# SPUMS ANNUAL SCIENTIFIC MEETING 1998

## CEREBRAL PROTECTION BY LIGNOCAINE DURING CARDIAC OPERATIONS

Simon Mitchell, Ora Pellett and Des Gorman

**Abstract**

*Background.* Lignocaine improves outcome in animal brain injury models. Cardiac operations often cause post-operative neuro-psychological (NP) impairment. We investigated cerebral protection by lignocaine in cardiac surgical patients.

*Methods.* Sixty-five patients undergoing left heart valve procedures completed 11 pre-operative NP tests, a self-rating inventory for memory, and inventories measuring depression and anxiety. These were repeated 10 days, 10 weeks, and 6 months post-operatively. Patients received a 48-hour double-blinded infusion of either lignocaine in a standard antiarrhythmic dose or placebo, beginning at the induction of anaesthesia. A post-operative deficit in any test was defined as a decline by more than or equal to the group pre-operative standard deviation. In addition, sequential post-operative percentage change scores were calculated for each patient in all NP tests and the inventories for memory, depression and anxiety.

*Results.* Forty-two patients completed all three reviews, 8 completed two reviews, and 5 patients were reviewed once. Significantly more placebo patients had a deficit in at least one NP test at 10 days ($p < 0.025$) and 10 weeks ($p < 0.05$). The lignocaine group achieved superior sequential percentage change scores in 6 of the 11 NP tests ($p < 0.05$) and in the memory inventory ($p < 0.025$). There were no group differences in the remaining NP tests or the depression and anxiety inventories.

*Conclusions.* These data demonstrate that cerebral protection by lignocaine, unrelated to any effect on depression or anxiety, at a level that is noticed by the patients.

**Key Words**

Bubbles, drugs, research, treatment sequelae.

**Introduction**

Neurological problems, such as delirium, cognitive difficulty, convulsions, persistent somnolence and stroke, were reported more than 30 years ago after cardiac procedures.[1] Despite efforts to prevent sequelae, post-operative stroke and cognitive dysfunction are still seen in up to 4.9%[2] and 59%[3] of patients, respectively. Although there are some data to the contrary[4] patients undergoing cardiac operations exhibit more stroke syndromes,[5] new clinical neurological signs,[6] and neuropsychological deficits[6] than non-cardiac surgical controls, particularly in the early post-operative period. Cerebral embolism and hypoperfusion are the most likely explanations for this difference[7] and peri-operative cerebral emboli exposure correlates with the risk of post-operative stroke[2] and cognitive deficit.[8] Strategies to prevent embolic brain injury in cardiac operations have included intra-operative hypothermia;[9] filtration of the cardiopulmonary bypass (CPB) arterial line;[10] reduced manipulation of the atheromatous aorta;[11] improved removal of residual air and debris from the heart after open chamber procedures;[12] carbon dioxide field flooding during open chamber procedures;[13] and prevention of bubble formation in CPB machines.[14]

There is also interest in pharmacological cerebral protection in cardiac operations. Thiopentone reduced the incidence of early post-operative neuropsychiatric problems,[15] although patients were slower to wake, remained intubated longer and required more inotropic support than controls. This result was not replicated in a subsequent trial and routine use of thiopentone for this purpose is not recommended.[16] Nimodipine produced equivocal preservation of memory function 6 months post-operatively in a small controlled cardiac surgical trial.[17] However, a larger placebo-controlled trial of nimodipine in this context was terminated early because of higher rates of death and major bleeding in the treatment group.[18]

Lignocaine, used as a local anaesthetic and class Ib antiarrhythmic agent, has been shown in vivo to preserve neuroelectric function;[19] reduce infarct size;[20] preserve cerebral blood flow;[21] reduce cerebral oedema;[22] and reduce intracranial pressure[21] in models of cerebral arterial gas embolism,[19] focal,[20] and global[21] brain ischaemia and brain oedema.[22] Possible mechanisms for cerebral protection by lignocaine include deceleration of ischaemic trans-membrane ion shifts;[23] reduction in cerebral metabolic rate;[24] modulation of leucocyte activity;[25] and reduction of ischaemic excitotoxin release.[26] There are reports of the successful use of lignocaine as an adjunct to recompression in divers with neurologic decompression illness[27] and lignocaine has received speculative mention as a possible cerebral protective agent in cardiac operations.[28] However, there are no controlled clinical data to support these uses of lignocaine. This is a report of a randomised, prospective, double-blind trial of lignocaine versus placebo in cerebral outcome after left heart valve operations.

