Copyright Statement

The digital copy of this thesis is protected by the Copyright Act 1994 (New Zealand).

This thesis may be consulted by you, provided you comply with the provisions of the Act and the following conditions of use:

- Any use you make of these documents or images must be for research or private study purposes only, and you may not make them available to any other person.
- Authors control the copyright of their thesis. You will recognise the author’s right to be identified as the author of this thesis, and due acknowledgement will be made to the author where appropriate.
- You will obtain the author’s permission before publishing any material from their thesis.

To request permissions please use the Feedback form on our webpage.
http://researchspace.auckland.ac.nz/feedback

General copyright and disclaimer

In addition to the above conditions, authors give their consent for the digital copy of their work to be used subject to the conditions specified on the Library Thesis Consent Form.
PREVENTION OF BRAIN INJURY IN CARDIAC SURGERY

Dr Simon J. Mitchell

A thesis submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Medicine.

Faculty of Medicine and Health Sciences
University of Auckland
2000
DEDICATION

This work is dedicated to my parents:

Alan Grant Mitchell

and

Jennifer Mitchell
ABSTRACT

Background: Stroke and neurocognitive deficits may follow heart surgery and have been linked to peri-operative cerebral embolism. Lignocaine exhibits cerebral protection in animal models of cerebral arterial gas embolism. This study began as a randomised trial of lignocaine in brain protection in left heart valve surgery patients. Carotid Doppler emboli counting, developed to control for emboli exposure in the trial groups, revealed that most emboli occurred at the termination of cardiopulmonary bypass (CPB), and that “deairing” techniques used to remove air from the heart were not effective. Doppler monitoring also suggested that emboli were generated by the hard shell venous reservoir (HSV) component of the CPB circuit, and that contrary to popular perception, air entrained into the CPB venous return line did pass through the circuit back to the patient.

Methods: Salvaged CPB circuits were used in vitro to investigate emboli generation by Medtronic Maxima HSVRs, and the passage of entrained venous line air through the CPB circuit. The efficacy of a novel left heart deairing technique was audited clinically using the Doppler device. Finally, a randomised double blind trial of lignocaine in cerebral protection during cardiac surgery was conducted. Sixty-five patients underwent pre-operative neuropsychological (NP) testing and were randomised to receive lignocaine in a standard antiarrhythmic dose, or a placebo, in a double blinded infusion over 48 hours beginning at surgery. The NP tests were repeated at 10 days, 10 weeks and 6 months post-operatively.

Results: The Medtronic Maxima HSVRs were found to generate bubbles when operated at blood volumes well above the manufacturer’s recommended minimum. These bubbles, and air entrained to the CPB venous return line, were found to readily
transit the CPB circuit. Patients deaired using the novel technique were exposed to more than 10-fold less emboli after removal of the aortic clamp and withdrawal of CPB. Lignocaine treated patients exhibited a significantly reduced incidence of NP deficits at 10 days and 10 weeks postoperatively, and reported better memory at 10 weeks and 6 months postoperatively.

Conclusions: The Medtronic Maxima HSVRs should not be operated at blood volumes lower than 600 – 700 ml. Attempts should always be made to eliminate air entrainment to the CPB venous line, especially where vacuum assisted drainage is used. The novel de-airing technique is markedly superior to conventional methods. Lignocaine is a potentially useful cerebro-protective agent during cardiac surgery.
ACKNOWLEDGEMENTS

The following individuals and groups are acknowledged for their assistance in the conduct of this work:

Professor Des Gorman for being my mentor as I broke into the field of diving medicine, and for his simply outstanding supervision and encouragement in this work;

Mr Timothy Willcox for making the *in vitro* work possible, and for his friendship;

Dr Paget Milsom who let me share in his inventiveness and innovation;

Ms Ora Pellett whose rapport with the patients ensured their successful follow-up;

Dr Alan Kerr for championing this work at his cardiac surgery unit;

Professor Mervyn Merrilees for getting me started in my PhD program;

Dr John McDougall whose lateral thinking led me to Green Lane;

Dr Neil Middleton for his early encouragement and enthusiasm;

Dr Alan Merry for his insightful academic input;

Dr Michael Davis for his encouragement and some fine ideas from afar;

Dr John Faris for being the discrete guardian of all secrets related to the blinding of patients and researchers until the time was right;

The English Freemasons of New Zealand for their long term financial support which made the project possible;

The Health Research Council of New Zealand, also for their financial contribution;

The Green Lane Hospital Perfusion Team for their humour and their unwavering support of the *in vitro* work;

The Green Lane cardiac anaesthetists for their collegial good will, and for never complaining (publicly) about my invasion of their very limited work space;
The Green Lane cardiac surgeons for their co-operation and for never taking the emboli counts personally;

The Green Lane nursing staff for their expert and uncomplaining management of the trial infusions on the wards;

The Royal New Zealand Navy for encouragement and vital flexibility with my working hours;

The Auckland Hospital Biochemistry Laboratory for 3 years of mistake-free assays.

I also thank Mr Martin Cawthorn for setting me on the medical path many years ago, Mr Bill Day for his limitless encouragement during my journey along it, and those other special friends who have supported me. They know who they are.

Finally, I thank my partner, Dr Clare Hamilton for her patience, loyalty and support over 5 rewarding but difficult years.
PUBLICATIONS, PRIZES, ABSTRACTS

Publications

The following peer reviewed journal articles based in this work have been published or accepted for publication,


Prizes

This work has received the following awards at international medical meetings.

1. Paper 2 won the Residents Prize for best paper presented by a resident / registrar at the Annual Scientific Meeting of the Undersea and Hyperbaric Medical Society, USA, 1996.

2. Paper 3 won the Terumo Award for best paper at the Annual Scientific Meeting of the Australasian Society of Cardiovascular Perfusionists, Sydney, Australia, 1997.

3. Paper 4 won the Committee Award for Excellence in Presentation at the Annual Scientific Meeting of the South Pacific Underwater Medical Society, New Zealand, 1997.

4. Paper 7 won the Terumo Award for best paper at the Annual Scientific Meeting of the Australasian Society of Cardiovascular Perfusionists, Sydney, Australia, 1999.
Published abstracts

The following abstracts have been published after presentation of this work at various medical meetings.


Presented at the Annual Scientific Meeting of the Undersea and Hyperbaric Medical Society, Alaska, May 1996


Presented at the Annual Scientific Meeting of the Undersea and Hyperbaric Medical Society, Cancun, Mexico, June 1997


Presented at the Annual Scientific Meeting of the Undersea and Hyperbaric Medical Society, Seattle, USA, May 1998

*Presented at the Annual Scientific Meeting of the Australasian Society of Cardiovascular Perfusionists, Sydney, Australia, September 1997*


*Presented at the Outcomes 98 Meeting, Key West, USA, June 1998*


*Presented at the Annual Scientific Meeting of the Undersea and Hyperbaric Medical Society, Boston, USA, May 1999*

*And:*

*The Outcomes 99 Meeting, Key West, USA, June 1999*

*And:*

*The Annual Scientific Meeting of the Australasian Society of Cardiovascular Perfusionists, Sydney, Australia, October 1999*
TABLE OF CONTENTS

TITLE PAGE .................................................................i
DEDICATION .......................................................................ii
ABSTRACT ........................................................................iii
ACKNOWLEDGEMENTS .........................................................v
PUBLICATIONS, PRIZES, AND ABSTRACTS .........................vii
TABLE OF CONTENTS .........................................................xii
TABLES AND FIGURES .......................................................xx
ABBREVIATIONS ............................................................xxv

1 INTRODUCTION AND LITERATURE REVIEW .........................1
1.1 Thesis overview and research chronology ...............................2
1.2 Historical perspective .......................................................5
1.3 Definition, measurement and incidence of brain injury in cardiac surgery .............................................7
   1.3.1 Peri-operative death secondary to brain injury
   1.3.2 Peri-operative stroke
   1.3.3 New neurological symptoms or soft neurological signs
   1.3.4 Neuropsychological deficits
      1.3.4.1 Neuropsychological testing
      1.3.4.2 The incidence of neuropsychological deficits
      1.3.4.3 Clinical significance of neuropsychological deficits
1.4 Comparison of cardiac surgical patients with appropriate control groups ........................................ 21

1.5 Mechanisms of brain injury in cardiac surgery ................................................................. 24

1.5.1 Pathological findings

1.5.2 Cerebral hypoperfusion during CPB

1.5.3 Cerebral embolisation during CPB

  1.5.3.1 Sources of solid emboli

  1.5.3.2 Sources of gaseous emboli

  1.5.3.3 Numbers and distribution of emboli through surgery

  1.5.3.4 Mechanisms of cerebral injury by emboli

  1.5.3.5 Clinical evidence for cerebral injury by emboli during cardiac surgery

1.5.4 The systemic inflammatory response to CPB

1.5.5 Other risk factors for cerebral injury

1.5.6 The cellular pathophysiology of peri-operative brain injury

  1.5.6.1 Initial events in ischaemia

1.6 Strategies for brain protection during cardiac surgery .................................................. 50

  1.6.1 Strategies to minimise cerebral emboli exposure

    1.6.1.1 Arterial line filtration

    1.6.1.2 Membrane oxygenation

    1.6.1.3 Cardiac deairing

  1.6.2 Strategies to optimise cerebral blood flow

    1.6.2.1 Carbon dioxide management

    1.6.2.2 Pulsatile perfusion

  1.6.3 Strategies to enhance cerebral resistance to hypoxia

    1.6.3.1 Hypothermia
1.6.3.2 Cerebro-protective drugs

1.6.4 Strategies to reduce the inflammatory response to CPB

1.6.4.1 Biocompatible components

1.7 Cerebral protection by lignocaine .................................. 62

1.7.1 In vivo evidence for cerebral protection by lignocaine

1.7.2 Clinical evidence for cerebral protection by lignocaine

1.7.3 Mechanisms of cerebral protection by lignocaine

1.7.3.1 Sodium channel blockade 1: prevention of the direct and indirect toxicity of sodium influx into neurones

1.7.3.2 Sodium channel blockade 2: alteration of cellular energy metabolism

1.7.3.3 Modulation of leukocyte activity and other rheological effects

1.7.3.4 Modulation of haemodynamic parameters

1.7.3.5 The multiple mechanism hypothesis

1.7.4 Optimising cerebral protection by lignocaine

1.8 Summary and hypothesis ............................................. 86

1.8.1 Summary

1.8.2 Hypothesis

2. DEVELOPMENT OF EMBOLI COUNTING ................................ 87

2.1 Introduction ............................................................ 88

2.2 Methods ................................................................. 90

2.2.1 Configuration and design of the emboli counter

2.2.2 Calibration of the Rimed emboli counter

2.2.3 Comparison against another Doppler counting device

2.3 Results ................................................................. 99
2.3.1 Calibration of the Rimed emboli counter

2.3.2 Comparison against another Doppler counting device

2.4 Discussion .................................................. 102

3 RANDOMISED TRIAL OF LIGNOCAINE IN BRAIN PROTECTION
DURING LEFT HEART VALVE SURGERY ................................. 104

3.1 Introduction .................................................. 105

3.2 Methods ..................................................... 107

3.2.1 Subjects

3.2.2 Neuropsychological testing

3.2.3 Trial medication administration

3.2.4 Anaesthesia and surgery

3.2.5 Statistics

3.3 Results ..................................................... 116

3.3.1 Completion of protocol

3.3.2 Baseline neuropsychological function

3.3.3 Demographic and peri-operative variables

3.3.4 Neurological outcome

3.4 Discussion .................................................. 129

3.4.1 Methodology

3.4.2 Results

3.4.3 Implications of the study

4. PATTERNS OF EMBOLI GENERATION .............................. 135

4.1 Introduction .................................................. 136

4.2 Methods ..................................................... 137
4.2.1 Patients
4.2.2 Conduct of anaesthesia, CPB and surgery
4.2.3 Right common carotid artery Doppler monitoring

4.3 Results .............................................. 141
4.4 Discussion ........................................ 144

5 AUDIT OF A NOVEL DEAIRING TECHNIQUE ........................................ 147
5.1 Introduction ...................................... 148
5.2 Methods ........................................... 150
  5.2.1 Patient groups
  5.2.2 Conduct of anaesthesia and CPB
  5.2.3 Right common carotid artery Doppler monitoring
  5.2.4 Deairing techniques
     5.2.4.1 Conventional deairing: Groups 1, 1a, 1b
     5.2.4.2 Dual vent deairing: Group 2
  5.2.5 Non-vented CABG patients: Group 3
  5.2.6 Myocardial damage
  5.2.7 Aortic vent flow
  5.2.8 Statistics

5.3 Results .............................................. 160
  5.3.1 Group characteristics
  5.3.2 Comparison of deairing in Groups 1, 2, and 3
  5.3.3 Flow through the aortic vent
  5.3.4 Myocardial damage in Group 2

5.4 Discussion ........................................ 166
6 EMBOLI AND THE CPB CIRCUIT ........................................170

6.1 Introduction .......................................................171

6.1.1 CPB venous reservoirs

6.1.2 Clinical observations

6.1.3 In vitro studies

6.2 Methods ............................................................175

6.2.1 Clinical intervention

6.2.2 Relationship between emboli generation and Maxima reservoir blood volume

6.2.2.1 Recirculation of emboli

6.2.3 Mechanism of emboli generation

6.2.3.1 Maxima reservoir design

6.2.3.2 Gas switching in a hollow fibre oxygenator

6.2.3.3 Gas switching in the reservoir atmosphere

6.2.3.4 Effect of increasing flow

6.2.4 Bubble generation by other venous reservoirs

6.2.4.1 Forte reservoir design

6.2.5 Passage of reservoir generated bubbles through the CPB circuit

6.2.6 Passage of venous air through the CPB circuit

6.2.6.1 Passage of venous air through hard shell venous reservoirs

6.2.6.2 Passage of venous air to the arterial line

6.2.6.3 Effect of vacuum assisted venous drainage on passage of venous air to the arterial line

6.2.6.4 Effect of controlling air entrainment rate on passage of venous air to the arterial line during vacuum assisted venous drainage
6.2.6.5 Effect of entrainment of CO\textsubscript{2} instead of air on passage of venous gas to the arterial line during gravity drainage and vacuum assisted venous drainage

6.3 Results

6.3.1 Clinical intervention

6.3.2 Relationship between emboli generation and Maxima reservoir blood volume

6.3.2.1 Recirculation of emboli

6.3.3 Mechanism of emboli generation

6.3.3.1 Maxima reservoir design

6.3.3.2 Gas switching in a hollow fibre oxygenator

6.3.3.3 Gas switching in the reservoir atmosphere

6.3.3.4 Effect of increasing flow

6.3.4 Bubble generation by other venous reservoirs

6.3.4.1 Effect of reservoir blood volume

6.3.4.2 Effect of increasing flow

6.3.4.3 Forte reservoir design

6.3.5 Passage of reservoir generated bubbles through the CPB circuit

6.3.6 Passage of venous air through the CPB circuit

6.3.6.1 Passage of venous air through hard shell venous reservoirs

6.3.6.2 Passage of venous air to the arterial line

6.3.6.3 Effect of vacuum assisted venous drainage on passage of venous air to the arterial line

6.3.6.4 Effect of controlling air entrainment rate on passage of venous air to the arterial line during vacuum assisted venous drainage
6.3.6.5 Effect of entrainment of CO$_2$ instead of air on passage of venous gas to the arterial line during gravity drainage and vacuum assisted venous drainage

6.4 Discussion

6.4.1 Bubble generation by hard shell venous reservoirs

6.4.2 Passage of venous air through the CPB circuit

7 SUMMARY

7.1 Prevention of emboli exposure

7.2 Cerebral protection by lignocaine

7.3 Summary statement

BIBLIOGRAPHY
LIST OF TABLES AND FIGURES

TABLES

<table>
<thead>
<tr>
<th>Name</th>
<th>Caption</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1.1</td>
<td>Studies reporting the incidence of fatal brain injury during cardiac surgery</td>
<td>7</td>
</tr>
<tr>
<td>Table 1.2</td>
<td>Studies reporting the incidence of peri-operative stroke during cardiac surgery.</td>
<td>9</td>
</tr>
<tr>
<td>Table 1.3</td>
<td>Studies reporting the incidence of new behavioural abnormalities and / or neurological signs following cardiac surgery.</td>
<td>10</td>
</tr>
<tr>
<td>Table 1.4</td>
<td>Studies reporting the incidence of NP deficits following cardiac surgery.</td>
<td>16</td>
</tr>
<tr>
<td>Table 1.5</td>
<td>Studies reporting the number of emboli recorded by Doppler devices used to monitor the cerebral circulation during cardiac surgery.</td>
<td>34</td>
</tr>
<tr>
<td>Table 1.6</td>
<td><em>In vivo</em> investigations of cerebral protection by lignocaine in ischaemic injury.</td>
<td>67</td>
</tr>
<tr>
<td>Table 2.1</td>
<td>Emboli count over 5 consecutive 1 minute periods in each of 7 sequential conditions during the calibration experiment.</td>
<td>99</td>
</tr>
<tr>
<td>Table 3.1</td>
<td>Tests and sub-scales of the NP test battery.</td>
<td>108</td>
</tr>
<tr>
<td>Table 3.2</td>
<td>Comparison of group mean raw scores for all test sub-scales in lignocaine and placebo groups at the pre-operative assessment.</td>
<td>117</td>
</tr>
<tr>
<td>Table 3.3</td>
<td>Comparison of lidocaine and placebo groups with respect to demographic and pre-operative variables.</td>
<td>119</td>
</tr>
<tr>
<td>Table 3.4</td>
<td>Comparison of lidocaine and placebo groups with respect to surgical and peri-operative variables.</td>
<td>120</td>
</tr>
<tr>
<td>Table 3.5</td>
<td>Comparison of lignocaine and placebo groups with respect to post-operative variables.</td>
<td>121</td>
</tr>
</tbody>
</table>
Table 3.6  Number and proportion of patients in the lignocaine and placebo groups exhibiting a decrement in at least one and at least two performance test sub-scales at each review

Table 3.7  Sequential group mean percentage change scores for lignocaine and placebo groups in performance test sub-scales where there was no significant difference between the groups.

Table 4.1  Emboli detection by operative phase.

Table 5.1  Patient groups: relevant medical and surgical parameters.

Table 5.2  Emboli count after aortic declamping in Group 2.

Table 5.3  Emboli count recorded after aortic declamping in Group 1 patients stratified according to selected patient and surgical variables.

Table 6.1  RCCA emboli counts during stable CPB in patients monitored before and after recommendation of the 1000 ml minimum venous reservoir volume.

FIGURES

Figure 2.1  Typical Colour flow Doppler displays during monitoring of an in vitro circuit

Figure 2.2  In vitro circuit configuration for the Doppler counter calibration.

Figure 2.3  Device for mounting the Doppler probe on the in vitro circuit tubing

Figure 2.4  Mean emboli count per minute after each alteration to the circuit during the calibration experiment.

Figure 2.5  Mean (± SEM) count recorded over 150 seconds by the Rimed and Hatteland Doppler devices downstream of the reservoir as reservoir blood volume was decreased.

Figure 3.1  Coded vial for trial infusion solutions.
Figure 3.2  Sequential group mean percentage change scores for lignocaine and placebo patients in those performance test subscales where there was a significant difference between the groups.

Figure 3.3  Sequential group mean percentage change scores for lignocaine and placebo groups in the two sub-scales of the Memory Assessment Clinics Self-Report Inventory.

Figure 3.4  Sequential group mean percentage change scores for lignocaine and placebo groups in the Beck Depression and State Trait Anxiety Inventories.

Figure 4.1  Operation of the Doppler emboli counter in the clinical setting.

Figure 4.2  Percentage of the total operative count recorded in each phase averaged over all patients.

Figure 5.1  Schematic of CPB circuit configured for conventional deairing.

Figure 5.2  Schematic of CPB circuit configured for dual vent deairing.

Figure 5.3  Schematic of dual vent deairing early during cardiac recovery.

Figure 5.4  Schematic of the final stage of dual vent deairing.

Figure 5.5  Median (range) emboli count after aortic declamping for each group.

Figure 6.1  In vitro circuit configuration for investigation of relationship between emboli formation and blood volume in the Medtronic Maxima HSVRs.

Figure 6.2  In vitro circuit configuration for investigation of the nature of the emboli generated by the Medtronic Maxima HSVRs.

Figure 6.3  Configuration of salvaged clinical CPB circuits for in vitro experiments.

Figure 6.4  Mean emboli count (± SEM) over 5 minutes measured downstream of the Medtronic Maxima bottom and top entry HSVRs as reservoir blood volume is reduced.
Figure 6.5  Cut-away view of the Medtronic Maxima Bottom Entry HSVR (from Medtronic promotional material) showing the upwardly directed venous line entry portal in an unconstrained chamber (white arrowhead).

Figure 6.6  Cut-away view of the Medtronic Maxima Top Entry HSVR (from Medtronic promotional material) showing the upwardly deflected venous line entry portal in an unconstrained chamber (white arrowhead).

Figure 6.7  Emboli count downstream of a Medtronic Maxima top entry HSVR and membrane oxygenator during manipulations of reservoir blood volume and oxygenator sweep gas.

Figure 6.8  Emboli count downstream of a Medtronic Maxima top entry HSVR and membrane oxygenator during manipulations of reservoir blood volume and reservoir atmosphere.

Figure 6.9  Mean emboli count (± SEM) over 150 seconds measured downstream of the Medtronic Maxima top entry HSVR as circuit flow rate is increased.

Figure 6.10  Mean (± SEM) emboli count over 150 seconds recorded downstream of the HSVRs tested as blood volume was progressively decreased.

Figure 6.11  Mean (± SEM) emboli count over 150 seconds downstream of the Medtronic Forte HSVR as reservoir blood volume is progressively lowered.

Figure 6.12  Mean (± SEM) emboli count over 150 seconds downstream of the HSVRs tested as flow rate was increased.

Figure 6.13  Cut-away view of the Medtronic Forte hard shell venous reservoir (from Medtronic promotional material) showing the upwardly deflected venous line entry portal in a constrained chamber (white arrowhead).

Figure 6.14  Mean (± SEM) emboli count over 150 seconds downstream of the reservoir, oxygenator, and filter as reservoir blood volume is decreased in Medtronic Maxima top entry HSVR.
Figure 6.15  Mean (± SEM) bubble count detected downstream of the HSVRs tested over 180 seconds of pulsed venous air exposure.

Figure 6.16  Mean (± SEM) bubble count in the arterial line downstream from a 40 μm filter after entrainment of air to the venous return line during gravity venous drainage.

Figure 6.17  Mean (± SEM) bubble count in the arterial line downstream from a 40 μm filter after entrainment of air to the venous return line during GVD and VAVD.

Figure 6.18  Mean (± SEM) time to complete entrainment of air under GVD and VAVD.

Figure 6.19  Mean (± SEM) bubble count in the arterial line downstream from a 40 μm filter after entrainment of 50 ml air to the venous return line at unrestricted and restricted rates during GVD and VAVD.

Figure 6.20  Mean (± SEM) bubble count in the arterial line downstream from a 40 μm filter after entrainment of air or CO₂ to the venous return line at unrestricted rates during GVD and VAVD.
### LIST OF ABBREVIATIONS AND SYMBOLS

Note: Abbreviations used only in tables or figures and explained in the captions to those tables or figures do not appear in this list.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate amino transferase</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>AVLT</td>
<td>Auditory – verbal learning test</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>Ca&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>Calcium</td>
</tr>
<tr>
<td>CAGE</td>
<td>Cerebral arterial gas embolism</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
</tr>
<tr>
<td>CK-MB</td>
<td>Creatine kinase (myocardial fraction)</td>
</tr>
<tr>
<td>cm</td>
<td>Centimetre</td>
</tr>
<tr>
<td>CO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CPB</td>
<td>Cardiopulmonary bypass</td>
</tr>
<tr>
<td>DCI</td>
<td>Decompression illness</td>
</tr>
<tr>
<td>EEG</td>
<td>Electro-encephalogram</td>
</tr>
<tr>
<td>EPSP</td>
<td>Excitatory post-synaptic potential</td>
</tr>
<tr>
<td>Fe&lt;sup&gt;3+&lt;/sup&gt;</td>
<td>Iron ion</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>GVD</td>
<td>Gravity venous drainage</td>
</tr>
</tbody>
</table>
H⁺  Hydrogen ion
HBO  Hyperbaric oxygen
HSVR  Hard shell venous reservoir
Hz  Hertz
ICP  Intracranial pressure
K⁺  Potassium ion
K/AMPA  Kainate / amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (receptors)
kg  Kilogram
L  Litre
LCCA  Left common carotid artery
m  Metre
MAC-S  Memory Assessment Clinics self-rating inventory
MAP  Mean arterial pressure
MCA  Middle cerebral artery
MHz  Megahertz
mmHg  Millimetres of mercury
mg  Milligram
Mg²⁺  Magnesium ion
min  Minute
ml  Millilitre
Na⁺  Sodium ion
[Na⁺]ᵢ  Intracellular concentration of sodium ions
[Na⁺]ₒ  Extracellular concentration of sodium ions
NO  Nitric oxide
NMDA  N methyl D aspartate (receptors)
NP  Neuropsychological
PaCO₂  Arterial partial pressure of carbon dioxide
PaN₂  Arterial partial pressure of nitrogen
PO₂  Partial pressure of oxygen
RCCA  Right common carotid artery
s  Second(s)
SD  Standard deviation
SDMT  Symbol digit modality test
SEM  Standard error of the mean
SER  Somatosensory evoked response
STAI  State – trait anxiety index
TOE  Transoesophageal echocardiography
μg  Microgram
μL  Microlitre
μm  Micrometer
μmol  Micromol
VAVD  Vacuum assisted venous drainage
VSCC  Voltage sensitive calcium channel
CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW
1.1 THESIS OVERVIEW AND RESEARCH CHRONOLOGY

Studies performed within the last 2 years report stroke in 5.9% and neuropsychological (NP) deficits in 69% of patients undergoing cardiac surgery. The most commonly cited mechanisms for these injuries are embolisation of the cerebral circulation by air or particulate matter, and intra-operative cerebral hypoperfusion. Numerous factors have been identified which either precipitate these events or alter the patient’s vulnerability to their ill-effects.

There is ongoing advocacy for development of cerebral protection strategies in cardiac surgery. Most previously reported strategies involved reduction of emboli exposure, prevention of cerebral hypoperfusion, or enhancement of cerebral resistance to these injurious processes. In the latter context, in vivo experiments have demonstrated cerebral protection by lignocaine in models of cerebral arterial gas embolism (CAGE), focal ischaemia and global ischaemia. In addition, there have been several case reports of apparent benefit following administration of lignocaine to divers with neurological decompression illness (DCI).

The present study began as a randomised, controlled, double blind trial of brain protection in left heart valve surgery patients by lignocaine, initiated at Green Lane Hospital in 1995. In order to control for emboli exposure in the patient groups, an emboli-counting capability based on colour flow Doppler ultrasound was developed. Subject recruitment took place from January 1995 until July 1997. In accordance with the trial protocol, all patients underwent Doppler monitoring of the right common
carotid artery (RCCA) throughout surgery to detect embolic activity. This resulted in several important incidental observations.

First, approximately 80% of the total operative emboli activity was recorded at the end of the surgical procedure when the aorta was declamped and the heart resumed ejection. This confirmed previous reports of ineffective removal of air and particulate matter from the heart chambers by contemporary “deairing” techniques. During 1996 a novel de-airing technique was evaluated.

Second, embolic activity appeared to increase when the Medtronic Maxima hard shell venous reservoir (HSVR) on the cardiopulmonary bypass (CPB) machine was operated at blood volumes that were low, but still above the manufacturer’s recommended minimum. During 1995, this observation was followed up with a series of in vitro experiments to confirm or refute bubble generation by these particular reservoirs. A second series of experiments in 1996 compared bubble generation by a range of these devices from other manufacturers.

Third, embolic activity appeared to increase when air was entrained into the CPB venous return line, a phenomenon considered by surgeons to be benign. During 1998 this observation was followed up with a series of in vitro experiments to investigate passage of venous line air through the CPB circuit, and to examine any exacerbation of the problem when venous drainage was assisted by a vacuum.

The remainder of Chapter 1 reviews the literature relevant to cerebral injury in cardiac surgery, and the literature indicating a protective role for lignocaine. The development
of an emboli-counting capability is briefly described in Chapter 2. The trial of lignocaine for brain protection during cardiac surgery is described in Chapter 3. The distribution of emboli detected in the RCCA throughout surgery is described in Chapter 4. The consequent investigation of a new deairing technique is described in Chapter 5. Finally, the investigation of apparent emboli generation by Medtronic Maxima HSVRs, and the passage of air entrained to the CPB venous line through the circuit is described in Chapter 6.
1.2 HISTORICAL PERSPECTIVE

Gibbon (1954) described the first successful application of CPB. Soon after, reports of cerebral morbidity during cardiac surgery emerged. Erenhaft and Claman (1961) and Erenhaft et al. (1961) retrospectively reviewed the case notes for 244 patients who had undergone CPB and open chamber left heart surgery, and identified 17 cases of cerebral complications including "protracted somnolence", convulsions and hemiplegia. On the basis of similar case note reviews, Egerton and Kay (1964) and Blachly and Starr (1964) reported the incidence of "delerium" following open chamber cardiac surgery as 41% and 57% respectively. A fifth study performed by Kornfeld et al. (1965) was notable in that retrospective notes reviews (119 cases) and prospective interviews (20 cases) identified post-operative "delerium" in 38% and 70% of cases respectively. This was the first of several studies to identify the insensitivity of retrospective methodology. In a prospective study, Gilman (1965) examined 35 adults prior to and after open chamber left heart surgery. He reported neurologic disturbances in 12 patients (34%), specifically: "gnostic" (cognitive) disorders in 6 (17.1%); hemiplegia in 2 (5.7%); visual field deficits in 2; and "convulsive disorders" in 2. Four of the 6 patients with cognitive disorders recovered completely over periods ranging from 8 days to 1 year post surgery.

The critical question of whether neurological sequelae were more frequent following cardiac surgery than other major surgical interventions was first addressed by Gilberstadt and Sako (1967). They were also among the first to utilise NP testing in evaluation of neurological outcome, and demonstrated significantly worse post-operative NP deterioration in the cardiac surgical group compared to surgical and non-
surgical controls. The possibility that this greater incidence of complications was related to the often obligatory period of CPB was raised by Lee et al. (1969). They reported either neurologic or psychiatric complications in 19% of 62 patients undergoing cardiac surgery with CPB, in contrast to no complications in patients having cardiac procedures not requiring CPB.

Such historical data are of questionable relevance in the modern context (Treasure 1989) since changes in the surgical population and substantial improvements in surgical techniques and CPB technology have irrevocably altered the milieu of peri-operative risk. However, these studies, and others, generated intense interest in the incidence, cause and prevention of peri-operative brain injury. This interest has intensified over the subsequent three decades as mortality in cardiac surgery has declined, focussing research on the epidemiology and prevention of peri-operative morbidity.

This review of the literature defines the various clinical brain injury syndromes in cardiac surgery and discusses their measurement and incidence. The causes of brain injury are subsequently reviewed, and putative protective strategies are discussed.
1.3 THE DEFINITION, MEASUREMENT AND INCIDENCE OF BRAIN INJURY IN CARDIAC SURGERY

Brain injury syndromes following cardiac surgery fall into one of four categories: death; stroke; abnormal neurological signs; and NP deficit.

1.3.1 Peri-operative death secondary to brain injury

Peri-operative mortality from all causes in cardiac surgery has declined since the 1960s (Gardner et al. 1985), although Cosgrove et al. (1984) suggest that the proportion of deaths attributable to brain injury has increased. This is difficult to substantiate since the exact cause of peri-operative death is often unclear. The few reports that attribute deaths specifically to brain injury are cited in Table 1.1. The overall incidence of peri-operative death due to brain injury in cardiac surgery is less than 1% in the modern context.

Table 1.1 Studies reporting the incidence of fatal brain injury during cardiac surgery

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Surgery</th>
<th>n</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branthwaite MA.</td>
<td>1972</td>
<td>IP</td>
<td>417</td>
<td>2.64%</td>
</tr>
<tr>
<td>Breuer et al.</td>
<td>1981</td>
<td>IP</td>
<td>418</td>
<td>0.72%</td>
</tr>
<tr>
<td>Coffey et al.</td>
<td>1983</td>
<td>EP</td>
<td>1669</td>
<td>1.02%</td>
</tr>
<tr>
<td>Sotaniemi KA.</td>
<td>1983</td>
<td>IP</td>
<td>100</td>
<td>2.00%</td>
</tr>
<tr>
<td>Gardner et al.</td>
<td>1985</td>
<td>EP</td>
<td>3279</td>
<td>0.21%</td>
</tr>
<tr>
<td>Shaw et al.</td>
<td>1987</td>
<td>EP</td>
<td>312</td>
<td>0.32%</td>
</tr>
<tr>
<td>Egloff et al.</td>
<td>1996</td>
<td>not specified</td>
<td>3593</td>
<td>0.37%</td>
</tr>
</tbody>
</table>

EP = extracardiac procedure; IP = intracardiac procedure
Due to the frequent occurrence of non-fatal brain injury (see sections 1.3.2 - 4), and the difficulty in precisely determining the cause of peri-operative death, death is neither a sensitive nor specific marker of brain injury cardiac surgery. Moreover, the low incidence of fatal brain injury prevents its use as an outcome measure in any other than the largest interventional studies.

### 1.3.2 Peri-operative stroke

Studies reporting the incidence of peri-operative stroke are cited in Table 1.2. Only those studies which specifically referred to “stroke” or which clearly described clinically significant persistent focal motor or sensory lesions were included in this table. The specific definition of “stroke” was unclear in some studies and this may contribute to any variation in incidence. Nevertheless it is clear that brain injuries which are persistent, clinically obvious, and significant do occur in up to 6% of patients, even in the modern context (Table 1.2).

Few would argue that stroke is not a specific marker of brain injury. However, more subtle yet functionally significant neurological and NP deficits may follow cardiac surgery in the absence of stroke (Tables 1.3 and 1.4). Thus “stroke” is an insensitive marker of brain injury, and like fatal brain injury, its relatively low incidence prevents its use as an outcome measure in any other than very large interventional studies.

### 1.3.3 New neurological symptoms or soft neurological signs

Many studies (Table 1.3) report the incidence of new neurological symptoms and signs following cardiac surgery. “Symptoms” are usually behavioural and include phenomena
Table 1.2  Studies reporting the incidence of peri-operative stroke in cardiac surgery.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Surgery</th>
<th>n</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al.</td>
<td>1969</td>
<td>not specified</td>
<td>62</td>
<td>12.9%*</td>
</tr>
<tr>
<td>Turnipseed et al.</td>
<td>1980</td>
<td>EP</td>
<td>170</td>
<td>4.7%</td>
</tr>
<tr>
<td>Ellis et al.</td>
<td>1980</td>
<td>EP</td>
<td>30</td>
<td>0%</td>
</tr>
<tr>
<td>Breuer et al.</td>
<td>1981</td>
<td>EP</td>
<td>421</td>
<td>5.2%</td>
</tr>
<tr>
<td>Breuer et al.</td>
<td>1981</td>
<td>IP</td>
<td>80</td>
<td>7.5%</td>
</tr>
<tr>
<td>Gonzales-Scarano and Hurtig</td>
<td>1981</td>
<td>EP</td>
<td>1427</td>
<td>1.2%</td>
</tr>
<tr>
<td>Coffey et al.</td>
<td>1983</td>
<td>EP</td>
<td>1669</td>
<td>0.8%</td>
</tr>
<tr>
<td>Gardner et al.</td>
<td>1985</td>
<td>EP</td>
<td>3279</td>
<td>1.7%</td>
</tr>
<tr>
<td>Shaw et al.</td>
<td>1987</td>
<td>EP</td>
<td>312</td>
<td>4.8%</td>
</tr>
<tr>
<td>Carella et al.</td>
<td>1988</td>
<td>EP</td>
<td>87</td>
<td>2.2%</td>
</tr>
<tr>
<td>Smith PL.</td>
<td>1988</td>
<td>EP</td>
<td>67</td>
<td>1.3%</td>
</tr>
<tr>
<td>Reed et al.</td>
<td>1988</td>
<td>EP</td>
<td>5915</td>
<td>0.8%</td>
</tr>
<tr>
<td>Towns et al.</td>
<td>1989</td>
<td>EP</td>
<td>65</td>
<td>0%</td>
</tr>
<tr>
<td>Towns et al.</td>
<td>1989</td>
<td>IP</td>
<td>25</td>
<td>0%</td>
</tr>
<tr>
<td>Kuroda et al.</td>
<td>1993</td>
<td>EP</td>
<td>638</td>
<td>1.0%</td>
</tr>
<tr>
<td>Kuroda et al.</td>
<td>1993</td>
<td>IP</td>
<td>345</td>
<td>1.0%</td>
</tr>
<tr>
<td>Wolman et al.</td>
<td>1994</td>
<td>EP</td>
<td>1999</td>
<td>3.0%</td>
</tr>
<tr>
<td>Wolman et al.</td>
<td>1994</td>
<td>IP</td>
<td>265</td>
<td>8.0%</td>
</tr>
<tr>
<td>Singh et al.</td>
<td>1995</td>
<td>EP</td>
<td>4190</td>
<td>1.1%</td>
</tr>
<tr>
<td>Heyer et al.</td>
<td>1995</td>
<td>IP</td>
<td>55</td>
<td>5.4%</td>
</tr>
<tr>
<td>Murkin et al.</td>
<td>1995</td>
<td>EP</td>
<td>316</td>
<td>2.5%</td>
</tr>
<tr>
<td>Hartman et al.</td>
<td>1996</td>
<td>EP</td>
<td>189</td>
<td>4.8%</td>
</tr>
<tr>
<td>Egloff et al.</td>
<td>1996</td>
<td>not specified</td>
<td>3593</td>
<td>1.9%</td>
</tr>
<tr>
<td>Barbut et al.</td>
<td>1997a</td>
<td>EP</td>
<td>82</td>
<td>4.9%</td>
</tr>
<tr>
<td>Johnsson et al.</td>
<td>1997</td>
<td>EP</td>
<td>440</td>
<td>2.5%</td>
</tr>
<tr>
<td>Borger et al.</td>
<td>1997</td>
<td>IP</td>
<td>2097</td>
<td>2.6%</td>
</tr>
<tr>
<td>Barbut et al.</td>
<td>1997 b</td>
<td>EP</td>
<td>84</td>
<td>5.9%</td>
</tr>
<tr>
<td>McKhann et al.</td>
<td>1997a</td>
<td>EP</td>
<td>456</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

* = “gross neurological deficit”;  EP = extracardiac procedure;

IP = intracardiac procedure
Table 1.3  Studies reporting the incidence of new behavioural abnormalities and / or neurological signs following cardiac surgery.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Patients</th>
<th>Surgery</th>
<th>Outcome</th>
<th>Method</th>
<th>0 - 14 days&lt;sup&gt;a&lt;/sup&gt;</th>
<th>4 - 12 week&lt;sup&gt;a&lt;/sup&gt;</th>
<th>4 - 12 month&lt;sup&gt;a&lt;/sup&gt;</th>
<th>&gt; 12 month&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kornfeld et al.</td>
<td>1965</td>
<td>79</td>
<td>IP</td>
<td>B</td>
<td>RD</td>
<td>38%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kornfeld et al.</td>
<td>1965</td>
<td>20</td>
<td>IP</td>
<td>B</td>
<td>PD</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Javid et al.</td>
<td>1969</td>
<td>85</td>
<td>IP</td>
<td>NS and B</td>
<td>PD</td>
<td>15%</td>
<td></td>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>1969</td>
<td>62</td>
<td>?</td>
<td>B</td>
<td>PD</td>
<td>9.7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotaniemi et al.</td>
<td>1981</td>
<td>49</td>
<td>IP</td>
<td>NS</td>
<td>PD</td>
<td>47%</td>
<td>26%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Slogoff et al.</td>
<td>1982</td>
<td>204</td>
<td>IP and EP</td>
<td>NS and B</td>
<td>PD</td>
<td>16.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotaniemi KA</td>
<td>1983</td>
<td>100</td>
<td>IP</td>
<td>NS</td>
<td>RD</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotaniemi KA</td>
<td>1983</td>
<td>100</td>
<td>IP</td>
<td>NS</td>
<td>PD</td>
<td>36%</td>
<td>15%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Coffey et al.</td>
<td>1983</td>
<td>1669</td>
<td>EP</td>
<td>B</td>
<td>RD</td>
<td>3.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topol et al.</td>
<td>1985</td>
<td>82</td>
<td>IP and EP</td>
<td>B</td>
<td>PD</td>
<td>8.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nussmeier et al.</td>
<td>1986</td>
<td>93</td>
<td>IP</td>
<td>NS and B</td>
<td>PD</td>
<td>7.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al.</td>
<td>1986</td>
<td>51</td>
<td>EP</td>
<td>NS</td>
<td>PD</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevin et al.</td>
<td>1987</td>
<td>312</td>
<td>EP</td>
<td>NS and B</td>
<td>PD</td>
<td>61.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carella et al.</td>
<td>1988</td>
<td>87</td>
<td>EP</td>
<td>NS</td>
<td>PD</td>
<td>48.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith PL</td>
<td>1988</td>
<td>67</td>
<td>EP</td>
<td>NS</td>
<td>PD</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slogoff et al.</td>
<td>1990</td>
<td>504</td>
<td>IP and EP</td>
<td>NS and B</td>
<td>PD</td>
<td>2.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murkin et al.</td>
<td>1992</td>
<td>245</td>
<td>EP</td>
<td>NS and B</td>
<td>PD</td>
<td>38%</td>
<td>22%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolman et al.</td>
<td>1994</td>
<td>2264</td>
<td>IP and EP</td>
<td>B</td>
<td>RD</td>
<td>2.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stump et al.</td>
<td>1994</td>
<td>125</td>
<td>IP and EP</td>
<td>B</td>
<td>PD</td>
<td>14.4%</td>
<td>8.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murkin et al.</td>
<td>1995a</td>
<td>316</td>
<td>EP</td>
<td>NS</td>
<td>PD</td>
<td>30%</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heyer et al.</td>
<td>1995</td>
<td>55</td>
<td>IP</td>
<td>NS</td>
<td>PD</td>
<td>23.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinberg et al.</td>
<td>1996</td>
<td>26</td>
<td>IP</td>
<td>NS</td>
<td>PD</td>
<td>15.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> time interval for follow-up reviews;  IP = intracardiac procedure;  EP = extracardiac procedure;  NS = (new) neurological signs;

B = (new) behavioural abnormality;  PD = prospective design;  RD = retrospective design;
such as "delerium" (Kornfeld et al. 1965), "psychosis and hallucinations" (Lee et al. 1969), "impaired mentation" (Murkin et al. 1992), and "somnolence". Signs are often referred to as "soft" (Pugsley 1994) and are distinguished from "stroke" on the basis of negligible functional significance or transience. Between 2.6 and 70% of patients are reported as exhibiting new neurological symptoms or signs in the early post-operative period (Table 1.3). While those studies with longitudinal design consistently report a trend toward resolution of these phenomena over time, a small proportion of patients continue to exhibit abnormality (Table 1.3).

