resistances for an empty tree. All emboli are allowed to dissolve, leading to a reduction in radius during each time step. Completely dissolved emboli are removed from the simulation. If the reduction in radius generates a change in the blockage state of the tree, flows and pressures are recalculated.

The emboli in the bifurcating tree move according to the following rules:

(i) If the pressure behind the deformed embolus is insufficient to overcome ‘static friction’ it does not move (fig 3.30).

(ii) If all arterioles downstream are blocked, the embolus may not move since there is no flow.

(iii) If the embolus radius becomes smaller than the current node and there is flow downstream then the embolus may move.

An air embolus encountering a bifurcation moves in direction A with a probability given by equation 3.4 where $f_A$ and $f_B$ designate flows in the A and B directions, $w_a$ is related to the orientation of the branches with respect to gravity ($w_a = (1 + A_g \cos(\theta))/2$), $A_g$ is a parameter that varies between 0 and 1:

$$P_A = f_A w_a/(f_A w_a + f_B w_B)$$

Equation 3.4
Otherwise, the embolus moves in direction B (fig 3.31).

**Figure 3.31** Pairs of parallel and serial resistances are repeatedly reduced to a single downstream resistance to facilitate calculation of pressures, flows and resistances at each level in the tree (Image reconstructed from Hague et al., 2013).

If progress of an embolus generates a new blockage, then the pressures and flows are recalculated. At this stage numerical measurements of the state of the tree are repeated.

This simulation incorporates the effects of bubble deformation, buoyancy, blood pressure, and friction between the surface of the bubble and the vessel wall, as shown in fig 3.30. The simulations give additional time dependent estimates of the total embolic burden in the arterial tree over time. The root node of the tree was chosen to match the diameter of the MCA, with 20 layers of bifurcations representing the MCA microvasculature, terminating in ~500,000 terminal arterioles (~26 µm in diameter). Bubble radii and blood pressure were input to the model MCA vasculature as a function of time and each simulation run 30 times to determine the average number and duration of obstructed end arterioles during surgery.
Chapter 4

4 Clinical study protocol and statistical analysis

To investigate a potential link between brain injury following cardiac surgery and intra-operative cerebral emboli, we aimed to study approximately 100 patients undergoing cardiac surgery. In addition to their normal hospital care, patients were monitored intra-operatively using TCD and underwent MRI scanning and neuropsychological testing before and after their surgery.

4.1 Ethical approval

Ethical approval for the project entitled ‘Causes of brain injury associated with cardiac interventions: A comparison of Doppler embolus detection and virtual patient predictions with post-surgical neurological outcomes quantified by MRI and neuropsychological testing’ was gained on the 18/05/2011 with an expected termination date of 31/12/2013 (UHL Ref: CLRN 51454, REC Ref: 10/H0401/78). My PhD studentship within the University of Leicester Department of Cardiovascular Sciences was funded by the Leicester Cardiovascular Biomedical Research Unit (BRU). All other costs associated with the project were funded by the British Heart Foundation. Patients provided written informed consent following a protocol approved by the University Hospitals of Leicester NHS Trust and Derbyshire Research Ethics Committee (REC reference:10/H0401/78). The study was sponsored by the University of Leicester.

It was mandatory for all investigators involved in patient recruitment to attain Good Clinical Practice (GCP) accreditation and patient consent training examined by the University Hospitals of Leicester Research & Development office (UHL R&D, Appendix 4.A and Ethical approval, Appendix 4.B). Once accreditation was achieved, I was added to the list of investigators (12/09/2011) and delegated to consent patients for this study, administrating neuropsychological tests, accompanying patients to MRI scans and carrying out intra-operative TCD monitoring during surgery.
4.2 Patient recruitment

4.2.1 Approaching the patients

We gained permission to approach potential cardiac surgery patients from 4 cardio-
thoracic surgeons practicing at the Leicester Glenfield Hospital: Professor Tomasz Jerzy
Spyt, Mr Mark St John Hickey, Mr Jacek Szostek and Mr Haitham Abunsara. Patients
who were scheduled to have coronary artery bypass graft (CABG), aortic valve
replacement/repair (AVR), mitral valve replacement/repair (MVR), or a combination of
these procedures, and who were not recruited to other studies, were eligible to take part.
Recruitment of patients took place at a pre-assessment clinic (Clinic C) on Tuesdays,
Wednesdays, and Thursdays. Patients who were confirmed at their pre-assessment
clinic to be undergoing cardiac surgery were approached with patient information
materials and invited to participate. During this process the purpose of the study was
explained to the patient and a study information sheet was provided for their
consideration (Appendix 4.C). The patient and their family also had an opportunity to
ask questions.

Patients were excluded if they were unable to have an MRI scan due to metal objects
within the body. Patients were also excluded if their first language was not English as
this would invalidate the neuropsychological tests. If the patient was willing to
participate in the study, they were given a minimum of 24 hours to consider the study
before being asked to provide written consent (Appendix 4.D). Patients who were
interested in taking part in the study were asked to stay a further 2 hours after their next
pre-operative appointment to allow us to obtain consent and carry out baseline MRI
scans and neuropsychological tests. On the day of the patient’s pre-operative
assessment, approximately 2 weeks before surgery, myself, or another member of the
research team approached the patient for written consent according to our standard
protocol. A copy of the consent form, patient information sheet, and details of the study
reference number in form of a sticker were added to the patient’s medical notes. The
original signed consent form was then retained within our project site file. On patient
request, a covering letter and study information sheet was also sent to the patient’s GP
(Appendix 4.E). A typical timeline experienced by patients participating in our study is
shown in fig 4.1.
<table>
<thead>
<tr>
<th>Week 1: New Referrals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatients clinic: New referral (NR) stage.</td>
</tr>
<tr>
<td>Patients are invited to participate and given a study information leaflet.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 4-5: Pre-operative assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative stage (maximum waiting time of 12 weeks after NR stage).</td>
</tr>
<tr>
<td>Patient is consented if keen and TCD screening is performed to locate the MCA signal. Neuropsychological tests &amp; MRI scans are performed if an MRI slots and neuropsychological test room is available.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 6-7: Peri-operative monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-admission stage (usually within 2 weeks of pre-operative stage)</td>
</tr>
<tr>
<td>Neuropsychological tests &amp; MRI scans can be performed at this stage if not completed during the pre-op stage.</td>
</tr>
<tr>
<td>TCD monitoring is performed the following day (date of surgery).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 13-15: Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up stage (usually within 6-8 weeks of the surgery date)</td>
</tr>
<tr>
<td>A follow-up appointment is scheduled to obtain post-operative MRI scans and post-operative neuropsychological tests results. This was usually scheduled to coincide with the patient’s surgical follow-up consultation.</td>
</tr>
</tbody>
</table>

**Figure 4.1** Typical timeline for patients approached and participating in this study.

Following informed consent, the TCD ultrasound machine was demonstrated to the patient and used to check for a suitable signal from MCA blood flow. If an MCA signal was found, the position of the probe, depth, angle and sample volume were recorded to facilitate accurate placement of the probe during surgery (Appendix 4.F). The TCD ultrasound setup used in the cardio-thoracic clinic is shown in fig 4.2.
Patient recruitment for the study began on the 31/08/2011 and was completed on 17/07/2013.

Figure 4.2 TCD ultrasound setup in the clinical assessment room available within the Leicester Cardiovascular BRU.

Where possible, patients were scheduled so that postoperative testing coincided with a routine 6-8 week follow-up appointment with their cardio-thoracic consultant. Patient appointment letters were sent out 2 weeks in advance with information containing the agreed time and location of both the MRI scan and the neuropsychological tests. Patients who were unable to complete the postoperative tests on this date were re-scheduled for the next available and convenient appointment.
4.3 Risk factor analysis

The patients’ medical notes contain useful information regarding the surgical procedure (surgeon's surgical log) and data from the perfusionist's transcript, such as type of cardiopulmonary bypass machine used and blood pressure and haematocrit changes during the surgery. Patients’ medical records were tracked by the University Hospitals of Leicester IT 'Track It' service. These medical records can also be used to identify whether the patient has any obvious neurological events following surgery (e.g. stroke or delirium). Medical notes were carefully examined to extract information regarding patient demographics and underlying risk factors for cardiovascular disease that had potential to be associated with adverse neurocognitive outcome (e.g. hypertension, diabetes, family history, smoking, and grade of cardiac atheroma). A full list of data recorded from the patient's medical notes is provided in Appendix 4.G.

4.4 Anaesthetic and surgical procedures

There were no specific alterations to standard surgical practice. Routine perioperative care was used in all patients, including direct arterial blood pressure monitoring using a radial cannula [Braun Medical Ltd]. Cold blood cardioplegia was used in all patients, and anaesthesia management usually consisted of a combination of isoflurane, propofol, midazolam and fentanyl. Body temperature was measured every 3 minutes with a nasal pharyngeal temperature probe. Non-pulsatile cardiopulmonary bypass (CPB) with a non-occlusive roller pump was used, along with adhering to perfusionist guidelines and a policy of keeping CPB perfusion pressure above 50 mmHg. The CPB circuit contained a membrane oxygenator and a 40 µm arterial line filter. Arterial blood pressure targets during surgery were based on usual clinical practice.

4.5 Magnetic Resonance Imaging

All patients who consented to participate in the study underwent MRI scans pre- and postoperatively. MRI scans were performed according to a detailed MRI protocol drafted by Professor Graham Cherrymen. The pre-operative scan was obtained approximately 2 weeks prior to surgery, and the post-operative scan was conducted 6-8
weeks after surgery at the patient’s next follow-up appointment. All scans were performed using the 3-Tesla NIHR-funded MRI whole body scanner (Magnetom Skyra, Siemens Medical, Erlangen, Germany) based at Leicester Glenfield Hospital by a qualified radiographer (Mrs. Joanne Wormleighton or Mr. Dean Mawby).

4.5.1 MRI scanning protocol

Scans were performed in the following order: 3-plane localiser; diffusion-weighted sequence; Time of Flight MR angiography; Susceptibility Weighted Imaging and Fluid-Attenuated Inversion Recovery (FLAIR) with a total imaging time of approximately 30 minutes (see Chapter 3.2). FLAIR images were obtained using a slice thickness of 3 mm with the number of slices set to cover the whole brain. Matrix size was 320×352, field of view was 240 mm, repetition time/echo time were 6770/108 ms, and inversion time was 2170 ms. MRI images were held on the Picture Archiving and Communication systems (PACS) and reviewed by a Senior Radiologist (Dr John Morlese) to identify incidental findings and confirm any changes in the pre- and post-operative scans. An example radiologist’s report is included in Appendix 4.H All MRI scans were archived to a CD for further analysis.

4.6 Neuropsychological assessment

The neuropsychological tests were carried out in clinical rooms located at the Leicester Biomedical Research Unit at Leicester Glenfield Hospital. Where possible, neuropsychological tests were performed in accordance to the ‘Statement of Consensus on Assessment of Neurobehavioral Outcomes After Cardiac Surgery’, which recommends a battery of neuropsychological tests including the Rey auditory verbal learning test, Trail-making A, Trail-making B and the Grooved pegboard test (Murkin et al., 1995). All tests were performed approximately 2 weeks before surgery and 6-10 weeks after surgery at the patient’s next follow-up appointment. Neuropsychological tests included: immediate & delayed memory, verbal IQ, performance IQ, trail-making exercise A & B, and grooved pegboard tests. Further detail for individual tests can be found in Chapter 3.4. In all domains, parallel test forms were used postoperatively, and
variations in patients’ test scores were minimised by ensuring ‘the same suitably trained and qualified individual administers the test to minimise subjectivity in the tests and they are performed in a standardised manner’ (Murkin et al., 1995). As assessment can also be negatively affected by mood (Funder et al., 2010), levels of depression and anxiety were gauged using the Hospital Anxiety and Depression scale (HADS) to allow adjustment for mood (Rasmussen et al., 2001).

4.6.1 Definition of neuropsychological decline

A variety of scoring methods can be used to quantify POCD which vary across studies. Criteria for decline can vary but are typically chosen to correspond to a ≥20% decline on 20% of the tests, or an absolute decline from baseline scores (e.g. of 1 or 2 SD) on one or more tests (Rudolph et al., 2010). Such criteria do not discriminate between decline due to surgery and normal variability associated with repeated measures. As patients are expected to improve with repeated testing, these assessment techniques are thought to underestimate the incidence of cognitive decline.

The proportion of patients estimated to experience POCD appears to be dependent on a number of methodological factors. Nearly all previous studies report a decline in neurocognitive function in some patients. In assessing short-term POCD, other factors that potentially influence cognitive performance include the effects of anaesthetic drugs and painkillers (Silbert et al., 2004; Wang et al., 2007), acute pain, nausea, limited mobility and fatigue (Heyer et al., 2000; Wang et al., 2007). Therefore, it was considered best not to assess POCD until at least a week has elapsed following surgery (Murkin et al., 1995; Blumenthal et al., 1995; Mackensen & Gelb, 2004).

All of the neuropsychological tests were scored according to standard instructions provided with each test and the scores were recorded in an excel spread sheet. An example of the scoring sheet used to summarise scores for the full battery of tests is shown in fig 4.3.
Figure 4.3 Neuropsychological test scores for patient 9; test scores associated with a >1 S.D. decline in ‘z-score difference’ are highlighted in red.

4.6.2 Postoperative decline

For the purpose of this study, a decline of a calculated z-score of 1 SD was considered clinically significant (Murkin et al., 1995). Individual neuropsychological test scores (x) were first converted to z-scores through comparison with published data describing the mean (X) and standard deviation (SD) of test scores measured from a population of healthy subjects (Equation 4.1):

\[
z = \frac{x - X}{SD}
\]

Equation 4.1

Post-operative z-scores were then subtracted from preoperative z-scores to calculate the pair-wise change in z-score; significant decline in cognition was assumed if there was a drop in z-score of more than 1 SD from baseline (figure 4.4).
Figure 4.4 The normal distribution curve for z-score data showing standard deviation (SD) from the mean.

For timed tests (Trail Making A/B and Grooved Pegboard tests), the sign of the z-score was reversed so that improved performance corresponded to a positive z-score. In addition to calculating the z-score change for each individual test, z-scores were summed and averaged to estimate the overall cognitive performance of each patient as a ‘composite’ cognitive performance score.

4.6.3 Pre-existing decline

Pre-existing decline was assessed by calculating the baseline composite score for each patient. If the patient’s composite score was ≤1 SD from the mean (0), the patient was considered to have pre-existing cognitive impairment. Individual cognitive test scores were also analysed along with their corresponding neuropsychological domains in an attempt to correlate the locations of lesions with decline in particular test functions. For individual test score analysis, a patient was considered to have experienced a deficit in a specific cognitive domain if the estimated z-score was ≤2 SD from the mean.
4.7 Intra-operative TCD monitoring and analysis of embolic signals

4.7.1 Transcranial Doppler sonography

Intra-operative TCD monitoring was performed bilaterally using a commercially available TCD system (DWL Doppler-Box™, Compumedics Germany GmbH, Germany) equipped with a pair of 2 MHz transducers. TCD probes were held firmly in place using an adjustable headset and settings were optimised to obtain a clear signal from MCA blood flow. A detailed transcript outlining the stages of surgery, fluctuations in blood pressure, and haematocrit values, were noted and cross-referenced with the perfusionist’s notes to match the timing of embolic signals with surgical and perfusionist’s interventions. An example transcript showing typical stages of the surgery is provided in Appendix 4.I.

4.7.2 Intra-operative data collection

TCD recordings were made throughout the surgical procedure and terminated roughly 30 minutes after the patient had been weaned from bypass. To correlate the timing of embolic showers with operative events, all actions of the surgeon, anaesthetist, and perfusionist were cross-referenced. Theatre staff were blinded to the results of embolus detection monitoring to avoid affecting clinical management. The main stages of the surgery included initiation of cardiopulmonary bypass, application of the aortic cross-clamp, cross-clamp removal, cardiac de-airing, weaning from bypass, and resumption of cardiac rhythm. During surgery, the blood was regularly sampled, and intravenous drugs, such as heparin and protamine, were introduced. Cardioplegia was also infused into the heart tissue during surgery via the aortic cannula to stop the heart from beating.

4.7.3 Obtaining the TCD data

Following surgery, recorded data files were compressed and transferred to a password protected external hard drive, which could be decompressed and analysed on another computer. The compressed TCD recordings were viewed offline using DWL QL 2.10.3 software to examine the recording and count the number of emboli, and were also
imported to MATLAB for detailed analysis and characterisation of embolic signals. Figure 4.5 shows examples of TCD data recorded from the left and right MCAs of patient 9 during de-airing of the heart.