## Material and Methods

### PATIENTS

Sixty-five patients scheduled for left heart valve operation gave written informed consent for participation in the study, which received ethics committee approval in August 1994. The exclusion criteria were as follows: age outside the 20- to 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.

### NEUROPSYCHOLOGICAL TESTING

All consenting patients underwent pre-operative neuropsychological (NP) testing on the day before operation. The test battery was selected on the basis of demonstrated efficacy in similar subject populations and negligible training effect and is listed in Table 1 (p 216). Six "performance" tests[29] with 11 sub-scales were chosen to measure cognitive function. A self-rating inventory with two sub-scales for memory function[30] was chosen to identify changes that were noticed by the patients themselves. Any spouses were also asked to rate the patient's memory using the latter inventory. Two inventories, one for depression and one for anxiety (two sub-scales)[29] were also used because both states influence NP test performance. All tests were repeated at 10 days, 10 weeks, and 6 months after operation, except the memory inventory, which was only repeated at 10 weeks and 6 months. Parallel forms of the Rey Auditory Verbal Learning Task[29] and Rey Figure test[29] were used in sequential testing to minimise any practice effect. Where possible, testing in the hospital was conducted in the same office. Some of the 10-day tests, and all of the 10-week and 6-month tests were performed in the patients' homes. A functional decrement was considered to exist in any of the post-operative 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.[31] In addition, each patient's preoperative scores were normalised to 100 and subsequent scores were recorded as percentage changes. All NP testing was conducted by the one psychologist.

### TRIAL MEDICATION ADMINISTRATION

The medication was repackaged by a pharmaceutical laboratory into coded vials. Dextrose 5% was used as the placebo solution to replicate the same mixing phenomenon as is seen when lignocaine is diluted in 0.9% sodium chloride solution. Patients were block randomised by surgeon to receive lignocaine or placebo, so that each of the five surgeons involved operated on the same number of patients in each group. The trial infusion was begun at induction of anaesthesia and continued for 48 hours. The infusion protocol was designed to deliver a 1 mg/kg "bolus" over 5 minutes, followed by 240 mg over the first hour and 120 mg over the second hour, and then 60 mg/h thereafter if the patient was receiving lignocaine. The target plasma concentration (6 to 12 μmol/L) was selected on the basis of successful in vivo[19,20] and in vitro[23] trials of lignocaine in brain injury. Blood specimens for lignocaine assay were taken to coincide with aortic cannulation and aortic declamping and at both 8 and 24 hours after starting the infusion. The latter two results were used to adjust the infusion rate. To preserve double blinding, the laboratory also reported sham levels for placebo patients.

### ANAESTHESIA AND OPERATION

Patients were premedicated with a benzodiazepine (usually midazolam), an $H_2$ receptor antagonist (usually famotidine), and in most cases, droperidol. Anaesthesia in all patients was based on moderate doses of fentanyl (10 to 50/μg/kg) and a non-depolarising muscle relaxant, supplemented when necessary with isoflurane and benzodiazepines. Any departure from this standard protocol was recorded. The CPB circuit included a hard shell combined venous and cardiotomy reservoir (Medtronic Blood Systems, Anaheim, California), roller pump (Stockert Instrumente, Munich, Germany), hollow fibre membrane oxygenator (Medtronic Blood Systems), and a Bentley AF1040D 40 micron screen arterial filter (Baxter Healthcare Corporation, Irvine, California) with a continuous purge. Perfusion was non-pulsatile with indexed flows set at 2.4 l/$m^2$/min during cooling and rewarming, and 2.0 l/$m^2$/min during stable CPB. The alpha-stat pH management protocol was used for all patients. All patients underwent hypothermic CPB. The lowest temperature was recorded.