A striking feature of these data is their variability. However, variability can be expected when studies report data for populations of differing age and illness severity undergoing various procedures by different surgeons using a range of techniques and equipment configurations (Newman 1989). In addition, even within a discreet population, the incidence of new post-operative neurological symptoms or signs may be profoundly influenced by study methodology. Following Kornfeld et al. (1965), Hazan (1966) was another early researcher who observed that estimates of incidence were influenced by the diligence of the observer and the methods employed in the investigation. This has been a recurring theme. Sotaniemi (1983) reported new neurological signs in the early post-operative period in 4% of patients on a retrospective review, and in 36% of the same cohort of patients reviewed prospectively. Other important aspects of study design include: the definition of abnormality; the expertise of the researcher (for example, Sotaniemi (1983) showed that a neurologist will detect more signs than a non-neurologist); and the timing of post-operative reviews, (for example, Smith (1988) showed that reviews conducted very early after surgery will detect more signs than those conducted later).
1.3.4 Neuropsychological deficits

Patients often complain of cognitive function disturbance following cardiac surgery, particularly with respect to memory. Relatives may notice personality change (Taylor 1982). Although not life threatening, such changes can constitute a considerable handicap (Taylor 1982) and may persist. For example, Sotaniemi et al. (1986) reported that 23% of a series of 44 valve surgery patients felt their memory was impaired 5 years after surgery.

1.3.4.1 Neuropsychological testing

NP testing is the best means of objectively quantifying cognitive function (Shaw et al. 1986). Individual NP tests invariably involve some form of intellectual or psychomotor exercise which targets a particular cognitive domain. A battery of NP tests is usually chosen to interrogate a variety of cognitive domains (McKhann et al. 1997b). The battery must be limited in scope since cardiac surgery patients are usually unwell and tire easily in the immediate pre-operative and early post-operative periods. A "typical" battery for use in cardiac surgery consists of 10 tests administered over one hour (Newman 1995). More than half the studies reviewed here utilised batteries of 9–12 tests (Table 1.4). The number of tests is significant since studies utilising larger test batteries tend to report a higher incidence of NP deficit (Shaw et al. 1986). Tests are usually administered under standardised conditions by an expert in NP test administration (Murkin et al. 1995b). The concurrent administration of inventories for depression and anxiety has been advocated since both phenomena may affect performance on NP testing (Murkin et al. 1995b).
The comparison of post-operative NP test performance to pre-operative performance is considered obligatory in any assessment of the impact of surgery on NP functioning (Murkin et al. 1995b). It is important to follow-up as many patients as possible at each post-operative review since those patients with poorer performance may be less inclined to present for review, thus introducing an important bias (Mahanna et al. 1996).

The analysis of data from such studies can be approached in two ways (Newman 1995). First, for each test, group mean raw scores or change scores (change from pre-operative baseline) can be compared over the range of assessments (Klonoff et al. 1989). However, since repeated testing can be expected to produce improvement in NP test performance by virtue of a practice effect alone (McCaffrey 1992), this approach may mask important deterioration in individual patients, particularly if the proportion of patients adversely affected is small. Indeed, to be valid, this approach essentially assumes deficits in all patients (Newman 1995). It follows that calculation of sequential group mean scores is infrequently seen in the literature.

The second approach is to calculate the change in performance (referenced to the pre-operative test) for each individual patient at each follow-up (Newman et al. 1987). Each patient acts as their own control (Newman 1995) and the proportion of patients who deteriorate significantly can be reported. One disadvantage of this approach is the lack of consensus over the definition of a “significant deterioration” (Mahanna et al. 1996). Several definitions have been used. Many authors (Table 1.4) calculate the standard deviation (SD) of the preoperative group mean for each test, and define a significant deterioration as a decline in performance by ≥ 1SD in a predetermined
minimum number of tests, usually one, two, or 20% of the total number. A disadvantage of the “1 SD criterion” is that some patients who perform poorly in the pre-operative test may not, by definition, be able to decline in performance by 1 SD: the so called “floor effect” (Mahanna et al. 1996). Another approach which avoids a floor effect is to calculate the percentage change in each patient’s performance in each test, and to define a significant deterioration as a 20% decline in performance in two or more (Hammon et al. 1997), or 20% or more of the total number of tests (Stump et al. 1997). However, this method may be excessively sensitive, since a relatively minor change from a low pre-operative score might meet the 20% decline criteria (Mahanna et al. 1996). Studies utilising the entire spectrum of these various criteria continue to appear in the literature (Table 1.4).

Practice effects in serial NP testing may result in underestimation of the incidence of deficit defined by threshold decrements in score (Kneebone et al.1998). It is possible to ameliorate this problem by choosing tests with a less prominent practice effect than others, or by using “parallel forms” (same test format but with different data) for repeated testing (Newman 1995). Jacobsen and Truax (1991) described a technique controlling for test-retest reliability by calculation of “reliable change indices”. Chelune et al.(1993) utilised this technique, and included a correction for practice effects. Test re-test reliability and practice effects were estimated by administration of the test battery to a group of matched non-surgical controls. This method was first applied to cardiac surgery (CABG) patients by Kneebone et al.(1998) who found the incidence of post-operative cognitive deficit to be significantly greater in 5 of 11 NP tests than when the more traditional “1 SD decrement” criterion was used.
In summary, the reported incidence of NP deficits following cardiac surgery may be influenced by: the definition of deficit (Mahanna et al. 1996); the number of tests utilised (Shaw et al. 1986); the timing of follow-up testing (Table 1.4); the proportion of patients available for follow-up testing (Mahanna et al. 1996); and the use of techniques which account for practice effect (Kneebone et al. 1998). A consensus paper encouraging uniformity in the approach to NP testing in cardiac surgery patients was published by Murkin et al. (1995).

1.3.4.2 The incidence of neuropsychological deficits

Studies reporting the incidence of post-operative NP deficits in cardiac surgery patients are listed in Table 1.4. Between 20% and 79% of patients are reported to suffer NP deficits in the early postoperative period, but the incidence decreases with time after surgery (Table 1.4). Indeed, an improvement (over baseline) in individual and group NP test performance has often been reported, especially in the medium term (Aberg and Kihlgren 1977, Sotaniemi et al. 1981, Townes et al. 1989, Forsman et al. 1990, Grote et al. 1992, Williams-Russo et al. 1994, Heyer et al. 1995, Vingerhoets et al. 1997a, Vingerhoets 1997b). There is no consensus on the relative contribution of practice effects (Newman 1995), reductions in anxiety and depression (Townes et al 1989), and any non-specific beneficial effects of cardiac surgery to these improvements. Despite this decline in the incidence of NP deficit over time, such deficits can persist in individuals for long periods. Sotaniemi et al. (1986) found that 13.6% of 44 valve surgery patients continued to exhibit new NP deficits 5 years after surgery.
Table 1.4. Studies reporting the incidence of NP deficits following cardiac surgery.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Patients</th>
<th>Surgery</th>
<th>Definition of deficit</th>
<th>Number of tests</th>
<th>0 - 14 days&lt;sup&gt;a&lt;/sup&gt;</th>
<th>4 - 12 week&lt;sup&gt;a&lt;/sup&gt;</th>
<th>4 - 12 month&lt;sup&gt;a&lt;/sup&gt;</th>
<th>&gt; 12 month&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellis et al.</td>
<td>1980</td>
<td>30</td>
<td>EP</td>
<td>Various</td>
<td>5</td>
<td>75%</td>
<td>17%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Sotaniemi et al.</td>
<td>1981</td>
<td>49</td>
<td>IP</td>
<td>fall in NP index&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8</td>
<td>85%</td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Savageau et al.</td>
<td>1982&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>245</td>
<td>IP and EP</td>
<td>≥1SD 1+</td>
<td>5</td>
<td>30%</td>
<td>24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotaniemi et al.</td>
<td>1986</td>
<td>44</td>
<td>IP</td>
<td>fall in NP index&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8</td>
<td>65%</td>
<td>27%</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>1986</td>
<td>51</td>
<td>EP</td>
<td>≥1SD 2+</td>
<td>10</td>
<td>79%</td>
<td>38%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>Shaw et al.</td>
<td>1987</td>
<td>312</td>
<td>EP</td>
<td>≥1SD 1+</td>
<td>10</td>
<td>79%</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevin et al.</td>
<td>1987</td>
<td>65</td>
<td>EP</td>
<td>&quot;Fail&quot; 2+</td>
<td>10</td>
<td>73%</td>
<td>37%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Newman et al.</td>
<td>1987</td>
<td>66</td>
<td>EP</td>
<td>≥1SD 2+</td>
<td>12</td>
<td>73%</td>
<td>37%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith PL.</td>
<td>1988</td>
<td>67</td>
<td>EP</td>
<td>≥1SD 2+</td>
<td>9</td>
<td>73%</td>
<td>37%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Blauth et al.</td>
<td>1988</td>
<td>20</td>
<td>EP</td>
<td>≥1SD 1+</td>
<td>4</td>
<td>35%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harrison et al.</td>
<td>1989</td>
<td>47</td>
<td>EP</td>
<td>≥1SD 2+</td>
<td>10</td>
<td>77%</td>
<td>36%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stump et al.</td>
<td>1990</td>
<td>27</td>
<td>EP</td>
<td>≥25% 2+</td>
<td>6</td>
<td>56%</td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murkin et al.</td>
<td>1992</td>
<td>245</td>
<td>EP</td>
<td>≥1SD 1+</td>
<td>5</td>
<td>56%</td>
<td>18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stump et al.</td>
<td>1992</td>
<td>68</td>
<td>EP</td>
<td>≥20% 3+</td>
<td>6</td>
<td>60%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sellman et al.</td>
<td>1993</td>
<td>54</td>
<td>EP</td>
<td>≥1SD 2+</td>
<td>8</td>
<td>17%</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newman et al.</td>
<td>1993</td>
<td>156</td>
<td>EP</td>
<td>≥1SD 20%+</td>
<td>5</td>
<td>35%</td>
<td>17%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Stump et al.</td>
<td>1993&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54</td>
<td>EP</td>
<td>≥20% 2+</td>
<td>10</td>
<td>76%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel et al.</td>
<td>1993</td>
<td>70</td>
<td>EP</td>
<td>≥1SD 2+</td>
<td>10</td>
<td>57%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pugsley et al.</td>
<td>1994</td>
<td>94</td>
<td>EP</td>
<td>≥1SD 2+</td>
<td>10</td>
<td>59%</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croughwell et al.</td>
<td>1994</td>
<td>240</td>
<td>EP</td>
<td>≥1SD 2+</td>
<td>10</td>
<td>38%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
<td>n</td>
<td>Surgery</td>
<td>Definition of deficit</td>
<td>Number of tests</td>
<td>0 - 14 days&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 - 12 week&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4 - 12 month&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt; 12 month&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>----</td>
<td>---------</td>
<td>-----------------------</td>
<td>-----------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
<td>---------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Toner et al.</td>
<td>1994</td>
<td>15</td>
<td>EP</td>
<td>≥1SD 2+</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>Goldsborough et al.</td>
<td>1994</td>
<td>149</td>
<td>EP</td>
<td>≥0.5SD 1+</td>
<td>8</td>
<td>33%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reinvang et al.</td>
<td>1994</td>
<td>26</td>
<td>IP</td>
<td>≥1SD 2+</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td>19%</td>
</tr>
<tr>
<td>McLean et al.</td>
<td>1994</td>
<td>155</td>
<td>EP</td>
<td>1 SD net drop summed across tests</td>
<td>4</td>
<td>48%</td>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Stump DA.</td>
<td>1995</td>
<td>167</td>
<td>EP</td>
<td>≥20% 2+</td>
<td>10</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heyer et al.</td>
<td>1995</td>
<td>55</td>
<td>IP</td>
<td>≥25% 2+</td>
<td>9</td>
<td>71%</td>
<td></td>
<td></td>
<td>32%</td>
</tr>
<tr>
<td>Murkin et al.</td>
<td>1995a</td>
<td>316</td>
<td>EP</td>
<td>Threshold change exceeded in 1+ test</td>
<td>4</td>
<td>79%</td>
<td></td>
<td></td>
<td>33%</td>
</tr>
<tr>
<td>Vingerhoets et al.</td>
<td>1997a</td>
<td>87</td>
<td>EP</td>
<td>≥1SD 2+</td>
<td>Unclear</td>
<td>44%</td>
<td></td>
<td></td>
<td>19%</td>
</tr>
<tr>
<td>Stump et al.</td>
<td>1997</td>
<td>22</td>
<td>EP</td>
<td>≥20% 20%+</td>
<td>11</td>
<td>59%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammon et al.</td>
<td>1997</td>
<td>395</td>
<td>EP</td>
<td>≥20% 2+</td>
<td>11</td>
<td>65%</td>
<td></td>
<td></td>
<td>23%</td>
</tr>
</tbody>
</table>

<sup>a</sup> time interval for follow-up reviews;   
<sup>b</sup> NP index is an integrative sum of scores from all tests;   
IP = intracardiac procedure; 
EP = extracardiac procedure;   
≥1SD = fall in performance by at least one standard deviation of the preoperative group mean;   
≥20% (or 25%) = fall in performance by at least 20% (or 25%) of patients own preoperative score;   
1+ = one or more tests;   
2+ = two or more tests;   
3+ = three or more tests;   
20%+ = 20% or more of total number of tests.
1.3.4.3 Clinical significance of neuropsychological deficits

There is debate over the clinical significance of arbitrarily defined NP deficits. A number of authors have attempted to address this issue by correlating the results of NP testing against other forms of post-operative neurological assessment in cardiac surgery patients. The assumption appears to be that NP test results assume more significance if they are demonstrably predictive of, or associated with, clinically obvious neurological abnormality.

Sotaniemi et al. (1981) compared sequential mean NP test change scores between two groups of valve surgery patients: one in which patients exhibited new clinical neurological complications, and one in which the patients were neurologically "normal". Those patients with no neurological complications were performing significantly better in 5 of 12 tests at 2 months after surgery in comparison with only 2 of 12 tests in the complicated group. By one year, the uncomplicated group recorded a highly significant performance improvement in 6 NP tests in contrast to no tests for the complicated group. A further review of this population at 5 years (Sotaniemi et al. 1986) revealed that the disparity in NP performance between the complicated and uncomplicated groups had continued to widen.

Smith et al. (1986), Shaw et al. (1986) and Williams-Russo et al. (1994) all reported concordance between the occurrence of new post-operative neurological signs and NP deficits in CABG patients. In a combined group of CABG and valve surgery patients Slogoff et al. (1982) found that early post-operative performance on the Trails B test (Reitan 1958) was sensitive but not specific for the presence of clinical neurological
abnormalities, and Aberg et al. (1984) reported a significant inverse correlation between NP deficit at 7 days and the post-operative levels of adenylate kinase (an indicator of membrane disturbance in neural tissue) in the cerebro-spinal fluid.

In contrast to these results, Smith (1988) and Heyer et al. (1995) failed to identify any correlation between the presence of NP deficit and new “hard or soft” neurological signs appearing post-operatively in CABG and valve surgery patients respectively. Stump et al. (1997) found no correlation between incidence of NP deficit at 7 days after CABG surgery and plasma levels of the S-100 protein (a biochemical marker of brain injury). They suggested that site specific deficits related to lesions of variable size are unlikely to correlate with volumetric indicators of brain injury such as the S-100 protein.

Thus, there is no consensus on the relationship between NP deficits and clinically detectable neurological abnormality following cardiac surgery. It could be argued that this is an irrelevant point for several reasons. First, “perfect parallelism” cannot be expected because of the different levels of function that the different methods measure (Sotaniemi et al. 1981). Second, the significance of “NP deficits” is probably not dependent on the demonstration of such a relationship. However, there is an unfortunate lack of data describing a relationship between arbitrarily defined NP deficits detected after cardiac surgery, and quality of life for patients. Newman (1995) argues that in view of the nebulous components of quality of life, and the equally nebulous range of influential factors, it would be difficult to definitively establish this relationship. He suggests that irrespective of concerns over the functional significance
of NP deficits as they are currently defined, NP testing remains a “sensitive tool of brain functioning” and an appropriate outcome measure for interventional studies.
1.4 COMPARISON OF CARDIAC SURGICAL PATIENTS WITH APPROPRIATE CONTROL GROUPS

The substantial attention given to the issue of brain injury in cardiac surgery has been predicated, at least in part, on the perception that cardiac surgery (especially that involving CPB) results in brain injury more often than other surgical procedures. Hazan (1966) was among the first to draw this conclusion on the basis of a review of the literature. Subsequent experimental studies have both supported and challenged this view.

Lee et al. (1969) prospectively compared neurological outcomes in patients undergoing cardiac surgery with and without CPB ("perfused" and "unperfused" groups respectively). A significantly greater proportion of perfused patients (12/62) exhibited "gross cerebral dysfunction" compared to unperfused patients (0/20). In addition, at 3 month follow up, perfused patients scored significantly lower on the "cardiac adjustment scale" (an index of rehabilitation), and exhibited significantly greater neurotic and abnormal behaviour as measured by the Minnesota Multiphasic Personality Inventory.

Aberg and Kihlgren (1977) reported significantly better performance in 2/3 and 1/3 NP tests at 1 week and 2 months post-operatively (respectively) for 46 thoracic surgery patients (no CPB), when compared to 124 patients undergoing open chamber (intracardiac) cardiac surgery. It was notable that the cardiac surgery patients underwent surgery according to a protocol designed to minimise brain injury. Aberg's group (Aberg et al. 1984) subsequently reported that 59% of 94 patients undergoing
cardiac surgery had a significantly raised level of adenylate kinase (ADK) in the cerebrospinal fluid (CSF) 24 hours post-operatively, compared with none of 8 patients undergoing lung surgery.

Smith et al. (1986) reported new neurological signs at 24 hours post-operatively in 64% of 55 patients undergoing CABG and 5% of 20 patients undergoing major thoracic or vascular surgery. However, there was no difference between the groups at 8 days and 8 weeks with respect to neurological signs or NP test results. In a similar study, Smith (1988) reported: new focal signs at 24 hours in 8% of 76 CABG patients and none of 29 (surgical) controls; new soft signs at 24 hours in 59% of CABG patients and 21% of controls; and NP deficits at 8 days in 73% of CABG patients and 50% of controls. There was no difference between groups in the incidence of soft signs at 8 days and 8 weeks, or NP deficits at 8 weeks.

Shaw et al (1987) performed what is perhaps the most widely cited controlled study of brain injury in cardiac surgery in which 312 patients undergoing CABG were compared to 50 peripheral vascular surgery patients. Stroke occurred in 4.8% of CABG patients and none of the controls. New neurological abnormalities were recorded in 61% of the CABG patients and 18% of controls. At 7 days post-operatively, NP deficits were recorded in 70% of CABG patients and 31% of controls. Hammeke and Hastings (1988) also compared CABG patients (n = 46) to peripheral vascular surgery patients (n = 14). The mean change-score (averaged from 12 NP tests) was lower (more negative) for the CABG group, and more CABG patients were defined as suffering a NP deficit (24% versus 7%). These differences did not reach statistical significance.
Williams-Russo et al. (1994) compared NP outcome in patients undergoing CABG (n = 248) and total knee joint replacement (n = 262), reporting a greater mean impairment in the CABG group at 1 week post-operatively. The difference was no longer detectable at 6 months. Similarly, Heyer et al. (1995) found a significantly greater incidence of NP deficit in cardiac valve surgery patients (n = 33) at 7 days post-operatively compared to non cardiac surgery patients (n = 13), which was no longer detectable at 6 weeks. Murkin et al. (1995) compared NP outcomes in 316 CABG patients and 40 patients undergoing major thoracic or abdominal surgery without CPB. There was a significantly higher incidence of NP deficit in the CABG patients at both 7 days and 2 months after surgery.

In the most recent study comparing cardiac (109 CABG patients) and non cardiac (20 major thoracic or vascular surgery patients) groups, Vingerhoets et al. (1997) found no difference in group mean NP performance or the incidence of individual NP deficits at 7 days or 6 months post-operatively.

Thus, the neurologic problems related specifically to cardiac surgery may be “relatively evanescent”, with longer term follow-up often revealing a similar rate of dysfunction in cardiac and control surgical populations. Nevertheless, it does seem that “CPB exerts an additional significant effect in the immediate postoperative period” and the consensus among researchers in this area is that cardiac surgery patients who undergo CPB are at greater risk of developing post-operative neurologic and NP complications than patients undergoing general anaesthesia and non cardiac surgery (Mora and Murkin, 1995).
1.5 MECHANISMS OF BRAIN INJURY IN CARDIAC SURGERY

From a mechanistic viewpoint, the above discussion can be interpreted as implying that some of the neurologic dysfunction seen in cardiac surgery patients arises from non specific effects of surgery (Vingerhoets et al. 1997), while other injurious processes specific to cardiac surgery and CPB are also important, especially in the immediate post-operative period (Mora and Murkin 1995). Gilman (1965) identified cerebral embolisation and peri-operative hypotension with consequently reduced cerebral perfusion as potentially important causes of brain injury during cardiac surgery. Subsequently, these have remained the most frequently cited mechanisms of specific relevance to cardiac surgery (Govier et al. 1989, Mora and Murkin 1995).

There is also increasing interest in a systemic inflammatory response to CPB as a possible mechanism for cerebral injury (Royston 1996, Smith 1996, Boyle et al. 1997).

1.5.1 Pathological findings

Neuropathological studies support both commonly cited etiologies for post-operative brain injury in cardiac surgery. Early post-mortem studies of human brains after heart surgery found changes indicative of: embolic injury; diffuse hypoxic damage consistent with circulatory arrest; and focal injury consistent with hypotension and reduced cerebral blood flow (CBF) (Ehrenhaft et al. 1961, Brierley 1963, Brierley 1967, Tufo et al. 1970, Aguilar et al. 1971). Only Tufo et al. (1970) speculated on the predominance of one mechanism, suggesting that the distribution and nature of the lesions in their small series of 10 cases identified hypoxic damage due to inadequate cerebral perfusion as most important. However, Brierley (1967) commented on the
significant difficulty in distinguishing between the neuropathology induced by severe rapid reduction in CBF and air embolism. Aguilar et al. (1971) published a large series of 214 cases and concluded that all of the various lesions must be looked for and may coexist.

It is possible that the relative importance of the various mechanisms of brain injury has changed since these early studies, as patients have become older and surgery for coronary artery disease (often indicative of more generalised arteriopathy) has become more common. For example, a more recent study by Blauth et al. (1992) found atheroembolic disease of the brain in 21 of 129 patients examined post-mortem. The incidence of stroke before death was significantly higher in the 21 patients with atheroembolism (52%) than in those without atheroemboli (18%). Risk of cerebral injury from atheroemboli is discussed further in section 1.5.3.5.

Another recent series of studies by Moody et al. (1990, 1995) and Challa et al. (1993, 1998) has identified a possible histopathological correlate for more subtle forms of brain injury in cardiac surgery. They used an endothelial alkaline phosphatase staining technique to identify numerous small capillary and arteriolar dilatations ("SCADs") which only occurred in the cerebral vessels of patients or animals who had undergone either CPB or instrumentation of the arterial circulation. In some cases, the SCADs numbered in their millions. Initially these were postulated to be air or fat emboli but there is increasing evidence that they are mainly lipoid in nature (Challa et al. 1993), and contaminated by aluminium and silicone (Challa et al. 1998). It has been demonstrated by experiments utilising sequential injection of coloured microspheres that SCADs are most likely emboli arising during CPB, although the exact source is
unknown. Moody et al. (1990) speculated that the diffuse microvascular obstruction caused by SCADs may be sufficient to impair neural function without producing cell death, thus producing post-operative NP dysfunction in the absence of overt cerebral infarction.

1.5.2 Cerebral hypoperfusion during CPB

Much attention has been given to the hypothesis that inadequate cerebral perfusion during CPB is the explanation for brain injury in cardiac surgery. Neuronal ischaemia and death may occur if CBF delivers insufficient oxygen to meet metabolic demands at a global or regional level. This may occur in a diffuse pattern in severe ischaemia, or on in a more regional pattern based on the selective vulnerability of "watershed" areas of the cerebral circulation (Graham 1977). Both patterns have been recognised in the pathological studies of cardiac surgery patients (see above).

Of the multiple determinants of cerebral blood flow, mean arterial blood pressure during CPB has most often been reported by studies in the cardiac surgical literature. Early studies by Javid et al. (1969), Tufo et al. (1970) and Stockard et al. (1973) suggested that the risk of cerebral injury during CPB was greater if mean arterial perfusion pressure fell below a threshold of 50 - 60 mmHg. It was observed: that such perfusion pressures represent the normal lower limit of preservation of cerebral autoregulation (Javid et al. 1969); that the presence of cerebrovascular disease might lower CBF at any given perfusion pressure (Gilman 1965, Javid et al. 1969, Tufo et al. 1970); and that for these reasons, the maintenance of "normal" extracorporeal circulation flow rates in excess of 2.2 L.min\(^{-1}.m^2\) could not be relied upon to
preserve adequate cerebral blood flow (Stockard et al. 1973). Stockard et al. (1973) recommended that pressor agents be used to maintain mean arterial pressure above 50 mmHg, and observed that since the ischaemic pressure threshold will vary as a function of venous pressure, perfusion pressures of 70 mmHg or more may be desirable.

More recently, Carella et al. (1988) found that peak hypotension during CPB was significantly greater in 5 patients with abnormal post-operative neurologic signs and / or behaviours, compared to 82 uncomplicated patients. Smith (1988) found that the incidence of NP deficit in the early post-operative period correlated with episodes of hypotension (< 50 mmHg for >10 minutes). Shaw et al. (1989) found that periods of hypotension (< 40 mmHg for >10 minutes) correlated with the appearance of the snout reflex, but not other primitive reflexes, psychosis, or NP deficits. Two studies (Gardner et al. 1985, Singh et al. 1995) report a higher incidence of stroke in patients suffering significant episodes of hypotension in the peri-operative period (either before or after CPB).

Many studies have failed to corroborate these findings. No correlation could be found between episodes of hypotension during CPB and post-operative: stroke (Gonzalez-Scarano and Hurtig 1981, Reed et al. 1988, McKhann et al. 1997a); abnormal neurologic signs and abnormal behaviours (Nussmeier et al. 1986); abnormal neurological signs and NP deficits (Sotaniemi et al. 1981, Slogoff et al. 1982); and NP deficits (Savageau et al. 1982a, Savageau et al. 1982b, Townes et al. 1989, Bruggemans et al. 1995).
These studies based assumptions about cerebral perfusion on measured arterial pressures. Few studies have actually attempted to examine CBF per se in relation to neurologic outcome in cardiac surgery patients. Stanley et al. (1990) correlated cerebral perfusion pressure (CPP) (CPP = MAP - CVP) and NP outcome at 5 - 11 days post-operatively in 19 patients undergoing CABG. There was no correlation between outcome and minimum CPP, mean CPP or the duration for which CPP was below 50 mmHg.

Studying 255 patients undergoing CABG and / or valve surgery, Croughwell et al. (1994) found an association between jugular bulb haemoglobin desaturation during rewarming after hypothermic CPB and early post-operative NP deficits. Jugular bulb desaturation (PO$_2$ ≤ 25 mmHg or saturation ≤ 50%) reflects increased oxygen extraction as compensation for inadequate oxygen delivery, and indicates transient cerebral ischaemia. All patients were managed according to an alpha-stat acid-base protocol (see below). The “desaturated patients” had both a significantly greater (and unexplained) increase in the cerebral metabolic rate for oxygen, and significantly reduced cerebral blood flow (CBF) on reaching normothermia. Although mean arterial pressure (MAP) was significantly lower than for the “saturated patients” at this time, the difference in MAP was not thought sufficient to explain the group differences in CBF. A failure in cerebral autoregulation leading to inadequate CBF was proposed. Such a failure might be due to a primary defect in autoregulation, or a cerebral autonomic (vasoconstrictive) response to non-pulsatile perfusion. Similar conclusions were drawn in a study by Prough et al (1991) who showed time dependent
reduction in CBF during hypothermic CPB unrelated to any fall in the cerebral metabolic rate for oxygen. NP outcomes were not measured in this study. Both studies mentioned the possibility of perturbation of cerebral autoregulation or vessel obstruction by the passage of emboli (see 1.5.3.4 below) although neither actually measured emboli exposure.

There are also data that suggest that "excessive" cerebral blood flow is disadvantageous. Stephan et al. (1992), Venn et al. (1995), and Patel et al. (1996) compared neurological and NP outcome in patient groups undergoing CPB using differing acid base management protocols: "pH stat" (in which PaCO₂ is maintained constant during hypothermia, and temperature corrected pH of 7.4 is achieved by addition of CO₂); and "alpha stat" (in which a constant temperature-uncorrected PaCO₂ is maintained, allowing the blood pH to rise in relation to temperature).

Stephan et al. (1992) found that CBF was greater in the pH stat group even though the cerebral metabolic rate for oxygen did not differ. The incidence of neurological abnormalities was significantly greater in the pH stat group. Venn et al. (1995) found that cerebral blood flow, flow velocity, and relative hyperaemia (based on the cerebral extraction ratio for oxygen) during CPB was significantly greater in the pH stat group, yet this group exhibited a greater incidence of significant NP deficit at 6 weeks postoperatively. It was suggested that the unnecessary cerebral hyper-perfusion may have resulted in exposure of pH stat patients to larger numbers of cerebral emboli (although emboli exposure was not measured). Patel et al. (1996) appear to present the same data in a different journal. The issue of pH versus alpha stat acid-base management is further discussed in section 1.6.2.1.
Thus, the relationships between MAP and CBF, and between CBF and the appearance of neurological complications during cardiac surgery are complex and incompletely understood. The data do support hypoperfusion as a mechanism of cerebral injury during cardiac surgery, but low perfusion pressures alone do not adequately explain the hypoperfused state (Croughwell et al 1994). The studies cited here suggest that the previous fashion for correlating MAP during CPB against neurologic outcome, based on the assumption that MAP alone is a reliable index of CBF, is too simplistic an approach.

### 1.5.3 Cerebral embolisation during CPB

Numerous sources of both solid and gaseous arterial emboli have been identified in cardiac surgery.

#### 1.5.3.1 Sources of solid emboli

Solid emboli may arise from either the CPB circuit or the surgical field. Contact of blood with the foreign surfaces of the CPB circuit activates the coagulation cascade and formation of fibrin aggregates is seen, especially in areas of stagnant blood flow or areas of turbulence (Kurusz and Butler 1993). In addition, contact activation and aggregation of platelets in CPB circuits is well documented (Blauth 1995). Gross coagulation is prevented by heparinisation during CPB (Young et al. 1978), and more recently, heparin bonded circuit components designed to reduce activation of coagulation have become available (Salazar et al. 1998). Nevertheless, recent work
has identified platelet-fibrin microaggregates in canine retinal vessels after CPB
despite anticoagulation (Blauth et al 1988).

Non-biological particulate emboli may also arise in the CPB circuit. Particles of PVC
or silicone may be released from that part of the circuit tubing in contact with the
roller pump head, although the vast majority of these are less than 10μm in size
(Uretzky et al. 1987). Particles of silicone antifoam material used in the CPB
oxygenator have been found in post-mortem examinations (Orenstein et al. 1982), but
more recent improvements in technology have resulted in significant reduction in
exposure to these particles (Kurusz and Butler 1993).

Solid emboli may also arise from the surgical field. Atheromatous material may be
mobilised from the aortic wall during manipulation, cannulation and clamping of the
aorta prior to CPB (Singh et al. 1995), and during declamping and decannulation after
CPB (Barbut et al. 1994a). Fat emboli are created by trauma to fat cells in the sternal
wound area and epicardium (Clark et al. 1975). These enter the CPB circuit through
the cardiotomy suction and are incompletely removed by the circuit components
(Clark et al. 1975). This mechanism may underpin the finding of numerous lipoid
SCADs on post-mortem examination after CPB (Brown et al. 1997). Other solid
embolic material arising from the surgical field includes: bone fragments; calcium
fragments; cotton fibres; talc; bone wax; and thread (Kurusz and Butler 1993).
1.5.3.2 Sources of gaseous emboli

Gaseous emboli (bubbles) may also arise from either the CPB circuit or the surgical field.

Air or CO$_2$ bubbles remaining after priming of the CPB circuit may be introduced to the arterial line, although van der Linden and Casimir-Ahn (1991) reported that this was infrequent. Other sources in the CPB circuit include bubbles arising from vaporous cavitation at the roller pump head (Hanneman and Barile 1973) and bubble formation arising from gas solubility changes during cooling and rewarming (Katoh and Yoshida 1976). Bubble oxygenators are known to introduce oxygen bubbles into the circuit, especially if the oxygen to blood flow ratio is increased or the arterial blood reservoir downstream is operated at low volumes (Loop et al. 1976). However, although widely quoted, this mechanism is of declining relevance in the modern context since bubble oxygenators have almost universally been replaced by membrane devices which produce few, if any bubbles (Padayachee et al. 1987).

Bubbles may arise from several sources in the surgical field. Aortic cannulation and decannulation during preparation for and termination of CPB usually results in detection of emboli, some of which are likely to be bubbles (van der Linden and Casimir-Ahn 1991, Stump et al. 1996). Cardiotomy suction during CPB invariably entrains both air and blood (Kurusz and Butler 1993), although there is no recent data describing passage of this air into the arterial line. The most significant source of bubbles in patients undergoing intracardiac procedures is air that remains in the heart.
chambers (Taber et al. 1970) and pulmonary veins (Fishman et al. 1969) after the heart is closed.

Despite the use of "de-airing" techniques (Kirklin and Barratt-Boyes 1993) not all residual air is removed (Padula et al. 1971, Mikaeloff et al. 1984, Oka et al. 1985, van der Linden and Casimir-Ahn 1991, Orihashi et al. 1993, Rescigno et al. 1995, Tingleff et al. 1995, Dalmas et al. 1996). Air in the pulmonary veins is particularly difficult to eliminate in the absence of physiological blood flow through the pulmonary circulation (Tingleff et al. 1995). By the time this is established, the aorta is declamped and emboli, most of which are gaseous, pass directly to the systemic arterial circulation including the cerebral circulation (van der Linden et al. 1991). The nature and efficacy of de-airing techniques is discussed further in section 1.6.1.3. and Chapter 5.

1.5.3.3 Numbers and distribution of emboli throughout surgery

Doppler ultrasound devices are most commonly used to detect emboli moving in the cerebral circulation, and this technology is discussed further in Chapter 2. While it is convenient to distinguish between solid and gaseous emboli in discussing mechanisms of emboli generation, current Doppler emboli detection technology does not allow ready distinction between emboli types (Stump et al. 1996), particularly where automated counting systems are used. It follows that studies of cerebral embolisation in the clinical setting usually report "emboli" counts rather than "bubble" or "particle" counts. In addition, there are numerous ways in which the accuracy of Doppler emboli counts can be confounded (Butler and Kurusz 1990, Kurusz and Butler 1993). Counts
obtained during similar surgical procedures may vary between studies according to the configuration and sensitivity of the Doppler device used (Butler and Kurusz 1990).

Despite these limitations, patterns of emboli detection do emerge which are consistent with the previous discussion of emboli generation. First, the total number of emboli detected is consistently greater in intracardiac as opposed to extracardiac procedures. Studies reporting total emboli counts measured in the carotid or cerebral circulation during cardiac surgery are listed in Table 1.5. It is clear that intracardiac procedures are associated with greater cerebral embolisation. Second, the greatest number of emboli in intracardiac procedures are detected after the aorta is declamped and when the heart begins to eject during weaning from CPB (Albin et al. 1991, Stein et al. 1991, van der Linden and Casimir-Ahn 1991).

**Table 1.5**  Studies reporting the number of emboli recorded by Doppler devices used to monitor the cerebral circulation during cardiac surgery.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Surgery</th>
<th>Mean</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villano et al.</td>
<td>1994</td>
<td>EP</td>
<td>135</td>
<td>-</td>
<td>1</td>
<td>1184</td>
</tr>
<tr>
<td>Hammon et al.</td>
<td>1994</td>
<td>EP</td>
<td>126</td>
<td>-</td>
<td>4</td>
<td>1184</td>
</tr>
<tr>
<td>Stump et al.</td>
<td>1995</td>
<td>EP</td>
<td>153</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Barbut et al.</td>
<td>1996</td>
<td>EP</td>
<td>133</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Barbut et al.</td>
<td>1997c</td>
<td>EP</td>
<td>-</td>
<td>-</td>
<td>21</td>
<td>508</td>
</tr>
<tr>
<td>Edmonds et al.</td>
<td>1997</td>
<td>EP</td>
<td>128</td>
<td>-</td>
<td>0</td>
<td>1196</td>
</tr>
<tr>
<td>Mikaeloff et al.</td>
<td>1984</td>
<td>IP</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>2000</td>
</tr>
<tr>
<td>Stump et al. and Stein et al.</td>
<td>1991</td>
<td>IP</td>
<td>1339</td>
<td>838</td>
<td>38</td>
<td>4455</td>
</tr>
<tr>
<td>Villano et al.</td>
<td>1994</td>
<td>IP</td>
<td>-</td>
<td>380</td>
<td>4455</td>
<td></td>
</tr>
<tr>
<td>Knauf et al.</td>
<td>1997</td>
<td>IP + EP</td>
<td>1207</td>
<td>-</td>
<td>4</td>
<td>12974</td>
</tr>
</tbody>
</table>

EP = extracardiac procedure; IP = intracardiac procedure.
These events generate far fewer cerebral emboli in extracardiac procedures (Albin et al. 1991, Stein et al. 1991, Stump et al. 1996). Other surgical and CPB events temporally linked to detection of cerebral emboli in both intra- and extracardiac procedures include: aortic cannulation and initiation of CPB (Stein et al. 1991, van der Linden and Casimir-Ahn 1991, Stump et al. 1993b, Stump et al. 1996); administration of cardioplegia; and clamping or declamping of the aorta with either total or side clamps (Stump et al. 1993b, 1996). It is notable that the source of many emboli detected during CPB is not obvious. In a recent study by Stump et al. (1996), more than 40% of the cerebral emboli detected during extracardiac surgery could not be attributed to any particular surgical or CPB event.