![Figure 4.5 Example of a shower of emboli observed in the left and right MCAs of Patient 9 during de-airing of the heart.](image)

As changes in haematocrit concentration can affect estimates of MEBR by up to 5 dB, backscattered intensities were adjusted for intra-operative haematocrit changes based on perfusionist blood sampling performed during bypass at 3 minute intervals. The Doppler sample length varied between 8 and 12 mm and the Doppler angle was assumed to be 30° to mimic a clinically realistic angle with respect to MCA geometry.

### 4.8 Statistical analysis

Statistical analyses were performed using a statistical software package (Statistical Product and Service Solutions, SPSS, version 20.0, SPSS Inc., IL, USA). Differences with a \( p \)-value of <0.05 were assumed to be statistically significant. Tests for normality were performed using the Kolmogorov-Smirnov test. Data are presented as mean ± SD unless stated otherwise. Comparisons of distributions were performed using either a Student’s \( t \)-test or a Mann-Whitney U test, as appropriate.
An exploratory data analysis was performed to check for possible associations of neuropsychological and MRI outcome with baseline and surgical risk factors, such as: type of procedure, age, sex, smoking status, hypertension, hypercholesterolemia, ischaemic heart disease, aortic stenosis, and pre-existing cerebral white matter disease. Type of surgery was dichotomised into those undergoing extra-cardiac procedures (CABG) and intra-cardiac (valve/combined) procedures. Statistical tests applied to the analysis of neuropsychological tests results have been described previously (section 4.6.2).

The distribution of new MRI lesions between left and right were analysed using a binomial test assuming a null hypothesis that lesions were distributed equally between hemispheres. Differences in average dimensions of lesions between the left and right sides were assessed using Student’s t-test. To assess whether new lesions were associated with poor cognition, differences in the characteristics of patients grouped by neurocognitive and MRI outcome were examined using Student’s t-test for continuous measures, and Pearson’s $\chi^2$ statistic for categorical data (or Fisher’s exact test if observed frequencies were less than 5). To assess whether surgical factors, timing of embolic events and size distribution of emboli were associated poor cognition and new MRI lesions, differences in characteristics of patients grouped by neurocognitive and MRI outcome were examined using a Mann-Whitney U test.
Chapter 5

5 Results – Part I: Cognitive and MRI outcome following cardiac surgery

5.1 Result of patient recruitment and demographics

5.1.1 Patient recruitment outcome

Patient recruitment for the study began on the 31/08/2011 and was completed on time in July 2013. During this study we approached a total of 362 patients and consented 114. Recruitment of patients and follow-up appointments were conducted over a period of 2 years. A total of 77 (68%) patients completed the MRI and neuropsychological test protocol. Full datasets (including additional TCD monitoring) were obtained for 71 (62%) patients. Of complete datasets obtained from 71 patients, 46 (40%) TCD recordings were suitable for detailed analysis of embolic signals. A full recruitment flow chart is provided in fig 5.1.
Figure 5.1 Diagram showing the flow of participants through each stage of the study.
5.1.2 Patient demographics

5.1.2.1 Age and sex

The mean age of the 77 patients was (age [SD]) 62.9 [10.3] years; range, 32 to 80 years, fig 5.2(a). The majority of patients were aged between 55 and 70 years (63 patients), with 13 patients below the age of 55 and only 1 patient above the age of 75. The majority of patients were male (72 males) with only 5 females Fig 5.2(b).

![Figure 5.2](image)

**Figure 5.2** (A) distribution of the patient’s ages and (B) sex

5.1.2.2 Associated risk factors

Associated risk factors for cardiovascular disease investigated as part of this study included smoking status, hypertension, hypercholesterolemia, family history of ischaemic heart disease, prevalence of aortic stenosis, left ventricle ejection fraction (LVEF). Figure 5.3 summarises the prevalence of associated risk factors within the study population.
Figure 5.3 Proportion of patients with the following risk factors: (a) smoking, (b) hypertension, (c) hypercholesterolemia, (d) aortic stenosis, (e) history of ischaemic heart disease, (f) good, fair, or poor left ventricle ejection fraction.
5.2 Magnetic Resonance Imaging Results

One-hundred and three patients were eligible to undergo MR imaging however, 19 patients did not have a pre-operative MRI scan due to scheduling difficulties, 3 patients were unable to undergo the postoperative scan due to postoperative contraindications (i.e. pacemaker) and 4 patients decided to withdraw from the study. Outcome data from all 77 patients (72 males; 63±10 years) with complete pre-and post-operative MRI scans were analysed.

5.2.1 Pre-existing chronic ischaemic white matter disease

Using the FLAIR MRI digital registration and subtraction technique outlined in chapter 5, section 5.3.1, new and pre-existing lesions were identified through comparison of before and after MRI scans. Figure 5.4 shows an example of the spatial distribution of pre-existing ischaemic lesions for patient 47. This patient had 70 pre-existing lesions, estimated to occupy a total brain volume of 3516 mm$^3$.

Pre-existing lesions, identified radiologically as chronic ischaemic white matter disease, were noted in 64% (49) of patients pre-operatively. Of patients with pre-existing lesions, the average number of lesions was 30.5 (range: 1 - 100), and the average size was 2474 mm$^3$ (range: 186 - 27950 mm$^3$) per person. Assuming 1.50 L and 1.32 L as the average volumes of the male and female brain, respectively (Luders et al., 2002), we estimate that pre-existing lesions in cardiac surgery typically affect up to 0.16% of total brain tissue.
Figure 5.4 Example of the spatial distribution of pre-existing ischaemic lesions for patient 47. This patient had 70 pre-existing lesions estimated to occupy a total volume of 3516 mm$^3$. This image was obtained by the semiautomatic contouring technique outlined in chapter 3, section 3.3.

5.2.2 New ischaemic lesions

Following surgery, 5/77 patients (7%) had perioperative strokes confirmed by the Radiologist’s MRI report: patients 13 and 62 had lacunar infarcts in the right corona radiata, patient 47 had a lacunar infarct in the left corona radiata, patient 63 had two small lacunar infarcts (one located in the right superior parietal lobule and one in the left
medial precentral gyrus), and patient 19 had a lacunar infarct in the right frontal lobe. Patient 19 was the only patient with perioperative stroke to also experience cognitive decline. ‘Before’ and ‘after’ MRI images for patients 13, 19 and 63 are shown along with the subtraction images in fig 5.5.

**Figure 5.5** Comparison of FLAIR MR images obtained 1-2 weeks before and 6-8 weeks after cardiac surgery. Registration and subtraction of MRI data were performed using ‘in house’ software to confidently distinguish new ischaemic lesions from pre-existing infarcts and provide an estimate of the position and volume of new lesions.

Nearly a third of patients, 31% (24/77), had new chronic lesions observed using FLAIR MRI. Nine patients (12%) exhibited multiple MRI lesions (up to a maximum of 5). Three patients had lesions located in more than one vascular territory. Of the 9 patients with multiple lesions, 7 possessed lesions that were larger than 100 mm$^3$. New lesions with estimated volume greater than 100 mm$^3$ were observed in 10 patients. The largest observed lesion had an estimated volume of 1383 mm$^3$ located in the right frontal lobe.
of patient 13, fig 5.5. The 10 patients with the largest lesions included 4 out of the 5 patients with perioperative stroke symptoms.

A 3-dimensional representation of the overall distribution of new MRI lesions, created by superimposing data from all 24 patients, is presented in fig. 5.6.

Figure 5.6 (A) superior view, (B) lateral view of new ischaemic lesions, compiled from the combined data of all 24 patients who received new lesions following surgery. The size and position of new lesions are consistent with a cardio-embolic pathogenesis. Lesions are highlighted in red against the background of a standard atlas image.
On average, right hemisphere lesions were three times larger (mean volume=264 ± 412 mm$^3$) than left hemisphere lesions (mean volume=87 ± 95 mm$^3$), $t$-test: $p=0.034$, fig. 5.7(a). However, the left hemisphere was the site of 74% of all new lesions compared to only 26% in the right hemisphere ($\chi^2=9.3: p=0.002$), fig. 5.7(b).

Overall, most new MRI lesions were found in the middle cerebral artery (MCA) territory (64%), followed by the anterior cerebral artery (ACA) territory (13%), posterior cerebral artery (PCA) territory (13%), superior cerebellar artery (SCA) territory (5%), and lateral lenticulostriate artery (LLA) territory (5%), fig. 5.7(b).
Figure 5.7 (A) Lesions observed in the left hemisphere tended to be smaller than those on the right ($n$ = number of lesions). (B) The majority (74%) of new lesions were located in the left hemisphere ($\chi^2$ test: $p=0.002$). Lesions appeared in multiple territories, but particularly favoured regions supplied by the middle cerebral artery (MCA). ACA = anterior cerebral artery, PCA = posterior cerebral artery, SCA = superior cerebellar artery, LLA = lateral lentistriate artery.

A detailed table summarising all data relating to the MRI results is provided in Appendix 5.A.
5.2.3 Comparison of old and new ischaemic lesions

Of the 64% (49) of patients with pre-existing lesions, 45% (22), went on to develop new lesions post-operatively compared to only 7% (2/28) of patients without pre-existing lesions (i.e. 92% (22/24) of patients with new lesions had pre-existing lesions). An example showing the location and volume of new (red) and pre-existing lesions (blue) in patient 47 is provided in fig. 5.8.

Figure 5.8 Spatial distribution of new ischaemic lesions (red), and pre-existing lesions (blue) for patient 47.
Comparison of the contribution from new and pre-existing lesions suggests that the accumulation of new lesions following surgery is relatively minor in comparison with the pre-existing burden due to chronic cerebrovascular disease. Figure 5.9(a) compares the volume of pre-existing and new lesions for the patients with new lesions. Figure 5.9(b) summarises the volume of pre-existing lesions for the patients without new lesions.
Figure 5.9  (A) Comparison of the total volume of pre-existing and new lesions in patients who received new lesions following cardiac surgery. Patients are ranked in order of the total volume of lesions and the number of pre-existing (and new) lesions is shown above each bar. (B) Volume and number of pre-existing lesions in patients who received no new lesions following surgery. * denotes patients who exhibited cognitive decline.
5.3 Neuropsychological Test Results

One-hundred and three patients were eligible to undergo neuropsychological assessment. Patients who were unable to undergo MRI were not asked to complete the neuropsychological tests. Data from all 77 patients (72 males; 63±10 years) with complete pre-and post-operative neuropsychological data were analysed.

5.3.1 Baseline cognitive scores

To investigate post-operative outcome, patient’s baseline test scores were used as their own controls. Figures 5.10 and 5.11 summarise the distribution of baseline test scores for immediate memory, delayed memory, verbal IQ, performance IQ, trial making A & B, grooved pegboard dominant and non-dominant hand respectively. Pre-operative test performances were similar to the general population in all tests apart from the grooved pegboard test where our cohort of patients exhibited a moderate pre-existing decline. Performance IQ was slightly better than the general population, which probably reflects the higher IQ of patients willing to participate in our research.

Overall, 22% of patients were estimated to have cognitive impairment in at least 1 test at baseline and 46% of patients experienced cognitive decline following surgery. A detailed breakdown of the results of neuropsychological testing is provided in the next few pages.
Figure 5.10 Baseline z-scores for (A) immediate memory, (B) delayed memory, (C) verbal IQ and (D) performance IQ. z-scores < 0 resulted in scores below the normal healthy population average and > 0 above average.
5.3.2 Pre-existing cognitive impairment

Pre-existing cognitive impairment at baseline was noted in 17 (22%) of 77 patients, as defined by a ‘composite z-score’ >1 SD below the normative population average. The most commonly affected tests were the Grooved pegboard exercise (dominant hand: 46% (36) and non-dominant hand: 23% (18)). More patients showed pre-existing impairment in the immediate memory exercise (12% (9)) than the delayed memory exercise (3% (2)). Likewise, a higher proportion of patients exhibited pre-existing
impairment in the Trail making-B test (10% (8)) than the Trail making-A (4% (3)). Five percent of the patients (4) had low scores in the verbal IQ tests. No patients had impaired performance IQ, fig 5.12. However, this may reflect selection bias as more highly educated individuals were more likely to agree to participate in our research.

Figure 5.12 Numbers of patients showing pre-existing decline in individual tests by >2 SD. TMA; Trail making-A, TMB; Trail making-B, GP; Grooved pegboard.

5.3.3 Postoperative cognitive decline

The mean raw and z-scores for the entire cohort were grouped by test and examined as a group to see if there were any significant differences overall between the baseline and postoperative scores. We found no evidence to suggest a statistically significant difference between the scores of our cohort before and after surgery in any of the 4 domains assessed, table 5.1.
Table 5.1 Mean raw and z-scores for baseline and postoperative test scores for each type of test performed. The S.D. refers to the raw scores.

<table>
<thead>
<tr>
<th>Cognitive function (n=77)</th>
<th>Baseline</th>
<th>6-8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (z-score)</td>
<td>SD</td>
</tr>
<tr>
<td><strong>Working memory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate memory</td>
<td>92.4 (-0.69)</td>
<td>14.1</td>
</tr>
<tr>
<td>Delayed memory</td>
<td>98.6 (-0.49)</td>
<td>13.1</td>
</tr>
<tr>
<td><strong>Visual and executive functioning</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance test</td>
<td>110.9 (0.63)</td>
<td>15.5</td>
</tr>
<tr>
<td>Trail making B</td>
<td>67.4 (-0.59)</td>
<td>25.1</td>
</tr>
<tr>
<td><strong>Attention and psychomotor speed</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making A</td>
<td>32.5 (-0.18)</td>
<td>11.2</td>
</tr>
<tr>
<td>Grooved pegboard (dom)</td>
<td>109.6 (2.44)</td>
<td>23.0</td>
</tr>
<tr>
<td>Grooved pegboard (non-dom)</td>
<td>110.1 (1.59)</td>
<td>17.8</td>
</tr>
<tr>
<td><strong>Verbal intelligence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal test</td>
<td>90.4 (-0.43)</td>
<td>18.3</td>
</tr>
</tbody>
</table>

Analysing data from individual patients where each patient acts as their own control, revealed a >1 SD decline in neuropsychological performance in at least one test for 35 (46%) of the 77 patients studied. Five patients (6%) declined in two or more tests. The most commonly affected domains were attention and psychomotor speed, affecting 23% (18) of patients (TMT-A: 5% and Grooved pegboard: 18%). Visual & executive domains were affected in 17% (13) of patients (performance: 4% and TMT-B: 13%), immediate memory was affected in 8% (6) of patients, while delayed memory was affected in 4% (3) of patients. Only one patient declined in the verbal intelligence test (1%). The magnitude of decline quantified as a z-score change for all patients who experienced cognitive decline are summarised in fig. 5.13. This figure shows the individual patient’s pre-operative z-score (●) and post-operative z-score (■).
Figure 5.13 Magnitude of z-score change for patients that declined postoperatively. ● denotes the pre-operative z-score and ■ denotes postoperative z-score. Shaded areas (in pink) within each graph indicate z-scores below the general population (normative) average.
Overall, more patients improved in their postoperative test scores than declined, however, only 2 patients showed an improvement in mean ‘composite’ z-score greater than 1 SD. The most commonly improved performances were in the Trail making-B test (18% (14)), delayed memory test (17% (13)) and the immediate memory test (16% (12)). Twelve percent of the 77 patients showed an improvement in the Trail making-A tests (9) and 7% (5) in both verbal IQ and the Grooved pegboard (dominant) tests. Five percent (4) showed an improvement in the Grooved pegboard (non-dominant) test and only 3% (2) showed an improvement in performance IQ. A comparison of the number of patients that declined and improved in each specific test is shown in fig 5.14.

![Comparison of the patients that declined and improved within specific tests. Bars shaded red indicate the number of patients that improved or declined by ≥2 SD in their respective cognitive tests.](image)

**Figure 5.14** Comparison of the patients that declined and improved within specific tests. Bars shaded red indicate the number of patients that improved or declined by ≥2 SD in their respective cognitive tests.

The majority of the patients had normal levels of depression and mild levels of anxiety on HADS at pre-operative assessment (anxiety: 6.3±3.8; depression: 3.3±2.7). The level of anxiety had dropped in some, but not all, patients after surgery (anxiety: 3.9±3.1; depression: 2.9±3.2). Depression levels were stable compared with baseline scores.
HADS assessment suggests that any decline in neuropsychological test scores was not due to an increase in anxiety or depression.