A Flowlink 300 colour flow Doppler machine (Rimed, Tel Aviv, Israel), operated in the 2-MHZ pulsed wave mode and interfaced to a purpose built emboli signal counter,[14] was used to monitor the right common carotid artery from 5 minutes before cannulation of the great vessels until 20 minutes after weaning from CPB. Physiological parameters were recorded during surgery by automatic data logging devices (HP Component Monitoring System, Hewlett Packard, Andover, Massachusetts). The product of time (minutes) during which perfusion pressure was below 50 mm Hg and the degree of hypotension (difference between 50 mm Hg and the observed perfusion pressure) during CPB was calculated.[32] This product is expressed as mm Hg minutes (mm Hg.min) and is known as the $TM^{-50}$. The cumulative duration of hypotension (systolic BP less than 80 mm Hg) before and after CPB was also calculated.

### STATISTICAL ANALYSIS

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 $\chi^2$ or Fisher's

**TABLE 1**

**TESTS AND SUB-SCALES OF THE NP TEST BATTERY** [29, 30]

| Test | Sub-scales | Modality Interrogated |
|---|---|---|
| **Performance tests** | | |
| Rey figure | Copy | Visuospatial memory |
| | Recall | |
| Inspection time | Traditional | Information processing speed |
| | Dynamic | |
| Rey Auditory Verbal Learning Task | Trials 1-5 | Verbal learning |
| (AVLT) | Distract list | Verbal memory |
| | Recall trial | |
| Symbol DigitModality Test | Oral | Complex scanning and visual tracking, manual agility |
| (SDMT) | Written | |
| | Written | |
| Trails A | Nil | Attention and spatial perception |
| Trails B | Nil | Sustained attention, spatial perception, visuomotor tracking |
| **Self-rating inventory** | | |
| Memory Assessment Clinic | How good at? | Memory |
| Self Rating Test (MAC-S) | How often do? | |
| **Control tests** | | |
| Beck depression | Nil | Depression |
| State Trait Anxiety Inventory (STAI) | State | State anxiety |
| | Trait | Trait anxiety |

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 $\chi^2$ 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 analysis of variance. This analysis was also used to assess any effect of time after operation 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 analysis of variance.[33] Patients missing two of the reviews were excluded from this analysis. A significance level of p less than 0.05 was chosen for all tests.

**Results**

Ten of the 65 consented patients did not enter the review phase of the trial. One withdrew after pre-operative NP testing and 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 before CPB. Two patients died after sudden cardiac arrest in the early post-operative period; one, who died on day 2, was receiving the placebo and the other, who died after discharge on day 7, had received lignocaine. Two patients had severe non-cerebral post-operative complications that would have significantly altered NP performance, 2 refused all post-operative testing, and 2 patients were lost to 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 patients completed all three post-operative reviews, 8 were reviewed twice, and 5 patients 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.

Group mean pre-operative NP test scores for these 55 patients did not differ and are listed in Table 2. Other

relevant demographic, operative, and post-operative data are listed in Tables 3, 4, and 5, respectively. The placebo patients had a significantly greater body mass index than the lignocaine patients (28.5 versus 25.3). Conversely, myocardial scores[34] indicated significantly worse coronary artery disease in the lignocaine patients. A significantly greater proportion of lignocaine patients underwent concomitant valve replacement and coronary grafting procedures. The lignocaine group patients had a significantly longer mean duration of aortic crossclamping. A significant (inverse) correlation with outcome was shown for only one factor, in one test, and at one testing time after controlling for lignocaine administration (body mass index 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 (micromoles per litre) in the lignocaine patients were 16.6 (8.5 standard deviation), 9.4 (3.3 SD), 7.8 (3.0 SD) and 10.6 (2.6 SD) at aortic cannulation, aortic declamping, 8 hours and 24 hours after initiation of the infusion.

One female placebo patient was recorded as suffering a mild peri-operative stroke, which resulted in new unilateral sensory changes. The number and proportion of lignocaine and placebo patients exhibiting a decrement in at least one or at least two performance test sub-scales at each review are presented in Table 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 NP "performance" tests are either shown in Figure 1 (five of the six sub-scales in which group differences were significant) or are listed in Table 7 (the five 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 to 5 component of the Rey Auditory Verbal Learning Task, 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; Auditory Verbal Learning Task (distract