1.5.3.4 Mechanisms of cerebral injury by emboli

Embolic brain injury is classically regarded as a focal ischaemic injury, caused when an embolus obstructs blood flow through a cerebral blood vessel. This concept is most valid in the context of large emboli comprised of solid material such as atheroma which is unlikely to disperse (Blauth 1995). Such a mechanism is probably responsible for many strokes in cardiac surgery, as is suggested by the strong association between stroke and aortic atheromatous disease (see section 1.5.3.5 below). However, the mechanism and manifestation of embolic brain injury may vary according to emboli composition, size, number, and distribution.

Gaseous emboli (bubbles) may cause focal ischaemia and stroke if large enough to occupy several generations of branching arterioles such that the net surface tension pressure acting on the column exceeds cerebral perfusion pressure (Gorman 1987).
Under such conditions the bubble can remain stuck for variable periods of time which are influenced by changes in perfusion pressure, any reflex vasodilation which occurs (Helps et al. 1990), and the absorption rate of the bubble gas into solution. The latter is, in turn, influenced by the initial size of the bubble and, for air bubbles, the \( \text{PaN}_2 \) (Dexter and Hindman 1998).

Smaller bubbles tend to redistribute through the cerebral vasculature (Gorman 1987) at a rate that is inversely proportional to their size (Feinstein et al. 1984). During the period of redistribution, flow through the affected vessel may be interrupted or reduced to a degree which is also influenced by bubble size (Helps et al. 1990). In addition, the passage of bubbles through cerebral vessels may damage the vascular endothelium (Haller et al. 1987; Hills and James 1991) inciting binding of leukocytes and platelets, and thus increasing vascular resistance and further decreasing blood flow (Francis and Gorman 1993). Damage to endothelium also disrupts the blood brain barrier resulting in an increase in brain water content (Nishimoto et al. 1978). It is notable that such changes have been recorded in vivo after exposure to bubbles as small as 15\( \mu \)m (Hills and James 1991).

These processes are illustrated by studies examining the effect of CAGE by progressively larger aliquots of air in vivo (Helps et al. 1990). Rabbits exposed to 25\( \mu \)L and 400\( \mu \)L of air introduced to the carotid artery exhibited an immediate decline in both cerebral blood flow and amplitude of the somatosensory evoked response (SER). In the rabbits exposed to 25\( \mu \)L the air transited the cerebral circulation almost without delay and this corresponded to immediate recovery of
cerebral blood flow and SER amplitude. However, over the following hours and in the absence of any further embolisation, there was a gradual secondary decline in SER amplitude which was correlated with a progressive reduction in CBF. In the rabbits exposed to 400μL the air took 2 - 5 minutes to transit the cerebral circulation, and although CBF recovered at this point, SER amplitude remained depressed throughout the remainder of the experiment. As in the 25μL rabbits, over several hours there was a gradual secondary decline in CBF in the absence of any further embolisation. Other studies showed that these secondary decrements in CBF and SER amplitude could be prevented by rendering the animals leukopenic prior to the embolic injury (Dutka et al. 1989; Helps and Gorman 1991).

Thus, CAGE by a small volume of gas produced a very brief period of ischaemia, and functional impairment that recovered after restoration of blood flow. Larger volumes of gas caused an initial ischaemic period long enough to cause sustained functional impairment despite restoration of flow within 2 - 5 minutes. In both cases, restoration of flow was followed by a delayed but progressive ischaemia, apparently mediated by leukocytes.

Several in vivo studies have investigated the relationship between cerebral embolisation during CPB and CBF. Brennan et al. (1971) demonstrated a fall in CBF by 25% from baseline over a 3 hour period, beginning with an hour on unfiltered CPB using a bubble oxygenator. This fall was abolished in filtered CPB, and bubble counting confirmed the efficacy of the filter in reducing emboli exposure. Patterson et al. (1976) subjected dogs to 2 hours of CPB using a bubble oxygenator operated in
such a way as to produce numerous microbubbles. Groups of dogs were sacrificed after progressively longer periods of recovery. Just prior to sacrifice, lamp black was injected to delineate the cerebral microvasculature. More than 50% of the vascular bed was abnormal in dogs sacrificed at day 1, with the incidence of filling defects steadily declining thereafter. The authors questioned the mechanism of this recovery without drawing conclusions, but the resolution of an inflammatory state induced by bubbles would be one plausible explanation. One study failed to find any reduction in global or regional brain perfusion in dogs during or after CPB with exposure to bubbles generated by a bubble oxygenator (Johnston et al 1993). However, the numbers of bubbles passing to the animals were orders of magnitude lower than in the experiments by Brennan et al. (1971) and Patterson et al. (1976), and these bubbles were probably much smaller than those created from a bolus injection of a gas aliquot as employed in the various non-CPB studies by Helps and his colleagues. In addition, bubbles were delivered in a “steady stream” over a long period, and were comprised of either 50% or 100% oxygen which predicts much faster spontaneous involution (Dexter and Hindmarsh 1998) than for the air bubbles used by Helps et al.

Thus, notwithstanding any minor discrepancies between studies, two distinct mechanisms for injury by CAGE have been identified by in vivo experiments. Both have ischaemia as a final common pathway. First, bubbles reduce blood flow when they lodge in or transit the cerebral vasculature. The magnitude and duration of this reduction determines the likelihood of functional damage, and is related to the volume of embolising gas (Helps et al. 1990). Second, although relatively small bubbles redistribute quickly (Feinstein et al. 1984, Helps et al. 1990) with immediate
restoration of CBF and function (Helps et al. 1990), their passage can incite a secondary inflammatory process which may progressively reduce CBF and impair function (Dutka et al. 1989, Helps and Gorman 1991).

There is some data that suggests such processes occur in clinical cardiac surgery. For example, Barbut et al (1997d) identified a relationship between emboli exposure, decline in cerebral blood flow velocity, and the appearance of cerebral complications. It must be noted that the “emboli” in this study were not characterised as either solid or gaseous.

1.5.3.5 Clinical evidence for cerebral injury by emboli

Clinical studies have found a relationship between stroke or NP deficit following cardiac surgery and peri-operative exposure to cerebral emboli.

Two studies published by the same group showed a relationship between emboli numbers and peri-operative stroke in CABG surgery. Barbut et al. (1997a) found that patients with and without stroke were exposed to a mean of 449 and 169 middle cerebral artery (MCA) emboli respectively. Another study by the same group (Barbut et al. 1997d) recorded mean emboli counts of 1106 in patients with stroke, 542 in patients with encephalopathy, and 157 in patients with no deficit. The extent to which data from these two studies overlap is not clear.
Other more circumstantial clinical evidence also suggests embolism as the cause for peri-operative stroke. For example, the severity of aortic atheromatous disease has been correlated with the risk of peri-operative stroke (Gardner et al. 1985, Singh et al. 1995, Hartmann et al. 1996). It is presumed that the diseased aorta is likely to release atheromatous emboli, especially when the aorta is manipulated during cardiac surgery. Several studies have detected cerebral emboli in relation to aortic manipulation (see Section 1.5.3.3), and a correlation between the severity of aortic atheromatous disease and cerebral emboli counts has been reported (Barbut et al. 1994b, Hammon et al. 1997), although this finding is not universal (Barbut et al. 1997b). Not surprisingly, mobile plaque in the aortic arch is associated with a particularly high risk for stroke (Barbut et al. 1997b, Barbut et al. 1997e).

Most studies in which neurological outcome has been correlated against emboli exposure have utilised NP testing rather than stroke as the outcome measure. Stump et al. (1993) reported a mean left common carotid artery (LCCA) emboli count of 130 in patients with an NP deficit 5 - 7 days after CABG surgery, and 63 in patients without deficit. These data are remarkably similar to those reported for similar groups of patients by Barbut et al. (1994a) (mean MCA counts of 166 and 73 in patients with and without deficits respectively), Stump (1996) (mean LCCA counts of 174 and 106 respectively), and Stump et al. (1997) (mean LCCA counts of 466 and 203 respectively). Pugsley et al. (1994) reported the percentage incidence of NP deficit at 8 weeks after CABG surgery as 9; 23; 31; and 43; in patients exposed to < 200; 201 - 500; 501 - 1000; and >1000 middle cerebral artery (MCA) emboli respectively. Clarke et al. (1995) reported cerebral complications after CABG surgery in 70% of patients
exposed to greater than 60 (mean 118) MCA emboli, and 30% of patients exposed to less than 60 MCA emboli. Arrowsmith et al. (1997) reported a significant correlation between MCA emboli counts and NP deficit measured 6 days after CABG surgery, but not when patients were assessed at 8 weeks post-operatively. Hammon et al. (1997) found early NP deficits in 60% of patients exposed to less than 100 LCCA emboli, and in 72% of those exposed to 100 or more emboli. In their relatively large patient population of 185, this difference was significant.

There are also several studies that present circumstantial evidence for causation of NP deficits by cerebral emboli exposure. Using peri-operative retinal fluorescein angiography, Blauth et al. (1988) identified more retinal vessel occlusions in CABG patients who exhibited a post-operative NP deficit than those without a deficit. Treasure (1989) reported that a greater proportion of CABG patients exhibited a post-operative improvement in NP test performance if a 40μm filter was employed in the arterial line during CPB. These studies were inferential by nature since the extent of perioperative embolism was not actually quantified.

Recent studies using biochemical markers such as the S-100 glial protein have also implicated embolism as the cause of brain injury in cardiac surgery. Grocott et al. (1998) showed a correlation between the number of emboli recorded at aortic cannulation and peri-operative S-100 levels in patients undergoing CABG. In addition, Taggart et al. (1997) showed that a significantly smaller proportion of CABG patients undergoing filtered CPB exhibited an elevation of S-100 when compared to unfiltered patients.
It is also notable that cerebral emboli exposure has been correlated with major cardiac complications following CABG, and to duration of stay in hospital. Barbut et al. (1997a) reported that patients with and without major cardiac complications were exposed to a mean of 392 and 163 MCA emboli respectively. Moreover, the mean hospital stay (days) in patients exposed to < 100; 101 - 300; 301 - 500; and > 500 MCA emboli was 8.6; 13.5; 16.3; and 55.8 days respectively.

Only one study has been found in which a correlation between neurological outcome and emboli exposure was not established. Topol et al. (1985) found no difference in the incidence of prolonged post-operative encephalopathy between two groups of patients in whom left ventricular intracavitary bubbles were either detected or not detected by transesophageal echocardiography just before and immediately after CPB. This study was too small (n = 82) to show any difference between the groups using the chosen outcome measures (stroke and encephalopathy). No NP testing was conducted.

The paucity of studies failing to show any correlation between cerebral embolisation and post-operative neurological outcome may reflect a bias for reporting positive findings. However, the fact remains that the overwhelming majority of the published literature suggests that exposure to emboli is an important cause of deterioration in cerebral function following cardiac surgery. It follows that methods to reduce cerebral microembolism are appropriate, and should be effective in reducing the incidence of postoperative cognitive dysfunction (Stump et al. 1996).
1.5.4 The systemic inflammatory response to CPB

Cardiopulmonary bypass initiates inflammatory processes, primarily by exposing the blood to foreign surfaces (Royston 1996, Boyle et al. 1997). The non-pulsatile flow often employed during CPB, hypothermia, relative anaemia, administration of blood and blood products, and administration of agents used to control coagulation are also thought to be pro-inflammatory (Royston 1996). Boyle et al. (1997) propose a schema for the “disseminated intravascular post-pump syndrome” in which the first step is complement activation by these processes. This leads to expression of adhesion molecules on both endothelium and leukocytes, with leukocyte sequestration and degranulation in end organ sites. There is also activation of platelets and both intrinsic and extrinsic coagulation pathways (Royston 1996). Heparin is routinely given during the period of CPB, and reversed with protamine at weaning from CPB for this reason.

Although more attention has been directed at the effects of inflammatory processes on the myocardium (Wilson et al. 1993), there is also speculation on the possible role of such processes in brain injury. For example, Harris et al. (1993) used MRI to demonstrate cerebral oedematous change in all patients in the first hours after CABG. Smith (1996) suggests that systemic inflammation might be an attractive explanation for this phenomenon. However, there is little or no data which clearly links cerebral injury in association with cardiac surgery to indices of systemic inflammation, or which demonstrates cerebral protection by modification of inflammatory processes. This subject is therefore not discussed in more detail. The role of local inflammatory processes in cerebral embolisation has previously been discussed (see section 1.5.3.4).
1.5.5 Other risk factors for cerebral injury

A variety of patient and surgical variables have been identified as influencing risk of cerebral injury during cardiac surgery (Shaw et al. 1989, Hammon et al. 1997, McKhann et al. 1977). Many (but not all) of these factors seem clearly linked to the injurious processes previously discussed. For example, the increased risk of stroke associated with the presence of severe aortic atheroma is almost certainly related to embolic injury (Barbut et al. 1994b).

It is notable that there is often disagreement in the literature regarding the prognostic significance of certain patient and surgical variables, and a full review of this debate and the data supporting or refuting various factors as “risks” is beyond the scope of this review. The relevance of the issue to the present work is in the choice of those factors that should be compared between the groups in the lignocaine trial (Chapter 3) in order to exclude possible confounding differences. Patient variables that have been associated with adverse neurological outcome include: greater age; female gender; history of stroke or transient ischaemic attack; history of hypertension; presence of a carotid or subclavian bruit; history of diabetes; history of cardiac failure; greater severity of myocardial disease; history of peripheral vascular disease; and presence of atheroma in the aortic arch. Surgical variables (other than emboli exposure and hypotension) that have been associated with adverse neurological outcome include: duration of CPB; extent of blood loss; “redo” (repeat) procedures; valve (intracardiac) procedures; and combined valve replacement and coronary graft procedures. (Shaw et al. 1989, Barbut et al. 1994b, Wolman et al. 1994, Nussmeier 1996, McKhann et al. 1997).
1.5.6 The cellular pathophysiology of peri-operative cerebral injury

The final common pathway for most of the mechanisms of injury discussed in sections 1.5.2 and 1.5.3 is ischaemia. Most contemporary reviews of the pathophysiology of cerebral ischaemia define two states: focal ischaemia and global ischaemia (Siesjo 1992a, 1992b, Siesjo et al. 1995). In the simplest of terms, focal ischaemia renders a region of tissue, usually defined by a vascular territory, critically and irreversibly ischaemic. This region becomes infarcted, leaving surrounding tissues partly compromised by reduced blood flow and exposure to chemical mediators of secondary damage (Siesjo et al. 1995). In contrast, global ischaemia is a “pan-ischaemia” of brief duration followed by reperfusion and recovery of function. Damage to neurones is often delayed and not confined to a single region, although some regions appear to be selectively vulnerable (Siesjo et al. 1995).

The pathophysiology of stroke occurring in cardiac surgery almost certainly conforms to classical descriptions of focal ischaemia. In contrast, the lesion underpinning NP deficits is undefined and difficult to classify according to these classical models of either focal or global ischaemia. Most commentators in the literature understandably avoid this issue. Patients with NP deficits generally do not have radiologically apparent infarctions, nor are they usually subject to periods of “pan-ischaemia” during their surgery. Yet the study by Croughwell et al. (1996) did demonstrate that NP deficits are related to periods of relative cerebral ischaemia. It seems likely that NP deficits result from ischaemic neuronal damage in which elements of both classical models may be relevant. For example, “focal” ischaemia induced by embolism, which is subsequently reversed by redistribution of the embolus, may be insufficient to cause
gross infarction but may result in selective neuronal necrosis. Such lesions have been demonstrated in primates after short periods of focal ischaemia (Jones et al. 1981, Marcoux et al. 1982). In this scenario, the injury is neither truly “focal” (since the ischaemia is reversible) nor truly “global” (while the ischaemia is transient, it involves only a region).

Irrespective of whether ischaemia is regional or global, or sustained or transient, the cellular pathophysiology of ischaemia is of some relevance to subsequent discussion of neuroprotection. A comprehensive review of the large body of related literature is beyond the scope of this review. However, some salient features of the injury process are discussed below.

1.5.6.1 Initial events in ischaemia

The pivotal event occurring early in ischaemia is depletion of adenosine triphosphate (ATP) stores. There are three important consequences (Siesjo 1992a). First, there is failure of ion homeostasis. Second, there is anaerobic glycolysis which causes intracellular acidosis. Finally, the production of macromolecules necessary to maintain cell integrity is interrupted.

The failure of ion homeostasis is of most interest in the context of this thesis, and is further discussed in the context of protection by sodium channel blocking agents in section 1.7.3.1. Ischaemia initiates dissipative ion fluxes according to prevailing concentration gradients and the membrane potential (Hanson 1985). Initially, a
conductance for K$^+$ is initiated, a slow increase in extracellular K$^+$ is recorded, and the membrane hyperpolarizes. Shortly after, a non-specific cation conductance results in rapid influx of Na$^+$, efflux of K$^+$, and depolarization of the membrane. There is influx of chloride accompanied by osmotically obligated water resulting in cellular oedema. While failure of the Na$^+$/ATPase “pump” due to lack of energy substrate is ultimately pivotal in this process, it is not certain that this is the primary event. It has been demonstrated that Ca$^{2+}$ is mobilised from intracellular stores early in ischaemia (Silver and Erecinska 1990), and it is suggested that this may be the signal responsible for the early increase in K$^+$ conductance (Siesjo 1992a).

Membrane depolarization initiates a complicated chain of events culminating in a dramatic increase in intracellular calcium concentration. When depolarization occurs at presynaptic membranes there is influx of Ca$^{2+}$ via voltage sensitive calcium channels (VSCCs) (Small and Buchan 1996) of the N type (Dunlap et al. 1995) which mediates release of glutamate or a similar neurotransmitter into the synaptic cleft (Small and Buchan 1996). Glutamate interacts with receptors on the postsynaptic membrane which are either ionotropic (ligand gated ion channels) or metabotropic (receptors which activate intracellular second messengers) (Small and Buchan 1996). The important ionotropic receptors are usually considered to be those selectively sensitive to kainate / amino-3-hydroxy-5-methyl-4-isozole propionic acid (K/AMPA) and N-methyl-D-aspartate (NMDA) (Siesjo 1990). The K/AMPA receptor gates a channel permeable to monovalent cations (Na$^+$, K$^+$, H$^+$) while the channel gated by the NMDA receptor also admits Ca$^{2+}$. Under resting conditions, Mg$^{2+}$ exerts a voltage dependent block on the NMDA receptor (Mayer et al. 1984). This is relieved by the
depolarization induced by sodium influx through concurrently activated K/AMPA gated channels (Siesjo 1990). Thus, activation of K/AMPA receptors induces postsynaptic depolarization, which in turn facilitates Ca\(^{2+}\) influx via NMDA receptor gated channels. Extracellular Ca\(^{2+}\) also enters the cell through VSCCs of the L and T types on depolarised postsynaptic membranes (Siesjo 1990). Finally, the increase in intracellular Na\(^{+}\), augmented by a Na\(^{+}\) - H\(^{+}\) exchanger driven by intracellular acidosis (Lazdunski et al. 1985), can reverse the normal direction of the Na\(^{+}\) - Ca\(^{2+}\) exchanger (Eisner and Lederer 1985), which normally shifts Ca\(^{2+}\) out of the cell.

Calcium is also released from intracellular stores during ischaemia. Activation of metabotropic receptors by glutamate results in release of Ca\(^{2+}\) from endoplasmic reticulum (Siesjo 1992a). Moreover, the normal intracellular buffering and sequestration mechanisms for calcium are inhibited by intracellular acidosis and reduced levels of ATP respectively (Siesjo 1992a).

The secondary adverse effects of raised intracellular Ca\(^{2+}\) are multiple (Siesjo 1991). For example, Ca\(^{2+}\) activates lipases that break down membrane phospholipids, producing free fatty acids and arachidonic acid. These substances may damage membranes in their own right (Siesjo 1992b). Moreover, in the presence of oxygen during reperfusion, arachidonic acid undergoes metabolism via the cyclooxygenase and lipooxygenase pathways to produce thromboxane A2 and leuktrienes. These metabolites promote platelet (thromboxane) and leukocyte (leukotrienes) aggregation, and increase vascular permeability (Samuelson 1983). Calcium activates proteases that convert xanthine dehydrogenase to xanthine oxidase (McCord 1985). In the
presence of oxygen during reperfusion, xanthine oxidase catalyses the conversion of hypoxanthine to xanthine and then xanthine to uric acid. Both reactions may produce oxygen free radical species. These, in turn, react with Fe$^{3+}$ and hydrogen peroxide in the Haber-Weiss reaction to produce the highly reactive and toxic hydroxyl radical (Halliwell 1989). The hydroxyl radical may also be produced when Ca$^{2+}$ induces nitric oxide (NO) synthetase to catalyse production of NO. Nitric oxide reacts with oxygen radical species to form the peroxynitrate ion, which in acidic conditions then decomposes to form the hydroxyl radical (Beckman et al. 1990).

The factors that determine death or survival of a hypoxic neuron are unclear. Siesjo (1992b) hypothesises that cell death only occurs if intracellular Ca$^{2+}$ rises above a minimum critical value for a minimum period of time. This will be influenced by the energy state of the cell and the activity of membrane pumps in relation to ion leaks.

In summary, neuronal energy failure causes rapid influx of sodium and other cations and depolarization of the membrane. Consequent release of excitotoxins from depolarised presynaptic terminals reinforces postsynaptic membrane cation leakage and precipitates a rapid increase in intracellular Ca$^{2+}$ concentration. Increased intracellular Ca$^{2+}$ catalyses a variety of injurious responses that may result in cell death, depending on the magnitude and duration of the rise in Ca$^{2+}$. 
1.6 STRATEGIES FOR BRAIN PROTECTION DURING CARDIAC SURGERY

Many strategies for reducing brain injury during cardiac surgery have been proposed. These can broadly be classified as those that focus on reducing peri-operative cerebral emboli exposure, those that optimise cerebral blood flow during CPB, those that increase cerebral resistance to hypoxic injury, and those that reduce the inflammatory response to CPB. Specific protection strategies that are either commonly used or often discussed are summarised below.

1.6.1 Strategies designed to minimise cerebral emboli exposure

1.6.1.1 Arterial line filtration

Since the early days of CPB technology, arterial line filters have been used in an attempt to reduce the passage of emboli from the CPB machine to the patient (Ehrenhaft et al. 1961). Initially these were coarse 400 μm metal screens (Ehrenhaft et al. 1961). Subsequently a finer 40 μm dacron wool screen was used (Osborn et al. 1970), and more recently synthetic mesh screen filters have been introduced. The 40 μm pore size remains the most popular.

Filters are effective in reducing the number of emboli reaching the distal arterial line (Padayachee et al. 1988). There is evidence from both in vivo and clinical studies that they are also effective in reducing brain injury. Using a canine model of CPB, Taylor et al. (1980) recorded significantly reduced levels of creatine kinase in spinal CSF during filtered versus unfiltered CPB. Improved postoperative N.P outcomes have been recorded in patients undergoing filtered versus unfiltered CPB (Aberg and
Kihlgren 1977, Treasure 1989, Pugsley et al. 1994), although this finding is not universal (Aris et al. 1986, Sellman et al. 1993). Notwithstanding these discrepant studies, the weight of evidence for clinical brain protection is now such that arterial line filters are widely considered mandatory.

1.6.1.2 Membrane oxygenation

Several investigators have recorded significantly fewer emboli during in vitro CPB (Hatteland et al. 1985) or in the cerebral circulation during clinical CPB (Padayachee et al. 1987a, Johnston et al. 1993) when a membrane oxygenator was used in comparison to a bubble oxygenator. There is less agreement on whether use of a membrane oxygenator results in less clinically detectable cerebral injury. Shaw et al. (1989) prospectively followed 312 patients undergoing CABG. Sixty six and 34 % of patients underwent CPB in which membrane and bubble oxygenators (respectively) were used. There was no difference in the rate of NP deficit at 7 days postoperatively between the groups. In contrast, Sotaniemi (1980) reported a trend toward a lower incidence of neurological abnormalities in patients undergoing CPB where a membrane oxygenator was used. Blauth et al. (1990) reported retinal microvascular occlusions in 44% of 34 and 100% of 30 patients undergoing CPB using membrane and bubble oxygenators respectively. Smith (1989), in a preliminary report of the latter study, noted that there was a trend toward a greater severity of NP deficit in the bubble oxygenator patients.

Although bubble oxygenators were more commonly used than membrane devices as recently as 10 years ago (Padayachee et al. 1987a), it is not surprising that this situation is now reversed.
1.6.1.3 Cardiac deairing

The numerical importance of emboli appearing in the cerebral circulation after aortic declamping and resumption of cardiac ejection has been discussed in section 1.5.3.3. Most of these emboli are bubbles retained in the left heart (Taber et al. 1970) and pulmonary veins (Fishman et al. 1969) after heart closure. Since reduction in emboli exposure has been demonstrated to result in less NP deficits (see section 1.5.3.5), the elimination of this air using “deairing” techniques has received much attention (see below). Although there are numerous variations, conventional techniques usually involve needle aspiration of the cardiac chambers and active venting of the left ventricle and ascending aorta. The free ejection of blood through a stab wound in the ascending aorta is sometimes allowed, and the lungs are usually ventilated during these manoeuvres to encourage mobilisation of air from the pulmonary veins (Kirklin and Barratt-Boyes 1993).

It is recognised that conventional techniques are not completely effective (van der Linden 1991, Tingleff et al. 1995). In particular, deairing often fails to adequately clear the pulmonary veins. Despite deairing by standard technique, Tingleff et al. (1995) observed bubbles emerging from the pulmonary veins intermittently for up to 28 minutes after withdrawal of CPB. These authors suggested that air entrapped in the pulmonary veins is “not mobilised until normal blood flow through the lungs has been established after weaning from CPB”, and that the importance of pulmonary venous air and “the difficulties associated with its removal by standard deairing techniques have been underestimated”.

52
Most efforts to improve deairing after open chamber surgery have focussed on the use of ultrasound imaging devices to guide existing techniques, rather than on the development of novel deairing techniques per se. Intra-operative transoesophageal echocardiography (TOE) (Duff et al. 1980, Oka et al. 1986, Orihashi et al. 1993, Tingleff et al. 1995, Dalmas et al. 1996), two dimensional echocardiography (Diehl et al. 1987), and Doppler monitoring of the left ventricular vent (Rescigno et al. 1995) have been advocated as guides to the adequacy of deairing. However, these papers did not address the fundamental difficulty of improving pulmonary vein deairing per se.

This problem was recognised by Hoka et al. (1995) who reported a technique which emphasised establishment of pulmonary venous blood flow by increasing resistance in the CPB venous return line. The adequacy of pulmonary flow was assessed by measurement of end tidal CO₂. Pulmonary venous blood was actively vented from the left ventricle until no further air was seen using TOE. The authors claimed “satisfactory elimination” of residual air, but no data describing the time course of this procedure and no emboli quantification after aortic declamping, either by TOE or cerebral vessel Doppler, was presented.

In another recent study, Rescigno et al. (1995) reported no left carotid microemboli at the point of aortic declamping and weaning from CPB in three of six patients when conventional deairing efforts were maintained until no further emboli signals could be detected by Doppler in the left ventricular vent. It is unclear whether emboli were detected between or after these events. Nor were the emboli quantified in the 3 patients where they were detected. Nevertheless, this technique would seem to be the most successful reported to date and the emphasis on establishing a clear LV vent
before allowing the heart to eject freely seems appropriate. It is likely that by monitoring flow down the LV vent, these authors were able to optimise flow through the pulmonary veins within the constraints of conventional deairing technique.

Carbon dioxide is markedly more soluble in solution than nitrogen or oxygen, and results in fewer and / or smaller gas emboli when entrained into blood (Kessler and Patterson 1970). Indeed, Gorman (1987) reported that a significantly greater volume of CO$_2$ (compared to air or oxygen) was required to produce vascular occlusion in a rabbit model of CAGE. It follows that displacement of air by carbon dioxide in the surgical field has been proposed as a means of reducing the impact of gaseous embolism (Nichols et al. 1958). Although the technique was not universally adopted it continues to have proponents, and there is renewed interest. Webb et al. (1997) used TOE during weaning from CPB to demonstrate fewer and less persistent intracardiac bubbles in patients where CO$_2$ field flooding had been used, compared to a control group. However, the technique has been criticised as unreliable (Taber et al. 1970) and in addition, bubbles of CO$_2$ are still capable of exerting pathogenic effects (Spencer et al. 1965).

Research to refine deairing techniques continues, and a novel technique is described in Chapter 5.

1.6.2 Strategies to optimise cerebral blood flow during CPB

1.6.2.1 CO$_2$ management strategy

The last decade has seen considerable debate over the relative cerebro-protective merits of the pH stat and alpha stat acid-base management strategies that were
discussed previously in the context of their effect on cerebral blood flow. Bashein et al. (1990) found no difference in NP outcome measured at 8 days and 7 months post-operatively between groups of patients randomly assigned to either technique. In contrast, Stephan et al. (1992), Murkin et al. (1995), Venn et al. (1995), and Patel et al. (1996) all reported neurological or NP outcome advantages for the alpha stat group. Murkin et al. (1987) demonstrated that under mildly hypothermic conditions, pH stat management results in pressure dependent CBF with impairment of both cerebral autoregulation and flow-metabolism coupling, whereas alpha stat management was found to preserve these physiological mechanisms. The “luxury perfusion” that occurs in pH stat management may expose the brain to greater numbers of emboli during CPB (Murkin et al. 1987). In addition, if there are regions of relative ischaemia, then increased blood flow to non-ischaemic areas may result in a “steal phenomenon” (Boysen et al. 1971). In a recent review of the issue, O'Dwyer et al. (1996) acknowledge the increasing evidence suggesting a disadvantage for pH stat management, and observe that the alpha stat technique is “more commonly used”.

1.6.2.2 Pulsatile perfusion

Pulsatile perfusion has been shown to ameliorate changes in the cerebral circulation that are seen during non-pulsatile perfusion, such as capillary collapse, sludging and marked venodilation (Matsumoto et al. 1971, Sanderson et al. 1972). A controlled experiment in a canine model of focal cerebral ischaemia showed that pulsatile perfusion both increased regional blood flow by 55% and conferred neuroelectrical protection (measured by EEG) (Tranmer et al. 1986). In clinical CPB, pulsatile perfusion significantly increases CBF (Murkin and Farrar 1989), decreases shunting in
the cerebral microcirculation (Kono et al. 1990), and prevents intraoperative hypothalamic and pituitary stress responses (Taylor et al. 1978).

There is controversy over whether these apparent advantageous effects translate into clinical brain protection (O’Dwyer et al. 1996). Hammeke and Hastings (1988) speculated that the low incidence of neurocognitive deficits recorded in their study group of patients undergoing CABG may have, at least in part, been explained by their use of pulsatile CPB. There was, however, no experimental evidence on which to base any conclusions. Shaw et al. (1989) found no advantage for pulsatile over non-pulsatile CPB in terms of neurological outcome in a prospective study of 312 patients undergoing CABG. Murkin et al. (1993) compared patients undergoing CABG during pulsatile or non-pulsatile CPB. They reported a significantly greater incidence of perioperative myocardial infarction and death in the non-pulsatile group, although neurological outcomes were not different between the groups. To complicate the matter further, Hyde et al. (1997) recently reported that serum levels of the S-100 protein, a marker of neuronal injury, increase more during pulsatile than non-pulsatile CPB. It follows that no conclusions can be drawn on the neuroprotective properties of pulsatile CPB.

1.6.3 Strategies to enhance cerebral resistance to hypoxic injury

1.6.3.1 Hypothermia

Mild to moderate hypothermia has been used during CPB to provide both myocardial and cerebral protection (Rogers et al. 1993). Hypothermia has traditionally been considered to protect the brain by reducing the cerebral metabolic rate (CMR) (Astrup 1982). The recent observation that experimental hypothermic neuronal protection is
not proportional to reduction in CMR (Todd and Warner 1992) has called this classical notion to question. Indeed, alternative mechanisms of protection have been recently identified. For example, mild hypothermia reduces the elaboration of excitotoxins during ischaemia (Busto et al. 1989, Illievich et al. 1994), and it is not surprising that recent *in vivo* studies have shown mild hypothermia to confer "extra" protection even when CMR is already lowered by administration of isoflurane (Sano et al. 1992).

Notwithstanding this controversy over the mechanism of protection by hypothermia, there has also been debate over its efficacy in the clinical setting, particularly since there is increasing interest in using warm blood cardioplegia for myocardial protection (Engelman 1991). The patient can only be rendered hypothermic between initiation and weaning from CPB. Since this interval does not include the high embolic risk periods around aortic manipulation and separation from CPB, the value of hypothermic protection has been questioned (Nussmeier et al. 1986). Recent studies comparing groups subjected to normothermic and hypothermic CPB have shown no difference in the incidence of stroke (Warm heart investigators 1994, Singh et al 1995) or neurocognitive deficit (McLean et al 1994). This finding is not universal. In a randomised prospective trial involving CABG patients, Martin et al (1994) recorded a significantly higher rate of stroke following normothermic CPB (3.1%) than after moderately hypothermic CPB (1.0%). The issue is further complicated by inconsistencies in the definition of hypothermia. In the studies that showed no difference in outcome, the body temperature in the "normothermic" control group was allowed to passively "drift" down by several degrees, whereas in Martin's study normothermia was actively maintained. Thus, it may be that even very mild
hypothermia is an effective brain protection strategy whereas actively maintained normothermia is hazardous. The lack of additional benefit from deeper hypothermia during CPB may be explained by the disadvantageous cerebral hyperthermia that can occur during rewarming from moderate hypothermia unless great care is taken to control temperature gradients (Newman 1999). In the case of open chamber surgery patients, this will occur during the period of maximal risk of embolisation.

The optimal degree of hypothermia for cerebral protection during CPB remains an area of debate. Not surprisingly, many centres are opting for compromise by using temperatures ranging between 32 and 35°C (Murkin 1995c).

1.6.3.2 Cerebro-protective drugs

There are many steps in the neurochemical cascade of ischaemic brain injury where protective pharmacological intervention may be possible and on-going research into such interventions has been strongly advocated (Roach 1997). Unfortunately, to date, there have been few convincing demonstrations of pharmacological brain protection in humans undergoing heart surgery.

Four agents: thiopentone; prostacyclin; nimodipine; and remacemide have undergone prospective clinical investigation for neuroprotective properties in cardiac surgery. Thiopentone is the most extensively investigated and discussed. Possible mechanisms of cerebral protection by thiopentone include: a decrease in CBF and cerebral blood volume with a consequent fall in intracranial pressure; decreased cerebral metabolic rate; cerebral vasoconstriction causing blood to be shunted toward an ischaemic area;
and increased scavenging of free radicals (Michenfelder 1988). Slogoff et al. (1982) found that a smaller proportion of cardiac surgery patients given thiopental (15 mg kg\(^{-1}\)) prior to going on CPB had neurological and behavioural abnormalities in the immediate post operative period when compared to a control group not given barbiturates. The difference did not reach statistical significance however. In a subsequent controlled study in which larger doses of thiopental (mean 39.5 mg kg\(^{-1}\)) were used to maintain EEG silence throughout CPB, Nussmeier et al. (1986) found that a significantly smaller proportion of the thiopental patients had neurological and behavioural abnormalities in the early postoperative period. It was notable that the thiopental patients required larger doses of inotropic and chronotropic drugs, and prolonged ventilatory support. Nevertheless, it was recommended that administration of thiopental be subsequently considered in high risk cardiac surgical procedures (Michenfelder 1986, Nussmeier et al. 1986). The practice has never been widely adopted (Rogers 1997), and another more recent controlled clinical trial in CABG patients has failed to show any benefit for thiopental administration (Zaidan et al. 1991).

Prostacyclin infused prior to and during CPB has been demonstrated to preserve platelet numbers and reduce the mass of microaggregates produced (Radegran et al. 1982). On this basis, it was speculated that it may reduce embolic brain injury (Smith 1989). However a prospective randomised and controlled study by Fish et al. (1987) failed to show any advantage in NP outcomes in the treated group.

Forsman et al. (1990) speculated that nimodipine’s ability to increase CBF during ischaemia (Barnett et al. 1986) might be protective during CPB. Their small
controlled trial (n = 35) demonstrated a significant advantage for the nimodipine patients in 2 of 31 NP test scales administered 6 months after surgery. It was notable though that there was no difference in CBF during CPB between the groups. In contrast, Legault et al. (1996) reported a larger controlled trial of nimodipine administered intravenously during CPB, which was terminated prematurely because the rates of both major peri-operative bleeding and death over the 6 months following surgery were significantly higher in the nimodipine group. Moreover, there was no evidence of cerebral protection in the nimodipine group. In explanation, it has been suggested that a cerebral dilator might confer disadvantage during CPB by increasing cerebral exposure to emboli (Rogers 1997).

Arrowsmith et al. (1998) conducted a randomised double-blind trial of remacemide, an agent exhibiting NMDA receptor antagonism, for neuroprotection during CABG. Two months after surgery, patients receiving remacemide exhibited a significantly improved “z score”, an integrative measure of performance over a variety of NP tests, when compared to the placebo patients. It is notable however, that when the data was analysed using the more traditional definitions of NP deficit (see section 1.3.4.1.), the difference between the groups did not reach significance.

Prior to the trial reported in Chapter 3, no other drugs have been specifically tested for neuroprotection during cardiac surgery. However, aprotinin, a serine protease inhibitor that has both antifibrinolytic and platelet preserving activity, was serendipitously found to significantly lower the incidence of stroke in patients undergoing redo CABG (Levy et al. 1995). There is speculation about other agents based on their efficacy in either animal models of brain injury or other clinical settings. Those that have been
speculatively mentioned as potentially useful in cardiac surgery include: lignocaine, phenytoin, midazolam, etomidate (Govier 1989); aspirin, vitamin E, desferrioxamine, mannitol, anti-neutrophil monoclonal antibodies (Royston 1989); and ketamine (Tempelhoff et al. 1995).

1.6.4 Strategies designed to reduce the inflammatory response to CPB

1.6.4.1 Biocompatible components

There has been much interest in the use of heparin bonded components in the CPB circuit in order to reduce contact activation of coagulation and inflammatory cascades. Indeed, such products are widely available and have been demonstrated to reduce the duration of post-operative ventilatory support and hospital stay, reduce chest drain blood loss and body temperature, improve renal function indices, and reduce the peri-operative release of the S100 glial protein (a marker of cerebral injury) (Svenmarker et al. 1997). There have not, however, been any unequivocal demonstrations of functional neuroprotection through the use of biocompatible componentry.
1.7 CEREBRAL PROTECTION BY LIGNOCAINE

Cerebral protection by lignocaine was the original focus of this investigation. Lignocaine is a cationic amide compound belonging to the pharmacological family of “sodium channel blocking agents”. It is used clinically as an injectable or topical local anaesthetic, and as an injectable antiarrhythmic agent in the prophylaxis of ventricular tachycardia and fibrillation (Hoffman and Bigger 1991). Lignocaine readily crosses the blood brain barrier (Sakurai et al. 1992), has a high volume of distribution, and is rapidly metabolised by the liver with the metabolites undergoing renal excretion (Hoffman and Bigger 1991). The therapeutic index for lignocaine is relatively low, the therapeutic range for antiarrhythmic action is 6 – 21 μmol L⁻¹, and plasma levels are often monitored to prevent toxicity which may be manifest as cerebral irritability, bradycardia, atrioventricular block, or myocardial depression (Hoffman and Bigger 1991).