The incidence of cognitive decline in our study population was 46%, which was independent of the presence of new lesions, and irrespective of whether new lesions were large or multiple. We found no association between declining $z$-score and the presence of new MRI lesions (denoted ○) (filled circles ● denote no new MRI lesions) (fig. 5.15 and 5.16). Similarly, as previously shown in fig 5.9, there was no association between the volume of new MRI lesions and >1 SD cognitive decline.
Figure 5.15 Summary of changes in neuropsychological test performance (z-score change) for 77 patients taking non-timed cognitive tests. Overall, test performance tended to improve slightly on retesting, indicated by a positive mean z-score change (mean: ■, 1 SD). Patients who had a drop in z-score of more than 1 SD (shaded) were assumed to have significantly declined in at least 1 test (indicated by the shaded grey regions). Visual inspection suggests no obvious correlation between z-score decline and the presence of new MRI lesions (denoted ○).
Figure 5.16 Summary of changes in neuropsychological test performance (z-score change) for 77 patients taking timed cognitive tests. Overall test performance tended to improve slightly on retesting, indicated by a positive mean z-score change (mean: ■, 1 SD) apart from the Grooved pegboard (non-dom.) which showed a small decline. Patients with a drop in z-score of more than 1 SD (shaded) were defined as having significantly declined. Visual inspection suggests no obvious correlation between z-score decline and the presence or characteristics of new MRI lesions (denoted ○).
Grouping patients by neuropsychological outcome showed similar demographic and surgical factors between groups with the exception of age ($t$-test, $p=0.022$) and aortic stenosis ($\chi^2$ test, $p=0.042$), table 5.2.

**Table 5.2** Comparison of potential risk factors grouped by cognitive outcome.

<table>
<thead>
<tr>
<th></th>
<th>Cognitive decline $N=35$</th>
<th>No cognitive decline $N=42$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: female</td>
<td>33:2</td>
<td>39:3</td>
<td>1.000*</td>
</tr>
<tr>
<td>Age, years ± SD</td>
<td>66±7</td>
<td>60±12</td>
<td>0.022†</td>
</tr>
<tr>
<td>CABG: intra-cardiac procedures</td>
<td>12:23</td>
<td>15:27</td>
<td>0.896‡</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>14 (40)</td>
<td>23 (55)</td>
<td>0.254‡</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>23 (66)</td>
<td>32 (76)</td>
<td>0.311‡</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>27 (77)</td>
<td>31 (74)</td>
<td>0.735‡</td>
</tr>
<tr>
<td>Ischaemic heart disease, n (%)</td>
<td>23 (66)</td>
<td>20 (48)</td>
<td>0.111‡</td>
</tr>
<tr>
<td>Aortic stenosis (mild/severe), n (%)</td>
<td>24 (69)</td>
<td>18 (43)</td>
<td>0.042‡</td>
</tr>
<tr>
<td>Pre-existing white matter disease, n (%)</td>
<td>23 (66)</td>
<td>26 (62)</td>
<td>0.727‡</td>
</tr>
<tr>
<td>New FLAIR MRI lesions, n (%)</td>
<td>11 (31)</td>
<td>13 (31)</td>
<td>0.964‡</td>
</tr>
</tbody>
</table>

*Fisher’s exact test, †$t$-test, ‡Chi-squared test; CABG=Coronary Artery Bypass Graft, FLAIR=Fluid Attenuated Inversion Recovery. Significant risk factors are highlighted.

There were no significant differences between the characteristics of patients with and without new lesions other than an association between new and pre-existing lesions. Ninety-two percent (22/24) of patients with new lesions had pre-existing lesions, compared to only 51% (27/53) of patients with no new lesions ($\chi^2$ test: $p=0.001$), see table 5.3

**Table 5.3** Comparison of potential risk factors grouped by FLAIR MRI outcome.

<table>
<thead>
<tr>
<th></th>
<th>New lesions (N=24)</th>
<th>No new lesions (N=53)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: female</td>
<td>21:3</td>
<td>51:2</td>
<td>0.172*</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>64±10</td>
<td>63±11</td>
<td>0.606†</td>
</tr>
<tr>
<td>CABG: intra-cardiac procedures</td>
<td>6:18</td>
<td>21:32</td>
<td>0.213‡</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>9 (38)</td>
<td>28 (53)</td>
<td>0.212‡</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>15 (63)</td>
<td>40 (75)</td>
<td>0.243‡</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>17 (71)</td>
<td>41 (77)</td>
<td>0.538‡</td>
</tr>
<tr>
<td>Ischaemic heart disease, n (%)</td>
<td>12 (50)</td>
<td>31 (59)</td>
<td>0.487‡</td>
</tr>
<tr>
<td>Aortic stenosis (mild/severe), n (%)</td>
<td>16 (67)</td>
<td>26 (49)</td>
<td>0.151‡</td>
</tr>
<tr>
<td>Pre-existing lesions, n (%)</td>
<td>22 (92)</td>
<td>27 (51)</td>
<td>0.001‡</td>
</tr>
<tr>
<td>Neuropsychological decline, n (%)</td>
<td>11 (46)</td>
<td>24 (45)</td>
<td>0.964‡</td>
</tr>
</tbody>
</table>

*Fisher’s exact test, †$t$ test, ‡Chi squared test. CABG=Coronary Artery Bypass Graft, FLAIR=Fluid Attenuated Inversion Recovery. Significant risk factors are highlighted.
5.4 Summary

In summary, the results of this chapter confirm that neurological injury is common in patients undergoing cardiac surgery; 7% of patients suffered a perioperative stroke, 31% had new MRI lesions, and 46% exhibited signs of neuropsychological impairment at 6-8 weeks postoperatively. Older patients and patients with aortic stenosis were confirmed to be most likely to experience cognitive decline. Patients with pre-existing lesions were most likely to receive new lesions following surgery. Pre-existing lesions, affecting up to 0.16% of total brain volume, were observed in 64% of patients and were associated with a high risk of receiving new lesions following surgery.

We found no evidence to support a link between new lesions on MRI and cognitive decline. Of those patients who experienced neuropsychological decline, 69% (24/35) had no new postoperative MRI lesions. Similarly, over half (54%) of the 24 patients with new MRI lesions (13/24) did not experience any discernable neuropsychological decline. No association between the magnitude of cognitive decline and the size or number of new lesions was found. On average, patients with new MRI lesions did not experience a greater magnitude of decline than patients without new MRI lesions (mean composite z-score change, 0.07 versus 0.11, respectively; t-test, p=0.7) and there was no association between having multiple new lesions and larger decline in composite z-score (t-test, p=0.6).
Chapter 6

6 Results – Part II: Intra-operative risk factors and detailed embolic signal analysis

6.1 Patient recruitment outcome

Of the 77 patients with complete sets of outcome measures, 73 received bilateral intra-operative transcranial Doppler (TCD). Of these recordings, data from 46 patients (43 males; mean age [range] 64 [41-80]) were of a sufficiently high quality to be used for detailed embolic signal analysis. Data were excluded from analysis for the following reasons: (i) Signal saturation (i.e. the dynamic range of the recording was insufficient for estimation of embolic signal intensity) (24), (ii) unilateral monitoring only (1), (iii) perfusionist records absent (1), (iv) poor quality recording (1).

6.2 Intra-operative exploratory data analysis

Intra-operative data collected as part of this study for all 77 patients included the type of surgery, duration of cardiopulmonary bypass, and duration of aortic cross-clamp application. Intra-operative blood pressure, haematocrit levels, temperature, rate of re-warming, and carbon dioxide levels are also reported for the 46 patients whose Doppler data were analysed.

6.2.1 Type of surgery

All patients underwent one of the following procedures; coronary artery bypass graft (CABG), valve procedure, or a combination of both. The number of patients within each surgical group is summarised in table 6.1.
### Table 6.1 Number of patients undergoing each type of surgical procedure.

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>No. of patients with complete MRI and cognitive tests</th>
<th>No. of patients with complete TCD data</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG (x1 graft)</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>CABG (x2 graft)</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>CABG (x3 graft)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total CABG</strong></td>
<td><strong>27 (35%)</strong></td>
<td><strong>18 (39%)</strong></td>
</tr>
<tr>
<td>Aortic valve</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Mitral valve</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td><strong>CABG &amp; aortic valve</strong></td>
<td><strong>9</strong></td>
<td><strong>4</strong></td>
</tr>
<tr>
<td><strong>CABG &amp; mitral valve</strong></td>
<td><strong>3</strong></td>
<td><strong>3</strong></td>
</tr>
<tr>
<td><strong>Mitral &amp; tricuspid valve</strong></td>
<td><strong>1</strong></td>
<td><strong>1</strong></td>
</tr>
<tr>
<td><strong>CABG &amp; mitral/tricuspid valve</strong></td>
<td><strong>1</strong></td>
<td><strong>1</strong></td>
</tr>
<tr>
<td><strong>Total Intra-cardiac</strong></td>
<td><strong>50 (65%)</strong></td>
<td><strong>28 (61%)</strong></td>
</tr>
<tr>
<td><strong>Total patients</strong></td>
<td><strong>77</strong></td>
<td><strong>46</strong></td>
</tr>
</tbody>
</table>

6.2.2 Cardiopulmonary bypass and aortic cross-clamp

The start and end of cardiopulmonary bypass (CPB) were noted and later cross-referenced with the perfusionist’s records. CPB duration for CABG ranged between 35 and 122 minutes (mean [SD] 71 [22]), fig 6.1(a) and aortic cross-clamp times ranged between 13 and 58 minutes (41[12]) fig 6.1(b). CPB duration for intra-cardiac surgery ranged from between 44 and 271 minutes (103 [57]), fig 6.1(c), and aortic cross-clamp times ranged from 34 to 234 minutes (72[48]) fig 6.1(d).
Results Part II: Intra-operative risk factors and embolic signal analysis

6.2.3 Blood pressure and haematocrit levels during CPB

**Blood pressure**

Arterial blood pressure targets during surgery were based on usual clinical practice. Blood pressure readings were taken every 5 minutes by the perfusionist during CPB,

---

**Figure 6.1** (A) CPB time for CABG, (mean [SD]) 71 [22], (B) aortic cross-clamp time for CABG, 41[12], (C) CPB time for intra-cardiac (103 [57]), and (D) aortic cross-clamp for intra-cardiac (72[48]) (n=77).
and the mean blood pressure during CPB for each patient was estimated. Blood pressure typically varied by 5-10 mmHg between recordings. Mean blood pressure varied considerably between patients, ranging from 45 to 85 mmHg with a mean of 62 mmHg, fig 6.2(a).

**Haematocrit**

Haemodilutional anaemia is inevitable during CPB and has potential to generate ischaemic organ injury. Normal haematocrit values are usually lower in adult females (38-46%) than adult males (42-54%). Haematocrit values can vary during CPB, but the majority of studies suggest that haematocrit less than 22% increases the risk of morbidity and neurological injury (Murphy *et al.*, 2009). Percentage haematocrit was recorded every 3 minutes during CPB and varied between 22% and 38% with a mean value of 29%, fig 6.2(b).

![Figure 6.2](image)

**Figure 6.2** Mean blood pressure during CPB (mean [SD]) 62.4 [8.8] (n=46), (B) mean haematocrit levels during CPB (mean [SD]) 29.0 [3.8] (n=46). Areas shaded red highlight patients experiencing cognitive decline.

### 6.2.4 Carbon dioxide levels during CPB

Respiratory carbon dioxide (CO₂) measurements provide instantaneous information during surgery about how effectively CO₂ is being eliminated by the pulmonary system.
(via ventilation), and how effectively CO₂ is being transported through the vascular system (perfusion). The level of respiratory CO₂ in kilopascals (KPa) was measured every 3 minutes during CPB and varied between 4.3 and 6.4 KPa with a mean CO₂ level of 5.2 KPa, fig 6.3.

![Figure 6.3](image)

**Figure 6.3** Mean carbon dioxide levels during CPB (mean [SD]) 5.2 [0.5] (n=46). Areas shaded red highlight patients experiencing cognitive decline. The normal range of CO₂ levels during CPB are 4.6 – 6.0 KPa outlined in The Society of Clinical Perfusion guidelines (Department of Health, [http://www.scps.org.uk/pdfs/GuidetoGoodPractice.pdf: accessed on 25/08/2014]).

### 6.2.5 Body temperature and the rate of re-warming during CPB

**Temperature**

Mild hypothermia is thought to be protective for the brain during surgery by reducing metabolic demand. Body temperature was measured every 3 minutes with a nasal pharyngeal temperature probe. The majority of our patients were operated on under mild hypothermia, during which the average body temperature during CPB was lowered
to between 30°C and 34°C with a mean temperature of 32°C. Seven patients were not cooled, fig 6.4(a).

**Rate of re-warming**

The average rate of re-warming was calculated by subtracted the first reading after the commencement of re-warming from the last reading of the temperature before re-warming. The distribution of re-warming rates is summarised in fig 6.4(b). Patients under ‘0’ on the histogram were not cooled during their surgery.

![Figure 6.4](image)

**Figure 6.4** (A) Average body temperature during CPB (mean [SD]) 32 [1.7] (n=46), (B) average rate of re-warming during surgery (mean [SD]) 5.2±0.5 (n=46). Areas shaded red highlight patients experiencing cognitive decline.

Blood pressure, haematocrit, carbon dioxide and temperature readings were similar between procedure types (table 6.2) in patients with and without new MRI lesions (table 6.3), and in patients with and without cognitive decline (table 6.4), with the exception of patient age which was significantly higher in patients experiencing cognitive decline ($t$-test: $p=0.022$). The rate of rewarming was significantly higher during intra-cardiac procedures ($t$-test: $p=0.039$).
### Table 6.2
Comparison of age, blood pressure, haematocrit, CO₂ levels, temperature and re-warming (post 3 mins) during CPB with type of procedure. All values describe median and IQR.

<table>
<thead>
<tr>
<th></th>
<th>CABG</th>
<th>Intra-cardiac</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=18</td>
<td>n=28</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67</td>
<td>61-73</td>
<td>64</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>62</td>
<td>56-70</td>
<td>60</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>29</td>
<td>26-32</td>
<td>28</td>
</tr>
<tr>
<td>Carbon dioxide levels</td>
<td>5</td>
<td>4-5</td>
<td>5</td>
</tr>
<tr>
<td>Temperature</td>
<td>32</td>
<td>31-34</td>
<td>32</td>
</tr>
<tr>
<td>†Re-warm temp.</td>
<td>3</td>
<td>2-4</td>
<td>4</td>
</tr>
</tbody>
</table>

IQR; Interquartile Range (25th – 75th percentile) AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass. *t-test, significant factors are highlighted, †7 patients were not cooled, CABG: 15 patients, Intra-cardiac: 24 patients.

### Table 6.3
Comparison of age, blood pressure, haematocrit, CO₂ levels, temperature and re-warming (post 3 mins) during CPB in patients with and without new MRI lesions. All values describe median and IQR.

<table>
<thead>
<tr>
<th></th>
<th>No new MRI lesions</th>
<th>New MRI lesions</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=28</td>
<td>n=18</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64</td>
<td>56-72</td>
<td>66</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>61</td>
<td>56-63</td>
<td>62</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>29</td>
<td>27-31</td>
<td>28</td>
</tr>
<tr>
<td>Carbon dioxide levels</td>
<td>5</td>
<td>5-6</td>
<td>5</td>
</tr>
<tr>
<td>Temperature</td>
<td>31</td>
<td>31-33</td>
<td>32</td>
</tr>
<tr>
<td>†Re-warm temp.</td>
<td>4</td>
<td>3-5</td>
<td>4</td>
</tr>
</tbody>
</table>

IQR; Interquartile Range (25th – 75th percentile) AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass. *t-test, †7 patients were not cooled, No new lesions: 26 patients, New MRI lesions: 13 patients.

### Table 6.4
Comparison of age, blood pressure, haematocrit, CO₂ levels, temperature and re-warming (post 3 mins) during CPB in patients with and without cognitive decline. All values describe median and IQR.

