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PREVENTION OF BRAIN INJURY IN CARDIAC SURGERY

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

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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 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 (HSVR) 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.

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PUBLICATIONS, PRIZES, ABSTRACTS

Publications

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

1. **Mitchell SJ.** The role of lignocaine in the treatment of decompression illness - A review of the literature. SPUMS J 1995;25(4):182-194
2. **Mitchell SJ, Willcox T, McDougall C, Gorman DF.** Emboli generation by the Medtronic Maxima hardshell adult venous reservoir in cardio-pulmonary bypass circuits: a preliminary report. Perfusion 1996;11:145-155
3. **Mitchell SJ, Willcox T, Gorman DF.** Bubbles generation and venous air filtration by hard-shell venous reservoirs: a comparative study. Perfusion 1997;12:325-333
4. **Mitchell SJ, Pellett O, Gorman DF.** Open chamber cardiac surgery: a clinical injury model for arterial gas embolism. SPUMS J 1997;27:230-235

5. Milsom FP, **Mitchell SJ**. A novel dual vent heart de-airing technique markedly reduces carotid artery microemboli. *Ann Thorac Surg* 1998; 66:785-91

6. **Mitchell SJ**, Pellett O, Gorman DF. Cerebral protection by lidocaine during cardiac operations. *Ann Thorac Surg* 1999;67:1117-24

7. Willcox TW, **Mitchell SJ**, Gorman DF. Venous air in the bypass circuit: a source of arterial line emboli exacerbated by vacuum assisted drainage. *Ann Thorac Surg* 1999;68:1285-9

8. **Mitchell SJ**, Willcox T, Milsom FP, Gorman DF. Physical and Pharmacological neuroprotection. *Sem Thorac Cardiovasc Anesth* 2000: In press

9. **Mitchell SJ**, Benson M, Vadlamudi L, Miller P. Cerebral arterial gas Embolism by helium: an unusual case successfully treated with hyperbaric oxygen and lidocaine. *Ann Emerg Med* 2000: In press

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.

1. **Mitchell SJ**, Willcox T, Gorman DF. Bubble generation by the Medtronic Maxima hard shell adult reservoir in cardiopulmonary bypass circuits. *Undersea Hyperbaric Med* 1996;23(supp):13
Presented at the Annual Scientific Meeting of the Undersea and Hyperbaric Medical Society, Alaska, May 1996

2. Milsom FP, **Mitchell SJ**. A superior heart de-airing technique reduces cerebral arterial gas embolism following left heart surgery. *Undersea Hyperbaric Med* 1997;24(supp):24
Presented at the Annual Scientific Meeting of the Undersea and Hyperbaric Medical Society, Cancun, Mexico, June 1997

3. **Mitchell SJ**, Gorman DF, Pellett O. Cerebral protection in cardiac surgery patients by lidocaine: a randomised double blind trial. *Undersea Hyperbaric Med* 1998;25(supp):22
Presented at the Annual Scientific Meeting of the Undersea and Hyperbaric Medical Society, Seattle, USA, May 1998

4. **Mitchell SJ**, Willcox T, Gorman DF. Bubble generation by hard shell venous reservoirs: a comparative study. *Perfusion* 1998;13:88
Presented at the Annual Scientific Meeting of the Australasian Society of Cardiovascular Perfusionists, Sydney, Australia, September 1997

5. **Mitchell SJ**, Pellett O, Gorman DF. Cerebral protection in cardiac surgery patients by lidocaine: a randomized double blind trial. *Ann Thorac Surg* 1998;66:1491
Presented at the Outcomes 98 Meeting, Key West, USA, June 1998

6. Willcox TW, **Mitchell SJ**, Gorman DF. Venous air in the bypass circuit: a source of iatrogenic arterial gas embolism exacerbated by vacuum assisted drainage. *Undersea Hyperbaric Med* 1999;26(supp):63
Presented at the Annual Scientific Meeting of the Undersea and Hyperbaric Medical Society, Boston, USA, May 1999
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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.

ANOVA	Analysis of variance
AST	Aspartate amino transferase
ATP	Adenosine triphosphate
AVLT	Auditory – verbal learning test
BMI	Body mass index
Ca ²⁺	Calcium
CAGE	Cerebral arterial gas embolism
CBF	Cerebral blood flow
CK-MB	Creatine kinase (myocardial fraction)
cm	Centimetre
CO ₂	Carbon dioxide
CPB	Cardiopulmonary bypass
DCI	Decompression illness
EEG	Electro-encephalogram
EPSP	Excitatory post-synaptic potential
Fe ³⁺	Iron ion
g	Gram
GVD	Gravity venous drainage

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-isoazole 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
Mg ²⁺	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
PaCO ₂	Arterial partial pressure of carbon dioxide
PaN ₂	Arterial partial pressure of nitrogen
PO ₂	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