1.7.1 In vivo evidence for cerebral protection by lignocaine

Since 1980, a number of in vivo studies have been published which demonstrate functional and / or structural (histological) cerebral protection by lignocaine. The earliest of these was performed by researchers whose primary interest was in the pathophysiology of CAGE. In vivo CAGE was followed by cardiac arrhythmias, acute hypertension, elevation of intracranial pressure (ICP) and an increase in plasma catecholamines (Evans et al. 1980, Evans et al. 1981a). It was observed that lignocaine eliminated or significantly attenuated these changes (Evans et al. 1980, Evans et al. 1987) and it was proposed that these beneficial effects might translate into protection of cerebral function. The first experiment specifically investigating cerebral
protection by lignocaine in CAGE was reported by Evans et al. (1981b, 1984).

Anaesthetised cats were pretreated with lignocaine (5 mg kg\(^{-1}\)) 5 minutes before a single bolus of 0.4 ml air was injected into the vertebral artery. The mean sciatic / cerebral somatosensory evoked response (SER) in an untreated control group initially fell to 28% of baseline, recovering to 60% and 73% over 1 and 2 hours respectively. In the treatment group, the mean SER initially fell to 68% of baseline, recovering to 89% and 95% over 1 and 2 hours. The differences were statistically significant at all times. Lignocaine also attenuated the increases in heart rate, blood pressure, and ICP recorded in the control group.

The same group subsequently published another controlled study using a modified CAGE model, and administration of lignocaine after the injury (McDermott et al. 1986, Evans et al. 1989). Cats received 0.08 ml increments of air to the carotid artery until the SER was reduced to 10% of baseline levels for a period of 5 minutes. Five minutes later, treatment group cats received lignocaine in a bolus and infusion regimen designed to produce plasma levels of 8 – 16 \(\mu\)mol L\(^{-1}\) for the duration of the experiment. Mean control and treatment group SER recovered to 32.6% and 77.3% of baseline respectively over 100 minutes (\(p < 0.001\)).

In the third and most recently published experiment using CAGE as the injury model, Dutka et al. (1992) introduced 0.4 ml of air to the carotid artery of dogs, and pharmacologically induced a post-embolic hypertensive spike. All animals in whom the SER was reduced to \(\leq\) 10% of baseline then underwent recompression treatment according to the US Navy Table 6A protocol (Navy Department 1979). In addition, the treatment group dogs received lignocaine according to the same infusion regimen.
used by Evans et al. (1989). On completion of recompression therapy, the mean treatment group SER had recovered to 60% of baseline versus 32% for the control group (p < 0.01), and mean cerebral blood flow was significantly greater in the treatment group (p < 0.025).

Early success in the CAGE injury model prompted interest in lignocaine as a protective agent in other forms of ischaemic cerebral injury. Gelb et al. (1987, 1988) demonstrated significant transient preservation of the SER in treatment group cats receiving a bolus of lignocaine (5 mg kg\(^{-1}\)) immediately prior to 6 hours of focal cerebral ischaemia. Nagao et al (1988) demonstrated significant preservation of the SER and cerebral blood flow, and significant reduction of cortical oedema, in treatment group cats receiving a pre-injury lignocaine bolus (3 mg kg\(^{-1}\)), and then an infusion (2 mg kg\(^{-1}\) hr\(^{-1}\)) throughout 12 hours of cerebral air exposure. This model precipitates progressive cerebral oedema and ischaemia. Sutherland et al. (1989) examined rats 7 days after a 10 minute period of incomplete global ischaemia and found significantly less neuronal injury in the CA3 region of the hippocampus in those given lignocaine (5 mg kg\(^{-1}\)) prior to ischaemia, compared to untreated controls.

Lantos et al. (1990a) demonstrated significant prolongation of cerebral electrical activity during global ischaemia in dogs given a large bolus dose of lignocaine. Shokunbi et al. (1990) demonstrated significant preservation of the SER and significantly smaller cerebral infarcts in treatment group cats receiving a lignocaine infusion (plasma levels 12.85 – 20.63 \(\mu\)mol L\(^{-1}\)) immediately prior to and then throughout 3 hours of middle cerebral artery occlusion and 3 hours of reperfusion.

Rasool et al. (1990) demonstrated significant preservation and superior recovery of the SER in treatment group rabbits receiving a lignocaine infusion (0.2 mg kg\(^{-1}\) min\(^{-1}\))
prior to, throughout, and following a 20 minute period of incomplete global cerebral
ischaemia. Ayad et al. (1994) demonstrated a significant shortening of both the
isoelectric EEG period and the SER recovery time in lignocaine treated rabbits
(infusion at 0.2 mg kg$^{-1}$ min$^{-1}$) subjected to 3 minutes of complete cerebral ischaemia.
There was no difference in these parameters between lignocaine treated and control
rabbits subjected to 5 minutes of ischaemia. Fujitani et al. (1994) reported a dose
dependent reduction in CA1 pyramidal cell necrosis 7 days after 4 minutes of global
ischaemia in gerbils prophylactically given lignocaine by intracerebroventricular
injection. Doses of $\geq 0.8 \mu$mol were effective, whereas doses $\leq 0.2 \mu$mol were not. No
in-between doses were tested, and these doses represent absolute amount of drug
given, not concentrations in the cerebro-spinal fluid. In a similar study, Mizumuma et
al. (1996) reported a reduction in CA4 and neocortical cell necrosis 7 days after 10
minutes of forebrain ischaemia in rats prophylactically given lignocaine (5 mg kg$^{-1}$) by
subarachnoid injection. Most recently, Zhou et al. (1998) demonstrated less
neurological deficit and less hippocampal neuronal necrosis 7 days after a 90 minute
period of hypothermic circulatory arrest in dogs prophylactically treated with
lignocaine in conventional doses, than in dogs subjected to hypothermic circulatory
arrest alone. The same group also demonstrated significantly fewer ischaemic
hippocampal neurones in dogs given lignocaine (versus controls not given lignocaine)
during 120 minutes of hypothermic retrograde cerebral perfusion (Wang et al 1999).

Several in vivo studies of cerebral protection have failed to demonstrate any benefit
for lignocaine. Shokunbi et al. (1986) reported no difference in infarct size in
treatment group cats receiving lignocaine in an unconventionally high dose (50 mg
followed by 50 mg kg$^{-1}$ hr$^{-1}$) beginning prior to and continuing throughout 6 hours of
left middle cerebral artery clamping. However, this study was superseded by that published by the same authors in 1990 which did show benefit (see above). Warner et al. (1988) reported no difference in post ischaemic EEG recovery, brain water content at 90 minutes post ischaemia, or neuronal necrosis at 7 days post ischaemia in rats treated with a bolus dose of lignocaine titrated to produce a pre-epileptogenic EEG pattern (mean dose $23.5 \text{ mg kg}^{-1}$) prior to 10 minutes of global ischaemia. McDermott et al. (1990) reported SER recovery in three groups of cats subsequent to arterial gas embolism: no treatment; hyperbaric oxygen (HBO) only, HBO and lignocaine infused to achieve plasma levels of $8 - 16 \text{ pmol L}^{-1}$. Both treatment groups recorded significantly better SER recovery than the no treatment group, but the treatment groups were not significantly different from each other. While there was no additive benefit for lignocaine and HBO demonstrated by this study, conclusions about the efficacy of lignocaine alone cannot be drawn since there was no lignocaine-only group.

The salient features of these in vivo studies which have investigated cerebral protection by lignocaine in ischaemic injury models are summarised in Table 1.6.

Varying results have been reported from less directly relevant studies of protection by lignocaine in other neurological injuries. Using cats, Kobrine et al. (1984) infused lignocaine to achieve plasma levels of $8 - 16 \text{ pmol L}^{-1}$, or a placebo, 15 minutes after a balloon catheter was inflated in the T6 epidural space for 15 seconds. There was significant return of the sciatic SER in 3 of 5 lignocaine-treated cats versus equivocal return in 1 of 5 controls. Moreover, there was markedly less haemorrhagic damage in
Table 1.6. *In vivo* investigations of cerebral protection by lignocaine in ischaemic injury.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Model</th>
<th>Lesion</th>
<th>Dose initiation</th>
<th>Dose size&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dose regimen</th>
<th>Outcome parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al. (1984)</td>
<td>Cat</td>
<td>CAGE</td>
<td>Pre-injury</td>
<td>Conventional</td>
<td>Bolus only</td>
<td>SER</td>
</tr>
<tr>
<td>Gelb et al. (1988)</td>
<td>Cat</td>
<td>Fl</td>
<td>Pre-injury</td>
<td>Conventional</td>
<td>Bolus only</td>
<td>SER</td>
</tr>
<tr>
<td>Nagao et al. (1988)</td>
<td>Cat</td>
<td>Air exp</td>
<td>Pre-injury</td>
<td>Conventional</td>
<td>Bolus / infusion</td>
<td>SER</td>
</tr>
<tr>
<td>Evans et al. (1989)</td>
<td>Cat</td>
<td>CAGE</td>
<td>Post-injury</td>
<td>Conventional</td>
<td>Bolus / infusion</td>
<td>SER</td>
</tr>
<tr>
<td>Sutherland et al. (1989)</td>
<td>Rat</td>
<td>IGI</td>
<td>Pre-injury</td>
<td>Conventional</td>
<td>Bolus only</td>
<td>Histopathology</td>
</tr>
<tr>
<td>Lantos et al. (1990)</td>
<td>Dog</td>
<td>CGI</td>
<td>Pre-injury</td>
<td>&gt; Conventional</td>
<td>Bolus only</td>
<td>EEG</td>
</tr>
<tr>
<td>Rasool et al. (1990)</td>
<td>Rabbit</td>
<td>IGI</td>
<td>Pre-injury</td>
<td>Conventional</td>
<td>Bolus / infusion</td>
<td>SER</td>
</tr>
<tr>
<td>Shokunbi et al. (1990)</td>
<td>Cat</td>
<td>Fl</td>
<td>Pre-injury</td>
<td>Conventional</td>
<td>Bolus / infusion</td>
<td>SER / Histopathology</td>
</tr>
<tr>
<td>Dutka et al. (1992)</td>
<td>Dog</td>
<td>CAGE</td>
<td>Post-injury</td>
<td>Conventional</td>
<td>Bolus / infusion</td>
<td>SER</td>
</tr>
<tr>
<td>Ayad et al. (1994)</td>
<td>Rabbit</td>
<td>CGI</td>
<td>Pre-injury</td>
<td>Conventional</td>
<td>Infusion</td>
<td>SER</td>
</tr>
<tr>
<td>Fujitani et al. (1994)</td>
<td>Gerbil</td>
<td>CGI</td>
<td>Pre-injury</td>
<td>Uncertain</td>
<td>Bolus to CSF</td>
<td>Histopathology</td>
</tr>
<tr>
<td>Mizunuma et al. (1996)</td>
<td>Rat</td>
<td>IGI</td>
<td>Pre-injury</td>
<td>Uncertain</td>
<td>Bolus to CSF</td>
<td>Histopathology</td>
</tr>
</tbody>
</table>

STUDIES DEMONSTRATING NO BENEFIT FROM LIGNOCAINE

<table>
<thead>
<tr>
<th>Authors</th>
<th>Model</th>
<th>Lesion</th>
<th>Dose initiation</th>
<th>Dose size&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dose regimen</th>
<th>Outcome parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shokunbi et al. (1986)</td>
<td>Cat</td>
<td>Fl</td>
<td>Pre-injury</td>
<td>&gt; Conventional</td>
<td>Bolus / infusion</td>
<td>Histopathology</td>
</tr>
<tr>
<td>Warner et al. (1988)</td>
<td>Rat</td>
<td>IGI</td>
<td>Pre-injury</td>
<td>&gt; Conventional</td>
<td>Bolus only</td>
<td>Histopathology</td>
</tr>
</tbody>
</table>

<sup>a</sup> "Conventional" implies a dose likely to produce lignocaine plasma levels within the antiarrhythmic reference range.

CAGE = cerebral arterial gas embolism; CGI = complete global ischaemia; CSF = cerebro-spinal fluid; Fl = focal ischaemia; IGI = incomplete global ischaemia; SER = somatosensory evoked response.
the cords of treated cats. In a similar experiment reported by Haghighi et al. (1987) where the injury was inflicted using a weight drop, no recovery occurred in either group. It is possible, however, that the weight drop spinal injury may be too severe to allow a realistic possibility of recovery with any treatment (Kobrine 1987). Oldfield et al. (1990) report a study in which lignocaine in larger than conventional doses significantly improved survival rates (followed to 40 days) in rats exposed to large doses of cerebral radiation. Muir et al. (1995) demonstrated preservation of reflexes and motor function in rats pre-treated with conventional doses of lignocaine and then exposed to fluid percussion brain injury. Broome and Dick (1996) reported no benefit for lignocaine administration in a porcine model of spinal cord decompression illness. However, only 20 animals were used in this study and the outcome measure (running on a treadmill 24 hours after the injurious dive) was somewhat crude. In addition, the lignocaine infusion was only continued for the 5 hours of recompression treatment.

Finally, it is worthy of note that lignocaine has been investigated as a protective agent in several in vivo models of myocardial ischaemia. Lignocaine has been reported to reduce infarct size (Nasser et al. 1980, Faria et al. 1983, Wendland et al. 1993), and enhance recovery of myocardial contractility (Wendland et al. 1993) during reperfusion.

1.7.2 Clinical evidence for cerebral protection by lignocaine

Prior to the study reported in Chapter 3, there have been no prospective controlled studies of lignocaine in cerebral protection in humans. Lignocaine has been advocated for reduction of intracranial pressure (ICP) in the clinical setting (Artru et al. 1991, Gao 1991) and there is speculation about its clinical neuroprotective potential (Govier
1989, Artru et al. 1991, Templehoff et al. 1995). However, there is a paucity of clinical literature attributing improved neurological outcome directly to lignocaine administration. Indeed, the literature is limited to 4 reports of apparent benefit in cases of central nervous system injury with a poor prognosis: 3 in the treatment of divers with decompression illness; and 1 in the treatment of accidental arterial gas embolism.

Drewry and Gorman (1992) instituted a lignocaine infusion immediately after two recompression treatments failed to resolve the symptoms and signs of spinal decompression illness in a 34 year old male diver. Complete recovery of all symptoms and signs occurred over the following 24 hours during which the infusion was continued, prior to any further recompression therapy. Cogar (1997) reported a case of rapidly progressive spinal decompression illness whose condition continued to deteriorate despite early institution of very aggressive recompression therapy. Progression of symptoms and signs was arrested with institution of a 24 hour lignocaine infusion. Despite a poor early prognosis, this patient went on to make a near complete recovery. Cogar (1997) also reported a second case; a 21 year old male who presented with complete paralysis of the legs 36 hours after diving. The prognosis for recovery of function in this setting was once again, poor (Ball 1993). On this occasion a 24 hour lignocaine infusion was begun concomitant with initiation of very aggressive recompression therapy, and the patient was able to walk from the recompression chamber after 53 hours of treatment. Our own group (Mitchell et al. 2000) described a case of CAGE with complete cortical blindness following inhalation of helium from an unregulated pressurised source. This patient remained blind 6 hours after the incident and had MRI changes initially called “patchy infarction” in the occipital lobes. After 4 hyperbaric oxygen treatments and a 48 hour
lignocaine infusion the patient had complete restoration of vision and almost complete regression of the lesions initially detected on MRI.

Although not directly relevant to brain protection, there are several recent clinical reports of lignocaine utilisation during cardiac surgery that are worthy of note. Perhaps not surprisingly, Lake et al. (1986) reported that lignocaine significantly reduced the number and energy of DC shocks during defibrillation after CABG surgery, and King et al. (1990) reported that lignocaine administration reduced the incidence of ventricular arrhythmias over the first post-operative day from 67% to 33%. More intriguing was a prospective myocardial protection study reported by Sunamori et al. (1982) in which patients undergoing CABG received a 24 hour infusion of either lignocaine or placebo beginning at initiation of anaesthesia. Compared to the controls, the lignocaine patients exhibited a smaller elevation of serum CK-MB and a significantly greater mean cardiac index and stroke volume at 24 hours post-operatively. The authors concluded that lignocaine appeared to ameliorate ischaemic changes in the myocardium during CABG. A similar study by Rinne and Kaukinen (1998) identified similar trends in a lignocaine treated group, but these trends did not reach statistical significance.

1.7.3 Mechanisms of cerebral protection by lignocaine

Not surprisingly, most attempts to explain neuroprotection by lignocaine have focussed on its sodium channel blocking properties. The physiological rationale for neuronal protection by sodium channel blockade has been thoroughly reviewed recently by Urenjak and Obrenovitch (1996). They propose that the advantages of sodium channel blockade in cerebral ischaemia include prevention of the direct and
indirect neurotoxicity arising from sustained influx of sodium into neurones, and the modification of neuronal energy metabolism. Other potential mechanisms of protection by lignocaine include modulation of white blood cell function (MacGregor et al. 1980) and advantageous haemodynamic effects (Shokunbi et al. 1990). These various protective mechanisms are discussed in turn below.

1.7.3.1 Sodium channel blockade 1: prevention of the direct and indirect neurotoxicity of sodium influx into neurones

The chain of events following ischaemic influx of sodium into neurones was broadly reviewed in section 1.5.6. The following issues are highlighted in view of their importance in the context of neuroprotection by sodium channel blockade. First, there is an intrinsic neurotoxicity associated with sustained sodium influx during ischaemia (Urenjak and Obrenovitch 1996), especially where anoxic depolarisation occurs (Ueda et al. 1992), and which is independent of any associated rise in intracellular calcium (Freidman and Haddad 1994). Second, indirect toxicity arises from an increase in intracellular calcium due to: reversal of the Na\(^+\)/Ca\(^{2+}\) exchanger (Blaustein 1988, Styss et al. 1992a); influx through voltage gated channels (Adam-Vizi and Ligeti 1986); influx through channels activated by glutamate released after pre-synaptic depolarisation (Nichols and Sihra 1986) or present because of reduced re-uptake by sodium driven exchangers (Szatkowski et al.1990); and release from intracellular stores (Zhang and Lipton 1995). Other indirectly toxic effects of intracellular sodium loading include: cellular oedema after influx of electrically obligated chloride and osmotically obligated water (Rothman 1985); and failure of cellular acid base regulation which depends in part on maintenance of the [Na\(^+\)]\(_o\)/[Na\(^+\)]\(_i\) ratio for operation of the Na\(^+\)/H\(^+\) exchanger (Aronsen 1985). The relative importance of these
various mechanisms may differ between grey matter where glutamate mediated toxicity seems important, and white matter where calcium influx via reversal of the Na\(^+\)-Ca\(^{2+}\) exchanger may be pivotal (Styss et al. 1991). Irrespective of the final pathway however, Urenjak and Obrenovitch (1996) conclude that prevention of anoxic depolarisation is “bound to be potentially cerebroprotective”, and they advocate sodium channel blockade as a rational means of achieving this end.

This stance is supported by experimental data. Delay or prevention of anoxic neuronal depolarisation by the “classical” sodium channel blocker tetrodotoxin has been demonstrated (Prenen et al. 1988, Xie et al. 1994). Moreover, neuroprotection by tetrodotoxin (Lysko et al. 1994), and other sodium channel blockers (Taft et al. 1989, Rataud et al. 1994, Smith and Meldrum 1995, Styss 1995, Wiard et al. 1995) has been demonstrated both in vivo and in vitro.

There is also considerable evidence that lignocaine administered prophylactically does delay sodium influx and anoxic depolarisation. Astrup et al. (1981a) and Lantos et al. (1990b) using dogs subjected to total circulatory arrest, showed that lignocaine administered prophylactically in extremely high doses (160mg kg\(^{-1}\) and 100mg kg\(^{-1}\) respectively) significantly decelerated the potassium efflux associated with anoxic depolarisation at normothermia. Astrup’s study also showed that the effect of lignocaine was additive to hypothermia (28 and 18\(^{\circ}\)).

These studies used unconventional doses of lignocaine, sufficient to abolish all EEG activity. Other groups, have tested the ability of clinically relevant doses to delay or prevent anoxic depolarisation. Ayad et al. (1994) administered lignocaine (0.2mg kg\(^{-1}\)
to rabbits undergoing 3 or 5 minutes of complete global ischaemia and found that the cortical negative potential reversal (reflecting anoxic depolarisation) was delayed by just over 3 minutes in each case. Fried et al. (1995) exposed rat hippocampal slices to lignocaine 10 µmol L\(^{-1}\), which corresponds to a plasma level in the low therapeutic range for clinical antiarrhythmic activity. This dose did not alter the pre-anoxic evoked population spike recorded from the CA1 pyramidal cell layer. However, it significantly reduced sodium influx and preserved intracellular ATP levels during 5 minutes of anoxia. Moreover, in the slices exposed to lignocaine, there was significantly improved recovery of the population spike measured 60 minutes after anoxia. It is notable that these outcome parameters were not further improved to a significant degree in slices exposed to 100 µmol L\(^{-1}\) lignocaine. Weber and Taylor (1994) exposed rat hippocampal slices to a 12 minute period of oxygen and glucose deprivation and recorded the proportion of slices undergoing anoxic depolarisation, the latency of anoxic depolarisation, and the proportion of slices in which the excitatory post synaptic potential (EPSP) recovered after anoxia. In addition, slices fixed 3.5 hours after anoxia were examined histologically to determine the percentage of morphologically intact pyramidal cell somata. Significantly fewer lignocaine treated slices exhibited anoxic depolarisation, and this event was significantly delayed in those that did. A significantly great proportion of lignocaine treated slices exhibited EPSP recovery, and pyramidal cell damage was significantly less. Most of these effects were dose dependent, but it is notable that both a significant delay of anoxic depolarisation and an increase in the proportion of slices recovering the EPSP were achieved with a perfusate lignocaine concentration of 2 µmol L\(^{-1}\) which did not alter the pre-anoxic EPSP. The same group subsequently published further (but similar)
data demonstrating protection by lignocaine during ischaemia in the same model without blockade of action potentials (Taylor et al. 1995).

In addition to delaying or preventing intracellular sodium loading and anoxic depolarisation, lignocaine has also been demonstrated both *in vivo* and *in vitro*, to ameliorate at least some of the associated secondary neurotoxic events.

Several studies have demonstrated that lignocaine delays and / or reduces release of excitatory amino acids during anoxia. Fujitani et al. (1994) showed that perfusion with a lignocaine solution during forebrain ischaemia delayed the rise in extracellular glutamate in the CA1 region of the gerbil hippocampus. The peak glutamate concentration was reduced by 79%. In addition, intracerebroventricular lignocaine significantly reduced pyramidal cell degeneration assessed 7 days after 4 minutes of ischaemia. The authors proposed that by inhibiting presynaptic depolarisation, lignocaine reduced glutamate release from synaptic vesicles, and that this effect explained the observed neuroprotection. Unfortunately, it is difficult to accurately interpret the lignocaine doses used in this study. Diaz et al. (1995) also demonstrated that lignocaine (17 µmol L⁻¹) markedly reduced release of an excitatory amino acid (aspartate) from rat striatal slices exposed to hypoxia *in vitro*. Probert et al. (1997) showed that lignocaine significantly delayed calcium influx and neuronal death in a dose dependent manner during a graded hypoxic / hypoglycaemic insult in rat neocortical cultures. Based on two observations: that lignocaine did *not* prevent calcium influx during *exogenous* administration of glutamate; and that pre-hypoxic administration tetrodotoxin (another sodium channel blocker) delayed the release of *endogenous* glutamate, they concluded that the observed protective effect of
lignocaine (and several other sodium channel blockers) may be due to inhibition of endogenous glutamate release. Zhang and Lipton (1999) also showed that lignocaine attenuated the rise in intracellular calcium during hippocampal ischaemia in vitro. They proposed that a reduction of sodium influx to the cell, and a consequent reduction of sodium dependent release of calcium from mitochondria was important.

Several other studies have demonstrated neuroprotection by lignocaine through prevention of other secondary consequences of sodium influx. Nagao et al. (1988) showed that lignocaine administered in clinically relevant doses reduced cerebral oedema during prolonged air exposure, a model known to produce progressive ischaemia, and both vasogenic and cytotoxic oedema (Prados et al. 1945). The authors attributed reduction in cortical cytotoxic oedema to a reduction in sodium influx across cell membranes. Lantos et al. (1996) showed that lignocaine administered in doses above the clinical range reduced the appearance of lipid peroxidation products 60 minutes after ischaemia induced by a 10 minute elevation of cerebro-spinal fluid pressure. Lipid peroxidation occurs in a number of processes initiated by cellular depolarisation and calcium influx (see section 1.5.6).

Thus, lignocaine administered prior to transient anoxia may delay or even prevent excessive intracellular sodium loading and neuronal depolarisation. Not surprisingly, this also prevents or ameliorates several of the secondary toxic events know to be consequent upon anoxic depolarisation. Importantly, these effects may be achieved with lignocaine doses low enough to preserve electrical function, implying that lignocaine interacts selectively with specific sodium channels or channel states during ischaemia to provide neuroprotection, while preserving function in non-ischaemic
areas (Urenjak and Obrenovitch 1996). It is possible that sodium channel blockade by lignocaine is enhanced in depolarising membranes because its action is use-dependant (Urenjak and Obrenovitch 1996). Alternatively, since the generation of action potentials depends in part on the ratio of sodium to potassium conductance, a concomitant partial blockade of both conductances by lignocaine might explain preservation of electrical activity (Styss et al. 1992b).

Of relevance to the above and following sections, it should be noted that Styss et al. (1992b) speculate that lignocaine, and the tertiary local anaesthetics in general, may not be the best suited sodium channel blocking agents for brain protection. This contention is based on the existence of sodium conductances that are both inactivating and non-inactivating after depolarisation (Stys et al. 1993). Lignocaine differentially blocks these conductances (Sugimori and Llinas 1980), being more effective at blocking inactivating channels, and less effective in preventing the continuous sodium leak which persists via non-inactivating channels. Styss et al. (1992b) propose that quaternary local anaesthetic derivatives which selectively block non-inactivating channels are potentially more effective agents and less likely to produce adverse effects. There are some in vitro data that do suggest superior protective effect by other sodium channel blockers when compared to lignocaine (Siniscalchi et al 1998).

1.7.3.2 Sodium channel blockade 2: alteration of cellular energy metabolism

In the context of brain protection, ischaemia is most appropriately regarded as an imbalance between energy supply and energy demand (Urenjak and Obrenovitch 1996). It follows that protection may be achieved not just by improving blood flow
(energy supply), but also by reducing cellular energy demand. Another useful construct is the separation of cerebral energy demand into that required for electrical and synaptic activity ("activation metabolism"), and that required for basal cellular processes that must continue, even after abolition of functional activity ("residual metabolism") (Michenfelder 1974). This is an important concept in the context of brain protection since residual metabolism corresponds to the energy necessary for preservation of non functional but still viable ischaemic brain regions (Urenjak and Obrenovitch 1996), such as the ischaemic penumbra of a focal infarction (Obrenovitch 1995).

Lignocaine administration may affect both residual and activation metabolism in a dose dependent manner. Early in vitro studies demonstrated that lignocaine in unconventionally high concentrations reduced the oxygen consumption of rat brain cortex (Geddes and Quastel 1956) and porcine brain mitochondria (Haschke and Fink 1975). Astrup et al. (1981b) administered lignocaine to dogs in a dose (160 mg kg\(^{-1}\)) sufficient to render the EEG isoelectric and recorded a reduction in both the cerebral metabolic rate for oxygen (CMRO\(_2\)) and glucose (CMR\(_{\text{gluc}}\)). This was attributed to the abolition of activation metabolism and was likened to a similar effect seen for pentobarbital. However, lignocaine administered after the EEG had already been rendered isoelectric by pentobarbital, caused a further reduction in both CMRO\(_2\) and CMR\(_{\text{gluc}}\). It is notable that the same phenomenon was not observed for pentobarbital when the drugs were administered in reverse order (Astrup et al 1981b).

This finding suggested that protection by barbiturates is derived from reduction of activation metabolism alone, and consequently, that barbiturates would not provide
protection in states such as complete global ischaemia where electrical activity is quickly abolished (Mrsulja et al 1984). In contrast, lignocaine appeared to depress both activation and residual metabolism. Astrup et al. (1981b) attributed reduction in residual metabolism by lignocaine to sodium channel blockade, reduced sodium leakage, and the consequently reduced need for ion pumping to maintain ion gradients. This seemed plausible since the same group had also demonstrated that 40 to 50% of basal energy requirements was expended on maintenance of ion gradients across the cell membrane (Astrup et al. 1981c).

Despite these promising findings, it remains unclear whether clinically useful depression of neuronal metabolism can be achieved with safe doses of lignocaine or any other sodium channel blocker. However, it is notable that Sakabe et al. (1974) administered lignocaine (3 mg kg\(^{-1}\)) to dogs and recorded a significant (10%) reduction in CMRO\(_2\) from baseline when plasma levels were well within the clinical therapeutic range (12 \(\mu\)mol L\(^{-1}\)). The decline in CMRO\(_2\) was dose dependent, increasing to 27% at the supra-therapeutic plasma concentration of 88 \(\mu\)mol L\(^{-1}\) (15 mg kg\(^{-1}\) lignocaine).

Sakabe et al (1974) also demonstrated that the lignocaine dose - CMRO\(_2\) response profile was complex. At doses high enough to induce seizures in their dogs (27 mg kg\(^{-1}\)) the CMRO\(_2\) was significantly increased from baseline. Another group has subsequently demonstrated selective activation of hippocampal neurones at pre-epileptogenic doses of lignocaine (Tommasino et al. 1986). It follows that pre-
epileptogenic and seizure-inducing doses of lignocaine should be avoided in any protocol designed to utilise lignocaine for clinical cerebral protection.

1.7.3.3 Modulation of leukocyte activity and other rheological effects

Leukocytes may accumulate in the microcirculation of reperfused ischaemic tissue (Schmid-Schonbein 1987) especially where endothelium has been damaged by the passage of emboli (Dutka et al. 1989, Helps and Gorman 1991). This can cause a secondary reduction in blood flow (Dutka et al. 1989, Helps and Gorman 1991), and tissue damage through the release of inflammatory mediators (Mullane et al. 1988). These processes have been suggested as potential contributors to brain injury during cardiac surgery (Royston 1989), and there is substantial evidence that they may be favourably modified by lignocaine.

Stimulated leukocytes exposed to lignocaine in concentrations higher than conventional antiarrhythmic plasma levels exhibit decreased superoxide release (Hoidal et al. 1979, Peck et al. 1985), oxygen consumption (Hoidal et al. 1979), lysosomal enzyme release (Goldstein et al. 1977), chemiluminescence (Peck et al. 1985, Hyvonen and Kowolik 1998), and bacterial killing (Peck et al. 1985) in vitro, and reduced leukocyte adhesion to venular endothelium in vivo (Giddon and Lindhe 1972). Of particular interest are the findings of Luostarinen et al. (1981) who exposed an everted hamster cheek pouch to standard laser induced injury and observed the rheological effects of topical saline, lignocaine, and other local anaesthetics on the injured microvasculature. When applied at the time of the injury, lignocaine prevented the irreversible thrombus formation that occurred in all control preparations. In
particular, leukocyte – endothelium binding was markedly reduced in the treatment
group preparations. When applied 15 minutes after injury, by which time thrombus
had inevitably formed, lignocaine restored flow in 5 of 6 trials. During this
restoration, leukocytes were observed to disadhere from each other and from the
endothelium. Tocainide and bupivacaine did not have a similar effect.

All of these investigations involved exposure to lignocaine at greater than
conventional antiarrhythmic concentrations, although the actual concentration (after
diffusion) to which the leukocytes were exposed in the experiment by Luostarinen et
al. (1981) is unknown. The relevance of these observations to clinical applications is
therefore in doubt. However, in a complex series of in vitro, in vivo and clinical
experiments using lignocaine in conventional concentrations, MacGregor et al. (1980)
reported reduced leukocyte adherence, reduced inflammation and reduced migration
of leukocytes into inflammatory exudate. Lignocaine was found to be a more effective
inhibitor of leukocyte migration than methylprednisolone, a result the authors
described as “surprising”. In another clinically relevant experiment, Peck et al. (1985)
recorded reduced superoxide anion release from human leukocytes exposed in vivo to
plasma concentrations of lignocaine 4 – 20 μmol L⁻¹ for a least 12 hours. Recently,
Nishina et al. (1998) showed that conventional doses of lignocaine, administered
either prior to or 10 minutes after installation of hydrochloric acid into rabbit lungs,
significantly reduced sequestration of neutrophils in the lungs and accumulation of
cytokines and albumin in lavage fluid, and significantly enhanced recovery of PaO₂.
The mechanism by which lignocaine modulates leukocyte activity is not clear. It may involve alteration of cytoskeletal function (Nicholson et al. 1976, MacGregor et al. 1980), or inhibition of stimulus response coupling at the leukocyte cell membrane (Goldstein et al. 1977, Tomoda et al. 1990). Irrespective of the basis for its modulation of leukocyte activity, these studies suggest that lignocaine may provide cerebral protection by reducing leukocyte adherence to damaged endothelium, migration into areas of ischaemic damage; and elaboration of cytotoxic substances.

1.7.3.4 Modulation of haemodynamic parameters


The mechanism for these effects is not certain (Evans et al. 1987). Lignocaine does reduce the release of catecholamines after brain injury (Evans et al. 1980). This may explain its intracranial hypotensive effect when administered intravenously during endotracheal suctioning (Donegan and Bedford 1980), endotrachial intubation (Hamill et al. 1981), and craniotomy (Bedford et al. 1980). In addition, lignocaine has vasomotor effects, but its dose – response profile in the healthy circulation is
complex. Both vasoconstrictive and vasodilatory effects have been observed depending on the dose of lignocaine used and the vascular bed being studied (Johns et al. 1985). Finally, favourable effects on the cerebral circulation after injury may result from a protective effect on cerebral blood vessels (Evans et al. 1987). One obvious mechanism for this is the modulation of leukocyte activity discussed in section 1.7.3.3. It is notable that although there is little data describing the effect of lignocaine in unconventionally high doses on postischaemic cerebral haemodynamics, such doses appear to cause hypotension and reduce cerebral blood flow in the healthy brain (Sakabe et al. 1974, Shokunbi et al. 1986). Thus, unconventionally high doses of lignocaine may haemodynamically disadvantage the injured brain.

1.7.3.5 The multiple mechanism hypothesis

It is likely that lignocaine mediates brain protection through a combination of the processes described in sections 1.7.3.1 - 3. A strong argument can certainly be made for amelioration of the intrinsic and secondary toxicity of sodium influx as an important component of any cerebral protection by lignocaine given prophylactically. This mechanism was well-established in in vitro studies (see section 1.7.3.1) where modulation of either leukocyte activity or haemodynamic effects was irrelevant. In addition, several in vivo studies (Nagao et al. 1988, Rasool et al. 1990) showed protection of neuroelectrical function before any haemodynamic effect became significant. This suggested another concurrent protective process. However, in view of the demonstrable importance of leukocyte activation in embolic brain injury in vivo (Dutka et al. 1989, Helps and Gorman 1991), the clearly demonstrated anti-
inflammatory properties of lignocaine may also be important, especially when lignocaine is given after the injurious event.

Given the "biphasic" pattern of injury by CAGE (Helps and Gorman 1991) lignocaine may be an "ideal" protective agent in this particular injury: first by establishing sodium channel blockade during transient vessel occlusion; and second, by ameliorating the subsequent inflammatory changes after bubbles redistribute. In view of this potentially multi-mechanistic mode of action, caution is necessary in interpreting predictions of the relative neuroprotective efficacy of sodium channel blockers (Styss et al. 1992b) based solely on in vitro experimentation.

1.7.4 Optimising cerebral protection by lignocaine

The data presented in the foregoing sections suggest a neuroprotective role for lignocaine. However, protection was not afforded in all models and factors that may influence the neuroprotective efficacy of lignocaine deserve attention. These include: the nature and severity of the injury; the dose and pattern of lignocaine administration; and the timing of lignocaine administration with respect to the injury.

The relevance of the nature and severity of the injury model to the neuroprotective efficacy of lignocaine has been emphasised by several authors (Shokunbi et al. 1986, 1990, McDermott et al. 1990). It is notable that lignocaine has been effective in all experiments using cerebral arterial gas embolism, a model known to cause transient cerebral ischaemia (Helps et al. 1990). There were variable results in experiments
involving focal and global ischaemia (Table 1.6). The two *in vivo* experiments demonstrating no benefit (Table 1.6) utilised a relatively severe ischaemic model. It appears that lignocaine is most effective in transient and/or incomplete ischaemia, and that its protective effect is overwhelmed if ischaemia is either severe or prolonged (Gelb et al. 1988). These observations might be of particular relevance to cardiac surgery where NP deficits may be the clinical correlate of a milder injury that is amenable to pharmacological amelioration.

Both *in vivo* studies that demonstrated no protection by lignocaine utilised doses considerably larger than conventional antiarrhythmic regimens. In contrast, all studies (except one) demonstrating protection, and where the dosing regimen could be interpreted, utilised conventional doses (Table 1.6). Although this may be coincidental, higher doses of lignocaine have been observed to selectively activate hippocampal neurones and increase metabolic stress (Munson et al. 1975, Ingvar and Shapiro 1981), and this may predispose to ischaemic injury (McDermott et al. 1990). Moreover, the previously mentioned observation of reduced cerebral blood flow during administration of unconventionally high doses of lignocaine (Sakabe et al. 1974, Shokunbi et al. 1986) is also suggestive of disadvantage from such regimens. Each of lignocaine’s potentially protective mechanisms has been observed *in vivo* and/or *in vitro* at conventional concentrations for clinical antiarrhythmic activity (sections 1.7.3.1 – 3). Considered together, these observations suggest that the ideal neuroprotective lignocaine concentration conveniently falls within the clinical reference range.
The pattern of lignocaine administration, that is, bolus versus bolus plus infusion, may be an important determinant of neuroprotective efficacy (Gelb et al. 1988). Maturation of an ischaemic lesion, and particularly an ischaemia – reperfusion injury, will take place over many hours, and will involve activation of leukocytes (Mullane et al. 1988) whose activities may be influenced by lignocaine (Section 1.7.3.3). It follows that for optimal neuroprotection, lignocaine may need to be present in adequate concentrations for some time (Gelb et al. 1988). Since plasma lignocaine levels decline rapidly after a single bolus, a sustained infusion may be necessary. In this context, those in vivo studies in which lignocaine was administered as a single bolus prior to cerebral ischaemia and which sought histological protection after a prolonged maturation period (Warner et al. 1988, Sutherland et al. 1989), should perhaps be considered methodologically flawed.

Finally, although the DCI cases reported by Drewry and Gorman (1992) and Cogar (1997) appeared to benefit after delayed administration of lignocaine, no experimental studies have addressed the effect of significant delay in its administration after ischaemic brain injury. In all in vivo studies cited here (Table 1.6), lignocaine was administered either prophylactically or within 15 minutes of the onset of ischaemia. If sodium channel blockade and prevention of hypoxic depolarisation are considered important goals, then protection would require administration of lignocaine either prior to or immediately after onset of ischaemia. Equally, it seems justified to suggest that protection by modulation of leukocyte activity may still be afforded by delayed administration, and there is at least some in vitro data to support this view.
(Luostarinen et al. 1981). However, there is no indication of maximum administration delay before a protective effect would decline or be absent altogether.

1.8 SUMMARY AND HYPOTHESIS

1.8.1 Summary

The key elements of this review as they pertain to the research subsequently reported in this thesis are:

1. Prospective studies show that up to 79% of cardiac surgery patients suffer early post-operative NP deficits, and these persist beyond 4 months in up to 47%.

2. The incidence of post-operative NP deficits has been positively correlated against peri-operative exposure to cerebral emboli and perioperative cerebral ischaemia.

3. Lignocaine administered prophylactically confers cerebral protection in animal models of embolic brain injury, focal ischaemia, and global ischaemia.