<table>
<thead>
<tr>
<th></th>
<th>No cognitive decline</th>
<th>Cognitive decline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=25</td>
<td>n=21</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62</td>
<td>56-70</td>
<td>68</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>61</td>
<td>59-67</td>
<td>61</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>29</td>
<td>26-31</td>
<td>28</td>
</tr>
<tr>
<td>Carbon dioxide levels</td>
<td>5</td>
<td>5-6</td>
<td>5</td>
</tr>
<tr>
<td>Temperature (during CPB)</td>
<td>32</td>
<td>31-33</td>
<td>32</td>
</tr>
<tr>
<td>†Re-warm temp.</td>
<td>4</td>
<td>3-4</td>
<td>4</td>
</tr>
</tbody>
</table>

IQR; Interquartile Range (25th – 75th percentile) AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass. *t-test, significant factors are highlighted, †7 patients were not cooled, No cognitive decline: 21 patients, Cognitive decline: 18 patients.
6.3 Timing of emboli during cardiac surgery

By manually analysing data from the entire procedure, and comparing the timing of the emboli showers with detailed intraoperative transcripts, we were able to identify sources of embolic showers during surgery. This was used to determine the number and estimated sizes of bubbles using the embolus analysis software and bubble sizing algorithm previously described in Chapter 3.5.6. Examples of detailed plots for specific patients, illustrating the timing and estimated sizes of individual air bubbles, and estimated total accumulated volume of air, are presented in figs 6.5-6.8. Each marker in the upper panel represents an individual embolic event. The y-axis and marker width indicates estimated bubble diameter and the x-axis displays the time during surgery.

Showers of emboli typically occurred in the left and right MCA simultaneously and included bubbles with a broad distribution of sizes. Showers typically coincided with the introduction and removal of cannulas, preparing and stitching the grafts, and injections. Dense showers, and curtains of emboli containing particularly large bubbles were consistently observed while restarting the heart following removal of the aortic cross-clamp.

To estimate the dynamic impact associated with accumulation and clearance of air bubbles within the vasculature over time, the diameters and timing of the bubbles were used as inputs for a Monte-Carlo simulation (see Chapter 3.6). Patient specific estimates for the instantaneous percentage of obstructed end arterioles in our model are plotted as the solid line in the lower panels of figures 6.5 to 6.8. Where possible, examples of patients have been selected to include patients undergoing differing procedures and with differing cognitive and MRI outcome.
Patient 39: AVR/CABG, POCD, no new MRI lesions

Figure 6.5 Bubble diameters estimated for patient 39 undergoing AVR/CABG. Each marker denotes an individual embolic event (blue: left MCA events, orange: right MCA events). The y-axis and marker size indicates estimated bubble diameter displayed on a log scale. The lower panel displays the predicted number of blocked arterioles obtained by Monte-Carlo simulation. The inset on the right-hand side summarises estimated total number of emboli and volume of air.

Figure 6.5 shows data from a 55 year old male with POCD (2/8 tests: delayed memory, z-score change: -2.12/grooved pegboard (non-dom.) z-score change: -5.14) with no new MRI lesions. This patient received a total of 4224 emboli with a total estimated volume of air of 0.12 ml. He had a CPB time of 102 mins (aortic cross-clamp time: 71 mins) with no major complications reported in the surgical transcript. Showers can be seen during blood sampling and anaesthetic interventions, initiation and weaning from bypass, stitching of grafts, release of the aortic cross-clamp and de-airing of the heart. The largest bubbles were seen after the release of the aortic cross-clamp, estimated to be...
up to ~3.48 mm in diameter (approximately the diameter of the MCA). Monte-Carlo simulations predicted <2% obstruction in both the left and right MCAs. The highest percentage of blocked end nodes appeared to be following the release of the aortic cross-clamp during de-airing (~1.8%).

**Patient 20: AVR, POCD, 1 new MRI lesion**

![Figure 6.6](image)

Figure 6.6 Bubble diameters estimated for patient 20 undergoing AVR. Markers denote individual embolic events (blue: left MCA events, orange: right MCA events) where the y-axis and marker size indicate estimated bubble diameter. The lower panel displays the predicted number of blocked arterioles obtained by Monte-Carlo simulation. The inset on the right summarises estimated total number of emboli and volume of air.

Figure 6.6 presents data from a 71 year old female with POCD (1/8 tests: grooved pegboard (dom.) z-score change: -1.23) and one new MRI lesion (309 mm$^3$ in the left-lateral lenticulostriate territory). This patient received a total of 1300 emboli with a total estimated volume of air of 0.02 ml. She had a CPB time of 66 mins (aortic cross-clamp time: 45 mins) with no major manoeuvres reported in the surgical transcript. Showers
were observed during surgical interventions (aortic cannulation and the opening of the pericardium). Large bubbles were observed in the right MCA during de-airing with the largest bubble estimated to be ~1.7 mm. Monte-Carlo simulations predicted <1% obstruction of the model vasculature in the right MCA, following the release of the aortic cross-clamp (~0.7%).

**Patient 4: CABG, no POCD, 1 new MRI lesion**

![Figure 6.7 Bubble diameters estimated for patient 4 undergoing CABG. Markers denote individual embolic events (blue: left MCA events, orange: right MCA events) where the y-axis and marker size indicate estimated bubble diameter. The lower panel displays the predicted number of blocked arterioles obtained by Monte-Carlo simulation. The inset on the right summarises estimated total number of emboli and volume of air.](image)

Figure 6.7 Presents data from a 71 year old female with no POCD and one new MRI lesion (1383 mm$^3$/right-MCA territory). This patient suffered from perioperative stroke confirmed radiologically to be a lacunar infarct in the right corona radiata. This patient
received a total of 1517 emboli with a total estimated volume of air of 0.03 ml. She had a CPB time of 108 mins (aortic cross-clamp time: 40 mins) with no major complications reported in the surgical transcript. Larger bubbles for this patient coincided with de-airing and filling the heart with blood with the largest bubble estimated to be ~1.92 mm. Monte-Carlo simulations predicted these bubbles to transiently obstruct just over 1% of the right MCA, and ~0.2% of the left MCA.

**Patient 45: MVR/TVR, POCD, no new MRI lesions.**

![Figure 6.8](image)

**Figure 6.8** Bubble diameters estimated for patient 45 undergoing MVR/TVR. Markers denote individual embolic events (blue: left MCA events, orange: right MCA events). The y-axis and marker size indicate estimated bubble diameter. The lower panel displays the predicted number of blocked arterioles obtained by Monte-Carlo simulation. The inset on the right summarises the estimated total number of emboli and volume of air.
Figure 6.8 presents data from a 72 year old male with POCD (1/8 tests: grooved pegboard (non-dom) z-score change: -2.86) and no new MRI lesions who underwent MVR/TVR. This patient received a total of 11646 emboli with a total estimated volume of air of 0.006 ml. He had a CPB time of 271 mins (aortic cross-clamp time: 225 mins). The number of emboli received by this patient was over 3 times greater than the average number. This patient underwent successful tricuspid valve replacement but unfortunately the mitral valve surgery had to be repeated, which is the reason why CPB was reinitiated at 12:48 pm. This patient experienced high numbers of emboli throughout CPB but did not receive any large macrobubbles and 95% of the bubbles detected were estimated to be less than <0.1 mm. The largest bubble this patient received was estimated to be 0.99 mm in diameter during de-airing. Monte-Carlo simulations predicted ~0.16% obstruction of the model vasculature in the left MCA and ~0.04% in the right MCA during de-airing of the heart and weaning from bypass.

Our Monte-Carlo simulations confirm that small showers of filtered bubbles (<40 µm) occurring during bypass do not have any negative impact on cerebral blood flow. The greatest threat to perfusion due to bubbles was consistently predicted to occur due to unfiltered bubbles in the later stages of surgery (following the removal of aortic cross-clamp).

6.3.1 Application and release of the aortic cross-clamp

As seen from figures 6.5-6.8, showers typically coincided with the introduction and removal of cannulas, preparing and stitching the grafts, and injections. Dense showers containing largest bubbles were consistently seen after restarting the heart following the release of the aortic cross-clamp. Bubbles occurring during CPB were found to be numerous but were estimated to be considerably smaller than those entering during the later stages of the surgery.

The majority of emboli were generated at stage 1 of the procedure (from the start of the surgery to the release of the aortic cross-clamp) (61385) compared to stage 4 (30830) release of aortic cross-clamp to the end of surgery. Approximately two-thirds of bubbles (67%) occurred prior to release of the aortic cross-clamp, fig 6.9(a).
The estimated median bubble diameter of 30 µm (IQR: 20 to 40 µm) prior to the release of the aortic cross-clamp is consistent with the use of a 38 µm filter, which is positioned in the aortic line of the CPB circuit. The majority of large bubbles were observed as the heart begins to eject following removal of the aortic cross-clamp. Although signals observed following the removal of the aortic cross-clamp only contributed to 33% of embolic signals, their estimated median diameter, and the spread of bubble sizes, was considerably broader, 56 µm (IQR: 20 to 72 µm) than during CPB (median [IQR] diameter (µm); 30 [20-40]), ($p=0.009$, $t$-test). Figure 6.9(b) presents the size distribution of bubbles for all 46 patients in stages 1 and 4.

6.3.2 One minute following application and release of the aortic cross-clamp

Embolic signals associated with the application and removal of arterial clamps were noted in patients undergoing CABG during release of the cross-clamp in 48 patients with severe aortic atheroma burden of which 7 (15%) had new ischaemic lesions (Kumral et al., 2001). Therefore embolic signals detected during the release of the aortic cross-clamp are of particular interest, since these are likely to contain solid emboli, which are potentially more hazardous than air.
We noted similar numbers of emboli in the minute following aortic cross-clamp application (median: 14.5) and release of the aortic cross-clamp (median: 17.5) (Mann Whitney U test, \( p = 0.568 \)). However, large macro-bubbles were more frequent following release of the aortic cross-clamp, with an average maximum diameter of 61 \( \mu \text{m} \) during CPB (IQR: 26 to 81) compared to 1160 \( \mu \text{m} \) (IQR: 510 to 1760 \( \mu \text{m} \)) (\( p = 0.001 \), \( t \)-test). The largest bubble detected during our study was estimated to be \( \sim 3.48 \text{ mm} \), approximately the size of the MCA (patient 39).

### 6.4 Total number and distribution of emboli and volume of air

Bilateral MCA monitoring of 46 patients during their surgery revealed a total of 92215 individual embolic signals over 115 hours of recordings. Details of the patient’s age and sex, type of surgery, duration of CPB, aortic-cross clamp time, numbers of emboli, curtain duration, estimated total volume of air and tests exhibiting cognitive decline are listed in table 6.5 (page 150). A total of 49485 (54\%) emboli were detected in the left MCA and 42730 (46\%) detected in the right MCA (fig. 6.10). Total numbers of emboli entering the MCAs during a single operation varied from 203 (patient 11) to 11646 (patient 45).
Total numbers of emboli entering the right/left MCA for all 46 patients. CABG patients are marked with ● and intra-cardiac patients with □.

Conversion of bubble diameters to volume of air (using $V = \frac{4}{3} \pi r^3$) was used to estimate the total volume of air entering the MCA territories for each patient. The estimated total volume of air entering the left MCA was 410 µl and 490 µl in the right MCA (fig. 6.11).
Figure 6.11 Estimated total volume of air (µl) entering the right/left MCA (n=46). CABG patients are marked with ● and intra-cardiac patients with □.

The estimated volumes of air entering the MCAs of individual patients ranged between 0.04 µl (patient 9, 16 and 28) and 216 µl (patient 30). Patients undergoing intra-cardiac procedures tended to receive a higher volume of air than CABG patients. Although bubble diameters ranged from 6.3 µm to 3.4 mm, the majority (87%) were less than 100 µm (fig 6.12). Patient-specific bubble sizing revealed that 87.1% of bubbles were less than 100 µm and only 0.3 % of bubbles were larger than 1 mm, fig 6.12.
Larger bubbles were more frequent during intra-cardiac procedures compared to CABG. Median bubble diameters were 20 µm during CABG and 30 µm during intra-cardiac surgery, but the upper size limit was considerably extended (fig 6.13).

**Figure 6.12** Estimated diameters of bubbles received during surgery

**Figure 6.13** Distribution of estimated bubbles sizes for CABG (n=865 emboli), valve (n=1995 emboli), and combined (n=2769 emboli) procedures shows that more complex intra-cardiac procedures attract a significantly higher number of large bubbles (>100 µm).
Bar charts showing patients ranked in order of the number of embolic signals received suggests that the number and sizes of bubbles are unrelated to cognitive decline. The distribution of bubble diameters for patients undergoing CABG, valve surgery and combined procedures are shown in fig 6.14, 6.15 and 6.16 respectively.

**Figure 6.14** Total estimated numbers of bubbles detected for each patient undergoing CABG, ranked in order of the total number of emboli. Patients exhibiting POCD in at least one test are indicated by the arrows. * denotes patients with new MRI lesions.
Figure 6.15 Total estimated numbers of bubbles detected for each patient undergoing valve procedures, ranked in order of the total number of emboli. Patients exhibiting POCD in at least one test are indicated by the arrows. * denotes patients with new MRI lesions.

Figure 6.16 Total estimated numbers of bubbles detected for each patient undergoing combined procedures, ranked in order of the total number of emboli. Patients exhibiting POCD in at least one test are indicated by the arrows. * denotes patients with new MRI lesions.
Higher numbers of emboli were experienced in patients undergoing valve and combined procedures. Visual inspection suggested no correlation between receiving high numbers of macrobubbles, or a high total number of bubbles with cognitive decline or new MRI lesions.

A detailed summary of the patients’ surgical characteristics and neurological outcome is provided in table 6.5. Patients are listed in order of procedure, showing their respective blood pressure (BP), haematocrit (HCT), carbon dioxide levels (CO₂) and body temperature (temp.), all measured during CPB. CPB and aortic cross-clamp times are also shown together with the total number emboli and number of emboli detected in the left and right MCA. Where emboli were too numerous to be individually analysed, curtain duration for each patient was noted in seconds. The estimated volume of air is given in µl. The table also presents the number of tests exhibiting cognitive decline for each patient and the number and volume (mm³) of new MRI lesions.
Table 6.5 Detailed summary of age, sex, type of procedure, blood pressure (BP), haematocrit (HCT), carbon dioxide levels (CO₂), body temperature during CPB (temp.), cardiopulmonary bypass (CPB) duration, aortic cross-clamp (AxC) duration, total number of emboli, length of dense embolic showers (curtain) total volume of air, and outcome of MRI and neurocognitive testing for all 46 patients whose TCD recordings were analysed in detail.

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<th>Mean values</th>
<th>Total number of emboli</th>
<th>Length of curtain (secs)</th>
<th>Estimated total volume of air (µl)</th>
<th>No. of tests exhibiting cognitive decline</th>
<th>New MRI lesions No./volume (mm³)</th>
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Results Part II: Intra-operative risk factors and embolic signal analysis

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<td>5/979</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>M/64</td>
<td>AVR/CABG</td>
<td>59.6</td>
<td>31.5</td>
<td>5.4</td>
<td>30.8</td>
<td>80 (50)</td>
<td>509</td>
<td>88</td>
<td>597</td>
<td>0</td>
<td>12.56</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>M/55</td>
<td>AVR/CABG</td>
<td>51.8</td>
<td>28.7</td>
<td>5.4</td>
<td>31.0</td>
<td>102 (71)</td>
<td>2080</td>
<td>2144</td>
<td>4224</td>
<td>130</td>
<td>122.89</td>
<td>2.8</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>M/69</td>
<td>AVR/CABG</td>
<td>60.9</td>
<td>36.4</td>
<td>5.3</td>
<td>31.7</td>
<td>111 (95)</td>
<td>1813</td>
<td>956</td>
<td>2769</td>
<td>180</td>
<td>2.62</td>
<td>8</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>M/65</td>
<td>AVR/CABG</td>
<td>60.9</td>
<td>25.3</td>
<td>5.6</td>
<td>33.4</td>
<td>219 (72)</td>
<td>191</td>
<td>391</td>
<td>582</td>
<td>0</td>
<td>7.07</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>M/66</td>
<td>MVR/CABG</td>
<td>45.7</td>
<td>27.8</td>
<td>4.7</td>
<td>30.5</td>
<td>110 (80)</td>
<td>349</td>
<td>322</td>
<td>671</td>
<td>0</td>
<td>15.80</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>M/74</td>
<td>MVR/CABG</td>
<td>64.6</td>
<td>33.1</td>
<td>4.6</td>
<td>36.3</td>
<td>53 (55)</td>
<td>2785</td>
<td>3691</td>
<td>6476</td>
<td>0</td>
<td>4.77</td>
<td>0</td>
<td>1/37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>M/56</td>
<td>MVR/CABG</td>
<td>63.1</td>
<td>22.5</td>
<td>5.8</td>
<td>31.0</td>
<td>119 (80)</td>
<td>730</td>
<td>742</td>
<td>1472</td>
<td>0</td>
<td>24.40</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>M/72</td>
<td>MVR/TVR</td>
<td>61.4</td>
<td>29.7</td>
<td>5.2</td>
<td>32.4</td>
<td>271 (225)</td>
<td>6691</td>
<td>4955</td>
<td>11646</td>
<td>0</td>
<td>6.03</td>
<td>8</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>M/61</td>
<td>MVR/TVR/CABG</td>
<td>54.1</td>
<td>28.7</td>
<td>5.5</td>
<td>31.8</td>
<td>254 (234)</td>
<td>3843</td>
<td>2565</td>
<td>6408</td>
<td>30</td>
<td>10.70</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients marked with * had perioperative stroke diagnosed clinically. CABG indicates coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve replacement; TVR, tricuspid valve replacement. Cognitive test 1 indicates immediate memory; 2, Delayed memory; 3, Verbal; 4, Performance; 5, Trail Making A; 6, Trail Making B; 7, Grooved Pegboard (dominant); 8, Grooved Pegboard (non-dominant).
6.5 Comparison of the number, timing and size distribution of emboli to type of procedure, MRI and neuropsychological outcome

6.5.1 Type of procedure

The number and timing of embolic events, and size distribution of emboli, were compared between patients undergoing CABG \((n = 18)\) and intra-cardiac \((n = 28)\) procedures. Cardiopulmonary bypass and aortic cross-clamp times were significantly higher in the intra-cardiac group fig 6.1. (Mann Whitney U test, \(p = 0.009\) and \(p = 0.001\) respectively), table 6.6.