**TABLE 2**
**COMPARISON OF GOUUP MEAN RAW SCORES FOR ALL TEST SUB-SCALES IN LIGNOCAINE AND PLACEBO GROUPS AT THE PREOPERATIVE ASSESSMENT[a]**

| Test | Units | Lignocaine Group | Placebo Group |
|---|---|---|---|
| **Performance tests** | | | |
| Auditory Verbal Learning Task (trials 1-5 total)[29] | Number correct | 39.4 ±9.3 | 40.4 ± 8.5 |
| Auditory Verbal Learning Task (distract list) | Number correct | 4.1 ± 1.3 | 4.6 ± 1.9 |
| Auditory Verbal Learning Task (recall trial) | Number correct | 8.0 ± 3.3 | 7.8 ± 2.6 |
| Inspection time (dynamic) | Time (ms) | 83.5 ± 27.1 | 82.9 ± 24.3 |
| Inspection time (traditional) | Time (ms) | 88.4 ±47.3 | 102.8 ± 51.6 |
| Rey figure (copy)[29] | Score | 32.8 ± 2.7 | 32.3 ± 4.1 |
| Rey figure (recall) | Score | 17.4 ± 5.7 | 16.0 ± 6.5 |
| Symbol Digit Modality Test (oral)[29] | Number correct | 48.7 ± 11.0 | 49.2 ±11.9 |
| Symbol Digit Modality Test (written) | Number correct | 41.0 ± 11.9 | 41.3 ± 11.7 |
| Trails A[29] | Time (s) | 31.6 ± 13.6 | 34.2 ± 11.5 |
| Trails B | Time (s) | 112.8 ± 102.5 | 103.5 ± 69.7 |
| **Self-rating inventory** | | | |
| MAC-S (How good at?)[30] | Score | 2.49 ± 0.58 | 2.42 ± 0.56 |
| MAC-S (How often do?) | Score | 2.61 ± 0.52 | 2.50 ± 0.47 |
| **Control tests** | | | |
| Beck depression[29] | Score | 7.2 ± 4.7 | 7.6 ± 6.8 |
| State Trait Anxiety Inventory (state anxiety)[29] | Score | 38.7 ± 11.4 | 38.4 ± 13.9 |
| State Trait Anxiety Inventory(trait anxiety) | Score | 35.3 ± 8.3 | 37.1 ± 8.3 |

a Data are means ± standard deviation. There were no significant differences.
MAC-S = Memory Assessment Clinics Self-Rating Test.

**TABLE 3**
**COMPARISON OF LIGNOCAINE AND PLACEBO GROUPS WITH RESPECT TO DEMOGRAPHIC AND PRE-OPERATIVE VARIABLES[a]**

| Pre-operative Factor | Lignocaine Group (n - 28) | Placebo Group (n = 27) |
|---|---|---|
| Age (years) | 56.9 ± 8.9 | 54.4 ± 9.7 |
| Men | 17 (60.7%) | 14 (51.9%) |
| Women | 11 (39.3%) | 13 (48.1%) |
| Body mass index | 25.3 ± 4.3[b] | 28.5 ± 5.2[b] |
| Secondary education (years) | 3.78 ± 3.0 | 3.81 ± 2.4 |
| Smoking (pack-years) | 4 (range 0-40) | 0 (range 0-40) |
| Cardiothoracic ratio | 53.6 ± 5.3 | 55.1 ± 5.4 |
| Mean aortic gradient in patient undergoing aortic valve procedures (mm Hg) | 55.1 ± 15.7 | 55.2 ± 14.5 |
| Admission systolic blood pressure (mm Hg) | 124 ± 16 | 127 +- 18 |
| Fractional shortening (%) | 33.8 -+ 10.8 | 37.8 +- 10.5 |
| Atrial fibrillation | 6 (21.4%) | 7 (25.9%) |
| Renal dysfunction | 3 (10.7%) | 1 (3.7%) |
| Carotid bruit | 1 (3.6%) | 2 (7.4%) |
| Clinical left ventricular failure | 6 (22.2%) | 4 (14.8%) |
| Coronary artery disease | 13 (46.4%) | 8 (29.6%) |
| Myocardial score[34] | 3 (range 0-12)[c] | 1 (range 0-11)[c] |
| Previous transient ischemic attack | 1 (3.6%) | 3 (11.1%) |
| Diabetes | 2 (7.1%) | 1 (3.7%) |
| Peripheral vascular disease | 1 (3.6%) | 1 (3.7%) |
| Hypertension (past history) | 2 (7.1%) | 6 (22.2%) |

[a]Data are mean ± standard deviation, number (%), or median (range); [b]p <0.025; [c]p <0.05 otherwise not significant.