1.8.2 Hypothesis

Lignocaine administered in a conventional bolus plus infusion regimen, beginning on induction of anaesthesia and continuing for a period of 48 hours, may reduce the incidence of NP deficit in patients undergoing CPB and valve replacement surgery.
CHAPTER 2

DEVELOPMENT OF EMBOLI COUNTING
2.1 INTRODUCTION

In view of the prevailing belief that embolism of the cerebral circulation is the most likely cause of neurological injury during cardiac surgery (Treasure 1989), any randomised study of a protective strategy should control for the number of emboli to which patients in the various treatment groups are exposed. This has become possible over the last decade as emboli detection has been achieved in several medical disciplines using Doppler ultrasound (Markus and Harrison 1995). Flow through blood vessels is detectable because of the velocity dependent change in frequency that occurs when ultrasound is reflected from an object moving toward or away from the ultrasound source; the so-called “Doppler effect”. Emboli are either larger and/or composed of a different material with different acoustic impedance compared to the red blood cells (Markus and Harrison 1995). The ultrasound signal is thus reflected and scattered differently at the interface between the embolus and blood, and this results in a brief signal of high intensity. Bubbles are particularly effective at scattering ultrasound and are more easily detected than solid emboli of similar size (Moehring and Klepper 1994).

There are various strategies for quantifying the high intensity Doppler signals generated by emboli moving in blood. These can be broadly classified into operator dependent counting or grading systems (Sawatzky and Nishi 1991, van der Linden and Casimir-Ahn 1991), and automated counting systems (Abts et al. 1978, Padayachee et al. 1987b, Sellman et al. 1990). In addition to counting emboli, there has been much interest in distinguishing between emboli of different composition (solid versus gaseous for example), and in determining embolus size. Both aims are
achievable in theory (Moehring and Klepper 1994). However, no device is readily available that automatically distinguishes emboli material (Stump et al. 1996) and despite some claims to the contrary (Hatteland and Semb 1985), accurate assessment of emboli size on the basis of the high intensity signals has proved difficult (Pugsley 1989).

A method for quantifying emboli was required for this study. A Rimed Flowlink 300 colour flow Doppler device (Rimed, Tel Aviv, Israel), which was designed for performing vascular investigations was available. Several "trial runs" in which the device was used to monitor flow through the RCCA during cardiac surgical procedures confirmed that it was capable of detecting Doppler-shifted signals typical of emboli. However, it had no in-built emboli counting capability and only limited capacity for recording the Doppler spectrum for later analysis. It was thus decided that a counting device should be interfaced to this Doppler to count emboli during the surgical procedures.

Dr Douglas Blomfield, a Biomedical Engineer, Auckland Healthcare designed and built this device with the author acting in a consultative role. The author conducted all testing and calibration.
2.2 METHODS

2.2.1 Configuration and design of the emboli counter

The Rimed Flowlink 300 Doppler was interfaced to a purpose built analogue signal processor and an 80C552 digital micro-controller (Mandeno Granville, Auckland, New Zealand) which quantified the signals. The Doppler was operated in the 2 MHz pulsed wave mode. The signal processor high-pass filtered the Doppler shifted flow signal to remove frequency components less than 500 Hz (which are predominantly due to either artefact or normal blood flow), before rectifying, amplifying, and splitting the signal into two paths: the first rectified signal was averaged with a time constant of four seconds; and the second signal was high-pass filtered again and passed through a variable attenuator. The two signals, representing the average Doppler signal amplitude and the instantaneous signal amplitude of higher frequencies respectively, were then compared. Each time emboli passing through the ultrasound beam caused the attenuated instantaneous signal to exceed the average, an output pulse 10 ms wide was generated and the comparator triggered a digital counter. During the 10 ms following this triggering, no further detection took place; however, if the instantaneous signal still exceeded the average after 10 ms, a further 10 ms output pulse was generated and the counter was activated again. The primary determinant of the “count” was therefore the number of emboli passing through the Doppler gate. However, the count was also potentially influenced by the size of emboli (since larger emboli produce a high intensity signal of greater duration), and by and the blood flow rate in the blood vessel or bypass tubing (since a slow moving embolus would remain within the Doppler “gate” for longer) (Furness and Wright 1985). It follows that while the raw Doppler “count” is cited in this work, it is
recognised that the “count” is perhaps best viewed as an “index of microembolic activity” in recognition of the ways in which such “counts” can be confounded.

In use, the colour flow display and audible flow signal were used to optimise the position of the Doppler probe over the RCCA (clinical cases) or CPB circuit tubing (in vitro experiments). The probe was continuously hand held during clinical monitoring, and a purpose built mounting bracket was manufactured for in vitro experiments. Once a flow signal was established in either context, the variable attenuator was set so that the comparator did not trigger the counter under normal flow conditions. Further attenuator adjustment was made so that the counter was incremented only when the characteristic harmonic chirps and pops of emboli (Spencer et al. 1990) were heard, and the characteristic disturbance of the colour flow display was seen (see Figure 2.1). This latter adjustment was facilitated by a diode that flashed each time the counter was incremented. Even when large numbers of emboli were being detected, the operator could readily confirm that the diode was flashing in synchrony with audible signals. Disturbances of the flow signal arising from artefactual sources such as probe movement were distinguishable from emboli signals by the circumstances and the sound of the signal. A control device allowed the Doppler operator to remove the data recorded over the previous five seconds if an artefactual signal caused the counter to increment.

2.2.2 Calibration of the Rimed Doppler emboli counter

The technique of Stump et al. (1991) was utilised to assess the response of the emboli counter after introduction of known numbers of microspheres to an in vitro circuit. A
Figure 2.1  Typical colour flow Doppler displays during monitoring of an \textit{in vitro} circuit.

A. Normal flow with no emboli

B. Three signal disturbances typical of emboli
C. Multiple signal disturbances typical of emboli
closed loop circuit (Figure 2.2) was constructed using a roller pump on the Stockert S3 CPB machine (Stockert Instrumente, Munich, Germany) and a 2.5 metre loop of PVC circuit conduit (Baxter Healthcare Corporation, Irvine, California, USA). The circuit included a Bentley AF1040D 40 μm screen arterial filter (Baxter Healthcare Corporation, Irvine, California, USA) in a short diversion loop. Following a CO₂ flush, the circuit was primed with date expired whole blood and Plasmalyte 148, and recirculated at 2.0 L min⁻¹. The loop containing the filter was clamped off after priming and a short period of recirculation. The circuit blood volume was 150 ml with the filter clamped off and 250 ml and with the filter loop open. Using a purpose built clamp (Figure 2.3), the Doppler probe was mounted on the circuit tubing at 45° to the direction of flow, and the air space between the probe head and tubing was filled with ultrasonic gel. The Doppler beam depth was set at 27 mm, machine power at 40%, and gain at level 6.

Five emboli counts were made over one minute after each of the following circuit manipulations:

a. normal recirculation; then

b. after stopping and restarting flow in the circuit with no additions; then

c. after stopping flow to add 40 μL of a 0.05% tween 80 surfactant / distilled water solution; then

d. after addition of 20 polystyrene microspheres of 200 μm diameter (E-Z Trac, Los Angeles, California, USA) suspended in 40 μL of surfactant solution; then

e. after addition of another 20 microspheres; then

f. after addition of another 20 microspheres; then
Figure 2.2  *In vitro* circuit configuration for the Doppler counter calibration.
Figure 2.3  Device for mounting the Doppler probe on the \textit{in vitro} circuit tubing
g. after routing the circuit through the filter loop.

2.2.3 Comparison against another Doppler counting device

The emboli "counts" obtained using the adapted Rimed Doppler were compared with those of a commercially available device that is commonly used for this type of investigation. A clinical circuit containing a Medtronic Maxima (Medtronic Inc, Anaheim, CA, USA) top entry hard shell venous reservoir (HSVR) was salvaged and operated in vitro under conditions in which the reservoir was known to generate gaseous microemboli (see Chapter 6). The circuit, in venous to arterial sequence, consisted of the HSVR, a roller pump on the Stockert S3 heart-lung machine (Stockert Instrumente, Munich, Germany), the Medtronic Maxima hollow fibre membrane oxygenator (Medtronic Inc, Anaheim, CA, USA) and a Bentley AF1040D 40 μm screen arterial filter (Baxter Healthcare Corporation, Irvine, California, USA) (see Figure 6.3). At termination of clinical CPB, the primed circuit was carefully preserved. The venous and arterial cannulae were plumbed into the shell of a Bentley Ben 10 bubble oxygenator (Baxter Healthcare Corporation, Irvine, California, USA) which was used to simulate a patient. The circuit volume was restored with date expired resuspended red cells and plasmalyte 148. During recirculation, the HSVR volume was regulated by fine adjustment of a venous line occluder (Stockert Instrumente, Munich, Germany).

The prime was recirculated at a constant rate of 3.5 L min⁻¹ and the circuit was simultaneously monitored for emboli downstream of the reservoir with both the Rimed Doppler and a Hatteland CMD-10 Cardiovascular Bubble Detector (Hatteland Instrumentering, Royken, Norway). The Hatteland Doppler was configured for
continuous detection at high resolution, with attenuation set at 0 dB, depth at 2.2 cm, and detection sensitivity at level 2. These settings gave the best correlation between audible emboli signals and count. The reservoir blood volume was set initially at 1000 ml; a volume at which bubble generation had previously been shown to be absent. A baseline count was recorded over 150 seconds. The reservoir volume was then lowered in 100 ml decrements and the count was recorded over 150 seconds at each new volume using both Doppler devices. This sequence was repeated 3 times in each of 2 separate circuits, a total of 6 repetitions. An unpaired t-test was used to compare the mean counts derived by each device at each reservoir blood volume.
2.3 RESULTS

2.3.1 Calibration of the Rimed Doppler emboli counter

The count recorded during each of the 5 one minute periods after each of the circuit manipulations is shown in Table 2.1. The mean count over the five recordings after each circuit manipulation is plotted in Figure 2.4.

Table 2.1. Emboli count over five consecutive 1 minute periods in each of 7 sequential conditions during the calibration experiment.

<table>
<thead>
<tr>
<th>Event</th>
<th>Minutes</th>
<th>Baseline</th>
<th>Stop/start</th>
<th>Add surfactant</th>
<th>Add 20 spheres</th>
<th>Add 20 spheres</th>
<th>Add 20 spheres</th>
<th>Open to filter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>83</td>
<td>62</td>
<td>47</td>
<td>128</td>
<td>175</td>
<td>210</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>61</td>
<td>73</td>
<td>59</td>
<td>113</td>
<td>160</td>
<td>228</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>55</td>
<td>64</td>
<td>78</td>
<td>132</td>
<td>175</td>
<td>223</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>74</td>
<td>60</td>
<td>71</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>57</td>
<td>54</td>
<td>63</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>72</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>66.0 ±</td>
<td>62.6 ±</td>
<td>63.6 ±</td>
<td>127.0 ±</td>
<td>159.2 ±</td>
<td>204.6 ±</td>
<td>73 ±</td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>5.4</td>
<td>3.1</td>
<td>5.3</td>
<td>5.8</td>
<td>5.0</td>
<td>5.4</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

No changes in the mean count per minute were seen as a result of circuit manipulations prior to the addition of spheres. The sequential addition of three aliquots of 20 spheres caused an increase in emboli numbers that was similar for each addition (increases in mean count per minute of 60.7, 45.7, and 50.3 respectively).

However, it was noted that there was a consistent decrease in count of 15 - 20 min\(^{-1}\) between the third and fifth minutes after sphere addition. This was interpreted as being due to sequestration of spheres somewhere in the circuit and consequently only the counts for the first three minutes following the addition of spheres were
considered for calibration purposes. Diverting the circuit through the 40 μm filter, after the cumulative addition of 60 spheres, returned the mean count min⁻¹ to baseline levels.

2.3.2 Comparison against another Doppler counting device

The mean count (± SEM) obtained from the two Dopplers over the range of reservoir blood volumes is plotted in Figure 2.5. Both devices showed similar trends in emboli counts, but counts by the Hatteland device were significantly lower at 600 and 500 ml (p < 0.01). The ratio of the mean count at each volume (Rimed : Hatteland) varied from 5.0 for the low counts at 800 ml, to 1.8 for the higher counts at 500 ml (mean 3.5).
Figure 2.4  Mean emboli count per minute after each alteration to the circuit during the calibration experiment.

Figure 2.5  Mean (± SEM) count recorded over 150 seconds by the Rimed and Hatteland Doppler devices downstream of the reservoir as reservoir blood volume was decreased.
2.4. DISCUSSION

The counter responded in an almost linear fashion to the sequential addition of identical aliquots of spheres to the in vitro circuit. This demonstrated that an increase in the “count” indicated an approximately proportional increase in emboli numbers. However, given the circuit volume (with the filter clamped off) of 150 ml and the pump flow rate of 2000 ml min$^{-1}$, and assuming that the spheres remained suspended in solution and circulated at the same velocity as the blood, the expected increase in emboli count for every 20 spheres added was approximately 266 min$^{-1}$. It follows that the recording device probably underestimated the circulating emboli, perhaps because solid spheres can be expected to produce a weaker perturbation in the Doppler-shifted signal than bubbles (Moehring and Klepper 1994).

These results illustrate how accurate counting of emboli in moving blood can be confounded (Butler and Kurusz 1990) and it is not argued here that the “count” is anything other than an “index of microembolic activity”. Nevertheless, for the purposes of this thesis, the data provided by the Doppler device is referred to as a “count”.

Simultaneous monitoring of a circuit with the Rimed and Hatteland Dopplers showed that although the absolute counts differed (see below), both devices detected near identical trends in emboli activity at the same reservoir volumes. The concordance between these devices with respect to the reservoir blood volumes at which bubbles formed (see Chapter 6) was reassuring, as it was known that studies of the same
phenomenon using different Doppler devices could produce markedly different results (Butler and Kurusz 1990).

Although both devices were configured so that the counters were responding only to audible signals typical of emboli, the Rimed Doppler count was consistently higher because it detected bubbles, unmistakable from the audible signal and colour flow output, which were not audibly detected by the Hatteland Doppler. The Rimed Doppler appears to be the more sensitive of the two units. Greater sensitivity might be considered disadvantageous because, for example, clinically insignificant bubbles may be counted. However, the size at which bubbles become "insignificant" has not been determined. Bubbles as small as 10 – 20 μm diameter have been shown to disrupt the blood brain barrier (Hills and James 1991).

It was concluded that the Rimed Doppler configured as described above, provided a "count" proportional to the number of circulating emboli. This subsequently enabled comparison of peri-operative emboli exposure between the clinical study groups in the lignocaine trial (see Chapter 3) and the "deairing" study (see Chapter 5). In addition, this emboli monitoring capability allowed a study of the temporal distribution of emboli throughout surgery (see Chapter 4) and comparison of emboli generation by various CPB circuit components and techniques (see Chapter 6).
CHAPTER 3

RANDOMISED TRIAL OF LIGNOCAINE IN BRAIN PROTECTION DURING LEFT HEART VALVE SURGERY
3.1 INTRODUCTION

Prior to the present study, cerebral protection by lignocaine had never been investigated in humans. Early in vivo studies were conducted by researchers whose primary interest was CAGE in compressed gas diving (Evans et al. 1984, 1989; Dutka et al. 1992), and lignocaine has repeatedly been mentioned as a potential pharmacological adjunct to recompression in this context (Moon and Gorman 1993). Indeed, lignocaine has been administered in the treatment of DCI (Drewry and Gorman 1992, Cogar 1997) and arterial gas embolism (Mitchell et al. 2000) with apparently good results.

The early intent of this project was to conduct the first prospective controlled trial of lignocaine in the treatment of DCI. However, the marked variability between divers in presentation latency and severity of disease (Gardner et al. 1996) makes comparison of outcomes between individuals and groups very difficult. Moreover, multiple pathological processes may contribute to DCI, including venous gas embolism, arterial gas embolism, and formation of bubbles in the tissues themselves (Francis and Gorman 1993). It is often not possible to determine which of these is the primary event in any case of DCI (Francis and Smith 1991) and this further complicates appropriate stratification into study groups.

Since cardiac surgery patients suffer NP deficits due to embolic brain injury (see section 1.5.3.5), this population was considered as an alternative study group. The use of cardiac surgery patients for this study was considered to confer several advantages over divers with DCI. First, premorbid neurocognitive function could be assessed so
that each of the patients could serve as their own control. Second, the exposure to various injurious events such as emboli and hypotension could be quantified and controlled in analysis of results. Third, the lignocaine could be given prophylactically and at a standard time in relation to the surgery. For these reasons, there seemed a better prospect of demonstrating any protective properties in this population. In addition, both cardiac surgery patients and compressed gas divers suffer neurological injury by CAGE, and hence there is cross-relevance between the two groups.

This chapter reports a randomised, prospective, double blind trial of lignocaine versus placebo in prevention of NP deficits arising from left heart valve surgery. The trial protocol was generated in 1994 and received ethics committee approval (North Health Ethics Committees) in the same year. Patient recruitment began in 1995 and was completed in 1997.
3.2 METHODS

3.2.1 Subjects

Sixty-five patients scheduled for left heart valve surgery gave written informed consent for participation in the study. The consent process in all cases included a verbal explanation of the study by the author and a written patient information leaflet. The exclusion criteria were as follows: age outside the 20 - 70 year range; any current neurological disorder; a first or most commonly used language other than English; residence outside the greater Auckland area; and, any past history of adverse reactions to lignocaine. It is notable that true type I hypersensitivity to lignocaine is very rare (Ball 1999). Only one patient refused to take part in the study when initially invited.

3.2.2 Neuropsychological testing

All consenting patients underwent pre-operative NP testing on the day prior to surgery. The test battery was selected on the basis of demonstrated efficacy in similar subject populations and negligible training effect; and is listed in Table 3.1. Six tests (Lezak 1995) comprising 11 sub-scales were chosen to measure cognitive performance. A self-rating inventory with 2 sub-scales for memory function was chosen to identify changes in memory that were noticed by the patients themselves (Crook and Larrabee 1990). The inclusion of a self-rating assessment of memory was considered important as cardiac surgery patients often complain of post-operative memory impairment. Any amelioration of this problem by lignocaine which was obvious to the patients themselves would imply clinically relevant cerebral protection. Spouses were also asked to rate the patient’s memory using this inventory. Inventories which assess depression and anxiety (two sub-scales) (Lezak 1995) were
Table 3.1  Tests and sub-scales of the NP test battery.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sub-scales</th>
<th>Modality interrogated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rey figure</td>
<td>Copy, Recall</td>
<td>Visuo-spatial memory</td>
</tr>
<tr>
<td>Inspection time</td>
<td>Traditional, Dynamic</td>
<td>Information processing speed</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Task (AVLT)</td>
<td>Trials 1 - 5, Distract list, Recall trial</td>
<td>Verbal learning, Verbal memory</td>
</tr>
<tr>
<td>Symbol - Digit Modality Test (SDMT)</td>
<td>Oral, Written</td>
<td>Complex scanning and visual tracking, manual agility</td>
</tr>
<tr>
<td>Trails A</td>
<td>nil</td>
<td>Attention and spatial perception</td>
</tr>
<tr>
<td>Trails B</td>
<td>nil</td>
<td>Sustained attention, spatial perception, visuomotor tracking</td>
</tr>
<tr>
<td><strong>Self rating inventory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory Assessment Clinic Self Rating Test (MAC - S)</td>
<td>How good at?, How often do?</td>
<td>Memory</td>
</tr>
<tr>
<td><strong>Control tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck depression</td>
<td>nil</td>
<td>Depression</td>
</tr>
<tr>
<td>State - Trait Anxiety Inventory (STAI)</td>
<td>State, Trait</td>
<td>State anxiety, Trait anxiety</td>
</tr>
</tbody>
</table>
also used because pre-operative levels of both states are strongly predictive of emotional distress after surgery (Vingerhoets 1998) and distress states may influence NP test performance (Lezak 1995). All tests were repeated at 10 days, 10 weeks, and 6 months after surgery, except the memory inventory, which was only repeated at 10 weeks and 6 months. Parallel forms of the Rey Auditory - Verbal Learning Task (AVLT) and Rey Figure test (Lezak 1995) were used in sequential testing to minimise any practice effect.

The same psychologist conducted all NP testing. Where possible, testing in the hospital was conducted in the same office but some patients did require testing in their ward beds. All pre-operative tests were completed in the hospital. Some of the 10 day post-operative tests were performed in the hospital, and others in the patient’s homes, depending on the duration of admission. All of the 10 week and 6 month post-operative tests were performed in the patients’ homes.

A significant reduction in performance was considered to exist in any of the post-operative cognitive performance tests if the patient scored at least one standard deviation (of the pre-operative population mean for that test) below their pre-operative score (Newman 1995). In addition, each patient’s pre-operative scores were normalised to 100 and percentage changes from baseline on sequential testing were either added to or subtracted from 100 depending on the direction of any change.

3.2.3 Trial medication administration

Patients were block randomised by surgeon to receive lignocaine or placebo, so that each of the 5 surgeons operated on the same number of patients in each group. Thus
for each surgeon, a series of coded vials (sequentially numbered sets of five) were prepared, half the sets containing lignocaine and half containing placebo. The patients were allocated the next set of vials in the surgeon’s series, in the order in which they underwent surgery. A medical officer who had no other role in the trial generated the code number to treatment allocations.

The trial solutions were repackaged by a pharmaceutical laboratory into coded vials (Figure 3.1). Each vial contained either lignocaine hydrochloride (1000 mg in 20 ml) or 20 ml of dextrose 5% (the placebo solution). The lignocaine and placebo solutions were indistinguishable by appearance, and 5% dextrose was chosen as the placebo to replicate the mixing phenomena seen when lignocaine is diluted in 0.9% sodium chloride solution. A set of five vials was prepared for each patient, thus ensuring sufficient lignocaine or placebo solution to maintain a 48 hour infusion.

The trial infusion was prepared by diluting the contents of one vial to a total volume of 50 ml using 0.9% sodium chloride. The 50 ml syringe was then mounted in an appropriate precision infusion pump. The infusion was begun at induction of anaesthesia and continued for a standard period of 48 hours. The infusion protocol was based on that described by Landow and Wilson (1991) who advocated a higher infusion rate over the first hour than the 2 mg min⁻¹ often recommended in “conventional” regimens. Their earlier work in cardiac surgical patients (Landow et al. 1990) had shown that the lower rate often resulted in sub-therapeutic levels in the first 2 hours of the infusion. Since maximal emboli exposure was likely to occur within this period in our patients, it was considered particularly important to establish and maintain a therapeutic lignocaine level from early in the infusion. Patients who were
Figure 3.1  Coded vial for trial infusion solutions
randomised to the lignocaine group received a 1 mg kg\(^{-1}\) “bolus” over 5 minutes, followed by 240 mg over the first hour and 120 mg over the second hour and then 60 mg hr\(^{-1}\) thereafter. The target plasma concentration (6 - 12 \(\mu\)mol L\(^{-1}\)) was selected on the basis of successful \textit{in vivo} (Evans et al. 1989, Shokunbi et al. 1990) and \textit{in vitro} (Fried et al. 1995) trials of lignocaine in brain injury.

Blood specimens for lignocaine assay were taken to coincide with aortic cannulation and aortic declamping, and at 8 and 24 hours after starting the infusion. The two peri-operative specimens were timed to coincide with surgical events previously reported to expose the patient to emboli. It was reasoned that should any protective effect for lignocaine be apparent, then the plasma levels achieved during the periods of maximal emboli exposure should be known. Since lignocaine pharmacokinetics are altered during (Morrell and Harrison 1983) and after CPB (Holley et al. 1984), the two post-operative specimens were taken to allow adjustment of the infusion and maintenance of plasma lignocaine levels within the target range. Infusion adjustments were based on the author’s clinical judgement. To preserve double blinding, the laboratory was provided with the unblinding codes. Specimens from patients receiving lignocaine were processed and the results reported in the standard fashion. Specimens from patients receiving the placebo were discarded and a sham result was reported. Sham results were supplied to the laboratory in advance of the trial and were designed to make pharmacological sense. For example, an 8 hour sham result higher than the reference range was followed by a lower 24 hour sham result in the expectation that the infusion rate would have been decreased.
3.2.4 Anaesthesia and surgery

Patients were premedicated with a benzodiazepine (usually midazolam), an H2 receptor antagonist (usually famotidine), and, in most cases, droperidol. Anaesthesia in all cases was based on moderate doses of fentanyl (10 - 50 μg kg⁻¹) and a non-depolarising muscle relaxant, supplemented when necessary with isoflurane and benzodiazepines. Any departure from this standard protocol was recorded. Monitoring was in accordance with the guidelines of the Australian and New Zealand College of Anaesthetists.

The CPB circuit included a hard shell combined venous and cardiotomy reservoir (Medtronic Blood Systems, Anaheim, CA), roller pump (Stockert Instrumente, Munich), hollow fibre membrane oxygenator (Medtronic Blood Systems, Anaheim, CA) and a Bentley AF1040D 40 micron screen arterial filter (Baxter Healthcare Corporation, Irvine, CA) with a continuous purge. In preparation, the circuit was CO₂ flushed, primed with plasmalyte 148 and 0.75g kg⁻¹ mannitol (Baxter Healthcare Corporation, Irvine, CA), and then recirculated through a 0.2μm pre-bypass filter (Pall Biomedical, Fajardo, PR, USA) to remove air. Perfusion was non-pulsatile with indexed flows set at 2.4L m⁻² min⁻¹ during cooling and rewarming, and 2.0 L m⁻² min⁻¹ during stable CPB. The alpha stat pH management protocol was utilised for all patients. All patients underwent hypothermic CPB. The lowest temperature was recorded.

The Doppler device described in Chapter 2 was used to monitor the right common carotid artery from 5 minutes prior to cannulation of the great vessels until 20 minutes following weaning from CPB. The Doppler monitoring protocol described in Section
4.2.3 was used throughout this trial. Physiological parameters were recorded during surgery by automatic data logging devices (HP Component Monitoring System, Hewlett Packard, USA). The product of time (minutes) during which perfusion pressure was below 50 mmHg and the degree of hypotension (difference between 50 mmHg and the observed perfusion pressure) during CPB was calculated (Stockard et al. 1973). This product is expressed as mmHg.min and is known as the TM\textsuperscript{50}. The cumulative duration of hypotension (systolic BP less than 80 mmHg) during the pre- and post-CPB periods was also calculated.

3.2.5 Statistics

The study was powered to show a difference in the proportion of patients exhibiting an NP deficit at 10 days post-operatively. It was assumed that 70\% of patients would exhibit a drop in performance by 1 SD in at least 1 test at this review. The data presented in Table 4 for studies utilising a similar number of tests as used in our protocol suggests that this was not an unrealistic expectation. It was then assumed that lignocaine might reduce this proportion to 35\%. Given these parameters, the sample size required for each group for power of 80\% at the 5\% significance level is 31 (Campbell et al. 1995), and hence 65 patients were enrolled. It is acknowledged that the expectation of reducing the rate of deficit from 70\% to 35\% is optimistic, although the in vivo data suggesting protection is strong. Moreover, it was considered that this small study might identify a less powerful effect for lignocaine in the form of a trend toward significant benefit, and this would facilitate the design of a larger study.

The group-mean scores for each test sub-scale at the pre-operative assessment were compared using an unpaired two-tailed t test. The groups were compared with respect
to potentially confounding variables using a Chi square or Fisher's exact test for proportions and an unpaired two-tailed t-test or a Mann Whitney U test for continuous variables. Any pre-operative or surgical factor that differed significantly between the lignocaine and placebo groups was tested by univariate regression analysis (continuous variables) or by appropriate stratification (categorical variables) against outcome; for each test and at all testing times. Factors showing a significant correlation or association (p < 0.1) with outcome, independent of lignocaine administration, were then tested by multivariate analysis.

Analysis of the NP test outcome data was approached in two ways. First, the proportion of patients in each group exhibiting a decrement in at least one or in at least two performance test sub-scales were compared at each review using a Chi square test. Second, in each of the performance tests, control tests and memory self-rating inventories, the sequential group mean percentage change scores were compared using repeated measures ANOVA. This analysis was also used to assess any effect of time after surgery on performance. Where a patient missed one of the three reviews, missing data were estimated from the average of the two that were completed and a degree of freedom was subtracted in the ANOVA (Myers and Well 1991). Patients missing two of the reviews were excluded from this analysis. A significance level of p < 0.05 was chosen for all tests.
3.3 RESULTS

3.3.1 Completion of protocol

Ten of the 65 consented patients did not enter the review phase of the trial. One female withdrew after pre-operative NP testing because she found the latter to be too stressful. This patient did not receive the trial infusion. Five of the remainder received the placebo and 4 received lignocaine. One placebo patient was unblinded in theatre after an episode of ventricular fibrillation prior to CPB. Two died after sudden cardiac arrest in the early post-operative period; one who died in the ICU on day two was receiving the placebo and the other who died after discharge on day 7 had received lignocaine. Two suffered severe non-cerebral post-operative complications which would have significantly altered subsequent NP performance, 2 refused all post-operative testing and 2 were lost to all follow up.

The remaining 55 patients completed pre-operative NP testing and the trial infusion (28 received lignocaine and 27 received the placebo). Forty-two completed all 3 post-operative reviews, 8 were reviewed twice and 5 were reviewed once. This represents 147 of 165 possible patient reviews (89.1%). Failure to complete the review program was variously attributable to difficulty in locating patients, refusal to undergo testing and development of non-cerebral post-operative complications.

3.3.2 Baseline neuropsychological function

Group mean pre-operative NP test scores for these 55 patients did not differ and are listed in Table 3.2.
Table 3.2. Comparison of group mean raw scores for all test sub-scales in lignocaine and placebo groups at the pre-operative assessment

<table>
<thead>
<tr>
<th>Test</th>
<th>Units</th>
<th>Lignocaine group</th>
<th>Placebo group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVLT (trials 1-5 total)</td>
<td>number correct</td>
<td>39.4 ± 9.3</td>
<td>40.4 ± 8.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>AVLT (distract list)</td>
<td>number correct</td>
<td>4.1 ± 1.3</td>
<td>4.6 ± 1.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>AVLT (recall trial)</td>
<td>number correct</td>
<td>8.0 ± 3.3</td>
<td>7.8 ± 2.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Inspection time (dynamic)</td>
<td>time (ms)</td>
<td>83.5 ± 27.1</td>
<td>82.9 ± 24.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Inspection time (traditional)</td>
<td>time (ms)</td>
<td>88.4 ± 47.3</td>
<td>102.8 ± 51.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Rey figure (copy)</td>
<td>score</td>
<td>32.8 ± 2.7</td>
<td>32.3 ± 4.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Rey figure (recall)</td>
<td>score</td>
<td>17.4 ± 5.7</td>
<td>16.0 ± 6.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>SDMT (oral)</td>
<td>number correct</td>
<td>48.7 ± 11.0</td>
<td>49.2 ± 11.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>SDMT (written)</td>
<td>number correct</td>
<td>41.0 ± 11.9</td>
<td>41.3 ± 11.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Trails A</td>
<td>time (s)</td>
<td>31.6 ± 13.6</td>
<td>34.2 ± 11.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Trails B</td>
<td>time (s)</td>
<td>112.8 ± 102.5</td>
<td>103.5 ± 69.7</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Self rating inventory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAC-S (How good at)</td>
<td>score</td>
<td>2.49 ± 0.58</td>
<td>2.42 ± 0.56</td>
<td>n.s.</td>
</tr>
<tr>
<td>MAC-S (How often do)</td>
<td>score</td>
<td>2.61 ± 0.52</td>
<td>2.50 ± 0.47</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Anxiety, depression tests</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck depression</td>
<td>score</td>
<td>7.2 ± 4.7</td>
<td>7.6 ± 6.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>STAI (state anxiety)</td>
<td>score</td>
<td>38.7 ± 11.4</td>
<td>38.4 ± 13.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>STAI (trait anxiety)</td>
<td>score</td>
<td>35.3 ± 8.3</td>
<td>37.1 ± 8.3</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*a Data are means ± SD

AVLT = Auditory Verbal Learning Task;   MAC-S = Memory Assessment Clinics Self Rating Test;   SDMT = Symbol - Digit Modality Test;   STAI = State - Trait Anxiety Inventory.
3.3.3 Demographic and peri-operative variables

Other relevant demographic, operative and post-operative data are listed in Tables 3.3, 3.4 and 3.5 respectively. The placebo patients had a significantly greater body mass index (BMI) than the lignocaine patients (28.5 versus 25.3). Conversely, myocardial scores (Brandt et al. 1977) indicated significantly worse coronary artery disease in the lignocaine patients. Accordingly, a significantly greater proportion of lignocaine patients underwent concomitant valve replacement and coronary grafting procedures. Since these procedures take longer, the lignocaine group had a significantly longer mean duration of aortic cross clamping. A significant (inverse) correlation with outcome was shown for only one of these variables which differed between the groups, in one test, and at one testing time after controlling for lignocaine administration (BMI in the MAC-S How Good self rating test at 10 weeks, p = 0.014).

There were no other significant differences in demographic or surgical variables. In particular, the TM\(^{50}\), total operative emboli exposure and the use of other putative brain protecting anaesthetic agents such as ketamine, etomidate and propofol did not differ between the groups. The lignocaine patients spent a significantly shorter immediate post-operative period in the Intensive Care Unit. There were no other significant differences between the groups with respect to post-operative variables.

Mean plasma lignocaine levels (µmol L\(^{-1}\)) in the lignocaine patients were 16.6 (8.5 SD), 9.4 (3.3), 7.8 (3.0), and 10.6 (2.6) at aortic cannulation, aortic declamping, 8 hours and 24 hours after initiation of the infusion respectively.
Table 3.3  Comparison of lidocaine and placebo groups with respect to demographic and pre-operative variables$^a$

<table>
<thead>
<tr>
<th>Pre-operative factor</th>
<th>Lignocaine group (n = 28)</th>
<th>Placebo group (n = 27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.9 ± 8.9</td>
<td>54.4 ± 9.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Males</td>
<td>17 (60.7%)</td>
<td>14 (51.9%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.3 ± 4.3</td>
<td>28.5 ± 5.2</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>Secondary education (years)</td>
<td>3.78 ± 3.0</td>
<td>3.81 ± 2.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Smoking (pack years)</td>
<td>4 (0 - 40 range)</td>
<td>0 (0 - 40 range)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>53.6 ± 5.3</td>
<td>55.1 ± 5.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Admission systolic BP (mmHg)</td>
<td>124 ± 16</td>
<td>127 ± 18</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>33.8 ± 10.8</td>
<td>37.8 ± 10.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (21.4%)</td>
<td>7 (25.9%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>3 (10.7%)</td>
<td>1 (3.7%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Carotid bruit</td>
<td>1 (3.6%)</td>
<td>2 (7.4%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Clinical left ventricular failure</td>
<td>6 (22.2%)</td>
<td>4 (14.8%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13 (46.4%)</td>
<td>8 (29.6%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Myocardial score</td>
<td>3 (0 - 12 range)</td>
<td>1 (0 - 11 range)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>1 (3.6%)</td>
<td>3 (11.1%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (7.1%)</td>
<td>1 (3.7%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1 (3.6%)</td>
<td>1 (3.7%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hypertension (past history)</td>
<td>2 (7.1%)</td>
<td>6 (22.2%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mean aortic gradient in aortic valve surgery patients (mmHg)</td>
<td>55.1 ± 15.7</td>
<td>55.2 ± 14.5</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

$^a$ Data are mean ± standard deviation, number (%), or median (range).

mmHg = millimetres of mercury; n.s. = not significant; TIA = transient ischaemic attack
Table 3.4  Comparison of lidocaine and placebo groups with respect to surgical
and peri-operative variables

<table>
<thead>
<tr>
<th>Surgical factor</th>
<th>Lignocaine group (n = 28)</th>
<th>Placebo group (n = 27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve replacement</td>
<td>20 (71.4%)</td>
<td>15 (55.6%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mitral valve replacement</td>
<td>6 (21.4 %)</td>
<td>9 (33.3%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dual valve replacement</td>
<td>2 (7.1 %)</td>
<td>3 (11.1%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Valve plus coronary grafts</td>
<td>13 (46.4%)</td>
<td>5 (18.5%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Redo operation</td>
<td>7 (25%)</td>
<td>4 (14.8%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ascending aorta atheroma</td>
<td>1 (3.6%)</td>
<td>3 (11.1%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>129.3 ± 42.6</td>
<td>109.5 ± 35.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cross clamping time (min)</td>
<td>112.3 ± 35.5</td>
<td>92.9 ± 27.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Emboli count</td>
<td>2042</td>
<td>1748</td>
<td>n.s.</td>
</tr>
<tr>
<td>Coolest temperature °C</td>
<td>28.2 ± 2.5</td>
<td>28.6 ± 2.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fractional fall in haemoglobin</td>
<td>0.34 ± 0.1</td>
<td>0.34 ± 0.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>TM&lt;sup&gt;50&lt;/sup&gt; mmHg.min</td>
<td>151</td>
<td>102.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pre and post CPB time</td>
<td>10</td>
<td>7.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>systolic BP &lt;80 mmHg (min)</td>
<td>(0 - 97 range)</td>
<td>(2 - 78 range)</td>
<td></td>
</tr>
<tr>
<td>Inotropes after CPB</td>
<td>11 (39.3%)</td>
<td>10 (37%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Etomidate used in anaesthetic</td>
<td>10 (35.7%)</td>
<td>9 (33.3%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ketamine used in anaesthetic</td>
<td>4 (14.3 %)</td>
<td>4 (14.8%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Isoflurane used in anaesthetic</td>
<td>17 (60.7%)</td>
<td>16 (59.3%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Propofol used in anaesthetic</td>
<td>10 (35.7%)</td>
<td>12 (44.4%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

* Data are mean ± standard deviation, number (%), or median (range).

CPB = cardiopulmonary bypass;  min = minutes;  mmHg = millimetres of
mercury;

n.s. = not significant.
Table 3.5  Comparison of lignocaine and placebo groups with respect to post-operative variables

<table>
<thead>
<tr>
<th>Post-operative factor</th>
<th>Lignocaine group (n = 28)</th>
<th>Placebo group (n = 27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU ventilation (hours)</td>
<td>12.6 ± 5.6</td>
<td>12.4 ± 6.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>ICU stay (hours)</td>
<td>24.1 ± 7.4</td>
<td>29.4 ± 11.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Inotropes required in ICU</td>
<td>10 (35.7%)</td>
<td>7 (25.9%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Intra-aortic balloon pump required</td>
<td>1 (3.6%)</td>
<td>0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Peak AST</td>
<td>55.9 ± 28.7</td>
<td>58.4 ± 18.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Peak AST &gt;100</td>
<td>1 (3.6%)</td>
<td>0</td>
<td>n.s.</td>
</tr>
<tr>
<td>New renal dysfunction in first 48 hours</td>
<td>9 (32.1%)</td>
<td>6 (22.2%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>New atrial fibrillation</td>
<td>7 (25%)</td>
<td>9 (33.3%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>9.0 ± 2.6</td>
<td>9.6 ± 2.8</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation, or number (%).

AST = aspartate aminotransferase;  ICU = intensive care unit;
n.s. = not significant.
3.3.4 Neurological outcome

One female placebo patient was recorded as suffering a mild peri-operative stroke that resulted in new unilateral sensory changes which gradually lessened with time. The proportion of lignocaine and saline patients exhibiting a decrement in at least one or at least two performance test sub-scales at each review is listed in Table 3.6. A smaller proportion of the lignocaine group exhibited decrements by either definition at all times. This was significant for decrements in at least one sub-scale at 10 days (p < 0.025) and 10 weeks (p < 0.05).

The sequential group mean percentage change scores in the performance tests are either shown in Figure 3.2 (5 of the 6 sub-scales in which group differences were significant) or are listed in Table 3.7 (the 5 sub-scales in which differences did not reach significance). The sixth sub-scale, in which the groups did differ significantly (p < 0.05), was the Trials 1 - 5 component of the AVLT which cannot be graphed easily. In all tests where group differences were significant, the lignocaine patients’ performance was superior. A significant time-dependent improvement in function was recorded in: Inspection Time (traditional); Trails A; Trails B; AVLT (distract list and recall trial); SDMT (written and oral); and Rey Figure (recall) tests (all p < 0.01).