Patients undergoing intra-cardiac procedures received over twice as many bubbles per procedure [median: 2000 vs. 865] (Mann Whitney U test, \(p = 0.004\)) (fig 6.17(a), & table 6.6), and 7 times as many macro-bubbles [median: 218 vs. 30] (Mann Whitney U test, \(p = 0.001\)) (fig 6.17(b)). However, some intra-cardiac procedures also tended to be associated with longer CPB times (median: intra-cardiac: 87 mins, vs CABG: 69 mins) (fig 6.17(c)) so higher numbers of emboli may also be consistent with a positive correlation between CPB time and number of emboli. The estimated volume of air entering the MCAs ranged from 0.04 µl (patients 9, 16 and 28) to 216 µl (patient 30). A significantly higher volume of air was received during intra-cardiac surgery than CABG [median: 11.6 vs. 0.7 µL] (Mann Whitney U test, \(p = 0.005\)), fig 6.17(d). Of the 92215 bubbles analysed, only 13% were classified as macro-bubbles > 0.1 mm. There was no significant difference in the incidence of new MRI lesions or cognitive decline between procedure types.
Table 6.6 Comparison of CPB duration, total number of emboli, emboli immediately following removal of the aortic cross-clamp, curtain duration, volume of air, bubble diameter, and number of micro (<0.1 mm) and macro (>0.1 mm) bubbles by type of procedure. All values describe median and IQR unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>CABG</th>
<th>Intra-cardiac</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 18</td>
<td>n = 28</td>
<td></td>
</tr>
<tr>
<td>CPB duration (mins)</td>
<td>69</td>
<td>87</td>
<td>0.009†</td>
</tr>
<tr>
<td>Total emboli</td>
<td>657</td>
<td>2000</td>
<td>0.004†</td>
</tr>
<tr>
<td>Emboli: &lt;0.1 mm</td>
<td>815</td>
<td>1498</td>
<td>0.013†</td>
</tr>
<tr>
<td>Emboli: ≥0.1 mm</td>
<td>30</td>
<td>218</td>
<td>0.001†</td>
</tr>
<tr>
<td>Emboli: 1 min after removal of AxC</td>
<td>7</td>
<td>37</td>
<td>0.103†</td>
</tr>
<tr>
<td>Curtain duration (seconds)</td>
<td>0</td>
<td>24</td>
<td>0.001†</td>
</tr>
<tr>
<td>Bubble diameter (µm)</td>
<td>20</td>
<td>30</td>
<td>0.824†</td>
</tr>
<tr>
<td>Total volume of air (µL)</td>
<td>0.7</td>
<td>11.6</td>
<td>0.005†</td>
</tr>
<tr>
<td>New FLAIR MRI lesions, n (%)</td>
<td>6 (33)</td>
<td>12 (43)</td>
<td>0.554‡</td>
</tr>
<tr>
<td>Neuropsychological decline, n (%)</td>
<td>9 (50)</td>
<td>12 (43)</td>
<td>0.764‡</td>
</tr>
</tbody>
</table>

IQR; Interquartile Range (25th – 75th percentile) AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass, †Mann-Whitney U test, ‡Chi-squared test, significant factors are highlighted
Figure 6.17 (A) Estimated number of emboli (median [IQR]) in CABG (865 [637-1526]) and intra-cardiac procedures (2000 [1067-3306]) (B) Estimated number of macro-emboli in CABG (30 [18-150]) and intra-cardiac procedures (218 [135-534]). (C) The total number of emboli increased slightly with CPB duration. CABG patients are marked with ● and intra-cardiac patients with □. (D) Estimated total volume of air in CABG (0.7 [0.1-8.1])) and intra-cardiac procedures (11.6 [2.6-24.3]). Mild outliers are marked with the patient number and o, extreme outliers are marked with the patient number and * in panels A and B.

6.5.2 Curtain of emboli

Curtains of emboli (seconds) were rarely observed during CABG (median [IQR]: 0 [0-1]) compared to a median curtain duration of 24 [0-101] seconds for intra-cardiac procedures (p=0.001). This is unsurprising given the more invasive nature of open chamber surgery. Figure 6.18 summarises curtain duration with respect to type of procedure and neurocognitive and MRI outcome for individual patients. Visual
inspection suggested no correlation between curtain duration >1 minute and either new MRI lesions or cognitive decline.

![Curtain duration distribution](image)

**Figure 6.18** Total curtain duration for all 46 operations. ○ denotes patients with no new MRI lesions, and □ denotes patients with new MRI lesions. Markers filled in red represents patients who experienced cognitive decline in one or more tests (indicated by a z-score change ≥1 SD).

### 6.5.3 Release of the aortic cross-clamp

The number of emboli detected within 1 minute following release of the aortic cross-clamp was over 5 times higher in the intra-cardiac group (37 [7-79]) compared to the CABG group (7 [2-29]), however, due to large variations between patients this did not reach significance ($p=0.103$) (table 6.6). Additionally, the incidence of large bubbles after the removal of the aortic cross-clamp was also higher in the intra-cardiac group (median [IQR]: 1.53 [0.70-2.14]) compared to the CABG group (median [IQR]: 0.55 [0.15-1.29]) (Mann Whitney U test, $p=0.018$).

Having explored the data to quantify differences in the number and size of emboli we went on to test the following hypotheses: (i) the total number of emboli, (ii) emboli > 0.1 mm, (iii) volume of air, (iv) curtain duration >60s, or (v) number of emboli detected...
1 min following removal of the aortic cross-clamp were linked to the presence of new MRI lesions or cognitive decline.

### 6.5.4 MRI outcome

The impact of surgical factors, number and timing of embolic events, and size distribution of emboli were tested for patients with \((n = 18)\) and without \((n = 28)\) new MRI lesions. The median number of emboli was higher in the MRI lesion group (median, [IQR]; 1761 [1087-2480]) compared to patients without new MRI lesions (median, [IQR]; 1073 [667-2070]) but this difference was not significant (Mann Whitney U test, \(p=0.130\)). With the current sample size, we found no evidence that bubble size had any significant impact on MRI outcome (table 6.7 and fig 6.19).

**Table 6.7** Comparison of CPB duration, total number of emboli, emboli immediately following removal of the aortic cross-clamp, curtain duration, volume of air, bubble diameter, and number of micro (<0.1 mm) and macro (>0.1 mm) bubbles with and without new MRI lesions. All values give median and IQR value unless stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>No new MRI lesions</th>
<th>New MRI lesions</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPB duration (mins)</td>
<td>78</td>
<td>62-110</td>
<td>76</td>
</tr>
<tr>
<td>Total emboli</td>
<td>1073</td>
<td>667-2070</td>
<td>1761</td>
</tr>
<tr>
<td>Emboli: &lt;0.1 mm</td>
<td>1003</td>
<td>561-1846</td>
<td>1390</td>
</tr>
<tr>
<td>Emboli: ≥0.1 mm</td>
<td>131</td>
<td>26-327</td>
<td>171</td>
</tr>
<tr>
<td>Emboli: 1 min after removal of AxC</td>
<td>8</td>
<td>0-39</td>
<td>46</td>
</tr>
<tr>
<td>Curtain duration (seconds)</td>
<td>2</td>
<td>0-35</td>
<td>11</td>
</tr>
<tr>
<td>Bubble diameter (µm)</td>
<td>30</td>
<td>20-40</td>
<td>30</td>
</tr>
<tr>
<td>Total volume of air (µL)</td>
<td>5.3</td>
<td>0.2-18.1</td>
<td>6.2</td>
</tr>
<tr>
<td>CABG: intra-cardiac procedures</td>
<td>12:16</td>
<td>-</td>
<td>6:12</td>
</tr>
<tr>
<td>Neuropsychological decline, (n) (%)</td>
<td>13 (46)</td>
<td>-</td>
<td>8 (39)</td>
</tr>
</tbody>
</table>

IQR: Interquartile Range (25th – 75th percentile), AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass, †Mann-Whitney U test, ‡Chi-squared test, significant factors are highlighted
Figure 6.19 (A) Numbers of emboli (median [IQR]) were higher in the new lesions group (1761 [1087-2480]) compared to the no new lesions group (1073 [667-2070]) but this difference was not significant (Mann-Whitney U test: \(p=0.130\)). (B) There was no significant difference in the estimated volume of air (\(\mu l\)) (median [IQR]) received by the patients with (6.2 [1.5-27.9]) and without (5.3 [0.2-18.1]) new lesions (Mann-Whitney U test: \(p=0.378\)).

The median value for the total duration of curtains (in seconds) was higher in patients with new lesions (median [IQR]; 11 [0-104]) compared to no new lesions (median [IQR]; 2 [0-35]) but, this difference was not significant (Mann Whitney U test: \(p=0.452\)). More than half of the patients who experienced ‘curtains’ lasting longer than 1 minute had new MRI lesions compared to one third of patients where curtains were absent or less than 1 minute. However, this difference was also not significant (Fisher’s exact test: \(p=0.170\)).

The median number of emboli detected within 1 minute of release of the aortic cross-clamp was higher in patients with new lesions (median, [IQR]; 46 [11-102]) compared to patients with no new lesions (median, [IQR]; 8 [0-39]), (Mann Whitney U test, \(p=0.037\)), fig 6.20. However, this finding was of borderline significance and due to the lack of a correction for multiple testing, this result should be interpreted with caution.
Figure 6.20 Estimated numbers of emboli following release of the aortic cross-clamp (AxC) against MRI outcome for all 46 patients (Mann Whitney U test, \( p=0.037 \)).

6.5.5 Neuropsychological outcome

Similar embolic burden was observed between patients with cognitive decline vs. no decline (see table 6.8). We found no evidence to support an association between total number of emboli, macro-emboli (\( \geq 0.1 \text{ mm} \)), emboli following aortic cross-clamp removal, total volume of air, or curtain duration, and subsequent cognitive decline (table 6.8). The only significant factor predicting post-operative cognitive decline was age (\( t \)-test: \( p=0.022 \), table 6.4), which is consistent with the findings of previous research (Moller et al., 1998; Carrascal et al., 2005).
Table 6.8 Comparison of CPB duration, total number of emboli, emboli immediately following removal of the aortic cross-clamp, curtain duration, volume of air, bubble diameter, and number of micro (<0.1 mm) and macro (>0.1 mm) bubbles by cognitive outcome. All values give the median.

<table>
<thead>
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<th></th>
<th>No cognitive decline</th>
<th>Cognitive decline</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n =25</td>
<td>n =21</td>
<td></td>
</tr>
<tr>
<td>CPB duration (mins)</td>
<td>75</td>
<td>62-92</td>
<td>71</td>
</tr>
<tr>
<td>Total emboli</td>
<td>1357</td>
<td>729-2453</td>
<td>1349</td>
</tr>
<tr>
<td>Emboli: &lt;0.1 mm</td>
<td>1008</td>
<td>632-2153</td>
<td>1191</td>
</tr>
<tr>
<td>Emboli: ≥0.1 mm</td>
<td>194</td>
<td>55-324</td>
<td>132</td>
</tr>
<tr>
<td>Emboli: 1 min after removal of AxC</td>
<td>12</td>
<td>4-68</td>
<td>23</td>
</tr>
<tr>
<td>Curtain duration (seconds)</td>
<td>10</td>
<td>0-52</td>
<td>0</td>
</tr>
<tr>
<td>Bubble diameter (µm)</td>
<td>30</td>
<td>20-40</td>
<td>30</td>
</tr>
<tr>
<td>Total volume of air (µL)</td>
<td>7.4</td>
<td>1.5-25.9</td>
<td>2.4</td>
</tr>
<tr>
<td>CABG: intra-cardiac procedures</td>
<td>9:16</td>
<td>-</td>
<td>9:12</td>
</tr>
<tr>
<td>New FLAIR MRI lesions, n (%)</td>
<td>10 (40)</td>
<td>-</td>
<td>8 (38)</td>
</tr>
</tbody>
</table>

IQR; Interquartile Range (25th – 75th percentile), AxC; Aortic cross-clamp, CPB; cardiopulmonary bypass, †Mann-Whitney U test, ‡Chi-squared test.

We found no evidence that the number of emboli observed within 1 minute of release of the aortic cross-clamp was linked to adverse cognitive outcome (Mann Whitney U test, \( p=0.839 \)), fig 6.21.

Figure 6.21 Estimated numbers of emboli following release of the aortic cross-clamp (AxC) against cognitive outcome (in one or more tests by a z-score change of ≥1 SD) for all 46 patients.
The total estimated number of emboli within the cognitive decline group (1349 [870-22096]) and the no cognitive decline group (median [IQR]); 1357 [729-2453]) were similar, fig 6.22(a) (Mann-Whitney U test: $p=0.844$). The estimated volume of air (µl) received per patient was lower in the cognitive decline group (median [IQR]); 2.4 [0.2-18.9]) compared to the no cognitive decline group (median [IQR]); 7.4 [1.5-25.9]), fig 6.22(b), but this difference was not significant (Mann-Whitney U test: $p=0.261$).

Figure 6.22 (A) Number of emboli (median [IQR]) were similar in the decline (1349 [870-2096]) and no decline groups (1357 [729-2453]) (Mann-Whitney U test: $p=0.844$). (B) There was no significant difference in the estimated volume of air (µl) (median [IQR]) received by the patients with (2.4 [0.2-18.9]) and without (7.4 [1.5-25.9]) cognitive decline (Mann-Whitney U test: $p=0.261$).
6.6 Summary

The main findings of this chapter are:

1. Patients undergoing intra-cardiac procedures experience greater embolic burden, including higher total numbers of emboli, higher numbers of macrobubbles, higher numbers of emboli following removal of the aortic cross-clamp, greater total volume of air, longer curtain durations, and longer CPB times.

2. We found no evidence that the total estimated number of emboli, volume of air or embolus size distribution influences cognition or MRI outcome.

3. Patients with higher numbers of emboli detected in the first minute following the release of the aortic cross-clamp were more likely to receive new MRI lesions ($p=0.037$). This is consistent with the release of some solid debris following clamp removal. However, our finding should be interpreted with caution as it is of borderline significance and would not be robust to adjustment, for multiple testing.

In summary, we found no evidence that the total number of emboli and volume of air received by patients during cardiac surgery is linked to cognitive decline or the presence of new MRI lesions. Assuming all emboli are gaseous, 87% have estimated diameters of less than 100 microns, with an average total estimated volume of air entering the MCA territory of approximately 5.4 µl.

Although cerebral microemboli during cardiac surgery have been implicated in the pathogenesis of cognitive decline, this study concludes that the overall impact of the majority of air bubbles is negligible and does not account for the 46% incidence of cognitive decline that was observed in our patients. Emboli released after the removal of the aortic cross-clamp were sufficiently large in size to cause temporary occlusion of arterioles, and patients with new MRI lesions tended to receive larger bubbles than patients with no lesions. However, the overall number of emboli appeared to have no bearing on MRI or cognitive outcome.
Chapter 7

7 Discussion

7.1 Introduction

In this clinical observational study of patients undergoing cardiac surgery, we sought to investigate proposed links between intraoperative cerebral emboli, declining cognitive test scores, and new post-operative lesions detected using MRI. With the aid of a novel MR image subtraction algorithm (Horsfield, Patel, et al., under revision in AJNR) we evaluated the volume and distribution of new lesions compared to pre-existing ischaemic lesions associated with chronic cerebrovascular disease (Patel et al., 2015). We compared CABG and intra-cardiac procedures and assessed whether new lesions were associated with a decline in cognition (Patel et al., 2015). Finally, we used transcranial Doppler ultrasound in conjunction with a specially developed bubble sizing algorithm (Banahan et al., 2012) and Monte-Carlo simulations (Hague et al., 2013) to estimate the size range and impact of bubbles entering the brain during surgery, and to assess whether high volumes of macro-bubbles were linked to an increased risk of cognitive decline or the development of new MRI lesions post-operatively (Chung et al., 2015).