**TABLE 4**
**COMPARISON OF LIGNOCAINE AND PLACEBO GROUPS WITH RESPECT TO SURGICAL AND PERI-OPERATIVE VARIABLES[a]**

| Surgical Factor | Lignocaine Group (n = 28) | Placebo Group (n = 27) |
|---|---|---|
| Aortic valve replacement | 20 (71.4%) | 15 (55.6%) |
| Mitral valve replacement | 6 (21.4%) | 9 (33.3%) |
| Dual valve replacement | 2 (7.1%) | 3 (11.1%) |
| Valve plus coronary grafts | 13 (46.4%)[b] | 5 (18.5%)[b] |
| Redo operation | 7 (25%) | 4 (14.8%) |
| Ascending aorta atheroma | 1 (3.6%) | 3 (11.1%) |
| Duration of cardiopulmonary bypass (CBP) (min) | 129.3 ± 42.6 | 109.5 ± 35.2 |
| Cross-clamping time (minutes) | 112.3 ± 35.5[b] | 92.9 ± 27.8[b] |
| Emboli count | 2,042 (range 247 - 6,959) | 1,748 (range 216 - 11,349) |
| Coolest temperature (°C) | 28.2 ± 2.5 | 28.6 + 2.0 |
| Fractional fall in haemoglobin | 0.34 ± 0.1 | 0.34 -+ 0.1 |
| $TM^{-50}$ mm Hg.minute | 151 (range 15 - 1,600) | 102.5 (range 0 - 590) |
| Pre- and post-CPB time systolic BP <80 mm Hg (minutes) | 10 (range 0-97) | 7.5 (range 2-78) |
| lnotropes after cardiopulmonary bypass | 11 (39.3%) | 10 (37%) |
| Etomidate used in anaesthetic | 10 (35.7%) | 9 (33.3%) |
| Ketamine used in anaesthetic | 4 (14.3%) | 4 (14.8) |
| Isoflurane used in anaesthetic | 17 (60.7%) | 16 (59.3%) |
| Propofol used in anaesthetic | 10 (35.7%) | 12 (44.4%) |

[a] Data are mean ± standard deviation, number (%), or median (range); [b] p <10.05, otherwise not significant. BP = blood pressure.

**TABLE 5**
**COMPARISON OF LIGNOCAINE AND PLACEBO GROUPS WITH RESPECT TO POST-OPERATIVE VARIABLES[a]**

| Post-operative Factor | Lignocaine (n = 28) | Placebo (n = 27) |
|---|---|---|
| ICU ventilation (hours) | 12.6 ± 5.6 | 12.4 ± 6.2 |
| ICU stay (hours) | 24.1 ± 7.4[b] | 29.4 ± 11.1[b] |
| ICU inotropes required | 10 (35.7%) | 7 (25.9%) |
| Intraaortic balloon pump required | 1 (3.6%) | 0 |
| Peak AST | 55.9 ± 28.7 | 58.4 ± 18.3 |
| Peak AST >100 | 1 (3.6%) | 0 |
| Renal dysfunction in first 48 hours | 9 (32.1%) | 5 (22.2%) |
| New atrial fibrillation | 7 (25%) | 9 (33.3%) |
| Hospital stay (days) | 9.0 ±2.6 | 9.6 ± 2.8 |

[a] Data are mean ± standard deviation, or number (%);
[b] $p < 0.05$, otherwise not significant.
AST = aspartate aminotransferase.
ICU = intensive care unit.

list and recall trial); Symbol Digit Modality Test (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 2. 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 who had spouses (n = 27). The sequential group mean percentage change scores in the Beck depression inventory and the two State Trait Anxiety Index (STAI) sub-scales are shown in Figure 3. Although there was no difference attributable to treatment, there was a significant time-dependent decrease in both depression and anxiety ($p < 0.01$).