The sequential group mean percentage change scores in the two sub-scales of the Memory Assessment Clinics Self-Report are shown in Figure 3.3. The lignocaine patients reported significantly better post-operative memory and fewer memory lapses than the placebo patients. Also, assessments of patients by their spouses using these sub-scales showed the same advantage for the lignocaine group, but the differences failed to reach our chosen significance level because of the small number of patients.
Table 3.6 Number and proportion of patients in the lignocaine and placebo groups exhibiting a decrement in at least one and at least two performance test sub-scales at each review.

<table>
<thead>
<tr>
<th></th>
<th>10 Day</th>
<th>10 Week</th>
<th>6 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lignocaine n = 25</td>
<td>Placebo n = 24</td>
<td>p</td>
</tr>
<tr>
<td>Timing of testing(a)</td>
<td>9.8 ± 2.6 (Days)</td>
<td>9.8 ± 1.7 (Days)</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>10.1 ± 1.8 (Weeks)</td>
<td>10.8 ± 2.4 (Weeks)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Decrement in at least 1 scale</td>
<td>10 (40%)</td>
<td>18 (75%)</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Decrement in at least 2 scales</td>
<td>5 (20%)</td>
<td>10 (42%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Decrement in at least 2 scales</td>
<td>3 (11.5%)</td>
<td>6 (25%)</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>2 (8%)</td>
<td>4 (17%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

\(a\) data are mean ± standard deviation.

n.s. = not significant.
Table 3.7  Sequential group mean percentage change scores for lignocaine and placebo groups in performance test sub-scales where there was no significant difference between the groups\(^a\).

<table>
<thead>
<tr>
<th>Test</th>
<th>10 Day</th>
<th></th>
<th>10 Week</th>
<th></th>
<th>6 Month</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lignocaine</td>
<td>Placebo</td>
<td>Lignocaine</td>
<td>Placebo</td>
<td>Lignocaine</td>
<td>Placebo</td>
</tr>
<tr>
<td>Rey figure (copy)</td>
<td>100.6 ± 1.7</td>
<td>99.7 ± 1.8</td>
<td>102.7 ± 2.1</td>
<td>100.6 ± 2.0</td>
<td>101.8 ± 1.5</td>
<td>102.5 ± 2.0</td>
</tr>
<tr>
<td>Rey figure (recall)</td>
<td>102.2 ± 5.8</td>
<td>111.9 ± 12.2</td>
<td>126.6 ± 7.0</td>
<td>123.6 ± 7.5</td>
<td>134.3 ± 8.3</td>
<td>139.9 ± 11.0</td>
</tr>
<tr>
<td>Inspection time (traditional)</td>
<td>104.8 ± 7.4</td>
<td>118.8 ± 14.7</td>
<td>120.1 ± 6.2</td>
<td>121.3 ± 10.9</td>
<td>124.9 ± 5.7</td>
<td>130.5 ± 16.2</td>
</tr>
<tr>
<td>Trails A</td>
<td>104.8 ± 3.4</td>
<td>112.1 ± 5.6</td>
<td>111.3 ± 5.5</td>
<td>112.2 ± 4.6</td>
<td>119.9 ± 5.8</td>
<td>115.8 ± 6.5</td>
</tr>
<tr>
<td>Auditory - verbal learning task: recall trial</td>
<td>99.4 ± 6.4</td>
<td>85.5 ± 6.8</td>
<td>111.0 ± 9.2</td>
<td>98.5 ± 7.0</td>
<td>127.6 ± 9.4</td>
<td>114.1 ± 7.8</td>
</tr>
</tbody>
</table>

\(^a\)data are mean ± standard error
Figure 3.2 Sequential group mean percentage change scores for lignocaine and placebo patients in those performance test subscales where there was a significant difference between the groups. Data are mean ± standard error.

AVLT = Auditory verbal learning task; SDMT = Symbol Digit Modality Test.
Figure 3.3  Sequential group mean percentage change scores for lignocaine and placebo groups in the two sub-scales of the Memory Assessment Clinics Self Report Inventory. Data are mean ± standard error.
who had spouses (n = 27). The sequential group mean percentage change scores in
the Beck depression inventory and the two STAI (anxiety) sub-scales are shown in
Figure 3.4. Although there was no difference due to treatment, there was a significant
time-dependent decrease in both depression and anxiety (p < 0.01).
Figure 3.4  Sequential group mean percentage change scores for lignocaine and placebo groups in the Beck Depression and State Trait Anxiety Inventories. Data are mean ± standard error. Note that an increase in score indicates a decrease in depression or anxiety.
3.4 DISCUSSION

3.4.1 Methodology

Left heart valve surgery patients were chosen for this investigation because of their high risk of peri-operative brain injury (Nussmeier 1996) and their previously documented exposure to greater numbers of emboli than other patients undergoing CABG alone (Table 1.5). It was concluded that this group of patients had most to gain from administration of any neuroprotective agent. Neuropsychological testing was chosen as the outcome measure since the incidence of NP deficits is high in the post-operative period. This allowed a trial with smaller numbers of subjects than if a less common adverse outcome such as stroke was utilised.

We used two methods in the analysis of the NP test outcomes. In the first, the groups were compared with respect to the proportion of patients exhibiting a significant deficit in one or more tests at each follow up. A “significant deficit” is defined as a decline in performance by $\geq 1$SD of the pre-operative population mean for that test. This is the most frequently used index to define cognitive decline (Mahanna et al. 1996), and this is apparent from our own recent literature review (Table 1.4). The number of tests in which a decline must be evident for a deficit to be defined does vary, but it is usually 1 or 2 (Table 1.4). The essential conclusions of the study could be drawn from the result of this analysis alone. However, in the second analysis, we calculated group mean percentage change scores (from pre-operative baseline) in each test at each review. The between group differences over the review period were assessed by repeated measures ANOVA. This is a less common approach to analysis
of NP data in this field, although it is not without precedent (Aberg and Kihlgren 1977).

Both methods of analysis have been criticised by various authors: the first for being subject to floor effects (Mahanna et al. 1996) and for failing to show that many cardiac surgery patients actually exhibit improved NP test performance after surgery; and the second for masking significant NP deficits in individual patients (Rogers et al. 1993). Both analyses were performed in this study in order to avoid at least some of these criticisms, and we do not rely on either in isolation for the fundamental conclusion of cerebral protection by lignocaine. It is also notable that the purpose of this study was not to establish the incidence of NP deficit in our patients, but rather to detect any difference in outcome between the treatment groups. Consequently the definition of “deficit”, which is essentially arbitrary (Kneebone et al. 1998), is less important than the discriminating ability of the method adopted. In this study, both methods of analysing the NP data demonstrated a significant difference between the groups and would have generated the same conclusion.

3.4.2 Results

These data suggest a strong and persistent cerebral protective effect for lignocaine. A significantly greater proportion of the placebo group showed discreet decrements in NP test performance at the 10 day and 10 week reviews. In addition, the sequential group mean percentage change scores for patients receiving lignocaine showed time dependant improvement in all tests except the Rey Figure Copy in which a ceiling effect prevented significant change. In contrast, improvement in the placebo group was significantly less in some tests or absent in others.
It is acknowledged that “decrements” shown to exist in NP tests may not result in any clinically discernible loss of function, such as usually seen after a stroke. However, other groups have previously reported correlation between NP test results and the incidence of objective clinical cerebral dysfunction (Shaw et al. 1986) and levels of biochemical brain injury markers (Aberg et al. 1984). In our own study, the advantage for lignocaine was not only detectable by objective NP testing, but with respect to memory at least, was also apparent to the patients themselves. Our data also illustrated the previously described phenomenon of time dependent improvement in group mean NP test scores despite discreet decrements in some patients, following cardiac surgery (Aberg and Kihlgren 1977). Group mean score improvements are particularly noticeable in later reviews. The precise basis for this post-operative improvement in function has not been determined but may include a decrease in depression and anxiety (Townes et al. 1989), a practice effect (Kneebone et al. 1998), selective attrition of poorly performed patients (Mahanna et al. 1996), and unidentified physiological benefit following surgery.

No confounding factors were identified that could explain the better outcome in the lignocaine patients. In particular, there were no significant differences between the groups with respect to exposure to cerebral emboli or hypotension during CPB. While anxiety and depression may affect NP test performance (Townes et al. 1989), the lignocaine and placebo patients did not differ either before or at any time after surgery with respect to depression or anxiety indices. There is no evidence here that lignocaine directly affects mood or anxious state. Although the lignocaine patients had a significantly smaller BMI, this has not previously been identified as a risk factor for
poor cognitive outcome after cardiac surgery and only a single test score (MAC-S: How Good, at the 10 week review) showed a significant inverse correlation with BMI. The lignocaine patients had significantly worse coronary artery disease. This resulted in a greater proportion undergoing concomitant coronary artery grafting and valve replacement, which exposes patients to the combined risk of both procedures (Wolman et al. 1994). The lignocaine patients also experienced longer aortic cross clamping times, which further increases relative risk of cerebral injury (Murkin 1993). While our data do not show a worsening of outcome in association with these latter factors, this is a probable consequence of subject distribution and the protective effect of lignocaine suggested by this study.

3.4.3 Implications of the study

This small study suggests that the cerebro-protective effect of lignocaine previously reported \textit{in vivo} may translate into clinically useful protection in cardiac surgery patients. This protective effect has been achieved using a dosing regimen designed to produce plasma lignocaine levels within the therapeutic reference range and to be consistent with those levels reported as effective for cerebral protection \textit{in vivo} (Evans et al. 1989, Shokunbi et al. 1990). We arbitrarily adopted a 48 hour infusion in recognition of a possible anti-inflammatory role (MacGregor et al. 1980), which might be important beyond the immediate peri-operative period. However, the 48 hour infusion does impose some logistical difficulties. It necessitates the patients remaining connected to an infusion pump during a period when they might not otherwise be so encumbered. Moreover, plasma lignocaine levels must be monitored. After unblinding it was determined that every patient receiving lignocaine had a plasma level which was within the therapeutic range at 24 hours. However, in most cases the lignocaine
level had risen since the 8 hour assay, necessitating that the infusion rate be reduced for the final 24 hours. Since we did not investigate dose response, we have not demonstrated that ours was the ideal dosing regimen for cerebral protection.

We have not demonstrated the mechanism of cerebral protection by lignocaine in cardiac surgery patients. Moreover, speculation on how lignocaine may have produced the benefits observed here is complicated by the debate over the pathophysiology of NP deficits. Although NP deficits may be apparent in the absence of radiological evidence of focal infarction, (Aberg et al. 1984), the positive correlation between these deficits and biochemical markers of neuronal injury (Aberg et al. 1984) confirms that neuronal injury does occur. Amelioration of this more subtle form of brain injury is consistent with the in vivo finding that lignocaine appeared most effective in “milder” injury (Shokunbi et al. 1990). Any or all of the protective mechanisms discussed in section 1.7.3 may be relevant here, and our data provide no basis for speculation about their relative importance.

Effective prevention of more severe injury such as stroke is more likely to be based on elimination of the precipitating event (such as macroembolisation) by modification of surgical and CPB technique, rather than on pharmacological protection (Rogers 1997). It is difficult to perceive that a drug could prevent infarction in a large vascular territory rendered densely ischaemic by a solid embolus. The work reported in the subsequent chapters of this thesis demonstrates that even in the modern context there remains considerable potential for reducing emboli exposure in cardiac surgery.

In conclusion, lignocaine administration to intensively monitored cardiac surgery patients appears safe and uncomplicated. These data support the hypothesis made in
section 1.8.2 and suggest that lignocaine be considered for the routine peri-operative care of patients undergoing left heart valve surgery. However, a larger repeat study is needed and should test different dosing regimens. Consideration could also be given to clinical investigation of a role for lignocaine in other forms of brain injury.
CHAPTER 4

PATTERNS OF EMBOLI GENERATION
4.1 INTRODUCTION

A capability for emboli counting based on colour flow Doppler technology was developed (Chapter 2) in order to control for cerebral emboli exposure in the lignocaine trial. The total cerebral emboli exposure was determined for each patient to enable comparison between the treatment and control groups (Chapter 3).

Emboli monitoring also enabled evaluation of patterns of emboli generation throughout surgery. These patterns are reported in this chapter, and were expected to reflect previous accounts of emboli distribution throughout left heart valve surgery (section 1.5.3.3). While this was the case in general terms, several unexpected sources of emboli were identified, and this finding was further investigated (see Chapter 6).
4.2 METHODS

4.2.1 Patients

Fifty eight patients enrolled in the lignocaine trial whose procedure included conventional methods of deairing the heart on completion of surgery were Doppler monitored throughout surgery. Five different surgeons operated on these patients. Those patients whose procedure included the novel de-airing technique described in Chapter 5 are not included here since these data are intended to illustrate the “typical” emboli distribution at inception of the lignocaine trial when “conventional” techniques were used. The median age was 54 years (range 20 – 70). Thirty two (55%) were male. Thirty eight patients underwent aortic valve replacement, 14 underwent mitral valve replacement or repair, and 6 underwent combined aortic and mitral procedures.

4.2.2 Conduct of anaesthesia, CPB and surgery

The preparation and configuration of the CPB machine and the conduct of CPB and anaesthesia was as described in section 3.2.4. Surgical techniques remained essentially “standard” throughout the period over which these 58 patients were monitored. In particular, despite minor variations between surgeons, the technique used to “deair” the left heart at the end of the operative procedure was as described by Kirklin and Barratt-Boyes (1993) (see sections 1.6.1.3 and 5.2.4.1).
4.2.3 Right common carotid artery Doppler monitoring

The RCCA was monitored using the Flowlink 300 Colour Flow Doppler interfaced to the purpose built emboli counting device described in Chapter 2. The RCCA was chosen after obtaining a cranial window for middle cerebral artery monitoring proved difficult in some cases during testing of the device. Other studies in the field have used carotid rather than cerebral monitoring for emboli counts (Stump et al. 1997, 1991). The right carotid was monitored in this study since it was easier to instrument given the prevalent configuration of the operating theatre. Moreover, there is some clinical evidence that emboli preferentially enter the right carotid system (Slogoff et al. 1982, Heikkinen 1985, Kuroda et al. 1993), although this is not an invariable finding (Reed et al. 1988, Kaps et al. 1995).

The Doppler was operated in the 2 MHz pulsed wave mode. The probe was continuously hand held (see Figure 4.1) with beam depth, probe angle, and signal gain adjusted to optimise both the audible flow signal and the colour flow display. A Doppler beam width of 10 mm and machine power of 40% were used for all patients. Artefact signals caused by probe movement were clearly distinguishable from the characteristic chirps and pops of emboli. The counting device sensitivity was set so that the count incremented with each embolus signal. As described in Chapter 2, the Doppler operator was able to remove the data recorded by the counter over the previous five seconds if an artefactual signal was identified. The author performed all Doppler monitoring.
Figure 4.1  Operation of the Doppler emboli counter in the clinical setting. Note the author’s right hand under the drapes to hold the Doppler probe over the right common carotid artery.
The operation was divided into eight Doppler monitoring phases (A - H), designed to reflect previously reported risk factors for emboli generation as follows:

A. the five minute period prior to placement of the first sutures in preparation for aortic and right atrial cannulation (a stable period in which no emboli were expected);
B. the end of A to the beginning of CPB (risk of introducing air, or dislodging particulate matter during aortic manipulation and cannulation);
C. The first 10 minutes following the beginning of CPB (risk of introducing bubbles from an incompletely deaired CPB circuit);
D. the end of C to the beginning of rewarming (a relatively stable period when few emboli were expected);
E. beginning of rewarming to 34°C (risk of bubble generation by reduction of gas solubility during rewarming);
F. 34°C to aortic declamping (a relatively stable period when few emboli were expected);
G. aortic declamping until withdrawal of CPB (risk of ejection of retained intracardiac / pulmonary venous air or particulate debris); and
H. the first 20 minutes following withdrawal of CPB (risk of continued ejection of retained intracardiac / pulmonary venous air or particulate debris).

The mean emboli count, and the mean fraction of the total operation count for each of these phases was calculated. Isolated events within each phase that seemed related to the appearance of emboli signals were also noted.
4.3 RESULTS

The total count recorded throughout surgery ranged from 342 to 6852 (median 1647). The range and median count by phase, and the percentage of the mean group total count recorded during each phase is given in Table 4.1 and graphed in Figure 4.2.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Median count</th>
<th>Count range</th>
<th>Percentage of total count for all phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>19</td>
<td>0 - 170</td>
<td>1.2</td>
</tr>
<tr>
<td>C</td>
<td>30</td>
<td>4 - 1340</td>
<td>2.5</td>
</tr>
<tr>
<td>D</td>
<td>37</td>
<td>0 - 5480</td>
<td>10.1</td>
</tr>
<tr>
<td>E</td>
<td>4</td>
<td>0 - 960</td>
<td>2.0</td>
</tr>
<tr>
<td>F</td>
<td>6.5</td>
<td>0 - 1942</td>
<td>3.4</td>
</tr>
<tr>
<td>G</td>
<td>971</td>
<td>50 - 6000</td>
<td>51.9</td>
</tr>
<tr>
<td>H</td>
<td>444</td>
<td>0 - 3610</td>
<td>28.4</td>
</tr>
</tbody>
</table>

Emboli were consistently absent during the 5 minute period prior to placement of the sutures in preparation for aortic or right atrial cannulation (phase A). Uncommonly, placement of the purse string sutures in either the aorta or the right atrium (early phase B)
Figure 4.2  Percentage of the total operative count recorded in each phase averaged over all patients.
resulted in detection of RCCA emboli. Both introduction of the aortic cannula and initiation of CPB usually produced a very transient period of embolisation.

There were highly variable levels of RCCA emboli activity (counts of 0 to 5480) during the relatively long period of stable CPB (phase D) prior to rewarming. Occasionally, the rapid injection of medications to the CPB circuit was associated with the appearance of small numbers of emboli in the RCCA. Repeated observation putatively linked periods of high RCCA embolic activity during phase D to the presence of air in the CPB venous return line, or low blood levels in the CPB hard shell venous reservoir.

Emboli were usually detected on removal of the aortic cross clamp (phase G). Greater embolic activity invariably occurred during weaning from CPB and the establishment of left heart ejection. This activity persisted for variable periods after CPB was withdrawn (phase H), but only rarely were emboli still detected at 20 minutes after withdrawal of CPB. Phases G and H were quantitatively the most important periods for cerebral embolisation, accounting for 80.3% of the total emboli count.
4.4 DISCUSSION

Both the number and temporal distribution of emboli recorded in this group of patients were similar to those reported previously.

Stump et al. (1991), monitored the left common carotid artery in 8 valve replacement patients and reported a mean total emboli count of 1339 (maximum 4455). The present study recorded a median count of 1647 and a maximum of 6852. Given the potential for discrepancies in counts because of differences in Doppler device sensitivity (Butler and Kurusz 1990), these “counts” are notably similar. Our higher total count may reflect a truly greater emboli exposure (for reasons that are not obvious), and as previously mentioned higher counts might be expected in the RCCA (Heikkinen 1985).

The distribution of microembolic activity in the present study was similar to that reported by Albin et al. (1991), Stein et al. (1991) and Van der Linden and Casimir-Ahn (1991) who monitored an unspecified middle cerebral artery, the left common carotid artery and the right middle cerebral artery respectively. All groups also found that the vast majority of emboli appeared after aortic declamping, especially in the period of weaning from CPB. Stein et al. (1991) cite 71% of emboli recorded during valve replacement surgery as being detected during resumption of cardiac ejection, similar to our corresponding figure of 80.3%. The present study also recorded embolic activity in association with other events previously identified as generating emboli, such as aortic cannulation and
initiation of CPB (van der Linden and Casimir-Ahn 1991, Stump et al. 1996), and addition of fluids and medications (Loop et al. 1976).

In contrast, not all previously proposed sources of emboli were corroborated. For example, it has been suggested that bubbles may form from dissolved gas if the temperature differential between blood and the heat exchanger is sufficiently high during attempts to rapidly rewarm the patient (Govier 1989). No evidence for this was found in the present study, perhaps because steep rewarming gradients (>10°C) were avoided in accordance with current recommendations (Kurusz and Butler 1993).

While Stein et al. (1991) detected no emboli during stable CPB (with the aorta clamped), emboli were recorded during phases D - F in the present study. Indeed, several potentially important sources of emboli that have not been discussed in the recent literature were noted during this period. First, there was an apparent relationship between RCCA emboli activity and low venous reservoir blood volume. If the volume fell below 500 - 600 ml, RCCA emboli were detected. It is notable that the manufacturer's recommended operating volume minimum was 300 ml. Second, despite an initial belief that any air in the venous return line (bringing blood from the patient to the CPB machine) would be removed by the various components of the CPB circuit, the appearance of visible bubbles in the venous line invariably resulted in the detection of emboli in the RCCA. Adjustment of the venous cannulae and / or their sutures usually resolved this problem, although occasionally attempts to rectify the problem failed. This resulted in the very high phase D
count of 5480 recorded in one patient. These findings suggested that the venous reservoir, oxygenator and arterial line filter cannot be relied upon to remove all venous air.

The finding of apparent emboli generation by venous reservoirs when operated at low blood volumes (which still fell well within the manufacturer’s recommended minimum) was a notable observation and clearly needed systematic investigation. A series of in vitro experiments designed to confirm the observation and elicit the cause are reported in Chapter 6. Similarly, the detection of RCCA emboli when air was entering the venous return line was surprising given that air removal is considered an advantage of hard shell venous reservoirs (Hessel 1993), and that surgeons generally believed that venous line air was removed by the CPB circuit and was consequently harmless. In vitro experiments were also conducted to confirm this observation, and are reported in Chapter 6.

Finally, this study demonstrated once again that conventional cardiac deairing techniques, designed to remove air and debris from the left heart in preparation for resumption of cardiac ejection, were not completely effective (Section 1.6.1.3.). The efficacy of a novel deairing technique developed and routinely used by one of the Green Lane Hospital cardiac surgeons was audited. The results of this audit are reported in Chapter 5.
CHAPTER 5

AUDIT OF A NOVEL DEAIRING TECHNIQUE
5.1 INTRODUCTION

This work (see Chapter 4) and that of others (see Section 1.5.3.2) has identified the period of weaning from CPB after removal of the aortic clamp as that of greatest cerebral embolisation during open ventricle left heart surgery. The emboli are mainly bubbles arising from air retained in the heart chambers and pulmonary veins after heart closure (see Section 1.5.3.2), and it has been concluded that "standard" methods for removing air from these sites ("deairing" techniques) are not effective (see Section 1.6.1.3).

Investigations into the poor efficacy of conventional deairing techniques were described in Section 1.6.1.3. Conventional techniques fail to establish sufficient blood flow through the heart chambers, and the pulmonary veins in particular (Tingleff et al. 1995), to wash out bubbles that become trapped during surgery. Flow sufficient to elute most bubbles is only established in conventional deairing when the aorta is declamped and the working heart is free to eject into the systemic circulation. At this point, however, there is nothing to prevent gas from embolising the cerebral vessels.

One of the 5 Green Lane surgeons (Dr F.P. Milsom) developed and began to routinely use a novel "dual vent" deairing technique designed to establish near normal cardiac output and pulmonary blood flow prior to aortic declamping. A CPB circuit modification allowed arterial blood to be ejected from the beating heart back to the CPB circuit rather than into the systemic circulation. This technique was considered likely to be more effective than conventional methods and its efficacy was audited using the emboli counting techniques developed for the lignocaine trial. The
technique, and the comparison of its efficacy with that of conventional methods is described in this chapter.
5.2 METHODS

5.2.1 Patient groups

Subjects were adult left heart valve surgery patients aged 20 to 73 years who underwent surgery between December 1995 and July 1997. The control group (Group 1) was a cohort of 58 consecutive patients who underwent conventional de-airing by 5 surgeons. This group included patients who participated in the lignocaine trial. Two sub-groups within Group 1 were defined: Group 1a was a cohort of 10 consecutive patients operated on by the individual surgeon most successful in conventional de-airing (although there was no statistically significant difference between surgeons); and Group 1b was a cohort of 16 consecutive patients de-aired conventionally by Dr Milsom before adoption of the dual vent technique. Group 2 was a cohort of 14 consecutive patients undergoing de-airing by the dual vent technique. Four patients (Group 3) who underwent non-vented coronary artery bypass grafting (CABG) were also Doppler monitored to obtain emboli counts illustrative of closed chamber procedures where de-airing is not required.

5.2.2 Conduct of anaesthesia and CPB

The preparation and configuration of the CPB machine, and the conduct of CPB and anaesthesia was described in section 3.2.4.

In all patients the CPB arterial line was introduced into the ascending aorta using a 24 French aortic cannula (Sherwood Medical, St Louis, USA). A two stage atrial cannula (Research Medical, Midvale, Utah, USA) was used for CPB venous return. Cardiac arrest was obtained following aortic cross clamping by antegrade and/or retrograde
blood cardioplegia. The left heart vent (a 17 French Research Medical catheter) was positioned through the right superior pulmonary vein into the left heart chambers. This vent was connected for active suction (through a pump) to the CPB circuit venous reservoir. When aortic valve surgery was undertaken the vent was advanced into the left ventricle.

5.2.3 Right common carotid Doppler monitoring

Doppler monitoring was conducted within predefined operative phases throughout surgery as described in section 4.2.3. The emphasis for this particular audit was on emboli counts in phases G and H, since the count in these phases directly reflects the adequacy of deairing.

5.2.4 Deairing techniques

5.2.4.1 Conventional deairing: Groups 1, 1a, 1b

Although there were minor differences in practice between the 5 surgeons, conventional de-airing followed the technique described by Kirklin and Barratt-Boyes (1993). Prior to withdrawal of CPB, the left heart vent was turned off and resistance on the CPB venous line was increased to allow left heart filling. Heart filling was achieved with careful attention to displacement of air out of the atriotomy and / or aortotomy. This was promoted by ballotting the heart and application of intermittent positive pressure pulmonary ventilation to aid mobilisation of intracardiac and pulmonary venous air respectively. With the left heart full of blood and with as much air as possible displaced from the heart chambers, the surgical wound was closed. The left heart chambers were aspirated using a needle and syringe with particular attention to those sites known to trap air, such as the atrial appendage. The heart was
defibrillated if necessary. More blood was “given back” to the left heart through the pulmonary circulation by increasing resistance in the CPB venous line. This blood was actively vented from the left heart vent. Before aortic declamping, the left heart vent was removed. Some surgeons actively vented the aortic root through the cardioplegia cannula both before and after declamping, although only very low volumes of blood could be vented because of the narrow gauge of the cannula. No echocardiographic guidance of de-airing was employed. Two surgeons routinely used a head down position during these manoeuvres, while 3 did not. The layout of the CPB circuit for conventional CPB and deairing is illustrated in Figure 5.1.

5.2.4.2 Dual vent deairing: Group 2

The dual vent de-airing technique was designed to establish near normal cardiac output from the working heart, and therefore near normal pulmonary blood flow, while keeping the aortic clamp in place and routing the ejected arterial blood back into the CPB circuit. This was achieved as follows:

1. Preparation of the CPB circuit, conduct of anaesthesia, and the initial establishment of CPB were as described in Section 5.2.2 above with one important exception. In the conventional configuration, the cardioplegia line was connected to a small (16 g) cannula placed in the aortic root. For the dual vent technique, the usual narrow gauge cardioplegia line was connected into a \( \frac{1}{2} \) inch conduit and a 21 French Argyle cannula (Sherwood Medical, St Louis, USA), placed in the aortic root proximal to the aortic clamp. This larger conduit was connected into the CPB circuit venous line so that during deairing it could function as an aortic vent. This aortic vent was subject to constriction by a variable resistor that was initially fully
Figure 5.1  Schematic of CPB circuit configured for conventional deairing.

LA = left atrium;  LV = left ventricle;  RA = right atrium;  RV = right ventricle
PA = pulmonary artery;  PV = pulmonary veins

= direction of blood flow during CPB. Note that the LV vent is plumbed to the reservoir through a pump (not shown) to enable active suction. The vent is used during CPB to keep the surgical field free of blood.
closed, and was pressure monitored on the aortic root side of the resistor. The left heart vent was established as described in Section 5.2.2 above, except that it was also connected for passive venting into the CPB circuit venous line in addition to active venting to the venous reservoir. The layout of the circuit for dual vent deairing is illustrated in Figure 5.2. It should be noted that the two vents connected into the venous line allow potentially unrestricted drainage of blood and emboli from the heart into the CPB reservoir.

2. On completion of surgery, cardiac resuscitation was by retrograde and antegrade reperfusion cardioplegia, followed by blood infused via the cardioplegia line to obtain controlled aortic root reperfusion. The left ventricle was passively vented into the CPB venous line. Defibrillation was either spontaneous or electrical.

3. During cardiac recovery with the left ventricular vent still in situ (see Figure 5.3), the atrial pressures were elevated to obtain a working heart. Positive pressure ventilation was commenced to help mobilise air in the pulmonary veins. Aortic root pressures were manipulated by varying inflow from the cardioplegia line, manipulating left ventricular loading, and by adjusting the variable resistor to alter resistance to outflow into the aortic vent. The heart was allowed to develop output through both the left ventricular and aortic vents.

4. Following cardiac recovery, the left ventricular vent was removed (see Figure 5.4). The working heart continued to eject into the venous line via the aortic vent. The variable resistor, cardioplegia line blood flow rate, and atrial pressures were adjusted to maximise cardiac output while maintaining appropriate aortic root pressures (120 mmHg systolic and 30 - 40 mmHg diastolic). Insufficient afterload would cause aortic root pressure to fall with a consequent reduction in myocardial perfusion. Excessive aortic root pressure was avoided by left heart venting (while
Figure 5.2  Schematic of CPB circuit configured for dual vent deairing.

CL = cardioplegia line;  VR = variable resistor

= direction of blood flow during CPB. Note that during stable CPB the aortic vent is closed at the variable resistor, and the LV vent is plumbed to the reservoir as in the conventional circuit. In addition, the communication between the two vents and the venous line is closed during stable CPB. The left ventricle can still be vented to the CPB reservoir in the usual manner during stable CPB.
Figure 5.3  Schematic of dual vent deairing early during cardiac recovery.

CL = cardioplegia line;  VR = variable resistor

= direction of blood flow during CPB. Note that the dual vent conduit is now open to the venous line. As the heart recovers, it develops output down both vents. Aortic root pressures are maintained by adjustment of the variable resistor. Early in recovery blood cardioplegia can be infused into the aortic root (black arrow) through the cardioplegia cannula to help maintain root pressures.
Figure 5.4  Schematic of the final stage of dual vent deairing.

CL = cardioplegia line;  VR = variable resistor

= direction of blood flow. Note that the LV vent is now removed and the heart continues to eject through the aortic vent. Physiological cardiac output can be developed through this large conduit. Bubbles and emboli are flushed back to the CPB circuit. Aortic root pressures are maintained by manipulation of the variable resistor.
this vent was in place), attention to atrial loading conditions, and adjustment of the variable resistor. There was no fixed period for which the heart was allowed to eject back to the CPB circuit in this manner. The timing of CPB withdrawal and aortic declamping was at the surgeon’s discretion. The period between reaching 34°C during rewarming and aortic declamping was designated as the time spent performing deairing manoeuvres and was recorded for all patients in both groups.

5. Immediately before aortic declamping, the systolic pressure in the aortic root was reduced below mean systemic perfusion pressure by cessation of blood inflow into the cardioplegic line, widely opening the variable resistor, and reduction of atrial filling pressure. The aorta was declamped and CPB was then withdrawn.

5.2.5 Non-vented CABG patients: Group 3

To obtain post-declamping emboli counts from patients who did not require deairing, 4 consecutive patients undergoing CABG without venting of the left ventricle underwent RCCA monitoring through phases G and H.

5.2.6 Myocardial damage

Group 2 patients had their pre-operative and post-operative ECGs examined by an independent cardiologist for evidence of myocardial infarction. Serum was collected on the day following surgery for evaluation of the serum aspartate amino transferase (AST) as an index of myocardial infarction (Merry et al. 1992).

5.2.7 Aortic vent flow

In order to confirm the contention that this deairing technique facilitates development of physiological cardiac output through the aortic vent prior to declamping, a
Medtronic Biopump flow probe (Medtronic Blood Systems, Anaheim, CA) was cut into the vent line on two occasions, and flows through the vent were measured during the latter stages of deairing.

5.2.8 Statistics

Non parametric analysis was utilised as embolic activity was not normally distributed. Data were expressed as median value with ranges.

Group comparisons were made using a Mann Whitney U test for continuous variables, and a chi square test for categorical variables. A p value < 0.05 was taken to indicate statistically significant trends.
5.3 RESULTS

5.3.1 Group characteristics

Relevant medical and surgical data for Groups 1, 1a, 1b, and 2 are shown in Table 5.1. The groups are similar, showing no statistically significant differences except for the shorter duration of both CPB and cross clamping in the Group 1a patients (p < 0.01 and < 0.025 respectively). It is of note that there was no significant difference between the groups with respect to time spent de-airing (defined as the period between reaching 34°C during rewarming and withdrawal of CPB). In addition to the data presented in the table, there was no significant difference between the groups with respect to the number undergoing reoperations, or combined valve replacement and CABG procedures.

5.3.2 Comparison of deairing in Groups 1, 2 and 3

The range and median emboli count recorded after aortic declamping for each patient group is shown in Figure 5.5. The count recorded after aortic declamping in Group 2 patients was markedly lower than recorded in Groups 1, 1a, or 1b (p < 0.0001). The Group 2 patients are listed in chronological order in Table 5.2. The efficacy of the dual vent technique improved through the series with 7 of the last 10 patients being exposed to embolic activity similar to that seen after aortic declamping in the Group 3 patients. Two Group 2 patients were recorded as not being exposed to a single embolus.
Table 5.1  Patient groups: relevant medical and surgical parameters.

<table>
<thead>
<tr>
<th>Group</th>
<th>Group 1</th>
<th>Group 1a</th>
<th>Group 1b</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 58</td>
<td>n = 10</td>
<td>n = 16</td>
<td>n = 14</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Male</td>
<td>32 (55)</td>
<td>7 (70)</td>
<td>11 (69)</td>
<td>10 (71)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (45)</td>
<td>3 (30)</td>
<td>5 (31)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>AVR</td>
<td>38 (66)</td>
<td>7 (70)</td>
<td>12 (75)</td>
<td>11 (79)</td>
</tr>
<tr>
<td>MVR</td>
<td>14 (24)</td>
<td>3 (30)</td>
<td>3 (19)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>AVR and MVR</td>
<td>6 (10)</td>
<td>0</td>
<td>1 (6)</td>
<td>1 (7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Median</th>
<th>Median</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(range)</td>
<td>(range)</td>
<td>(range)</td>
<td>(range)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>54 (20-70)</td>
<td>54 (29-69)</td>
<td>60 (37-70)</td>
<td>57 (43-73)</td>
</tr>
<tr>
<td>Pre-op FS (%)</td>
<td>34 (20-63)</td>
<td>31 (24-47)</td>
<td>39 (20-46)</td>
<td>35.5 (17-48)</td>
</tr>
<tr>
<td>Pre-op EF (%)</td>
<td>62 (28-87)</td>
<td>65 (50-77)</td>
<td>68 (61-73)</td>
<td>62 (34-73)</td>
</tr>
<tr>
<td>Duration CPB (mins)</td>
<td>115 (50-225)</td>
<td>81 (70-129)</td>
<td>127.5 (77-177)</td>
<td>106 (85-138)</td>
</tr>
<tr>
<td>Cross clamp time (mins)</td>
<td>106.5 (38-179)</td>
<td>81.5 (61-125)</td>
<td>124 (66-160)</td>
<td>104 (70-216)</td>
</tr>
<tr>
<td>De-airing time(^a) (mins)</td>
<td>28 (11-48)</td>
<td>34 (19-45)</td>
<td>30 (16-42)</td>
<td>24 (15-44)</td>
</tr>
</tbody>
</table>

\(^a\) from 34°C during rewarming to withdrawal of CPB

AVR = aortic valve replacement;  CPB = cardiopulmonary bypass;

FS = fractional shortening;  EF = ejection fraction;  MVR = mitral valve replacement
Figure 5.5  Median (range) emboli count after aortic declamping for each group.
Table 5.2  Emboli count after aortic declamping in Group 2.

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age</th>
<th>Gender</th>
<th>Procedure</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>M</td>
<td>AVR</td>
<td>652</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>M</td>
<td>MVR</td>
<td>363</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>M</td>
<td>AVR</td>
<td>562</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>F</td>
<td>AVR + 1 CABG</td>
<td>167</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>M</td>
<td>AVR + CABG</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>M</td>
<td>AVR</td>
<td>865</td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>M</td>
<td>AVR + 1 CABG</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>M</td>
<td>MVR</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>51</td>
<td>M</td>
<td>AVR + 1 CABG</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>65</td>
<td>F</td>
<td>AVR + 2 CABG</td>
<td>7</td>
</tr>
<tr>
<td>11</td>
<td>60</td>
<td>F</td>
<td>AVR</td>
<td>208</td>
</tr>
<tr>
<td>12</td>
<td>46</td>
<td>F</td>
<td>MVR + Tricuspid</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>43</td>
<td>M</td>
<td>AVR</td>
<td>35</td>
</tr>
<tr>
<td>14</td>
<td>66</td>
<td>M</td>
<td>AVR + 2 CABG</td>
<td>219</td>
</tr>
<tr>
<td>Median</td>
<td>57</td>
<td></td>
<td></td>
<td>101</td>
</tr>
</tbody>
</table>

AVR = aortic valve replacement;  CABG = coronary artery bypass graft;  F = female;
IMA = index of microembolic activity;  M = male;  MVR = mitral valve replacement.
The emboli counts after declamping in Group 1 patients stratified according to selected surgical or patient variables are shown in Table 5.3. None of these variables significantly influenced the count after declamping, although there were trends towards a decreased number of cerebral emboli associated with: aortic valve replacement, first time operations (non “redo” procedures), and valve replacement with concomitant CABG (Table 5.3). When Group 1 was stratified, to include only those patients receiving these “favourable” procedures (n = 12), then the median count after declamping was 977 (range 342 - 5008). Even this “favourable” subgroup was still exposed to significantly more emboli than Group 2 (p < 0.0005).

5.3.3 Flow through the aortic vent

On both occasions when aortic vent flow was monitored, flows between 4 - 5 L min\(^{-1}\) were recorded during the latter stages of de-airing.

5.3.4 Myocardial damage in Group 2

There was no Q wave evidence of myocardial infarction on the ECG, nor was the serum AST elevated (\(\geq 100\) u/l) in any Group 2 patient.
Table 5.3 Emboli count recorded after aortic declamping in Group 1 patients stratified according to selected patient and surgical variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median count (Range)</th>
<th>Variable</th>
<th>Median count (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>1647 (494-5008)</td>
<td>vs Females</td>
<td>1682(342-6852)</td>
</tr>
<tr>
<td>Age ≥ 55 (yrs)</td>
<td>1628 (549-4360)</td>
<td>vs Age ≤ 54 years</td>
<td>1667 (342-6852)</td>
</tr>
<tr>
<td>AVR</td>
<td>1502 (342-6852)</td>
<td>vs MVR</td>
<td>2226 (795-5670)</td>
</tr>
<tr>
<td>Redo procedure</td>
<td>3069 (954-6852)</td>
<td>vs No redo procedure</td>
<td>1522 (342-5248)</td>
</tr>
<tr>
<td>Valve + CABG(s)</td>
<td>1050 (342-5008)</td>
<td>vs Valve only</td>
<td>1717 (643-6852)</td>
</tr>
<tr>
<td>Dual valve</td>
<td>1820 (919-5248)</td>
<td>vs Single valve</td>
<td>1647 (342-6852)</td>
</tr>
<tr>
<td>CPB time ≥ 116 (mins)</td>
<td>1717 (342-6852)</td>
<td>vs CPB time ≤ 115</td>
<td>1582 (549-5248)</td>
</tr>
<tr>
<td>Deairing time ≥ 28 (mins)</td>
<td>1797 (342-5670)</td>
<td>vs Deairing time ≤ 27</td>
<td>1209 (494-6852)</td>
</tr>
</tbody>
</table>

AVR = aortic valve replacement; CABG = coronary artery bypass graft(s);
MVR = mitral valve replacement; CPB = cardiopulmonary bypass
Cerebral embolisation is responsible for both strokes and NP deficits occurring in cardiac surgery (section 1.5.3.5.). The data presented in Chapter 4 and that of others (section 1.5.3.3.) have demonstrated that open chamber surgery patients are exposed to greater numbers of emboli and that these appear after resumption of cardiac ejection. A superior method for removing these emboli prior to ejection into the systemic circulation is required.