The incidence of cognitive decline in our cohort was 46% and the prevalence of new cerebral ischaemic lesions was 31%. Outcomes were similar for both CABG and intra-cardiac procedures. The biggest factor predicting cognitive decline was confirmed to be advanced age. Whereas, the most influential factor predicting risk of acquiring new lesions during cardiac surgery was the presence of pre-existing lesions. Bilateral TCD monitoring of our patients during their surgery revealed a total of 92,215 individual embolic signals, with estimated volume of air entering the MCAs ranging between 0.04 µl and 216 µl (table 6.5). Our findings suggest that, 5.4 µl (median) of air typically enters the MCA territories during cardiac surgery, and that this is insufficient to result in impaired cognitive outcome. We found no strong evidence to support a link between large or numerous bubbles and cognitive decline or new MRI lesions.
7.2 Cerebral ischaemic lesions and post-operative neuropsychological outcome

FLuid Attenuated Inversion Recovery (FLAIR) is an inversion recovery pulse sequence which uses a combination of T₁ and T₂ weighting to null the signal from fluid so that it appears dark, while tissue damaged by ischaemia remains bright. Although some studies have used 1.5-T FLAIR MRI to identify new chronic ischaemic lesions following surgery (Agarwal et al., 2010; Lund et al., 2005; Floyd et al., 2006; Merino et al., 2013) few studies report the characteristics of pre-existing lesions, and only 2 studies have used FLAIR in conjunction with neuropsychological testing (Agarwal et al., 2010; Lund et al., 2005). Agarwal (2010) studied 10 CABG patients using 1.5-T FLAIR, but as none of their patients developed new MR lesions or cognitive decline, their results were inconclusive (Agarwal et al., 2010). Lund et al. (2005) previously detected new lesions (>2 mm) in 9 of 52 (17%) patients at 3 months post-operatively using 1.5-T FLAIR and found a correlation between new and pre-existing lesions. However, as cognitive decline had resolved at 3 months, no association was observed between post-operative lesions and cognitive decline (Lund et al., 2005). In this study, the higher resolution afforded by MRI at 3-T, coupled with subtraction of ‘before’ and ‘after’ FLAIR images, provided a highly sensitive means of detecting small ischaemic lesions and distinguishing new lesions from old. Overall, 31% of patients were found to possess at least one new FLAIR-MRI lesion 6-8 weeks post-operatively, compared to 17% in the 1.5-T FLAIR-MRI study conducted at 3 months by Lund et al. (2005). Our higher detection rate is most likely due to the use of digital subtraction to help confidently identify ischaemic changes, and the higher resolution afforded by 3-T MRI. Previous DW-MRI studies revealed perioperative cerebral ischaemia immediately following surgery in 29% to 61% of patients (Stolz et al., 2004; Messe et al., 2014) suggesting that many acute changes seen on DW-MRI translate to small persistent lesions on FLAIR, rather than completely resolving.

The distribution of new FLAIR lesions observed in our study was consistent with a cardio-embolic pathogenesis. Digital registration and subtraction of MR images, combined with the expertise of a qualified neuroradiologist, enabled us to confidently estimate the size and location of new lesions. The distribution of new lesions suggests that larger emboli favour the right side of the brain, predominantly coming to rest in territories supplied by the MCA. This is consistent with a cardio-embolic source, in
which larger pieces of embolic debris travel along the brachiocephalic artery (which emerges first from the ascending aorta), and is consistent with a tendency for larger emboli to disproportionately favour major vessels (Chung et al., 2010).

The total volume of new lesions estimated for each patient was generally small when compared to the volume of pre-existing cerebrovascular disease. Our analysis of pre-existing cerebrovascular ischaemic lesions suggested that \( \approx 0.16\% \) of total brain volume was typically affected by pre-existing ischaemic white matter disease prior to surgery. New lesions acquired peri-operatively comprised only \( \approx 4\% \) of the total burden of ischaemic white matter disease, occupying approximately 0.004\% of total brain volume.

Our findings concur with those of Lund et al., who also found that patients with pre-existing lesions identified using MR-FLAIR were at exceptionally high risk of developing new lesions post-operatively (Lund et al., 2005). In our study, patients with pre-existing lesions were ten times more likely to experience new lesions post-surgery than patients without pre-existing disease. Pre-operative MRI assessment may be useful for identifying high-risk patients for targeted intervention to reduce embolisation of atheromatous debris and reduce the risk of stroke.

Our study found no evidence that small subclinical lesions on MRI affect either baseline or post-operative cognitive test results. In comparing the incidence of new lesions with cognitive outcome, the incidence of cognitive decline was 46\%, regardless of whether new lesions were present (results Chapter 5). This is similar to the incidence reported by other studies using similar criteria (paired z-score analysis with 1 SD as significant) (Puskas et al., 2007; Toeg et al., 2013). Conversely, the proportion of patients with new MRI lesions was 31\% regardless of cognitive status. In previous research, the incidence of neurocognitive impairment ranged from 0 to 50\% when measured between 1 and 3 months following surgery and was found to be related to multiple risk factors, including age, pre-existing white matter disease, decline in pre-existing cognition, and complexity of surgery (Ahonen & Salmenpera, 2004). Our study failed to identify any link between new MRI lesions and cognitive decline, but confirmed that older patients with aortic stenosis are most likely to suffer post-operative neuropsychological impairment (Chapter 5, table 5.2). Since lesions tended to be small and highly localised, this may explain why new lesions identified by our study following surgery did not significantly impair cognition.
Strengths of our study included higher resolution afforded by 3-T MRI and a larger sample size than the majority of previous MRI reports. By performing scans at 6-8 weeks postoperatively, we were able to perform neuropsychological tests at the same time-points as the MRI scans. DW-MRI lesions observed in the acute phase are known to resolve with time (Hauth et al., 2005), so lesions and cognitive changes observed at 6-8 weeks will underestimate acute ischaemic burden, but are more likely to be representative of persistent changes than tests performed immediately following surgery, which can be affected by anaesthetics and other peri-operative factors.

Unfortunately, some of the patients recruited to our study were unable to undergo MRI scans, leading to full datasets for only 77 of 103 patients. As these data were missing prospectively at random, they are unlikely to have affected our conclusions. However, it is possible that with greater statistical power a small contribution of new lesions to neurocognitive decline could have been differentiated from other more dominant contributions such as age and pre-existing cardiovascular disease.

Our MRI study confirmed that:

1. New FLAIR lesions in the left hemisphere were significantly smaller and more numerous than those in the right hemisphere. The distribution of new lesions was consistent with a cardio-embolic pathogenesis.
2. The total volume of new lesions was small in comparison to the embolic burden from pre-existing cerebrovascular disease.
3. Patients with pre-existing lesions were at increased risk of receiving new lesions.
4. Increased age and mild/moderate atheroma burden were the only significant pre-operative risk factors found to be associated with postoperative cognitive decline.
5. We found no evidence that either pre-existing or new lesions had an adverse impact on baseline or post-operative cognitive test results.

This part of the thesis, which was published in *Stroke* (Patel et al., 2015), confirmed that neurological injury is common in patients undergoing cardiac surgery; 7% of patients suffered a perioperative stroke, 31% received new MRI lesions, and 46% exhibited signs of neuropsychological impairment 6-8 weeks postoperatively. Older patients with aortic disease were confirmed to be most likely to experience cognitive decline, but
there was no significant association between a decline in cognitive function and the presence, size, or number of new MRI lesions. Pre-existing lesions affected up to 0.16% of total brain volume, and were observed in 64% of patients prior to surgery. Patients with pre-existing lesions faced an exceptionally high risk of receiving new lesions perioperatively. New lesions did not appear to contribute significantly to the 46% incidence of cognitive decline observed in our cohort, however, with increased power it is possible that a small contribution of new lesions to cognitive decline could have been observed. The striking relationship between new and pre-existing lesions suggests that a deeper understanding of complex interactions between perioperative stressors and chronic cerebrovascular disease will be useful for gaining further insights into the causes of brain injury during cardiac surgery to inform personalised strategies for risk stratification and intervention.

7.3 Intraoperative management and cognitive decline

Comparison of intraoperative transcripts, physiological measurements and TCD embolus detection with neuropsychological and cognitive outcome were published in PLOS ONE (Chung et al., 2015) and highlighted a number of interesting observations.

Although patients undergoing intra-cardiac procedures received almost twice as many emboli during cardiopulmonary bypass than CABG patients these corresponded to small bubbles and were not predicted by our simulations to generate significant vascular obstruction. This confirms the results of previous RCTs comparing on and off pump surgery (see Chapter 2 for a literature review), demonstrating that the use of CPB does not contribute to perioperative cerebral injury. Several RCTs that randomised patients to on-pump or off-pump surgery have consistently shown no difference in neurocognitive outcomes, stroke rates, or mortality (Lamy et al., 2012; Lamy et al., 2013). In previous research, high numbers of cerebral emboli detected during CPB were not found to be associated with neurocognitive deficits (Liu et al., 2009; Hillis, 2011), which is consistent with our findings.

Our study found that blood pressures were similar between CABG and intra-cardiac procedures. Mean arterial pressure for the majority of our patients ranged between 50-70 mmHg. Low blood pressure (<60 mmHg) during surgery did not appear to increase
the risk of experiencing cognitive decline or acquiring new MRI lesions (see results Chapter 6). Several previous studies have attempted to define the optimum blood pressure that would result in fewer patients experiencing neurological complications (for a review see Chapter 1). Four out of the five studies reported in our review found a decline in postoperative outcome with lower blood pressure (50-60 mmHg) during CPB. Our results failed to confirm a link between low blood pressure (<60 mmHg) and poor cognitive outcome. However, our results concur with the largest RCT investigating blood pressure and cognitive outcome by Charlson et al who also failed to show any association (Charlson et al., 2007).

The majority of our patients underwent ‘mild hypothermia’ (31-34°C) during CPB. Analysis of the temperature and rate of rewarming of patients during surgery revealed no evidence that ‘mild hypothermia’, or an increased rate of re-warming, had any impact on the risk of cognitive decline or of acquiring new MRI lesions (see results Chapter 6). This agrees with previous research (see Chapter 1, page 25).

A higher number of patients with mild/severe aortic stenosis received new MRI lesions (67%) than patients without aortic disease (49%), but this difference did not reach statistical significance. However, a borderline significant (p=0.042) association between mild/severe aortic stenosis and cognitive decline was observed. Degree of aortic stenosis has previously been found to be associated with perioperative stroke (Hillis, 2011) and the presence of significant cardiac atheroma and has also been found by some researchers to be associated with an increased risk of cognitive decline (Hammon et al., 2006) and new lesions on MRI (Cook et al., 2007). A limitation of our study was that cardiovascular disease within the ascending aorta tends not to be visible using TOE and was therefore not routinely assessed as part of our study. Although surgeons did perform manual palpation of the aorta prior to cross-clamp application, ultrasound assessment of the aorta (epiaortic scanning) is recommended by the American Heart Association and would have provided a better technique for grading aortic plaque (Glas et al., 2008; Hillis, 2011). Whether epiaortic ultrasound-guided application of the aortic cross-clamp and site of cannulation would improve neuropsychological or MRI outcome is currently unclear as no trials have been conducted. The presence of particulate emboli associated with chronic cardiovascular disease provides the most likely explanation of why a high proportion of cardiac surgery patients exhibit new ischaemic lesions both pre- and post-operatively.
Our cohort of patients experienced lowered mean haematocrit between 25-33% during cardiopulmonary bypass. Haematocrit values were similar in both types of procedure and did not appear to be associated with an increased risk of cognitive decline or new lesions on MRI (see results Chapter 5). In some previous research a low haematocrit was found to be linked to a higher risk of stroke (Karkouti et al., 2005) and postoperative neuropsychological decline (Mathew et al., 2007), for a review see Chapter 1. However, the TRACS trial (Transfusion requirements After Cardiac Surgery) in 2010 compared cognition of patients with haematocrit targets of 24% and >30% and observed a 6% incidence of neuropsychological decline in both groups (Hajjar et al., 2010) suggesting that haemodilution has no major influence on cognition. Our findings also suggest that haematocrit values maintained between 25-33% had no adverse impact on cognition.

Analysis of intra-operative management provided no evidence that:

6. Bubbles during CPB contribute to cognitive decline.
7. Low intra-operative blood pressure, haematocrit, and temperature change are linked to cognitive decline.

### 7.4 Characteristics of intraoperative emboli detected during cardiac surgery

Embolic signals detected by Transcranial Doppler (TCD) are common during cardiac surgery, even in low-risk patients. However, the results of previous TCD embolus detection studies can be difficult to interpret due to differences in study methodology, such as intensity thresholds used to detect embolic signals (Rodriguez et al., 2006), inconsistencies in signal reviewing procedures (manual versus automated) (Ringelstein et al., 1998; Rodriguez et al., 2006), quality of TCD recordings (Ringelstein et al., 1998), and intermittent embolus detection (limited to selected times in the procedure). We sought to overcome these limitations by obtaining good quality bilateral TCD recordings throughout the entire procedure and insisting on adopting a consistent semi-automated offline procedure for reviewing embolic signals. To the best of our knowledge, this study represents one of the most detailed investigations to date of the timing and a characteristic of Doppler embolic signals detected during cardiac surgery,
and provides researchers with an initial estimate of the likely size distributions of bubbles and volume of air entering the cerebral circulation (Chung et al., 2015). It also provides a first insight into the likely impact of air entering the brain during cardiac surgery and the potential for air bubbles to influence neuropsychological outcome.

Our study confirms that showers of bubbles are generated during cardiopulmonary bypass (CPB), and are associated with specific operative procedures (e.g. aortic manipulation, grafting and cross-clamp applications). We found that the majority of embolic signals detected during heart surgery were generated by small microemboli (<100 µm) and are therefore likely to be benign. The majority (87%) of bubbles entering the cerebral circulation were found to correspond to microbubbles less than 100 µms in diameter. Only 0.3% of bubbles were estimated to be greater than or equal to 1 mm in diameter. The number and dimensions of air emboli revealed by our analysis was broadly consistent with previous autopsy studies by Moody et al., which revealed numerous small capillary arteriolar dilatations post-operatively (Moody et al., 1995). Moody and colleagues studied 100 µm thick slices of the basal ganglia of patients who died within one week of surgery and observed numerous empty ~40 µm dilatations, with a density of approximately 40 dilatations per cm² of tissue. The median diameter of air emboli of 33 µm (IQR: 18-71) estimated by our analysis is similar to Moody’s findings.

Patients undergoing intra-cardiac procedures received over twice as many bubbles per procedure, and 7 times as many macro-bubbles. Significantly higher volumes of air were received during intra-cardiac surgery than CABG. CPB times tended to be longer for intra-cardiac procedures than CABG. Curtains of emboli were rarely observed during CABG compared to intra-cardiac procedures. Although the number of emboli observed during the minute following the release of the aortic cross-clamp was over 5 times higher in the intra-cardiac group than the CABG group, there were large variations between patients and this did not reach significance. Our findings are in agreement with the majority of previous research suggesting that more complex procedures with a higher number of surgical interventions are associated with lengthier operations, and consequently, a greater chance of receiving a higher embolic load. Macrobubbles were most likely to be generated during the latter stages of the surgery.
(after the release of the aortic cross-clamp), and were more common during intra-cardiac procedures.

A detailed analysis of our TCD recordings suggests that the small volume of air received over the course of the surgery is unlikely to generate significant cerebral injury. The average (median) estimated total volume of air entering the MCA territory was 5.4 µl, which is exceedingly small in comparison with the area of the vasculature. Our findings demonstrate that up to 0.22 mL of air typically enters the MCA territories during cardiac surgery. This is lower than levels expected to cause acute cerebral injury. Previous animal studies by Haines et al., investigated the impact of air bubbles injected to the cerebral vasculature of dogs in the form of a microbubble mix over a period of ~20 mins (Haines et al., 2013). The authors found that the dogs presented multiple DWI lesions when a volume of air between 1-2 mL was introduced. Our findings in humans suggest that the volume of air entering the human brain during surgery is much less than this (0.22 mL), table 8.1. Given time taken for an air embolus to completely dissolve, and proportion of the vascular tree that becomes obstructed, are both sensitively dependent on bubble size (Barak & Katz, 2005); small bubbles are not expected to be harmful.