**Comment**

Patients undergoing left heart valve procedures were chosen for this study because of their high risk of peri-

**TABLE 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**

| | 10 Days | | | 10 Weeks | | | 6 Months | | |
|---|---|---|---|---|---|---|---|---|---|
| | Lignocaine (n = 25) | Placebo (n = 24) | p Value | Lignocaine (n = 26) | Placebo (n = 24) | p Value | Lignocaine (n= 25) | Placebo (n =23) | p Value |
| Timing of tests[a] | 9.8 ± 2.6 | 9.8 ±1.7 | NS | 10.1 ± 1.8 | 10.8 ± 2.4 | NS | 29.1 ± 2.4 | 29.2 ± 1.8 | NS |
| Decrement x 1 | 10 (40%) | 18 (75%) | <0.025 | 12 (46%) | 18 (75%) | <0.05 | 7 (28%) | 11 (48%) | NS |
| Decrement x 2 | 5 (20%) | 10 (42%) | NS | 3 (11.5%) | 6 (25%) | NS | 2 (8%) | 4 (17%) | NS |

Timing of tests units are days for the first test and weeks for the other two tests. [a]Data are mean ± standard deviation. Decrement x 1 = Decrement in at least 1 scale. Decrement x 2 = Decrement in at least 2 scales. NS = not significant.

**TABLE 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]**

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

[a] Data are means ± standard error.

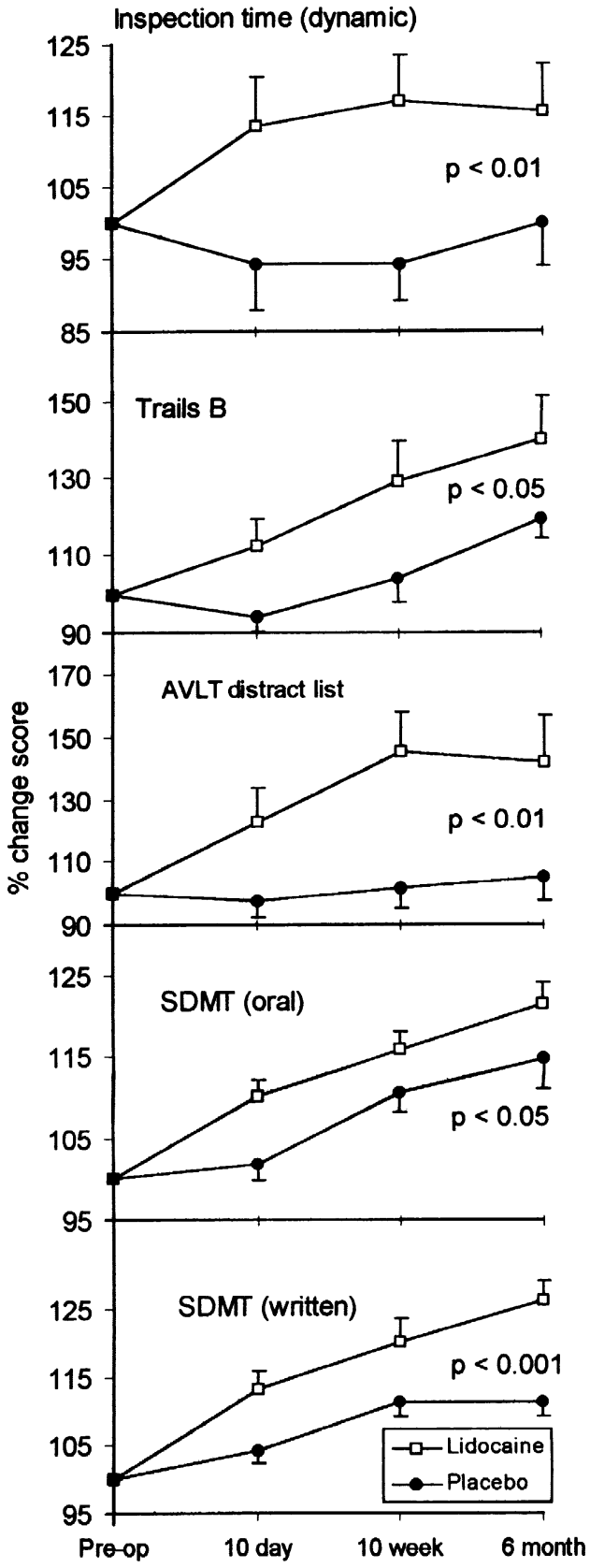


**Figure 1.** Sequential group mean percentage change scores for lignocaine and placebo groups in performance of test sub-scales where there was a significant difference between the groups. Data are mean ± standard error. (AVLT = Auditory Verbal Learning Task; SDMT = Symbol Digit Modality Test.)