Numerous attempts have been made to improve deairing techniques (Section 1.6.1.3.), and these are usually based on the use of TOE to guide conventional methods. For example, Oka et al. (1986) reported TOE guided removal of air from the left atrium by ensuring good filling, ballotment to mobilise air, and concurrent venting until no further air was present. However, there was no carotid or cerebral artery Doppler monitoring to indicate cerebral exposure to microemboli. Since the aorta was declamped during deairing manoeuvres, it is likely that some of the bubbles observed by TOE in the heart chambers were ejected into the aorta rather than removed into the vent. Furthermore, the authors acknowledge that in most patients, "low grades" of bubbles appeared in the left heart for up to five minutes after CPB was terminated, indicating that air was mobilised from the pulmonary circulation once physiological flows were re-established. Transoesophageal echocardiography is cumbersome and expensive (Resigno et al. 1995), and carries the risk of oesophageal trauma (Oka et al. 1986). These considerations may preclude its routine use as a de-airing tool. Moreover, if the de-airing technique is inherently inefficient at mobilising pulmonary venous air, then a sensible end point for de-airing attempts will be difficult to
establish. Clearly, there is a need for improved deairing techniques that achieve clearance of the pulmonary circulation.

This study utilised continuous quantitative monitoring of RCCA embolic activity to demonstrate complete or near complete left heart deairing by the dual vent technique. The efficacy of this technique is apparent when the experience with individual cases is considered (Table 5.2). Refinements to the technique resulted in four of the last five patients being almost completely deaired. Indeed, even without the need for TOE guidance, the dual vent technique can reduce the risk of post declamping cerebral embolisation to a level comparable to that for CABG patients. The complete deairing recorded in two patients (Table 5.2) was remarkable given that this Doppler device was demonstrated to be a more sensitive emboli detector than at least one of the devices commonly used for this purpose (section 2.4).

Establishment of physiological flow through the pulmonary circulation appears to be the prerequisite for removal of trapped air (Tingleff et al. 1995). The magnitude of pulmonary blood flow seems to be the essential difference between the dual vent and conventional techniques, including the modified techniques described by Oka et al. (1986) (see above), Hoka et al. (1995) and Rescigno et al. (1995) (section 1.6.1.3). Conventional technique achieves “passive” pulmonary flow by increasing CPB venous line resistance, thus “forcing” blood back through the pulmonary circulation, and actively venting this blood from the left heart. In contrast, the dual vent technique establishes a working heart and near physiological pulmonary flow which is passively vented to the CPB circuit. It must be conceded, however, that although enhanced flow is assumed to be the advantage of the dual vent technique, this has not been
definitively established by this study. Other processes may be important. For example, it seems plausible that both gaseous and solid emboli would be more likely to mobilise from trabeculae and recesses in the working myocardial wall.

The difference in efficacy between the conventional and dual vent deairing techniques apparent here did not appear to be explained by bias introduced by surgeon performance or patient selection. In this regard, it is notable that this study monitored the performance of 5 surgeons using conventional technique, each of whom was aware that their deairing efficacy was under scrutiny. The difference between the techniques remained significant even when the conventional technique group was stratified to include only those patients deaired by Dr Milsom, or by the individual surgeon who most successfully performed conventional deairing. Similarly, the difference remained significant when the conventional technique group was stratified to include only those patients whose surgical procedures appeared most conducive to successful deairing. Finally, the success of the dual vent technique cannot be attributed to prolonged and more fastidious efforts by Dr Milsom, since performance of his technique took no longer than conventional methods.

Concern has been expressed at several meetings where the dual vent technique has been presented that its use might increase the likelihood of coronary artery embolisation. There was no evidence of this in the ECGs or in the cardiac enzyme assays, either in Group 2 or in a much larger group of patients deaired in this manner since the present data was collected. Concerns about increased coronary embolisation could be justified if coronary artery flow was increased by the dual vent technique. However, it seems unlikely that coronary flow is enhanced given that aortic root
pressure (and therefore coronary perfusion pressure) is maintained within physiological limits.

The dual vent has been simplified since it was first used. Initially, the variable resistor consisted of artery forceps applied to the aortic vent and constantly adjusted by the surgeon. More recently an automatic and dynamically responding device has been constructed and successfully utilised. Future refinements may include the use of a Doppler to monitor the aortic vent for emboli so that decisions to end deairing attempts and withdraw CPB can be made more objectively.

It is acknowledged that this study did not establish that the reduction in emboli exposure achieved by the dual vent technique elicited an improvement in outcome for these patients. Advocacy for any method of reducing cerebral emboli can be based on the many studies that have shown a correlation between emboli exposure and cerebral dysfunction (section 1.5.3.5.). Nevertheless, the case for adoption of this technique would be advanced by clear demonstration of an advantage for patients undergoing dual vent deairing when compared to conventional technique controls. Funding has been obtained for a study that is powered to show any such advantage, and this commenced at Green Lane Hospital late in 1999.
CHAPTER 6

EMBOLI AND THE CPB CIRCUIT
6.1 INTRODUCTION

This chapter describes the results of experiments undertaken to investigate unexpected observations made during Doppler monitoring of the RCCA during the lignocaine trial. Specifically, emboli generation by hard shell venous reservoirs (HSVRs) and the passage of air in the venous return line through the CPB circuit were studied. Since both observations involve the HSVR, a brief description of these devices is given below. This is followed by accounts of the key clinical observations and the aims of the experiments.

6.1.1 CPB venous reservoirs

The venous reservoir is essentially a blood container. It is the first extracorporeal component of the CPB circuit that venous blood enters after leaving the patient’s systemic circulation, usually via a system of screen filters. The reservoir provides capacitance for the CPB circuit, allowing for example, changes in arterial line flow rate without these having to be immediately matched by changes in venous line flow. Most reservoirs incorporate an integral “cardiotomy reservoir” which receives blood suctioned from the surgical field and returns this to the venous blood via a screen filtration system.

There are two “generic” types of venous reservoirs: hard shell and soft bag. Hard shell venous reservoirs are analogous to a “roofed bucket” with rigid walls and a blood / air interface between blood and the reservoir atmosphere. Soft bag reservoirs are plastic bags that expand to receive blood and collapse when emptying. There is a minimal blood / air interface. At the time of inception of the lignocaine trial, Green lane
Hospital was using the Medtronic Maxima (Medtronic Blood Systems, Anaheim, CA) HSVR for all adult CPB. There were two versions of this device designated “bottom entry” and “top entry”, in reference to the inward flow path of the venous line. It was understood that the two versions were provided by Medtronic only to facilitate easy configuration of the reservoir to any particular CPB machine.

### 6.1.2 Clinical observations

As reported in Chapter 4, several unexpected and potentially important observations were made while Doppler monitoring the lignocaine trial patients for RCCA emboli during the period of stable CPB.

First, an increase in RCCA Doppler signals typical of emboli was recorded whenever the blood volume in the Medtronic HSVRs fell below 500 to 600 ml, and in the apparent absence of any explanatory surgical or CPB event. A clinical study (see methods and results) indicated that maintaining higher blood volumes significantly reduced emboli numbers. This apparent relationship between emboli occurrence and reservoir blood volume was unexpected since the minimum recommended operating volume for these reservoirs was 300 ml.

Second, the appearance of air in the venous return line seemed to reliably result in the appearance of emboli in the RCCA, implying that gas from the venous line was passing through all the components of the CPB machine and back to the patient. Once again, this was unexpected as removal of venous air is one of the reported advantages of an HSVR (Hessel 1993). In addition, other elements of the CPB circuit, such as the
oxygenator and filter, were expected to remove emboli. Because of these expectations, venous air was perceived by the Green Lane surgeons to be benign, and there was usually reluctance to interrupt the surgical procedure in order to take corrective action such as tightening the purse string sutures at the venous line cannulation site.

Towards the end of the Green Lane program, a new technique known as “vacuum assisted venous drainage” (VAVD) was introduced (Anon. 1998). In contrast to gravity venous drainage (GVD), in which venous blood flows from the patient to the CPB venous reservoir passively under the influence of gravity, VAVD utilises a vacuum applied to the venous line. This facilitates flow to the CPB machine and allows the use of narrower tubing conduit in paediatric cases or during the use of so-called “minimally invasive” techniques. This has several advantages, including the use of lower circuit priming volumes, and improvement of access to the surgical field through a smaller portal (Taketani et al 1998). Although no clinical cases undergoing VAVD were monitored during this research program, it was reasoned that application of a vacuum to the venous return line might influence the number of emboli generated if air was entrained.

6.1.3 In vitro studies

Neither emboli generation by HSVRs nor arterial line emboli as a result of air in the venous return line have been recently reported in the cardiac surgery literature. In response to the clinical observations, a series of in vitro experiments was instituted with the following aims:

1. to identify any relationship between emboli formation and blood volume in the Medtronic Maxima HSVRs;
2. to identify the nature of any emboli generated by these reservoirs;
3. to identify the mechanism of any emboli generation by these reservoirs;
4. to investigate emboli generation by a range of other HSVRs;
5. to investigate the relationship between air in the venous return line and numbers of emboli appearing downstream in the arterial line; and
6. to investigate any relationship between the application of VAVD during air entrainment to the venous return line and numbers of emboli appearing downstream in the arterial line.
6.2 METHODS

The experiments conducted to investigate emboli generation by the Medtronic Maxima HSVRs (sections 6.2.1 – 6.2.5) and the passage of venous air (section 6.2.6) through the CPB circuit are described below in approximate chronological order. In many cases, the results of one experiment dictated the aim and / or methodology of the next. It follows that the “logical thread” of this work is most clearly seen if both the method and result (section 6.3) of each experiment is considered before progressing to the next.

6.2.1 Clinical intervention

The RCCA was continuously monitored in adult patients undergoing valve replacement at Green Lane Hospital according to the protocol described in section 4.2.3. The conduct of anaesthesia and CPB was as described in section 3.2.4. After repeated “casual” observation by the Doppler operator (the author in all cases) linked the appearance of RCCA emboli during “stable CPB” (phase D as described in section 4.2.3) to blood levels in the HSVR below 500 – 600 ml, the CPB protocol was changed. Five consecutive valve replacement patients were Doppler monitored during use of the new protocol which required the HSVR blood volume to be maintained above 1000 ml during CPB. The protocol was to be abandoned if maintenance of the higher volume necessitated administering a donor blood transfusion, but this did not occur in any patient. The actual minimum reservoir volume during these 5 procedures was recorded.
The mean emboli count during phase D in these 5 patients was compared to that for
the 5 consecutive patients monitored prior to introduction of the modified minimum
volume using a t-test. A significance level of $p < 0.05$ was chosen.

6.2.2 Relationship between emboli generation and Maxima reservoir
blood volume: the “fixed flow – variable volume” experiment

After the clinical manipulation described in sections 6.2.1 and 6.3.1 reinforced the
suspicion of emboli production by the Medtronic Maxima HSVRs, any further
assessment of the effect of reservoir volume in clinical circuits was considered
unethical. A standard clinical practice of maintaining high reservoir volumes was
adopted and all other experiments were conducted in vitro.

In vitro circuits (Figure 6.1) were constructed using the shell of a Bentley Ben 10
bubble oxygenator (Baxter Healthcare Corporation, Irvine, California, USA) as a
reservoir to simulate a patient. Each circuit included either a Maxima bottom entry or
top entry adult HSVR (Medtronic Blood Systems Inc, Anaheim, California, USA),
and a roller pump on the Stockert S3 CPB machine (Stockert Instrumente, Munich,
Germany). The “patient” reservoir was mounted at the height of a normal operating
table, and the test HSVR was mounted in the normal position on the CPB machine,
close to the ground, in order to simulate normal gravity venous drainage. A venous
line occluder (Stockert Instrumente, Munich, Germany) was placed on the circuit
tubing between the patient and test reservoirs so that the volume in the latter device
could be regulated. The circuit was primed with Plasmalyte 148 and date-expired
human whole blood or resuspended red cells. Each circuit was primed with blood at a
different haematocrit to evaluate any effect of haematocrit on emboli generation.
Figure 6.1  *In vitro* circuit configuration for investigation of relationship between emboli formation and blood volume in the Medronic Maxima HSVRs.
Prime temperature was maintained between 24 and 26°C. Each circuit was monitored downstream of the test reservoir using the Doppler emboli counting device in the same manner as described in sections 2.2.1 and 2.2.2.

Prior to any experimental work in each circuit, the prime was recirculated for at least 30 minutes at 3.5 L min\(^{-1}\) while the reservoir blood volume was maintained at 1000 ml. Large numbers of emboli were usually detected when flow was initiated but after a period of recirculation numbers fell markedly. The emboli were assumed to be bubbles left behind by the priming process, and their disappearance was considered secondary to a “filtering” effect of the two reservoirs included in the circuit.

After construction and “pre-circulation” of each circuit as above, a series of trials was performed. A “trial” consisted of sequential 5 minute emboli counting periods made as the reservoir volume was decreased in stepwise 100 ml decrements during recirculation at a constant rate of 3.5 L min\(^{-1}\). Each trial started with the reservoir blood volume at 1000 ml. Based on the clinical observations, neither Medtronic HSVR was expected to generate emboli at this volume. A baseline count was made over 5 minutes, after which the reservoir volume was reduced to 900 ml, and then to the sequentially lower volumes. These decrements in test reservoir volume were achieved by increasing resistance in the venous return line using the venous line occluder. This caused inflow to the test reservoir to diminish, and “transfer” of circuit blood volume to the “patient” reservoir. The test reservoir volume stabilised when a new equilibrium was established between head of pressure in the patient reservoir and resistance to flow in the venous line. Each new 5 minute counting period began as soon as the new volume was achieved. It was intended to continue these stepwise
volume reductions until the manufacturer's recommended minimum volume was reached. However, emboli generation was so great at volumes much higher than the recommended minimum that the trials had to be curtailed when very high counts (> 300 min⁻¹) caused the counter to interpret the emboli signals as the average Doppler signal amplitude.

Each of the bottom and top entry Medtronic Maxima HSVRs was tested in 3 separate circuits, with 4 or 5 trials conducted in each circuit according to the above protocol (a total of 13 trials for each reservoir). Pooled data from all trials of each reservoir type were analysed by one way ANOVA to assess the significance of any changes in emboli count over the range of blood volumes. In addition, the pooled data for each reservoir type were analysed by paired t-test to determine the volume at which any change in emboli count first became statistically significant. A significance level of p < 0.05 was chosen.

6.2.2.1 Recirculation of emboli

There was concern that since these in vitro circuits did not contain an oxygenator or filter, the design might be flawed. Specifically, the circuit might allow greater recirculation of emboli through the "patient" reservoir and back to the test reservoir than if these components were present. If so, the emboli counts recorded downstream of the test HSVR might be falsely elevated. In order to investigate this possibility, a fourth circuit containing a Medtronic Maxima bottom entry HSVR was constructed and a series of trials conducted according to the protocol described above. In this instance however, 3 trials were conducted with the Doppler probe positioned downstream of the test reservoir as previously and 3 trials with the probe positioned
immediately upstream. The upstream and downstream positions were alternated between trials. Although simultaneous monitoring of both sites during the each trial would have been ideal, a second identical Doppler device was not available.

6.2.3 Mechanism of emboli generation

The experiments described in section 6.2.2 indicated that the Medtronic Maxima HSVRs did produce emboli when operated volumes much higher than the manufacturer's recommended minimum (see section 6.3.2), and that emboli numbers increased exponentially as volume was lowered. The character of the audible Doppler emboli signals suggested that they were bubbles, although there was no immediately obvious mechanism by which the reservoir might generate bubbles.

6.2.3.1 Maxima reservoir design

An example of each reservoir was dismantled and carefully examined for possible causes of bubble generation. The findings are discussed more fully in section 6.3.3.1. To summarise, it was proposed that upward direction or deflection of the venous inflow created a fountain that entrained gas from the reservoir atmosphere into the blood. The 3 experiments described in sections 6.2.3.2 - 4 (below) were undertaken to further investigate this theory.

6.2.3.2 Gas switching in a hollow fibre oxygenator

The first step in validating the "fountain" theory was to confirm that the emboli were bubbles. Another circuit was constructed (Figure 6.2) to include a Medtronic Maxima Plus hollow fibre membrane oxygenator (Medtronic Blood Systems Incorporated, Anaheim, California, USA) between a Medtronic Maxima top entry HSVR and the
Figure 6.2  *In vitro* circuit configuration for investigation of the nature of the emboli generated by the Medtronic Maxima HSVRs.
Doppler probe. The oxygenator functions like a lung. The “sweep gas” flows through thousands of fine hollow fibres with gas-permeable membrane walls. In contrast to the older “bubble oxygenators”, the recirculating blood bathes these fibres and gas exchange occurs across the membrane without the sweep gas and blood directly mixing. The circuit was primed as described in section 6.2.2. After the usual period of pre-circulation, the prime was circulated at 3.5 L min⁻¹. A trial consisted of five sequential 1 minute emboli counts in each of the following conditions:

a. oxygenator sweep gas 4 L min⁻¹ oxygen, reservoir volume 1000 ml; then
b. oxygenator sweep gas 4 L min⁻¹ oxygen, reservoir volume 400 ml; then
c. oxygenator sweep gas 4 L min⁻¹ nitrous oxide, reservoir volume 400 ml; then
d. oxygenator sweep gas 4 L min⁻¹ oxygen, reservoir volume 400 ml.

The rationale for these manipulations of reservoir volume and oxygenator sweep gas was: first, to recirculate blood with the reservoir volume above that likely to result in emboli generation; then to introduce emboli to the circuit by lowering reservoir volume; and finally to expose those emboli to a highly diffusable gas across the highly permeable oxygenator membrane. If the emboli were bubbles, their volume would change due to unequal gas fluxes across the membrane when the sweep gas was changed from oxygen to nitrous oxide (Munson and Merrick 1966); with a consequent change in the nature of the emboli signals or a change in the emboli count. If the emboli were solid, neither the signal quality nor count would change in response to a change in oxygenator sweep gas. Two trials in each of two separate circuits were conducted (a total of 4 trials).
6.2.3.3 Gas switching in the reservoir atmosphere

The experiment described in section 6.2.3.2 demonstrated that the emboli were bubbles (see section 6.3.3.2). The next step in validating the fountain theory was to demonstrate that the bubbles detected downstream of the reservoir originated in the reservoir atmosphere. To investigate this, another circuit was constructed as described in section 6.2.3.2 and as depicted in Figure 6.2. Once again, the prime of expired human blood was circulated at 3.5 L min\(^{-1}\), but in this protocol the oxygenator sweep gas was maintained at 4 L min\(^{-1}\) oxygen throughout, while the reservoir atmosphere gas was manipulated. A trial consisted of five sequential 1 minute emboli counts in each of the following conditions:

a. reservoir volume 1000 ml, reservoir atmosphere air; then
b. reservoir volume 400 ml, reservoir atmosphere air; then
c. reservoir volume 400 ml, reservoir atmosphere carbon dioxide; then
d. reservoir volume 400 ml, reservoir atmosphere air.

Control of the reservoir atmosphere was achieved by flushing the appropriate gas at 4 L min\(^{-1}\) from a regulated high pressure cylinder directly into the enclosed reservoir atmosphere through one of the available accessory ports. All other ports were sealed except one which was left open to room air to allow “flow through” of the infused gas.

The rationale for these manipulations of reservoir volume and atmosphere was: first, to recirculate blood with the reservoir volume above that likely to result in emboli generation; then to introduce bubbles to the circuit by lowering reservoir volume; and finally to change the reservoir atmosphere, the putative source of the bubbles, to a
more soluble and rapidly diffusing gas. The number of any bubbles originating from
the reservoir atmosphere would consequently be reduced due to rapid dissolution into
blood. If the bubbles did not originate from the reservoir atmosphere, changes in the
atmosphere gas would have no effect on bubble numbers. Two trials in each of two
separate circuits were conducted (a total of 4 trials).

6.2.3.4 Effect of increasing flow: the "fixed volume – variable flow"
    experiment

The experiment described in section 6.2.3.3 demonstrated that the bubbles emanating
from the Medtronic Maxima HSVRs arose from the reservoir atmosphere (see section
6.3.3.3). Final confirmation of a "fountain" mechanism was sought. It was reasoned
that any fountain would be exacerbated by not only a reduction in reservoir volume
(as previously demonstrated) but also by an increase in circuit flow rate while volume
was held constant. A "fixed volume – variable flow" experiment was therefore
conducted to investigate the effect of changes in flow rate on the number of emboli
detected downstream of the Medtronic Maxima top entry HSVR.

An important change in methodology was introduced in this experiment. The trial
described in section 6.2.2.1 confirmed that bubbles did recirculate in the original
circuits depicted in Figure 6.1. Although this did not detract from the essential
conclusion of the experiment described in section 6.2.2, it introduced a degree of
uncertainty over actual emboli numbers generated by the reservoirs. A new strategy
for obtaining an experimental circuit was therefore adopted for this and subsequent
investigations. Instead of constructing and priming an experimental circuit de novo,
clinical circuits were salvaged post-operatively. These circuits included an oxygenator
and an arterial line filter, neither of which had been included in the circuit for the fixed flow - decreasing volume experiment because of cost concerns, and both of which might contribute to reduction of emboli recirculation. Indeed, it was confirmed early in the development of our circuit salvage technique that almost no emboli recirculated back to the venous line in these circuits.

To salvage a clinical circuit, the circuit priming was carefully preserved at termination of clinical CPB. The venous and arterial cannulae were plumbed into the shell of a Bentley Ben 10 bubble oxygenator that was used, as previously, to simulate a patient. The circuit volume was restored with plasmalyte 148 and date expired resuspended red cells which were either Group O+ or matched to the blood type of the patient perfused from that circuit. The circuits were left recirculating at 1 L min$^{-1}$ until the experiment began.

In venous - arterial sequence, the salvaged circuits consisted of the Medtronic Maxima top entry HSVR, a roller pump on the Stockert S3 heart - lung machine (Stockert Instrumente, Munich, Germany), the Medtronic Maxima hollow fibre membrane oxygenator (Medtronic Blood Systems, Anaheim, CA) and a Bentley AF1040D 40 μm screen arterial filter (Baxter Healthcare Corporation, Irvine, California, USA) with continuous purge. For this experiment, in which flow rates as high as 6 L min$^{-1}$ were anticipated, the roller pump was replaced by a Medtronic centrifugal Biopump (Medtronic Inc., Anaheim, California, USA). Roller pumps had earlier been seen to generate bubbles by cavitation at flow rates greater than 5.5 L min$^{-1}$. As previously the HSVR volume was regulated by fine adjustment of a venous line occluder. The circuit layout is depicted in Figure 6.3.
Figure 6.3  Configuration of salvaged clinical CPB circuits for *in vitro* experiments.
During the experiment, the blood volume in the HSVR was maintained at 600 ml, previously shown to be the approximate threshold at which fountaining seemed to begin in the top entry HSVR when the flow rate was 3.5 L min\(^{-1}\) (see section 6.3.2). The Doppler probe was positioned immediately downstream of the reservoir. The prime was initially recirculated at 3.5 L min\(^{-1}\) and a baseline count was recorded over 150 seconds. The flow was then increased in 500 ml min\(^{-1}\) increments, with a 150 second count made at each new flow rate. The maximum flow rate achieved was 5 L min\(^{-1}\) since bubbles became too numerous to be accurately counted at rates greater than this. This procedure was repeated 4 times in each of 2 separate circuits (a total of 8 studies).

One way ANOVA was used to assess the significance of any change in the mean count over the range of different flow rates. A paired t-test was used to compare the mean count at different flow rates. A significance level of \(p < 0.05\) was chosen.

### 6.2.4 Bubble generation by other venous reservoirs

After the above experiments established that the Medtronic Maxima HSVRs entrained bubbles into the blood when operated at blood volumes well in excess of the manufacturers recommended minimum, a series of experiments was conducted to determine whether this was an invariable phenomenon associated with the operation of all HSVRs.

The “fixed flow – variable volume” protocol described in section 6.2.2 and the “fixed volume – variable flow” protocol described in section 6.2.3.4 was repeated for the Medtronic Maxima top entry HSVR and 4 other HSVRs. The HSVRs investigated in
this comparative experiment (and the manufacturer’s recommended minimum operating volumes) were: the Medtronic Maxima Top Entry HSVR (Medtronic Inc., Anaheim, California, USA), 300 ml; the Terumo Capiox SX HSVR (Terumo Corp., Tokyo, Japan), 200 ml; the Sorin Monolyth HSVR (Sorin Biomedical Inc., Irvine, California, USA), 300 ml; the Baxter Bentley HSR-4000 HSVR (Baxter Healthcare Corporation, Irvine, California, USA), 300 ml; and the new generation Medtronic Maxima Forte HSVR (Medtronic Inc., Anaheim, California, USA), 500 ml. Salvaged clinical circuits were used as described in section 6.2.3.4 and depicted in Figure 6.3 since they had the clear advantage of near zero emboli recirculation. When circuits were prepared for testing the Maxima Forte HSVR, the protocol for circuit salvage differed from that previously described. This device could not be used clinically since neither suitable holders nor the dedicated Maxima Forte oxygenator were available at the time. Instead, a Forte HSVR pre-primed with plasmalyte 148 was carefully cut into a salvaged clinical circuit to replace the Terumo HSVR that had been used during surgery. The Terumo Capiox SX membrane oxygenator was left in place for the *in vitro* experiment. Once again, for the “fixed volume – variable flow” experiments the centrifugal pump was utilised as previously described (section 6.2.3.4) because of concerns over cavitation at the roller pump head at high flow rates. In the “fixed flow – variable volume” experiment the roller pump was not replaced because flow was maintained at 3.5 L min\(^{-1}\).

Count periods at each new volume or flow rate were standardised at 150 seconds in both protocols. Three or 4 trials of each reservoir were performed in each of 2 salvaged circuits in both protocols. This represented a total of 6 – 8 trials of each reservoir in both protocols. For each reservoir, one way ANOVA was used to assess
the significance of any change in emboli count as volume was decreased or flow was increased. A paired t-test was used to compare the mean count for the same reservoir operating at different volumes or flows, and an unpaired t-test was used to compare mean count between reservoirs operating at the same volume or flow. A significance level of $p < 0.05$ was chosen.

6.2.4.1 Forte reservoir design

The above experiment did demonstrate a (comparatively) minor degree of emboli generation by the Medtronic Forte reservoir (see section 6.3.4.1). It follows that an example of this reservoir was dismantled and the design closely examined for possible causes of emboli generation.

6.2.5 Passage of reservoir generated bubbles through the CPB circuit

The experiments described above established that a unique fountaining phenomenon in the Medtronic Maxima HSVRs generated bubbles when the reservoirs were operated at volumes well in excess of the manufacturer's recommended minimum. However, the number of these bubbles that appeared in the CPB circuit arterial line and therefore the number that actually reached the patient was not determined. An experiment was conducted to determine the degree to which bubbles generated by a Medtronic Maxima top entry HSVR were removed by the membrane oxygenator and the arterial line filter.

Salvaged clinical circuits as described in section 6.2.3.4 incorporating a Medtronic Maxima top entry HSVR were used. The protocol was as described above for the "fixed flow - decreasing volume" experiments (section 6.2.2), except that three studies
were performed with the Doppler probe positioned downstream of the reservoir, the
oxygenator and the filter, in each of two circuits (a total of six studies for each
position). The oxygenator sweep gas was set at 1.5 L min$^{-1}$ oxygen.

For each monitoring site, the significance of any change in count as reservoir volume
was decreased was tested by one way ANOVA. In addition, for each reservoir volume,
the significance of the difference in count recorded at the three monitoring sites was
also assessed using a one way ANOVA. A significance level of $p < 0.05$ was chosen.

Since the Medtronic Forte HSVR did generate some bubbles in the comparative fixed
flow – decreasing volume experiment (section 6.2.4), a truncated version of the above
protocol was conducted in one circuit incorporating the Forte HSVR. Five trials were
performed in which the reservoir volume was first kept at 1000 ml, and then at 400
ml, with a 150 second count made with the probe downstream of the arterial line filter
at each volume.

6.2.6 Passage of venous air through the CPB circuit

6.2.6.1 Passage of venous air through hard shell venous reservoirs

During the comparative study of bubble generation by HSVRs described in section
6.2.4 the ability of these devices to remove incoming venous air was also investigated.
This seemed a logical prelude to a study of venous air passage through the entire
circuit since one of the perceived advantages of HSVRs is their ability to remove
venous air (Hessel 1993).
Salvaged clinical circuits as described in section 6.2.3.4 were utilised. The roller pump was retained for all trials since high flow rates were not used. Each circuit was configured to be identical with respect to standard tubing length between components, total blood volume, and the vertical distances between the venous air entry site (see below) and the blood levels in the reservoir simulating the patient and the HSVR under test. The prime was recirculated at a constant rate of $3.5 \text{ L min}^{-1}$. The blood volume in the HSVR under test was maintained at 1000 ml, chosen as both a “typical” clinical level, and a volume at which no bubble generation by any of the reservoirs would be expected. The Doppler probe was positioned immediately downstream of the reservoir. A venous air entry site was created by introducing a 26 gauge hypodermic needle attached to a two way stop cock into the venous line tubing just distal to the venous occluder. After a 180 second baseline emboli recording period, the stop cock was alternatively opened fully for 5 seconds, allowing air to be entrained into the venous line, and then closed for 25 seconds over a three minute period. Thus, the stop cock was open for a total of 30 seconds in the 180 second period. This “pulsed” method of venous air introduction became necessary after trials of continuous exposure resulted in too many emboli distal to the HSVRs to be reliably counted. During periods of opening, the needle allowed a stream of bubbles into the venous line. These bubbles were visible through the venous line tubing and appeared very similar in terms of size and number to those seen in a typical clinical situation. Emboli were continuously counted in the HSVR exit line throughout the 180 second period of intermittent air introduction.

All the HSVRs tested in the comparative study of bubble generation (section 6.2.4) were tested according to this protocol. The procedure was repeated 6 to 8 times in
each of 2 separate circuits (a total of 12 - 16 studies) for each HSVR. The mean emboli count downstream of the reservoir over a 180 second period of pulsed venous air exposure was calculated after subtracting the baseline count from the number recorded during each study. An unpaired t-test was used to compare reservoir performance. A significance level of $p < 0.05$ was chosen.

6.2.6.2 Passage of venous air to the arterial line

The experiments described in section 6.2.6.1 established that while some HSVRs appeared better than others at removing venous air from the circuit, large numbers of bubbles still appeared downstream of all reservoirs (see section 6.3.6.1). However, the number of these bubbles appearing in the CPB circuit arterial line and therefore the number that would actually reach the patient was not determined. An experiment was conducted to test the hypothesis that entrained venous air is incompletely removed by the CPB circuit during gravity venous drainage (GVD) and that entrainment of greater volumes of air result in larger numbers of arterial line bubbles.

Salvaged clinical circuits as described in section 6.2.3.4 and depicted in Figure 6.3 were utilised. At the time these experiments were performed the Medtronic Forte reservoir was in routine clinical use at Green Lane and we were therefore able to use these reservoirs in the salvaged clinical circuits. In the experiment described in section 6.2.6.1 the Forte had proven the most effective HSVR in venous air removal. It follows that the arterial line counts obtained in this experiment could be considered as a “best case scenario”.
In order to control the volume of venous air entrained, the entrainment system was modified from that described in section 6.2.6.1. The venous air injection site was created by inserting a standard ¼” luer lock connector into the venous line beyond the venous occluder, and an injection plug (B | Braun, Melsungen, Germany) was placed into the luer. A 3 cm stainless steel 21 gauge hypodermic needle was introduced into the venous line through the injection plug and a three way stopcock was attached to the needle. Opening the stopcock enabled “venous air” entertainment. In this experiment, the volume of air was limited by connecting a 1.0 L blood transfer pack (Baxter Healthcare Corp), pre-filled with the desired volume of gas, to the stopcock. In this mode, the volume was controlled but there was no restriction on the rate at which air could be entrained. In subsequent experiments requiring control of volume and entrainment rate, air was introduced from a pre-filled syringe at the desired rate. In practice, the new venous air delivery system generated venous line bubbles that were indistinguishable to the eye from those observed in the clinical situation.

The salvaged circuit prime was recirculated at 3.5 L min⁻¹ and the volume of the HSVR maintained at 1000 ml. The oxygenator was ventilated with a sweep gas flow rate of 2.5 L min⁻¹ and a FiO₂ of 0.50. The Doppler probe was mounted on the arterial line tubing distal to the filter. A baseline emboli count was recorded over 180s prior to each experimental intervention. Twenty five ml of air was entrained at an uncontrolled rate and the entrainment time was recorded. The bubble count was recorded over 180 seconds beginning at initiation of air entrainment. The net experimental emboli count was obtained in all cases by subtracting the baseline count from the count following entrainment of venous air. The procedure was repeated for 50, 75, and 100ml of entrained air, and this sequence was repeated 3 times in each of 3 separate circuits (a
total of 9 studies for each volume of venous air). One way analysis of variance (ANOVA) was used to assess the significance of any trend in the mean emboli count with the increasing volumes of entrained venous air. A significance level of $p < 0.05$ was chosen.

6.2.6.3 Effect of vacuum assisted venous drainage on passage of venous air to the arterial line

After the above experiment (section 6.2.6.2) recorded bubbles in the arterial line after venous air entrainment (see section 6.3.6.2), an experiment was conducted to test the hypothesis that this process might be exacerbated under the influence of VAVD. The protocol described in section 6.2.6.2 was repeated for 2 volumes of air (25 ml and 50 ml) under conditions of GVD and VAVD. For the VAVD trials, all leurs and inlet ports on the HSVR were sealed and a 60 mmHg vacuum was applied to the reservoir vent port. The vacuum was controlled using a thoracic low-vacuum regulator (Clements Medical Equipment, Sydney, Australia) and monitored using a pressure transducer module on the CPB machine. Once again, the protocol was repeated 3 times in each of 3 separate circuits (a total of 9 trials for each volume of air under each condition). An unpaired t-test was used to compare the mean arterial line bubble count recorded after entrainment of equal volumes of air during GVD and VAVD. The mean time for these volumes of air to be entrained under each condition was similarly compared. A significance level of $p < 0.05$ was chosen.
6.2.6.4 Effect of controlling air entrainment rate on passage of venous air to the arterial line during vacuum assisted venous drainage

The experiment described at 6.2.6.3 showed that markedly greater numbers of bubbles reached the distal arterial line when air was entrained during VAVD. It was also demonstrated that air was entrained significantly more quickly during VAVD (see section 6.3.6.3). An experiment was conducted to test the hypothesis that this difference in the rate of venous air entrainment accounts for the greater number of bubbles reaching the distal arterial line during VAVD. The experimental circuit was configured and operated as described in section 6.2.6.2. A disposable syringe was filled with 50 ml of air and attached to the three way tap on the venous air injection site. Injection of the air at 2 ml s\(^{-1}\) and a 180s bubble counting period were then begun simultaneously. This was repeated 6 times during both GVD and VAVD in each of 2 separate circuits (a total of 12 trials under each condition). An unpaired t-test was used to compare mean arterial line bubble count under GVD and VAVD. A significance level of \( p < 0.05 \) was chosen.

6.2.6.5 Effect of entrainment of \( \text{CO}_2 \) instead of air on passage of venous gas to the arterial line during gravity drainage and vacuum assisted venous drainage

Flooding of the surgical field with \( \text{CO}_2 \) has been advocated for reducing circulation of bubbles left behind in the heart chambers and pulmonary veins after heart closure (see section 1.6.1.3.). The same argument could be applied to bubbles entrained to the venous line from the surgical field. An experiment was conducted to test the hypothesis that entrainment of \( \text{CO}_2 \) instead of air reduces the resultant arterial line bubble counts during both GVD and VAVD. Once again the experimental circuit was
configured and operated as described in section 6.2.6.2. Gas entrainment followed the
unrestricted rate protocol. Arterial line bubble counts were recorded over 180s from
the onset of gas entrainment under the following conditions: first during GVD,
entrainment of 75 ml of air and 100 ml of air, and then 75 ml of CO₂ and 100 ml of
CO₂; and second during VAVD, entrainment of 25 ml of air and 50 ml of air, and then
25 ml of CO₂ and 50 ml of CO₂. Each combination of gas, volume and drainage
condition was tested 9 times. An unpaired t-test was used to compare the arterial line
bubble counts for air and CO₂ at each combination of entrained gas volume and
drainage condition. A significance level of p < 0.05 was chosen.
6.3 RESULTS

6.3.1 Clinical intervention

Individual and group data for the 5 consecutive patients undergoing CPB before and after introduction of the modified minimum reservoir volume recommendation are shown in Table 6.1. The mean rate of embolisation (emboli minute\(^{-1}\)) and the mean total emboli exposure during stable CPB were significantly lower for the “after” group in which an effort was made to keep the reservoir volume at 1000 ml (p < 0.01). Patient 1 in the “before” group had a count comparable to the patients in the “after” group, suggesting that the reservoir may have been kept at high volumes in this patient. Since reservoir volumes in the “before” group were not recorded, this cannot be confirmed.

6.3.2 Relationship between emboli generation and Maxima reservoir blood volume

Progressive lowering of the reservoir volume in the \textit{in vitro} circuit caused an exponential increase in the number of emboli recorded over five minutes in circuits containing both bottom and top entry reservoirs. The haematocrit of the circuit prime had no effect on emboli generation, and the data from all trials (n = 13) in each reservoir type was pooled and are presented in Figure 6.4. The increase in count as reservoir volume was lowered was significant in both reservoir types (p < 0.01). The increase in count compared to that made at the 1000 ml “baseline” volume was significant in the bottom entry reservoir at 900 ml (p < 0.01) and in the top entry reservoir at 700 ml (p < 0.01).
Table 6.1. RCCA emboli counts during stable CPB in patients monitored before and after recommendation of the 1000 ml minimum venous reservoir volume.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Operation</th>
<th>Actual minimum reservoir volume (ml)</th>
<th>Stable CPB emboli min⁻¹</th>
<th>Stable CPB total emboli</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENTS PRIOR TO NEW MINIMUM RESERVOIR VOLUME</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>AVR/MVR</td>
<td>unrecorded</td>
<td>0.43</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>AVR + 2 CABG</td>
<td>unrecorded</td>
<td>16.1</td>
<td>1562</td>
</tr>
<tr>
<td>3</td>
<td>AVR</td>
<td>unrecorded</td>
<td>10.7</td>
<td>1059</td>
</tr>
<tr>
<td>4</td>
<td>AVR</td>
<td>unrecorded</td>
<td>9.7</td>
<td>708</td>
</tr>
<tr>
<td>5</td>
<td>AVR + 2 CABG</td>
<td>unrecorded</td>
<td>12.9</td>
<td>1525</td>
</tr>
<tr>
<td><strong>Mean ± SEM</strong></td>
<td></td>
<td></td>
<td>9.97 ± 2.6</td>
<td>978.4 ± 283.1</td>
</tr>
<tr>
<td><strong>PATIENTS AFTER NEW MINIMUM RESERVOIR VOLUME</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>AVR</td>
<td>1600</td>
<td>1.5</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>AVR</td>
<td>900</td>
<td>1.0</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
<td>AVR</td>
<td>1000</td>
<td>0.82</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>MVR</td>
<td>900</td>
<td>1.6</td>
<td>111</td>
</tr>
<tr>
<td>5</td>
<td>AVR</td>
<td>1000</td>
<td>1.9</td>
<td>103</td>
</tr>
<tr>
<td><strong>Mean ± SEM</strong></td>
<td></td>
<td></td>
<td>1.37 ± 0.2</td>
<td>82.2 ± 11.8</td>
</tr>
</tbody>
</table>

AVR = aortic valve replacement; CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; MVR = mitral valve replacement; SEM = standard error of the mean
Figure 6.4. Mean emboli count (± SEM) over 5 minutes measured downstream of the Medtronic Maxima bottom and top entry HSVRs as reservoir blood volume is reduced.
6.3.2.1 Recirculation of emboli

The suspicion of emboli recirculation was confirmed when the *in vitro* circuit was Doppler monitored both upstream and downstream of the reservoir. However, Table 6.2 shows that even if all emboli entering the reservoir redistribute through it, recirculation can account for no more than 40% of emboli detected downstream. Thus, while recirculation occurred, the reservoir itself was clearly demonstrated to generate emboli.