To better understand the relationship between vascular obstruction and bubble size relative to the dimensions of the arterial tree we used a Monte-Carlo simulation of gas bubbles moving through a model MCA vasculature (Chung et al., 2007; Hague & Chung, 2009; Hague et al., 2013). Based on the results of these simulations, showers containing bubbles less than ~38 µm in diameter did not generate any significant obstruction. Showers of larger (>100 µm) macrobubbles detected following removal of the aortic-cross clamp and during weaning from bypass were predicted to affect up to 2.2% of the model vasculature for several hours. However, as the dissolve time for an individual bubble depends crucially on surface area, and multiple bubbles have potential to coalesce, the potential for more subtle localised injuries cannot be completely discounted.

Strengths of our embolus detection study include estimation of bubble size and use of Monte-Carlo simulations to provide a deeper understanding of the likely impact of air emboli on cerebral blood flow. The presence of dense showers and curtains of emboli made it difficult to distinguish individual emboli during some sections of our recordings.
(see table 6.5 for curtain durations). This impacted mainly valve and combined procedure patients, where showers were particularly heavy. Based on these limitations, the numbers of emboli reported in our study for patients 18, 20, 23, 27, 37, 39 and 40 should be considered conservative estimates. The total number of emboli and estimated volume of air entering the circulation is therefore expected to be underestimated. Unfortunately, we were unable to distinguish solid from gaseous emboli. Therefore, our estimates of bubble size are based on an assumption that the majority of emboli were bubbles. Our estimates of bubble size are associated with additional inaccuracies, particularly when the MCA diameters were difficult to measure, or in the event of poor vessel-beam alignment. To reduce errors in bubble sizing, every effort was taken to accurately measure MCA diameter and to optimise beam-vessel alignment. However, the true errors associated with our bubble size estimates are difficult to confirm. Since bubbles are likely to be harmless, our findings also underline the importance of developing and validating methods to confidently distinguish solid and gaseous emboli, along with technologies aimed at preventing particulate embolic debris from reaching the brain.

A limitation of our Monte-Carlo model was the absence of a mechanism for allowing multiple small bubbles to coalesce. Large bubbles pose a much greater threat to blood flow because they take longer to dissolve and become lodged higher up in the arterial tree. If our existing model can be considered to reflect true levels of microvascular obstruction and rates of embolus clearance, the greatest threat to cerebrovascular perfusion is predicted to occur following removal of the aortic cross-clamp during weaning from bypass.

Overall, our TCD embolus detection study confirms that:

8. Assuming all emboli are gaseous, 87% have estimated diameters of less than 100 µm with the average total estimated volume of air entering the MCA territory of approximately 5.4 µl.

9. Patients undergoing intra-cardiac procedures tend to experience significantly greater overall embolic burden than patients undergoing CABG-only procedures. This includes higher total numbers of emboli, more macro-bubbles and greater volume of air, longer curtain durations, and high numbers of emboli following release of the aortic cross-clamp.
Our Monte-Carlo simulations predict that small bubbles (<38 µm) do not impair cerebral perfusion. However, macro-bubbles were predicted to obstruct a small percentage of the model vasculature for several hours.

### 7.5 Cerebral emboli and neuropsychological and MRI outcome

Previous research has suggested that embolisation of gaseous and solid material into the cerebral vasculature has potential to result in cerebral damage (Pugsley et al., 1994). However, evidence for a direct association between embolic load and postoperative cognitive dysfunction (POCD) in a cardiac surgery setting has proved elusive (Stump et al., 1996; Bar-Yosef et al., 2004; Hogue et al., 2006). Although several studies reported a significant correlation between high numbers of embolic signals and cognitive decline (see literature review, Chapter 2), as the majority of studies are observational, associations could also be explained by confounding factors such as the length and complexity of surgery, which are also likely to be associated with higher emboli counts. As embolic signal analysis is time consuming, sample sizes tend to be small (<100 patients), and there are also differences in methodologies used for the collection and analysis of TCD recordings between studies.

Overall, we found no evidence to support a link between the volume of air received by the patient during cardiac surgery and cognitive decline (results Chapter 6). This is consistent with previous research (Gaunt et al., 1994; Dittrich & Ringelstein, 2008) confirming that gaseous emboli are less damaging to the brain than solid emboli. The biggest risk factors predicting cognitive decline in previous research were the patient’s age, cognitive status at baseline, and presence of pre-existing chronic cardio and cerebro-vascular disease. As the number of older patients undergoing cardiac surgery is increasing there are likely to be higher rates of cognitive decline in the future (Andrell et al., 2005). Other intra-operative risk factors and mechanisms leading to brain injury such as cerebral oedema, inflammation, response to surgical insult, cerebral hypoperfusion and ischaemia (Boodhwani et al., 2007; Bayram et al., 2013) may also require further investigation.
Regarding the proportion of patients with new MRI lesions following surgery, patients with new lesions tended to have received a greater embolic burden during surgery, but differences were not statistically significant. The only association observed in our data was between new MRI lesions and the total number of emboli observed in the first minute following release of the aortic cross-clamp. However, this result was of borderline significance and was not robust to adjustment for multiple testing. This stage of the surgery is of particular interest, since removal of the cross-clamp has potential to release a mixture of bubbles and solid pieces of atheromatous debris into the bloodstream. Although, our finding of a potential association should be interpreted with caution, it seems consistent with previous research suggesting a link between cardiac and aortic atheroma and new lesions following surgery (Katz et al., 1992; Stern et al., 1999; Djaiani et al., 2004; Cook et al., 2007). In a recent randomised trial by Bolotin et al., which investigated 66 patients undergoing valve or combined surgery, a special arterial cannula (Cardio Cannula) was used to capture solid emboli during cross-clamp manipulation. A lower proportion of patients exhibited new DW MRI lesions in the group receiving the novel cannula (44%) than the control group (66%) (Bolotin et al., 2014). In a previous RCT featuring 1,289 patients randomised to receive the Embol-X filter, particulate emboli were identified in 598 (97%) of 618 filters, demonstrating that significant numbers of solid emboli are released (Banbury et al., 2003), particularly following release of the aortic cross clamp (Christenson et al., 2005).

Although bubbles have long been hypothesised to be a cause of cognitive decline, our findings and simulations concur with mounting evidence suggesting that bubbles during surgery are largely benign. Our analysis suggests that the volume of air received by patients during cardiac surgery does not strongly influence cognition or generate focal ischaemic lesions seen on MRI. However, due to difficulties in obtaining high quality recordings, and the time consuming nature of Doppler embolus detection, our sample size of 46 patients was too small to confidently reach reliable conclusions regarding bubble properties and clinical outcome measures. Although a small contribution of bubbles to cognitive decline cannot be ruled out, we can confidently conclude that bubbles alone do not provide an explanation for the 46% incidence of cognitive decline observed in our cohort, the majority of which will need to be explained by other mechanisms.
Overall, we conclude that:

1. Patients with higher numbers of emboli detected in the first minute following release of the aortic cross-clamp may be more likely to receive new MRI lesions due to solid emboli.
2. We found no evidence of a link between the number of bubbles, volume of air, or bubble size distribution and cognitive or MRI outcome.
3. The 46% incidence of cognitive decline observed in our patients is not explained by the impact of bubbles on cerebrovascular perfusion.
Chapter 8

8 Conclusions

8.1 Main findings and conclusions

As numbers of elderly patients undergoing cardiac surgery increase, neurological complications remain a common source of morbidity. It is clear from the results of this study, together with previously published data, that cerebral injury following cardiac surgery is likely to involve complex multifactorial mechanisms.

From this study, we conclude that patients with pre-existing lesions are at an increased risk of receiving new lesions during cardiac surgery; however, there was no evidence to suggest that either pre-existing or new lesions had an adverse impact on baseline or post-operative cognitive test results. We estimate that the majority of air emboli received during cardiac surgery are small and likely to be benign, and found no link between bubble properties or volume of air and adverse cognitive or MRI outcome. The 46% incidence of cognitive decline observed in our patients is not explained by the impact of bubbles on cerebrovascular perfusion and is not directly associated with new postoperative MRI lesions.

Solid emboli resulting from manipulation of the aorta during the application and removal of the aortic cross-clamp, hypoperfusion, perioperative arrhythmias, blood loss, inflammation (both cerebral and systemic), rapid re-warming, and genetic vulnerability to injury all provide alternative mechanisms for brain injury (Newman et al., 2006; McKhann et al., 2006; Grocott, 2007). Improved cognitive safety during cardiac surgery might be accomplished by hindering one or more of these factors and countering cascading events, but so far no single pathway for the successful prevention of cognitive decline has been identified. The current study is important for confirming that bubbles associated with surgery are not a major cause of cognitive decline, enabling future researchers to focus on other potential targets. New approaches may include novel neuroprotective agents, development of biochemical and genetic markers to facilitate risk stratification, and novel surgical and perfusionist strategies to minimise
physiological stress on the brain during surgery. Although most efforts currently focus on preventing decline, strategies could also be developed to strengthen and restore neurocognitive function.

Our study suggests that the number and timing of intraoperative emboli, haemodilution, temperature and blood pressure management during cardiac surgery do not individually increase the risk of acquiring new MRI lesions or cognitive decline. It seems likely that predisposing cerebrovascular disease, together with the stress of undergoing surgery may trigger a multifactorial cascade of events that leads to cerebral injury. New advances in personalised medicine potentially provide a better means of understanding complex diseases than cohort studies, and more stringent efforts may be needed to focus on preventing adverse outcomes on an individual basis. Ischaemic damage to the brain, regardless of whether it is correlated to cognitive decline after cardiac surgery is still worrying and should be minimised. Whether brain injury following cardiac surgery also has potential to contribute to the acceleration of serious chronic diseases such as dementia has yet to be discovered.

8.2 Future work

Cognitive protection in the future may include careful assessment to identify high-risk patients, coupled with improvements in perfusion guided by perioperative monitoring. Screening patients before they undergo surgery could also help with directing appropriate adjustment for co-existing morbidities and allow surgeons to modify their techniques (Selim, 2007). Other interventions may include preventing and treating secondary cerebral damage through the use of filters, or administration of anti-inflammatory drugs (Grocott, 2007). It would also be useful in future studies to be able to identify patients with pre-existing cerebrovascular disease, and to see how other pre-existing risk factors such as impaired cerebral autoregulation could have an impact on postoperative cognition. It would also be worthwhile using an appropriate control population to accurately validate the neuropsychological assessments, and assess whether surgery has any long-term impact on cognition or risk of dementia when separated for changes to the brain associated with progression of cardiovascular disease.
8.3 Closing remarks

Cardiac surgery is one of the great triumphs of 20th century medicine, and has become so safe that it is now regarded as a routine procedure. However, subtle cognitive decline remains a common complaint. As cardiac surgery procedures are now being challenged by less invasive methods, perhaps neuropsychological tests and neuroimaging will play an increasingly important role in optimising treatment. Although it is important to try to reduce the burden of cerebral ischaemia in patients undergoing cardiac surgery, our research suggests that we must try to better understand the relationship between surgery and progressive pre-existing cerebrovascular disease. By selecting patients with pre-existing cognitive and cerebrovascular diseases, and treating this subgroup of patients more carefully, patient specific treatment in the future might better assist in reducing cognitive deficits and eliminating the risk of stroke in patients undergoing heart surgery.
9 Appendices

9.1 Appendix 4.A R&D approval

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DIRECTORATE OF RESEARCH & DEVELOPMENT

Director: Professor D Rowbotham
Assistant Director: Dr David Hetmanski
R&D Manager: Carolyn Maloney

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Leicester General Hospital
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Leicester
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18th May 2011

Dr Emma ML Chung
British Heart Foundation Research Fellow
University of Leicester
Medical Physics
Level 1, Sandringham Building
Leicester Royal Infirmary
LE1 5WW

Dear Dr Chung

Ref: CLRN 51454
Title: Causes of brain injury associated with cardiac interventions; A comparison of Doppler embolus detection and virtual patient predictions with postsurgical neurological outcome quantified by MRI and neuropsychological testing

Project Status: Approved
End Date: 31-12-2013

I am pleased to confirm that with effect from the date of this letter, the above study now has Trust Research & Development permission to commence at University Hospitals of Leicester NHS Trust.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

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Version 5, 20-04-10
Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study in this trust.

We are aware that undertaking research in the NHS comes with a range of regulatory responsibilities. Attached to this letter is a reminder of your responsibilities during the course of the research. Please ensure that you and the research team are familiar with and understand the roles and responsibilities both collectively and individually.

You are required to submit an annual progress report to the R&D Office and to the Research Ethics Committee. We will remind you when this is due.

The R&D Office is keen to support research, researchers and to facilitate approval. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office.

We wish you every success with your research.

Yours sincerely,

[Signature]

Carolyn Maloney
R&D Manager

Encs: Researcher Information Sheet.

Please note that some of the documents may not apply to your study.
9.2 Appendix 4.B Ethical approval

Dear Dr Chung,

Study Title: Causes of brain injury associated with cardiac interventions; A comparison of Doppler embolus detection and virtual patient predictions with postsurgical neurological outcome quantified by MRI and neuropsychological testing.

REC reference number: 10/H0401/78

Thank you for your letter of 23 September 2010, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

This Research Ethics Committee is an advisory committee to East Midlands Strategic Health Authority. The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England.
Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed
guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.nosa.nhs.uk.

| 10/H0401/78 | Please quote this number on all correspondence |

Yours sincerely

[Signature]

Mr Apostolos Falta
Vice-Chair

Email: lisa.gregory@nottspct.nhs.uk

Enclosures: “After ethical review – guidance for researchers” SL- AR2 for other studies

Copy to: Graham Hewitt, University of Leicester
        R&D office for NHS care organisation at lead site - UHL
Appendices

9.3 Appendix 4.C Study information sheet

RESEARCH PARTICIPANT INFORMATION SHEET (23/08/11, version 3a)

Causes of brain injury associated with cardiac surgery

Investigators: Dr E. Chung\(^1\), Dr C. Banahan\(^2\), Dr M Horsfield\(^1\), Prof. T. Spy1\(^1,3\), Mr N. Masala\(^3\), Mr H. Alimara\(^3\), Mr J. Szostek\(^3\), Mr M. Hickey\(^3\), Prof V Egan\(^3\), Prof. G. Cherryman\(^3\), Prof. D.H. Evans\(^1,3\), Mrs J. Janus\(^1\), Mr D. Spiers\(^3\), Mr N. Patel\(^1\)

1 Department of Cardiovascular Sciences, University of Leicester
2 Medical Physics Department, University Hospitals of Leicester NHS Trust
3 Department of Cardiothoracic Surgery, University Hospitals of Leicester NHS Trust
4 Department of Psychology, University of Leicester
5 Department of Neuroradiology, University Hospitals of Leicester NHS Trust

Introduction
You have been invited to take part in a research study. Before deciding if you wish to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if anything is not clear to you, or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of this study?
The aim of this study is to improve our understanding of the adverse effects of particles and gas bubbles (emboli) that enter arteries supplying the brain during cardiac surgery. During your operation we would like to use ultrasound to detect emboli moving through the arteries. Ultrasound signals recorded during this study will be used to predict the risk of brain injury for comparison with the results of neurological tests and Magnetic Resonance Imaging (MRI) scans performed before and after surgery.

How long will it take?
The study involves a number of additional investigations which will be completed alongside your routine care so that no extra hospital visits other than those associated with your normal care will be required.

Before surgery:
As a preliminary examination we will use ultrasound to measure blood-flow through the arteries in the head and neck. These checks will take approximately 30 mins. We will then
ask you to complete a series of neuropsychological tests (questionnaires and puzzles) to assess brain function, reaction times, memory and IQ. These tests will take approximately 1 hour. We will then ask you to undergo an MRI scan of the brain. This will take approximately 30 mins.

**During surgery:**
Ultrasound monitoring for emboli will be performed for the duration of your surgery. Ultrasound signals will be recorded to computer for later analysis.

**After surgery:**
During your routine outpatient’s appointment (approximately 6 weeks following surgery) we will ask you to repeat the neuropsychological tests (1 hour) and MRI scan (30 mins).