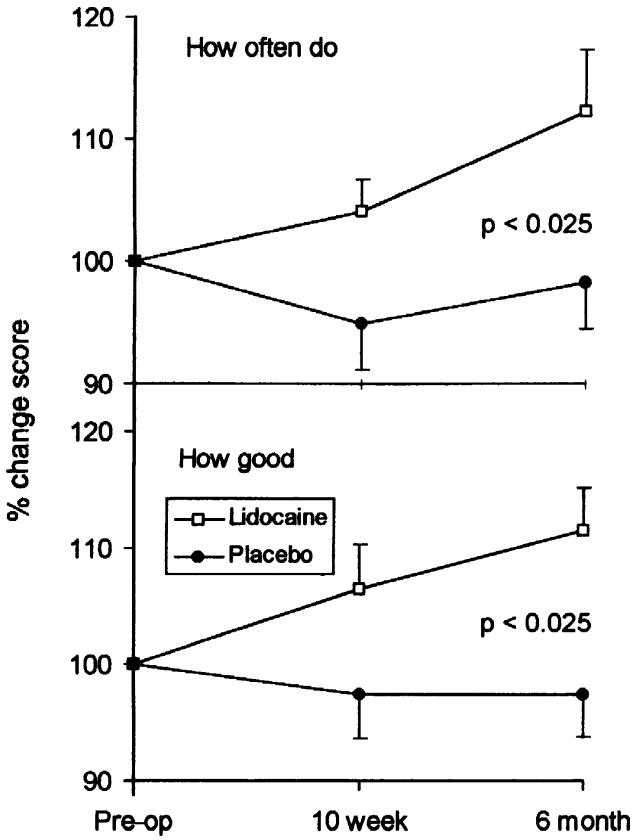


**Figure 2.** Sequential group mean percentage change scores for lignocaine and placebo groups in the two sub-scales of the Memory Assessment Clinics Self Report Inventory. Data are mean ± standard error.

operative brain injury.[35] In addition, the elective nature of the operation enabled pre-operative NP testing such that the patients could act as their own controls. Together, these allowed a trial of many fewer subjects than if stroke had been used as an end point.

A significantly greater proportion of the placebo group showed discrete 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 improvement in all tests except the Rey Figure Copy in which a ceiling effect prevented significant change. In contrast, improvement in the placebo group mean was significantly less in some tests or absent in others. These findings suggest a strong and persistent cerebral protective effect for lignocaine. They also illustrate the previously described phenomenon of improvement in group mean NP test scores,[36] despite discrete decrements in some patients, after cardiac operations. Group mean score improvements are particularly noticeable in later reviews and are not surprising here given that we demonstrated a significant post-operative decrease in depression and anxiety in both groups. A practice effect, selective attrition, and physiological factors may also be important, but none of the latter have been identified.