**Table 6.2** Emboli count over 5 minutes recorded upstream and downstream of a Medtronic Maxima bottom entry HSVR at progressively lower volume.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reservoir blood volume (ml)</th>
<th>PROBE DOWNSTREAM OF RESERVOIR</th>
<th>PROBE UPSTREAM OF RESERVOIR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1000</td>
<td>900</td>
<td>800</td>
</tr>
<tr>
<td>1</td>
<td>47</td>
<td>42</td>
<td>190</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>32</td>
<td>213</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>26</td>
<td>237</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>29.3 ± 9.1</td>
<td>33.3 ± 4.7</td>
<td>213.3 ± 13.6</td>
</tr>
</tbody>
</table>

6.3.3 Mechanism of emboli generation

6.3.3.1 Maxima reservoir design

An example of each of the Medtronic Maxima reservoirs was carefully dismantled and examined for possible causes of emboli generation. The notable feature of both designs was the venous flow-path. In the bottom entry reservoir the venous line was
plumbed into the base of the reservoir shell, and then passed upward to open into an unconstrained chamber in the main body of the device (see Figure 6.5). It seemed possible that swiftly flowing blood might "fountain" upward and that bubbles from the reservoir atmosphere might be entrained in turbulence created at the fountain / blood interface. This theory was compatible with the observation of increasing numbers of emboli as blood volume was lowered, since any fountain would be more pronounced as the venous outlet became progressively more exposed. In the top entry reservoir the venous line passed through the roof of the reservoir, and then through a conduit to the base of the main body of the device where the incoming venous blood was upwardly deflected by a cup-like baffle (see Figure 6.6). Once again, a fountain of upwardly deflected blood could be expected to entrain bubbles from the reservoir atmosphere. It was proposed that upward deflection of blood would not produce such a prominent fountain as a direct upward flow-path, and that this explained why the top entry reservoir did not generate emboli until it reached lower volumes (see Figure 6.4). It was notable that 3 other brands of HSVR examined (see Section 6.3.4) all had downwardly directed venous flow-paths. No other obvious mechanisms for emboli generation were noted.

6.3.3.2 Gas switching in a hollow fibre oxygenator.

The pattern of change in emboli count during the various circuit manipulations was identical in all four trials. The changes recorded in one of the trials are depicted in Figure 6.7. Few emboli were detected during the period of recirculation while reservoir volume was held at 1000 ml. As expected, there was an immediate increase in emboli numbers when the reservoir volume was reduced to 400 ml. The numbers of emboli remained relatively constant minute by minute until the oxygenator sweep gas
Figure 6.5  Cut-away view of the Medtronic Maxima Bottom Entry hard shell venous reservoir (from Medtronic promotional material) showing the upwardly directed venous line entry portal in an unconstrained chamber (white arrowhead).
Figure 6.6  Cut-away view of the Medtronic Maxima Top Entry hard shell venous reservoir (from Medtronic promotional material) showing the upwardly deflected venous line entry portal in an unconstrained chamber (white arrowhead).
Figure 6.7  Emboli count downstream of a Medtronic Maxima top entry HSVR and membrane oxygenator during manipulations of reservoir blood volume and oxygenator sweep gas.
was changed from oxygen to nitrous oxide. Over the 5 minute period of nitrous oxide substitution there was a dramatic fall in the numbers of emboli detected downstream of the oxygenator, and this trend was reversed soon after the sweep gas was changed back to oxygen. This change in count, elicited merely by changing the nature of the gas to which the emboli were exposed in the oxygenator, strongly supported the proposal that the emboli were bubbles.

6.3.3.3 Gas switching in the reservoir atmosphere

Once again, the pattern of change in emboli count during the various circuit manipulations was identical in all four trials. The changes recorded in one of the trials are depicted in Figure 6.8. The changes in emboli count were almost identical to those described for the oxygenator gas switching experiment described above. Few emboli were detected during the period of recirculation while reservoir volume was held at 1000 ml. There was an immediate increase in emboli numbers when the reservoir volume was reduced to 400 ml. The numbers of emboli remained relatively constant until the reservoir atmosphere gas was changed from air to carbon dioxide. Over the 5 minute period of carbon dioxide substitution there was a dramatic fall in the number of emboli detected downstream of the oxygenator, and this trend was reversed soon after the reservoir atmosphere was changed back to air. This change in count, elicited by changing the reservoir atmosphere to a more soluble rapidly diffusing gas, strongly supported the proposal that the bubbles were entrained from the reservoir atmosphere.

6.3.3.4 Effect of increasing flow

Progressively increasing the flow rate in the in vitro circuit caused a significant and exponential increase in the number of emboli recorded over 150s downstream of the
Figure 6.8  Emboli count downstream of a Medtronic Maxima top entry HSVR and membrane oxygenator during manipulations of reservoir blood volume and reservoir atmosphere.
Medtronic Maxima top entry reservoir (p < 0.001) (see Figure 6.9). This increase was first significant (compared to the “baseline” count made at a flow rate of 3.5 L min\(^{-1}\)) when flow rate was increased to 4.0 L min\(^{-1}\) (p < 0.001). These observations were consistent with the exacerbation of fountaining at an upwardly deflected inlet portal as flow was increased.

6.3.4 Bubble generation by other venous reservoirs

6.3.4.1 Relationship between emboli formation and reservoir volume.

As previously, progressive lowering of the reservoir volume caused an exponential increase in the number of bubbles recorded over 150s downstream of the Medtronic Maxima top entry reservoir (p < 0.001) (see Figure 6.10.). This increase was first significant at 700 ml (p < 0.001). There was also a significant increase in numbers of emboli detected downstream of the Medtronic Maxima Forte (p < 0.001). This increase was consistently biphasic (see Figure 6.11); significant changes occurred between 1000 and 700 ml (p < 0.001) and then between 500 and 400 ml (p < 0.001). Emboli were significantly more numerous downstream of the Forte than for all other reservoirs (except the Medtronic Maxima top and bottom entry devices) at volumes below 700 ml (p < 0.05). It is notable however, that although increases in emboli numbers downstream of the Forte were significant, the absolute numbers remained very low. The clinical significance of apparent emboli generation by the Forte is addressed in section 6.2.5. Emboli numbers did not increase downstream of any of the other reservoirs tested, even when they were operated at volumes well below the recommended minimum.
Figure 6.9  Mean emboli count (± SEM) over 150 seconds measured downstream of the Medtronic Maxima top entry HSVR as circuit flow rate is increased.
Figure 6.10  Mean (± SEM) emboli count over 150 seconds recorded downstream of the reservoirs tested as reservoir blood volume was progressively decreased. Note: MM-BER = Medtronic Maxima bottom entry reservoir; MM-TER = Medtronic Maxima top entry reservoir. Data for the MM-BER is from the previous experiment reported in Figure 6.4, adjusted for the shorter recording period utilised here.
Figure 6.11  Mean (± SEM) emboli count over 150 seconds downstream of the Medtronic Forte HSVR as reservoir blood volume is progressively lowered.
6.3.4.2 Relationship between emboli formation and flow rate

As reported in section 6.3.3.4 there was a significant increase in bubble numbers downstream of the Medtronic Maxima top entry HSVR as reservoir volume was held steady and flow rate was increased. There was also a significant increase in the emboli count recorded downstream of the Medtronic Forte as flow increased \((p < 0.001)\) (see Figure 6.12). The counts recorded downstream of the Forte were greater than for any of the other 3 HSVRs at any volume \((p < 0.025)\). However, as in the fixed flow – variable volume protocol, although the increase downstream of the Forte was statistically significant, the actual increase in emboli numbers was small. Similarly, an increase in emboli numbers downstream of the Terumo and Sorin HSVRs as flow increased did reach statistical significance \((p < 0.05)\), but the actual numbers of emboli were very small. There was no significant change in emboli numbers recorded downstream of the Baxter HSVR as flow increased.

6.3.4.3 Forte reservoir design

Once again, the notable feature of the Forte design was the venous flow-path. As with the Medtronic Maxima top entry HSVR, the venous line passed through the roof of the reservoir, and then through a conduit toward the base of the main body of the device where the incoming venous blood was upwardly deflected by a cup-like baffle. In the Forte however, any fountaining is constrained by enclosure of the outlet portal in a roofed chamber (see Figure 6.13). Limited fountaining could still occur within the chamber if a blood - air interface developed, and it is notable that the 1000 – 700 ml volumes over which emboli were first detected downstream of this device corresponded to the volumes over which the chamber gradually became uncovered. Moreover, the “second phase” of emboli production in the Forte (between 500 and
Figure 6.12  Mean (± SEM) emboli count over 150 seconds downstream of the HSVRs tested as flow rate was increased. Note: MM-TER = Medtronic Maxima top entry HSVR.
Figure 6.13  Cut-away view of the Medtronic Forte hard shell venous reservoir (from Medtronic promotional material) showing the upwardly deflected venous line entry portal in a constrained chamber (white arrowhead).
400 ml volume) corresponded to the development of a "waterfall" from the entry chamber down to the main blood pool. It should be noted that the minimum recommended operating volume for the Forte is 500 ml. This theory of "constrained fountaining" to explain emboli generation by the Forte HSVR was not investigated further.

6.3.5 Passage of reservoir generated bubbles through the CPB circuit

There was a significant increase in bubble count downstream of the reservoir, the oxygenator and the arterial line filter as reservoir volume was lowered (p < 0.001) (see Figure 6.14). With the exception of the measurements made with the reservoir volume at 1000 ml (not shown in the Figure) and 800 ml, the count at each volume was lower downstream of the oxygenator, and even lower downstream of the filter, although this trend did not become significant until the reservoir volume reached 500 ml (p < 0.001). Nevertheless, with the reservoir operated at 400 ml blood volume and at a clinically relevant flow rate of 3.5 L min\(^{-1}\), 175 bubbles still passed back to the "patient" every minute.

In the abridged experiment to determine the extent to which emboli generated by the Forte HSVR appeared downstream of the filter, the mean count over 150 seconds at reservoir volumes of 1000 and 400 ml were 0.4 and 5.4 respectively. Thus even when operated below the manufacturer's recommended minimum volume, emboli entry to the arterial line was only 2.16 min\(^{-1}\).
Figure 6.14  Mean (± SEM) emboli count over 150 seconds downstream of the reservoir, oxygenator, and filter as reservoir blood volume is decreased in Medtronic Maxima top entry HSVR.
6.3.6 Passage of venous air through the CPB circuit

6.3.6.1 Passage of venous air through hard shell venous reservoirs.

Emboli were recorded downstream of all HSVRs during pulsed introduction of venous air over a 3 minute period (see Figure 6.15). Because of the temporal relationship between air introduction to the venous line and the appearance of the emboli downstream of the reservoir, the emboli were assumed to be bubbles. Significantly fewer bubbles appeared downstream of the Medtronic Forte HSVR than the Sorin HSVR ($p < 0.01$), and downstream of the Sorin than the Baxter HSVR ($p < 0.01$). There was no difference between the Baxter, Medtronic Maxima top entry and Terumo HSVRs.

6.3.6.2 Passage of venous air to the arterial line

Bubbles were detected in the arterial line downstream of the filter every time air was entrained into the venous line during GVD (see Figure 6.16). The bubble count increased with increasing volumes of entrained venous air ($p < 0.001$).

6.3.6.3 Effect of vacuum assisted venous drainage on passage of venous air to the arterial line

Once again, bubbles were detected in the arterial line downstream of the filter every time air was entrained into the venous line. For both volumes of air, an almost 10-fold increase in arterial line bubble count was seen under VAVD when compared to GVD ($p < 0.0001$) (see Figure 6.17). Air was entrained at a significantly faster rate under the influence of VAVD ($p < 0.0001$) (see Figure 6.18).
Figure 6.15  Mean (± SEM) emboli count detected downstream of the HSVRs tested over 180 seconds of pulsed venous air exposure. MM-TER = Medtronic Maxima top entry HSVR.
Figure 6.16  Mean (± SEM) bubble count in the arterial line downstream from a 40 μm filter after entrainment of air to the venous return line during gravity venous drainage.
Figure 6.17  Mean (± SEM) bubble count in the arterial line downstream from a 40 μm filter after entrainment of air to the venous return line during GVD and VAVD.
Figure 6.18  Mean (± SEM) time to complete entrainment of air under GVD and VAVD.
6.3.6.4 Effect of controlling air entrainment rate on passage of venous air to the arterial line during vacuum assisted venous drainage

The mean arterial line bubble count after restricted rate entrainment of 50 ml of venous air was higher during VAVD than GVD, but the difference was markedly less than during unrestricted rate entrainment (see Figure 6.19) and did not reach our chosen level of significance. Note that the bubble counts following entrainment of 50 ml air at an unrestricted rate have been transposed from Figure 6.17.

6.3.6.5 Effect of entrainment of CO$_2$ instead of air on passage of venous gas to the arterial line during gravity drainage and vacuum assisted venous drainage

Arterial line bubble counts recorded after entrainment of CO$_2$ were significantly lower than for air entrainment at all gas volumes, and during both GVD and VAVD (p < 0.001) (Figure 6.20). Nevertheless, large numbers of bubbles still appeared distal to the arterial line filter when CO$_2$ was entrained into the venous line.
Figure 6.19  Mean (± SEM) bubble count in the arterial line downstream from a 40 µm filter after entrainment of 50 ml air to the venous return line at unrestricted and restricted rates during GVD and VAVD.
Figure 6.20  Mean (± SEM) bubble count in the arterial line downstream from a 40 μm filter after entrainment of air or CO₂ to the venous return line at unrestricted rates during GVD and VAVD.
6.4 DISCUSSION

Two unexpected and previously unreported phenomena were investigated in this series of experiments after incidental observations made during Doppler monitoring of the RCCA in patients undergoing left heart valve surgery.

6.4.1 Bubble generation by hard shell venous reservoirs

The first, an apparent association between blood volume in the Medtronic Maxima HSVRs and the detection of emboli in the RCCA, was supported by a reduction in RCCA emboli when higher volumes were maintained. The association could not be confirmed by our clinical audit of the effect of higher volumes, and once this association was made, no further intentional manipulation of reservoir volume in the clinical setting was undertaken because it was considered unethical.

Emboli generation by the Medtronic Maxima reservoirs as blood volume decreased was confirmed in vitro. Even though the design of our early in vitro circuits was flawed in allowing recirculation of emboli, such recirculation did not account for the majority of emboli emanating from these HSVRs. A change in emboli count after exposure to nitrous oxide in a membrane oxygenator confirmed that the emboli were bubbles. The decline in emboli numbers after switching the HSVR atmosphere to CO₂ was a predictable outcome of a more soluble and rapidly diffusing gas being entrained into the blood and showed that the bubbles came from the reservoir atmosphere.

Inspection of the Maxima designs revealed the potential for fountaining at the venous blood inflow portal. Since flow in the top entry device was upwardly deflected rather than upwardly directed as in the bottom entry device, the fountaining effect was likely
to be less prominent. This was consistent with the observation that the top entry device did not generate bubbles until it reached lower volumes. An increase in bubble detection downstream of both devices as flow rate increased was consistent with bubble generation in a fountain. These bubbles were not completely removed by the circuit oxygenator and arterial line filter. Thus, when the top entry device was operated at a blood volume of 400 ml and a clinically relevant flow rate of 3.5 L min⁻¹, more than 150 bubbles could be expected to pass to the patient every minute. On the basis of these findings, the recommended minimum operating volumes for these reservoirs during use at Green Lane Hospital was changed to 600 – 700 ml, and greater if possible.

Prior to these findings, there were no published reports of bubbles generated by modern CPB circuit reservoirs. The passage of microemboli through cardiotomy, oxygenator, or arterial reservoirs has previously been described, and some studies have cited low blood volume as a risk factor (Patterson and Kessler 1969, Gallagher and Pearson 1973, Loop et al. 1976). However, these studies describe equipment configurations that are now several generations out of date, and any concern about microemboli entering the arterial line as a result of low reservoir volume appears to be based upon an assumed compromise of the reservoir’s ability to “filter” incoming emboli, rather than on any generation of emboli by the reservoir per se.

An in vitro circuit similar to that reported here was used by the manufacturer to investigate emboli generation by the Medtronic Maxima bottom entry reservoir prior to its market release in the late 1980s (Medtronic Blood Systems Inc [undated]). No evidence of emboli generation by this HSVR was found. However, the Medtronic
study focussed on the effects of recirculation flow rate and of air introduced to the venous line, rather than the effect of blood volume in the reservoir. Indeed, the reservoir blood volume used in the Medtronic trials was not cited. The reservoir may have been operated at too high a volume to detect the problem revealed in the present study. In addition, the Medtronic test program used the Hatteland BD-100 Doppler (Hatteland Instrumentering, Royken, Norway) for bubble detection. This is a predecessor to the CMD-10 device which we compared to our own Doppler, and which we found to be less sensitive in emboli detection (see Section 2.3.2).

Concomitant with publication of the data in sections 6.3.2 and 6.3.3, the author was invited to Anaheim to present the study to Medtronic biomedical engineers. Not surprisingly, the Medtronic laboratory repeated these experiments shortly after this visit and obtained similar results (van Driel 1997). Fortunately, the new generation Forte reservoir was available for release shortly after.

The comparative HSVR study demonstrated that bubble generation by these devices does not invariably occur in all models. Bubble generation by the Medtronic Forte and the Sorin, Terumo, and Baxter HSVRs at low volumes or high flow rates was either negligible or non-existent. Indeed, the Forte was the only other HSVR that we tested to clearly show bubble formation. This occurred as reservoir volume was lowered, but there were markedly fewer bubbles than generated by the Maxima top entry. In addition, very few of the bubbles generated by the Forte actually reached the distal arterial line, even when the reservoir was operated at 400 ml (100 ml less than its recommended volume).
The comparative HSVR study also enabled correlation between reservoir design and bubble generation characteristics. All reservoirs that did not generate bubbles under any circumstances (Sorin, Terumo, Baxter) had a downwardly directed venous inlet portal. All reservoirs that did generate bubbles had an upwardly directed (Maxima bottom entry) or deflected (Maxima top entry and Forte) venous inlet flown path. These observations strongly suggest that upward direction or deflection of the inlet flow path is likely to cause a fountaining and air entrainment unless the inlet portal is carefully enclosed in a chamber to constrain any fountain (as in the Forte).

It was concluded that the Medtronic Maxima HSVRs generated bubbles when blood volumes were in the lower operating range. Based on those studies that have previously shown a correlation between cerebral emboli exposure and stroke or NP deficits (section 1.5.3.5), it was argued in papers arising from this work (page viii) that these bubbles might adversely affect neurological outcome. These papers therefore suggested that the manufacturer’s recommended minimum of 300 ml be revised to 600 – 700 ml. At the time of completing this thesis, it is understood that very few centres now use the Maxima top entry HSVR, and that almost none use the bottom entry device.

6.4.2 Passage of venous air through the CPB circuit.

The second phenomenon noted clinically and investigated in vitro was the passage of air in the venous return line through the CPB circuit. The reported ability of HSVRs to remove such air during CPB (Hessel 1993) has led to an “acceptance” that venous air is consequently benign. Typically, when a HSVR is used, venous cannulae are not deaired and initiation of bypass is associated with a bolus of air returning to the CPB
circuit. During CPB, air may enter the venous line from the atriotomy, and around venous or retroplegia cannulae purse string suture.s, especially during retraction of the atrial wall. A single atrial cannula may be used in some congenital procedures to vent blood and coincidentally air from the left heart across a patent foramen ovale or an excised atrial septum.

The first experiment (sections 6.2.6.1 and 6.3.6.1) showed that air from incoming bubbles passed through all the reservoirs tested. The Maxima Forte and the Sorin HSVRs were significantly better at air removal than the others, and several design features may explain the superior performance of the Forte HSVR in particular. First, the outflow is positioned at the bottom of a relatively long snout that projects well below the reservoir base. This would make it less likely for bubbles large enough to be influenced by buoyancy to enter the outflow. Second, the outflow is comparatively distant from the venous inflow portal. Third, the venous inflow path is deflected upward into a constrained chamber. While this may be directly responsible for some bubble formation at low volumes, it may nevertheless hinder incoming venous bubbles from entering the outflow.

The second experiment (sections 6.2.6.2 and 6.3.6.2) established that even when the Forte HSVR was used, bubbles appeared in the arterial line distal to the filter after every addition of venous air. Moreover, there was a clear dose response relationship; the number of arterial line bubbles increased as larger volumes of venous air were introduced. It is notable that these experiments utilised restricted volumes of venous air, whereas in the clinical setting, the amount of air that can be entrained is "unlimited". This is a particularly pertinent observation when considering the results
of the VAVD experiments (Sections 6.2.6.3-5 and Sections 6.3.6.3-5). It was clearly demonstrated that air was entrained more quickly under VAVD and that this resulted in a much larger number of emboli appearing downstream of the arterial line filter. In the clinical setting where the entrainment time and volume are “unlimited” this could result in the patient being exposed to very large numbers of bubbles. It should be emphasised that these data do not imply that VAVD is a dangerous or undesirable technique. The important implication is that the presence of venous air should result in immediate steps to stop the entrainment, particularly where VAVD is used.

Flooding the surgical field with CO$_2$ has been advocated as an aid to deairing the heart at the end of surgery (see section 1.6.1.3). This technique would also cause entrainment of CO$_2$ rather than air to the venous line, and we have demonstrated that this would result in fewer bubbles reaching the patient (section 6.3.6.5), and therefore the patient’s cerebral circulation. This is consistent with the findings of Gorman (1987) who showed in vivo that larger volumes of intravascular CO$_2$ (compared to air and oxygen) were required in order to produce cerebral vascular occlusions. However, while flooding the surgical field with CO$_2$ would reduce CAGE, the problem would not be prevented. It follows that CO$_2$ field flooding should not be considered a “panacea” to the problem of gas entrainment to the venous return line.

It is acknowledged that the clinical significance of bubbles generated by the Medtronic HSVRs or bubbles of venous air that pass through the circuit has not been demonstrated by this study. However, given that both sources are easily rectifiable it is difficult to conceive an ethically acceptable protocol that would prospectively compare patients exposed to or not exposed to bubbles from either source. Moreover,
the correlation of emboli exposure against adverse NP outcome is well established (see section 1.5.3.5), and few would argue that eliminating readily identifiable and remediable sources of solid or gaseous emboli is not important.
CHAPTER 7

SUMMARY
7. SUMMARY

This project began as an investigation of brain protection by lignocaine in embolic brain injury. Prior to inception of the present protocol it was envisaged that the study would be carried out in divers with DCI. However, in DCI patients there is a lack of premorbid NP test data, a marked variability in both disease severity and presentation latency, and ambiguity in the pathological diagnosis. It follows that establishment of a homogeneous study population is very difficult. Cardiac surgery patients constitute a subject population with a proven incidence of brain injury by emboli. Moreover, pre-operative NP testing allows each patient to act as his or her own control, lignocaine can be administered in a standard relation to the injurious event, and the exposure to emboli can actually be measured for each patient. Finally, there is a predictable and readily accessible population of cardiac surgery patients which contrasts to the sporadic incidence of DCI. For these reasons, the lignocaine trial was performed in cardiac surgery patients. Patients undergoing left heart valve surgery were chosen because of their exposure to greater numbers of emboli (Stump 1991), and their higher risk of brain injury (Nussmeier 1996).

An emboli-counting capability was developed in order to control for emboli exposure in the trial groups. It became clear from an early stage in the development and use of the Doppler device that there may be potential for identification and elimination of sources of emboli. Any such initiative was considered a mandatory accompaniment to the lignocaine trial since prevention of exposure to emboli seemed preferable to protecting the brain after exposure.
7.1 Prevention of emboli exposure

As described in the various chapters, three sources of potentially remediable emboli exposure were identified: residual air (and surgical debris) remaining in the heart at closure of the surgical wound; bubbles passing through the CPB circuit after entrainment into the venous line; and bubbles generated by the Medtronic Maxima hard shell venous reservoirs that were in use at Green Lane Hospital during the study period.

The importance of residual air in the heart chambers and pulmonary veins after closure of the surgical wound was not a new discovery. Cerebral embolisation by this air (section 1.5.3.3) and various means of minimising this problem (section 1.6.1.3) have been described in the literature. It is therefore not surprising that the inadequacy of so-called “deairing” techniques was “understood” at Green Lane prior to the present study. Despite this, no strategies to improve deairing had been tried. However, the invariable demonstration by Doppler of emboli entering the cerebral circulation after aortic declamping prompted all surgeons to become more meticulous during deairing. One surgeon developed a novel technique that addressed the fundamental inadequacy of the conventional methods: failure to allow physiological ejection from the working heart before declamping the aorta.

The technique developed by Dr Milsom and audited here (Chapter 5) was demonstrably more successful than conventional methods. The success of the technique supports earlier claims that failure to establish physiological flow through the pulmonary veins prior to
aortic declamping results in entrapment of residual air (Tingleff et al. 1997).

Unfortunately, the technique is complex, requires a redesigned circuit, and commands careful attention to procedure from both the surgeon and perfusionist. Refinements have simplified matters since it was first applied, and attempts to further simplify and automate the process continue.

The finding that air entrained to the venous line did appear downstream of the arterial line filter was new in the sense that it had not been previously published. A number of authorities have expressed awareness of the problem since publication of the data in section 6.3.6. This was an important issue to report in the literature since there has been a perception among surgeons that venous air was inconsequential because of protective elements in the CPB circuit. In contrast, we have shown that if venous air entrainment is not corrected, the patient may be exposed to large numbers of bubbles throughout the procedure. Our data also suggest that this problem is potentiated if the case is perfused under conditions of VAVD. The latter finding has caused concern among industry groups promoting their CPB components for use during VAVD, and at least one large research grant has been disbursed to facilitate investigation of our results (DA Stump pers comm).

Perhaps the most unexpected finding in these studies was that of bubble generation by a market leading HSVR. A reported advantage of the HSVR is that it “protects” the circuit from air entrainment, yet for the Medtronic Maxima devices our data demonstrated the opposite. The potential clinical, commercial and legal importance of this finding necessitated that it was carefully verified *in vitro* prior to publication. Predictably,
publication of the data in sections 6.2.2 and 6.2.3 caused much attention to be focussed on our methodology and findings. Nonetheless, no one has attempted to refute these data. Indeed, it is known that Medtronic repeated this work in their own laboratory and obtained essentially the same results. The revised operating volume recommendations for the Medtronic Maxima reservoirs described in section 6.4.1 were published, but the reservoirs were phased out of use over a relatively short period thereafter, to be replaced by the new generation Forte device.

Thus, this study resulted in affirmation of one previously reported source of cerebral emboli, and revealed two previously unreported sources. In each case a strategy to reduce emboli exposure was proposed and published. With respect to bubble generation by the Maxima HSVRs, this resulted in changes in practice at a global level. A similar degree of attention is now being given to the possible disadvantages of VAVD in terms of air entrainment.

7.2 Cerebral protection by lignocaine

Few studies have ever described human cerebral protection in any context by a drug, despite an immense amount of attention to this issue in the literature. The trial of lignocaine described in Chapter 3 and published in the cardiac surgical literature is one of those few. The finding is made all the more compelling by the fact that lignocaine is an old, well understood, safe, cheap agent. However, the study was small and needs to be repeated in a larger patient population before lignocaine can be considered for incorporation into the routine care of patients undergoing cardiac surgery (Butterworth
1999). In response to the findings reported here a larger study has received funding and is underway at Duke University, North Carolina, USA.

7.3 Summary statement

This thesis describes both known and previously unknown sources of exposure to cerebral emboli during cardiac surgery, and proposes means of preventing this exposure. In addition, this work establishes lignocaine as a potentially useful cerebro-protective agent in patients undergoing left heart valve surgery.
BIBLIOGRAPHY

Aberg T, Kihlgren M. Cerebral protection during open heart surgery. Thorax 1977;32:525-33


Adam-Vizi V, Ligeti E. Calcium uptake of rat brain synaptosomes as a function of membrane potential under different depolarising conditions. J Physiol (Lond) 1986;372:363-77


Astrup J, Sorenson PM, Sorenson HR. Inhibition of cerebral oxygen and glucose consumption in the dog by hypothermia, pentobarbital, and lidocaine. Anesthesiology 1981b;55:263-8


Ball R. Effect of severity, time to recompression with oxygen, and re-treatment on outcome in 49 cases of spinal cord decompression sickness. Undersea Hyperb Med 1993;20:133-45


239
Barbut D, Hinton RB, Hartmann GS, Bruefach M, Hahn R, Szatrowski TP, Charlson ME, Gold JP. Number of emboli detected by TCD during CABG is related to aortic atheroma as assessed by TEE. Perfusion 1994b;9:414


Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA. Apparent hydroxyl radical production by peroxynitrate: implications for endothelial injury from nitric oxide and superoxide. Proc Natl Acad Sci USA 1990;87:1620-4


Clark RE, Margraf HW, Beauchamp RA. Fat and solid filtration in clinical perfusion. Surgery 1975;77:216-224


Crook TH, Larrabee GJ. A self rating scale for evaluating memory in everyday life. Psychology and Aging 1990;5:48-57


Diaz L, Gomez A, Bustos G. Lidocaine reduces the hypoxia-induced release of an excitatory amino acid analog from rat striatal slices in superfusion. Prog Neuropsychopharmacol Biol Psychiatry 1995;19:943-53


Donegan MF, Bedford RV. Intravenously administered lidocaine prevents intracranial hypertension during endotracheal suctioning. Anesthesiology 1980;52:516-8


Freidman JE. Haddad GG. Anoxia induces an increase in intracellular sodium in rat central neurons in vitro. Brain Res 1994;663:329-34


Gao CR. Cerebral protection in neurosurgical anesthesia. Chung Hua Wai Ko Tsa Chih 1991;29:170-3

Geddes IC, Quastel JH. Effects of local anesthetics on respiration of rat brain cortex. Anesthesiology 1956;17:666-71


Gilberstadt H, Sako Y. Intellectual and personality changes following open heart surgery. Arch Gen Psychiat 1967;16:210-14

Gilman A. Cerebral disorders after open-heart operations. NEJM 1965;272:489-98


Gorman DF. The Redistribution of Cerebral Arterial Gas Embolism. University of Sydney 1987, PhD Thesis in Medicine

Gorman DF, Browning DM, Parsons DW, Traugott FM. Distribution of arterial gas emboli in the pial circulation. SPUMS J 1987;17:101-15


Hamill JF, Bedford RF, Weaver DC, Colohan AR. Lidocaine before endotrachial intubation. Intravenous or laryngotracheal? Anesthesiology 1981;55:578-81


Hanson AJ. Effect of anoxia on ion distribution in the brain. Physiol Rev 1985;65:101-48


Heikkinen L. Clinically significant neurological disorders following open heart surgery. Thorac Cardiovasc Surg 1985;33:201-6


Hyde JAJ, Jones TJJ, Heafield MTE, Riddington DW, Graham TR. Pulsatile flow may increase the elevation in serum S100 produced by cardiopulmonary bypass. Ann Thorac Surg 1997;64:919


Ingvar M, Shapiro HM. Selective metabolic activation of the hippocampus during lidcaine induced pre-seizure activity. Anesthesiology 1981;54:33-7

Illievich UM, Zornow MH, Choi KT, Strmat AP, Scheller MS. Effects of hypothermia or anesthetics on hippocampal glutamate and glycine concentrations after repeated transient global cerebral ischaemia. Anesthesiology 1994;80:177-86


Johns RA, DiFazio CA, Longnecker DE. Lidocaine constricts or dilates rat arterioles in a dose dependant manner. Anesthesiology 1985;62:141-44


King FG, Addetia AM, Peters SD, Peachey GO. Prophylactic lidocaine for postoperative coronary artery bypass patients, a double-blind, randomized trial. Can J Anaesth 1990;37:363-8


Lantos J, Roth E, Temes G. Effects of lidocaine on cerebral lipid peroxidation and neutrophil activation following complete compression ischaemia. Arch Int Pharmacody Ther 1996;331:179-88

Lazdunski M Frelin C, Vigne P. The sodium/hydrogen exchange system in cardiac cells: its biochemical and pharmacological properties and its role in regulating internal concentrations of sodium and internal pH. J Mol Cell Cardiol 1985;17:1029-42


254
Legault C, Furberg CD, Wagenknecht LE, Rogers AT, Stump DA, Coker L, Troost BT, Hammon JW.


McCord JM. Oxygen derived free radicals in postischemic tissue injury. NEJM 1985;312:159-63


Michenfelder JD. The interdependency of cerebral function and metabolic effects following massive doses of thiopental in the dog. Anesthesiology 1974;41:231-6


Mizunuma T, Ohta S, Suzuki M. Subarachnoid administration of lidocaine reduces delayed neuronal damage due to forebrain ischemia in rats. Masui 1996;45:421-7


Munson ES, Merrick HC. Effect of nitrous oxide on venous air embolism. Anesthesiology 1966;27:783-7


Murkin JM, Farrar JK. The influence of pulsatile vs nonpulsatile cardiopulmonary bypass on cerebral blood flow and cerebral metabolism. Anesthesiology 1989;71(3A):A41


Murkin JM. Neurological dysfunction after CAB or valvular surgery: is the medium the miscreant? Anesth Analg 1993;76:213-4

Murkin JM, Martzke JS, Buchan AM, Sharma DS, Campbell P, Bentley CA. Pulsatile perfusion during hypothermic cardiopulmonary bypass significantly influences morbidity and mortality after coronary artery bypass surgery. Anesth Analg 1993;76:S280


Newman MF. Strategies to protect the brain during cardiac surgery. Proceedings of the Outcomes '99 Meeting, Key West, FLA, USA 27 – 29 May 1999


Newman SP. The incidence and nature of neuropsychological morbidity following cardiac surgery. Perfusion 1989;4:93-100


Nichols HT, Morse DP, Hilrose T. Coronary and other air embolization occurring during open heart surgery prevention by the use of gaseous carbon dioxide. Surgery 1958;43:236-44


Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology 1986;64:165-70


Obrenovitch TP. The ischaemic penumbra: 20 years on. Cerebrovasc Brain Metab Rev 1995;7:297-322


Patterson RH, Rosenfeld L, Porro RS. Transitory cerebral microvascular blockade after cardiopulmonary bypass. Thorax 1976;31:736-41


Prados M, Strowger B, Feindel WH. Studies on cerebral edema: I. Reaction of the brain to air exposure; pathologic changes. AMA Arch Neurol Psychiat 1945;54:163-74
Prenen GHM, Go KG, Postema F, Zuiderveen F, Korf J. Cerebral cation shifts in hypoxic-ischemic brain damage are prevented by the sodium channel blocker tetrodotoxin. Exp Neurol 1988;99:118-32

Probert AW, Borosky S, Marcoux FW, Taylor CP. Sodium channel modulators prevent oxygen and glucose deprivation injury and glutamate release in rat neocortical cultures. Neuropharmacology 1997;36:1031-8


Reitan RM. Validity of the trail making test as an indicator of organic brain damage, Percept Mot Skill 1958;8:271-6


Rogers A. Con: Preventing stroke after cardiopulmonary bypass does not require pharmacologic neuroprotection. J Cardiothorac Vasc Anesth 1997;11:796-800

Rothman SM. The neurotoxicity of excitatory amino acids is produced by passive chloride influx. J Neurosci 1985;5:1483-9


Royston D. Systemic inflammatory response to surgery with cardiopulmonary bypass. Perfusion 1996;11:177-89

Sakabe T, Maekawa T, Ishikawa T, Takeshita H. The effects of lidocaine on canine cerebral metabolism and circulation related to the EEG. Anesthesiology 1974;40:433-41


264

Samuelson B. Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation, Science 1983;220:568-75

Sanderson JM, Wright G, Sims FW. Brain damage in dogs immediately following pulsatile and non-pulsatile blood flows in extracorporeal circulation. Thorax 1972;27:275-86


Savageau JA, Stanton B-A, Jenkins CD, Frater RWM. Neuropsychological dysfunction following elective cardiac operation: II. A sixth month reassessment. Thorac Cardiovasc Surg 1982b;84:595-600


Slogoff S, Girgis KZ, Keats AS. Etiologic factors in neuropsychiatric complications associated with cardiopulmonary bypass. Anesth Analg 1982;90:3-11


Smith PLC. Interventions to reduce cerebral injury during cardiac surgery – introduction and the effect of oxygenator type. Perfusion 1989;4:139-45


Smith SE, Meldrum BS. Cerebroprotective effect of lamotrigine after focal ischemia in rats. Stoke 1995;26:117-22

Smith PLC. The systemic inflammatory response to cardiopulmonary bypass and the brain. Perfusion 1996;11:196-9

Sotaniemi KA, Juolasma A, Hokkanen ET. Neuropsychologic outcome after open-heart surgery. Arch Neurol 1981;38:2-8

Sotamiemi KA. Cerebral outcome after extracorporeal circulation. Comparison between prospective and retrospective evaluations. Arch Neurol 1983;40:75-77


Stump DA, Newman SP, Coker LH. Persistence of neuropsychological deficits following CABG. Anesthesiology 1990;73:A113


Stump DA, Tegeler CH, Rogers AT, Coker LH, Newman SP, Wallenhaupt SL, Hammon JW. Neuropsychological deficits are associated with the number of emboli detected during cardiac surgery. Stroke 1993a;24:509

Stump DA, Roger AT, Kon ND, Wallenhaupt SL, Hammon JW. When emboli occur during coronary artery bypass surgery. Anesthesiology 1993b;79:A49


Styss PK, Ransom BR, Waxman SG. Tertiary and quaternary local anesthetics protect CNS white matter from anoxic injury at concentrations that do not block excitability. J Neurophysiol 1992b;67:236-40


Taylor KM, Wright GS, Reid JM, Bain WH, Caves PK, Walker MS, Grant JK. Comparative studies of pulsatile and non-pulsatile flow during cardiopulmonary bypass. II. The effects on adrenal secretion of cortisol. J Thorac Cardiovasc Surg 1978;75:574-8


Taylor KM. Brain damage during cardiac surgery (editorial). Thorax 1982;37:873-6

Taylor CP, Burke SP, Weber ML. Hippocampal slices: glutamate overflow and cellualr damage from ischemia are reduced by sodium-channel blockade. J Neurosci Methods 1995;59:121-8


Tommasino C, Maekawa T, Shapiro HM. Local cerebral blood flow during lidocaine induced seizure. Anesthesiology 1986;64:771-6


Tufo HM, Ostfeld AM, Shekelle R. Central nervous system dysfunction following open-heart surgery. JAMA 1970;212:1333-40


Van Driel M. Biomedical Engineer, Medtronic Blood Systems, Inc. Pers Comm.


Vingerhoets G. Perioperative anxiety and depression in open-heart surgery. Psychosomatics 1998;39:30-7


Weber ML, Taylor CP. Damage from oxygen and glucose deprivation in hippocampal slices is prevented by tetrodotoxin, lidocaine and phenytoin without blockade of action potentials. Brain Res 1994;664:167-77


Wiard RP, Dickerson MC, Beek O, Norton R, Cooper BR. Neuroprotective properties of the novel antiepileptic lamotrigine in a gerbil model of global cerebral ischemia. Stroke 1995;26:466-72


Wilson I, Gullinov AM, Curtis WE, DiNatale J, Burch RM, Gardner TJ, Cameron DE. Inhibition of neutrophil adherence improves posts ischemic ventricular performance in the neonatal heart. Circulation 1993;88(Supp 2);372-9


Zhang Y-L, Lipton P. Mitochondria and endoplasmic reticulum are major sources of increased cytosolic calcium during ischemia in the rat hippocampus. Society for Neuroscience Abstracts 1995;21:217