**Do I have to take part?**
It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign a consent form. Even if you have given your consent, you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

**What will be involved if I take part in the study?**
Ultrasound equipment emitting inaudible sound waves will be placed gently on the head or neck and adjusted to monitor the flow of blood and particles through the arteries. The probe is covered in a small amount of gel and held by hand or fixed in place using an adjustable headset. Ultrasound monitoring is completely painless, and over 20 years of diagnostic measurements has not been shown to be harmful.

As with all patients who have an MRI scan, you will be asked to complete a questionnaire beforehand to make sure that it is safe for you to have a scan. You will be asked to remove any metal objects, including jewellery. The scanners are quite noisy, making a hammering noise during the scan. You will be provided with ear plugs to protect your ears. You will be asked to lie very still during the scans, which can be uncomfortable. However, you will be able to get comfortable again during the rest periods between scans. The MRI scanner is quite narrow, and some people feel claustrophobic within the scanner, but there is a ‘panic button’ which will enable staff to get you out of the scanner straight away if necessary. Many thousands of MRI scans are performed every day, and it is not thought that there are any long-term risks.

The neuropsychological tests involve you doing about an hour’s worth of puzzles and tasks of the kind you might see on game shows on television. However, the tasks measure different aspects of your memory, attention and problem-solving. All have been used in studies like this one many times before and help us to understand what kinds of practical problems any brain injury might cause.

**What are the possible disadvantages and risks of taking part?**
As you are aware, there is a small risk of stroke associated with your surgery. Involvement in this study has no effect on this risk.

MRI does not use X-rays and is safe for the majority of people. However, the strong magnet at the centre of the procedure can affect medical devices, such as heart pacemakers and inner ear implants. If you have metal close to an important organ then you will be advised not to have an MRI.
As with all additional medical tests, there is a risk that the brain MRI will reveal abnormalities that you may have been unaware of. MRI images will be examined by a Radiologist and any abnormalities will be reported to your GP.

**What are the benefits of taking part?**
There are no direct clinical benefits for participants but the information we get from the study may improve the safety of cardiac surgery in the future.

**Will the information obtained in the study be confidential?**
If you wish to take part in this study your participation will be noted in your medical records. All information that is collected about you during the course of the research will be kept strictly confidential. Researchers may have future access to the study data, but all information that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

**What if I am harmed by the study?**
It is highly unlikely that you will be harmed during this study and there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for a legal action against University Hospitals of Leicester NHS trust but you could have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated, the normal National Health Service complaints mechanisms would still be available to you.

**What if I have a complaint?**
If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions. (Please contact Dr Emma Chung, Tel: 0116 2385610). If you remain unhappy and wish to complain formally, please contact the University Hospitals of Leicester NHS Trust Patient Information and Liaison Service (PILS); Freephone: 0800 178 9337.

**What will happen to the results of the research study?**
The results of the study will be presented at medical conferences and will be published in specialised medical journals. The data will be completely anonymous and your identity will not be revealed in any publication or presentation of these results.

There will be an open lecture on research generated by the study to which all participants will be invited.

**Who has reviewed the study?**
All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits, and that you have been given sufficient information on which to make an informed decision.

**Contact for further information**
If you have any questions or queries about this research project please do not hesitate to contact Dr Emma Chung. (Tel: 0116 2385610 Email: emclt@le.ac.uk)

Thank you for reading this. This information leaflet is for you to keep.
9.4 Appendix 4.D Patient consent form

CONSENT FORM (23/08/11, version 3a)

Causes of brain injury associated with cardiac interventions

Principal investigator: Dr Emma Chung

1. I confirm that I have read and understood the patient information sheet dated 23/08/11, version 3a. I have had the opportunity to consider the information and ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected.

3. I consent for researchers involved in this study and regulatory authorities from the NHS Trust to have access to my medical records and imaging data where this is relevant to the research.

4. I agree to take part in the above study.

5. I would like my GP to be informed of my participation in the study.

Name and address of GP:

__________________________
Name of Patient

__________________________
Signature

Date

I confirm that I have explained the nature of the study, as detailed in the patient information sheet, in terms that in my judgement are suited to the understanding of the patient.

__________________________
Name of Researcher

__________________________
Signature

Date

Causes of brain injury associated with cardiac interventions, 23/08/11, version 3a. [1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.]
9.5 Appendix 4.E GP letter and patient appointment letter

Ref: 23/09/10_version2
Date:

Dear Dr

Your patient, Mr. has kindly agreed to participate in a research project.

Study title: Causes of brain injury associated with cardiac interventions
REC Reference number: 10/H0401/78

During this study we will be performing transcranial Doppler ultrasound detection of microemboli moving through the cerebral circulation for comparison with the results of neuropsychological tests and brain MRI conducted before and after cardiac surgery.

None of the diagnostic tests associated with this study have any known adverse clinical consequences. Participation in the study requires no changes to the normal treatment or medical management of your patient. If incidental findings are identified as a result of our imaging investigations you will be notified.

If you have any questions regarding this research, please do not hesitate to contact me.

Yours faithfully,

Dr Emma Chung
British Heart Foundation Research Fellow
University of Leicester, Department of Cardiovascular Sciences

Tel: +44 (0)116 2541414 ext 6065
Email: emlc1@le.ac.uk
Dear

Re: "Causes of brain injury associated with cardiac interventions".

Thank you for your participation in our research study. I am writing to confirm that an appointment has been made for you to attend:

For: Neuropsychological tests
On: at:

For: MRI scan of the head for research
On: at:

At: Glenfield Hospital, Radiology Department

Please report to the Radiology Department, which is situated just inside the MAIN ENTRANCE of the hospital, and proceed to Waiting Area C.

If you are unable to attend this appointment, please telephone Miss Bharti Patel on 0116 258 5626 or 0116258 5486

You will receive a green car parking pass from us at the day of your arrival. This will allow you to have a free parking for the whole day of your appointment at the clinic. You will need to add the registration no. of your car to the permit and then place it behind the windscreen.

If you have any questions or queries about this research project please do not hesitate to contact Dr. Emma Chung (Tel: 07757511633, email: eml1c1@le.ac.uk)

If you have any questions regarding the MRI scan procedure, please call 0116 2502353 to speak to one of the radiographers.

Dr Emma Chung
British Heart Foundation Research Fellow
University of Leicester, Department of Cardiovascular Sciences

Tel: +44 (0)116 2541414 ext 6065
Email: eml1c1@le.ac.uk
### 9.6 Appendix 4.F TCD screening sheet

**Appendix 4**

University Hospitals of Leicester NHS Trust

---

#### 9.6 Appendix 4.F TCD screening sheet

**Date**: 

**Patient name**: ............................................................

**UHL Number**: ............................................................

**Address**: ........................................................................

**Patient’s tel**: ............................................................

**GP Address**: ....................................................................

**Car reg**: .................................................................

---

**“BICI” study**

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#### TCD Settings for Cardiac Surgery Monitoring

**Date**: 

**TCD Operator**: ............................................................

**Date of surgery**: ............................................................

---

**Patient name**: ............................................................

**UHL Number**: ............................................................

---

**Right side**

**Artery Monitored**: ............................................................

**Depth (mm)**: ............................................................

**SVL (mm)**: ............................................................

**Mean velocity (cm/s-1)**: ............................................................

---

**Left side**

**Artery Monitored**: ............................................................

**Depth (mm)**: ............................................................

**SVL (mm)**: ............................................................

**Mean velocity (cm/s-1)**: ............................................................

---

**Headset settings**

**Front or back lock**: ............................................................

**Clip position at the back**: ............................................................

---

**Notes**: .................................................................

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Page 2
### 9.7 Appendix 4.G Medical records data collection

**Medical records data collection sheet**

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#### Part B: Psychological and emotional Well Being

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<th>Current [ ]</th>
<th>Pack years [ ]</th>
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<th>Pack years [ ]</th>
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<td>Y / N</td>
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</table>
### Appendices

#### Part C. Physiological data

1. Any ApoE-ε4 genotype Y/N
2. Systolic blood pressure
3. Diastolic blood pressure
4. Pulse pressure
5. LV dysfunction: Good 40% Fair 30-49% Poor <30%
6. Recent myocardial infarction: <6h, 6-24h, 1-30days, >30days
7. Emergency procedure Y/N
8. Post infarct septal rupture Y/N
9. Pre-op heart rhythm:
   - "SR": Sinus rhythm
   - "AF": Atrial fibrillation/flutter
   - "SVF": Ventricular fibrillation
   - "dead": Complete heart block/paced
   - "oA": Other abnormal rhythm
10. Previous non-surgical interventions (previous PCI)
11. Pre-op urea and electrolytes (U&Es)
12. Critical pre-operative state Y/N
13. MRI / CT scan result:
14. LVEF (Echocardiographic):
   - >50%
   - 30-49%
   - <30%
15. Preoperative laboratory variables:
   - Pre-op FBS (full blood count)
   - Partial Thromboplastin Time (PTT) [s]
   - International Normalized Ratio (INR) [U]
   - Hemoglobin [g/dL]
   - Creatinine [mg/dL]
16. Medicines:
   - Beta-blockers
   - ACE inhibitors
   - Calcium channel blockers
   - Nitrates
   - Others

#### Part D. Surgical and hospital parameters

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<th>Type of surgery</th>
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<td>On bypass on, Off bypass off, Total bypass time:</td>
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<tr>
<td>Type of anaesthesia &amp; duration</td>
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<td>Cardiopulmonary Bypass used</td>
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<td>Minimum temp on bypass</td>
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<td>Total complete cross-clamping time (min)</td>
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<tr>
<td>Myocardial ischemic time (min)</td>
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<td>Time of hypothermisation (min)</td>
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<td>Time of intubation</td>
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<tr>
<td>Time of superior vena cava obstruction</td>
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<tr>
<td>Total Heparin dose (U)</td>
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<tr>
<td>Prosthetic valve dose (U)</td>
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<tr>
<td>Intra-aortic balloon pump (IABP) use</td>
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### Appendices

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<th>Intraoperative vasopressor use</th>
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<td>Diveymetry plate position</td>
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<td>Dehydration</td>
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<td>Co2 insufflations</td>
<td>Blood Transfusion</td>
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<td>Auto transfusion</td>
<td>Packed red blood cells (U)</td>
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<td>Fresh Frozen plasma (U)</td>
<td>Platelets (U)</td>
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<td>Total blood loss</td>
<td>Drains (Y/N)</td>
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### Part E - Examination Intra-op

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<th>Glucose, fasting (mmol/l)</th>
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<td>LDL cholesterol (mmol/l)</td>
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<td>Diastolic BP (mmHg)</td>
<td>HDL cholesterol (mmol/l)</td>
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<td>Pulse pressure (mmHg)</td>
<td>Intra-op Laryngoscopy grade</td>
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<td>Intra-op TOE summary</td>
<td>Intra-op complications</td>
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<th>Drains used</th>
<th>Number of coronary grafts placed</th>
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<td>Left anterior descending graft placed</td>
<td>Right anterior descending graft placed</td>
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<td>Circumflex graft placed</td>
<td>Coronary artery graft conduit used</td>
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<td>Other</td>
<td>Intra-op Infusions</td>
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<td>CNS</td>
<td>Lines inserted on day of surgery:</td>
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<td>CVS</td>
<td>CVP (Y/N)</td>
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<td>Abdomen/Renal</td>
<td>Arterial Line (Y/N)</td>
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<td>Gases</td>
<td>IABP (Y/N)</td>
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<td>Peripheral lines (Y/N)</td>
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### Part F - Postoperative progress and complications

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<td>Pulmonary complications</td>
<td>Chest tube output (ml)</td>
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<td>Gastrointestinal problems</td>
<td>Intensive care unit (ICU) length of stay</td>
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<td>Infective complications</td>
<td>Post-operative morphine consumption</td>
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<td>Postoperative anxiety</td>
<td>Other:</td>
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9.8 Appendix 4.H MRI report

Please be aware that this printed report does not display the Time of the Examination. This report should only be read in conjunction with the Images to ensure the positive identification.

Summary:

Clinical History: BICI STUDY

Last Verified By: [Redacted]  
Reported By: [Redacted]

DR JOHN MORLESE  
26/02/2012 12:56

(MSKUH) MRI Head:

MRI Head:

- There is a 14mm x 4mm area of DWI hyperintensity and ADC hypointensity in the right cerebellum in keeping with a PICA infarct.
- No other areas of diffusion, trace and ADC show no acute infarct or restricted diffusion.
- No evidence of bleed or altered blood products on SWI. No microhaemorrhages are demonstrated.
- Old lacunar infarction are noted in the left thalamus and right caudate nucleus is demonstrated.
- Further old tiny cortical infarction is noted in the left middle frontal gyrus.
- Small subcortical and deep white matter T2 hyperintensities are noted in keeping with mild small vessel cerebrovascular disease.
- The basal cisterns and ventricles are within normal limits. No evidence of hydrocephalus. No significant generalised or focal cerebral atrophy or disproportionate hippocampal atrophy.

Conclusion: Small acute right pCOM territory infarct.

Last Verified By: [Redacted]  
Reported By: [Redacted]

DR JOHN MORLESE  
26/02/2012 12:56

(MAICA) MRA Head:

MRA Head:

- Variants of circle of willis: Hypoplastic right pCOM artery and absent left pCOM artery.
- No areas of intracranial stenosis or decreased forward flow.
Please be aware that this printed report does not display the Time of the Examination. This report should only be read in conjunction with the Images to ensure the positive identification.

**Summary:**

**Clinical History:** BICI STUDY

*Last Verified By:* [Redacted]  
*Reported By:* PROF G CHERRYMAN  
*16/12/2011 1041*

**(MSKUH) MRI Head:**

MRI Head: FIRST SCAN 29.11.11.  
No previous brain imaging.  
Diffusion trace and ADC show no restricted diffusion or acute infarction.  
No bleed or altered blood products.  
T2 and FLAIR show minimal burden small vessel CVD in the periventricular white matter and in the anterior limb right internal capsule. No previous infarcts.  
No global, lobar, focal or hippocampal atrophy.

No abnormality on the MRA. Both carotids show normal forward flow. Normal terminal vertebral arteries and basilar artery.  
Incomplete circle of Willis - no posterior communicating arteries on either side.

*Last Verified By:* [Redacted]  
*Reported By:* PROF G CHERRYMAN  
*16/12/2011 1041*

**Event Number:** [Redacted]  
**Examination Date:** 29/11/2011

**Ref:** SPYT TJ, GLENFIELD HOSPITAL, GROBY ROAD, LEICESTER, LEICESTERSHIRE. LE3  
**Source:** 9QP
There is a 14mm x 4mm area of DWI hyperintensity and ADC hypointensity in the right cerebellum in keeping with a PICA infarct. No other areas of diffusion, trace and ADC show no acute infarct or restricted diffusion. No evidence of bleed or altered blood products on SWI. No microhaemorrhages are demonstrated.

Old lacunar infarction are noted in the left thalamus and right caudate nucleus is demonstrated. Further old tiny cortical infarction is noted in the left middle frontal gyrus. Small subcortical and deep white matter T2 hyperintensities are noted in keeping with mild small vessel cerebrovascular disease.

The basal cisterns and ventricles are within normal limits. No evidence of hydrocephalus. No significant generalised or focal cerebral atrophy or disproportionate hippocampal atrophy.

Conclusion. Small acute right pCOM territory infarct.

MRA Head:

Variants of circle of willis: Hypoplastic right pCOM artery and absent left pCOM artery. No areas of intracranial stenosis or decreased forward flow.
9.9 Appendix 4.1 Surgical transcript

![Intra-Operative Transcranial Doppler Monitoring form](image-url)

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<th>Time</th>
<th>Surgery stages/ Interventions/Drugs</th>
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<table>
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<th>Time</th>
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### Appendix 5.A MRI results table

Detailed summary of age, sex, type of procedure, risk factors, cardiopulmonary bypass duration, number and size of MR FLAIR lesions, and outcome of neurocognitive testing for all 77 patients.

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<tr>
<th>Patient no.</th>
<th>Sex/Age</th>
<th>Procedure</th>
<th>Risk factors</th>
<th>CPB Time (mins)</th>
<th>Pre-existing lesions No./Volume (mm³)</th>
<th>New FLAIR lesions No./Volume (mm³)</th>
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Patients marked with * had perioperative stroke diagnosed clinically. CABG=Coronary Artery Bypass Graft; AVR=Aortic Valve Replacement; MVR=Mitral Valve Replacement; TVR=Tricuspid Valve Replacement. In the list of risk factors SMK=Smoker; HCL=hypercholesterolemia; HTN=hypertension; AS=aortic stenosis.
10 Bibliography


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