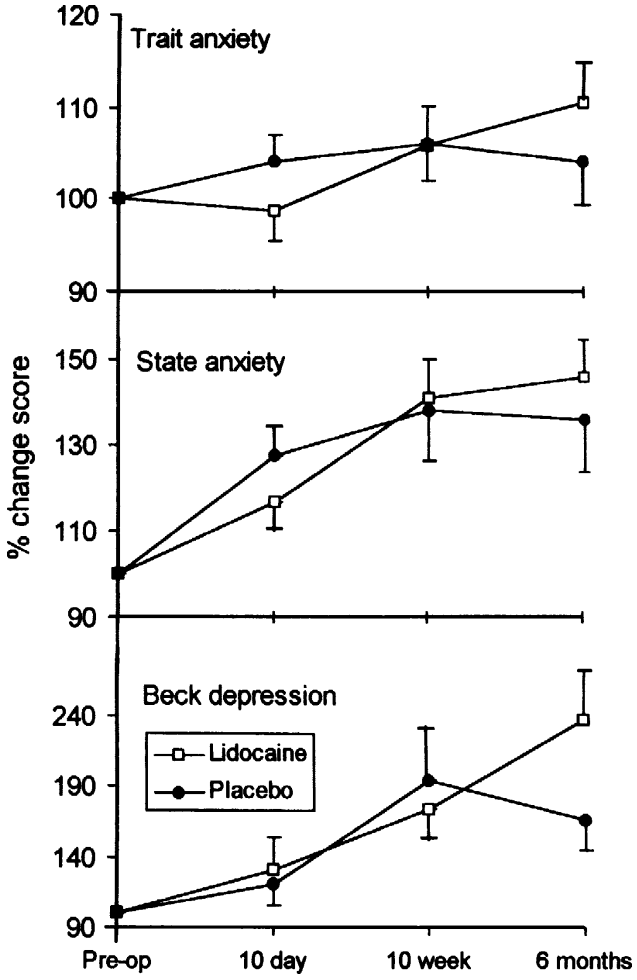


**Figure 3.** Sequential group mean percentage change scores for lignocaine and placebo groups in the Beck Depression and State Trait Anxiety Inventories. Data are mean ± standard error. Note that an increase in score indicates a decrease in depression or anxiety.

No confounding factors were identified that could explain the better outcome in the lignocaine patients. Although anxiety and depression may affect NP test performance,[37] the lignocaine and placebo patients did not differ either before or at any time after operation 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 body mass index, this has not previously been identified as a risk factor for poor cognitive outcome after cardiac operations and only a single test score (MACS-How Good, at the 10-week review) showed a significant inverse correlation with body mass index. 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.[38] The lignocaine patients also experienced longer aortic cross-clamping times, which further increases relative risk of cerebral injury.[39] Although 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.

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, the advantage for lignocaine shown here is not only detectable by objective NP testing, but with respect to memory at least, is also apparent to the patients themselves. In addition, a correlation between NP test results and the incidence of both objective clinical cerebral dysfunction[40] and biochemical markers of brain injury[41] has previously been demonstrated after cardiac operation.

Neither the mechanism of cerebral protection by lignocaine nor the ideal dosing regimen is demonstrated by this study. We chose a target plasma concentration consistent with that reported as effective for cerebral protection in vivo.[19,20] We arbitrarily adopted a 48-hour infusion in recognition of a possible anti-inflammatory role,[25] which might be important beyond the immediate peri-operative period. An expanded trial that will test different infusion durations is planned.

In the interim, we recommend that lignocaine be considered for the routine peri-operative care of patients undergoing left heart valve procedures. Consideration should also be given to investigating a role for lignocaine in other forms of brain injury.

This work was supported by grants from the English Freemasons of New Zealand and the Health Research Council of New Zealand. We thank the surgeons, anaesthetists, perfusionists, and nursing staff at Green Lane Hospital for their invaluable assistance in the conduct of this study. In particular, thanks are due to: Drs Alan Kerr, Neil Middleton and John McDougall; Tim Willcox; and to the patients for their co-operation.

## References

1 Fox HM, Rizzo ND and Gifford S. Psychological observations of patients undergoing mitral surgery: study of stress. *Psychosomat Med* 1954; 16: 186-208

2 Barbut D, Lo YW, Gold JP, et al. Impact of embolization during coronary artery bypass grafting on outcome and length of stay. *Ann Thorac Surg* 1997; 63: 998-1002

3 Stump DA, Fedorko L, Brooker R, Hilbawi H, Kon NA and Hammon JW, Jr. Biochemical markers of brain injury, embolic load, bypass time, and neurobehavioral deficits after CABG surgery: is there a relationship? [Abstract] *Ann Thorac Surg* 1997; 64: 920

4 Vingerhoets G, Van Nooten G, Vermassen F, De Soete G and Jannes C. Short-term and long term neuropsychological consequences of cardiac surgery with extracorporeal circulation. *Eur J Cardiothorac Surg* 1997; 11: 424-31

5 Ropper AH, Wechsler LR and Wilson LS. Carotid bruit and the risk of stroke in elective surgery. *N Engl J Med* 1982; 307: 1388-90

6 Shaw PJ, Bates D, Cartlidge NEF, et al. Neurologic and neuropsychologic morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. *Stroke* 1987; 18: 700-6

7 Mora CT and Murkin JM. The central nervous system: responses to cardiopulmonary bypass. In *Cardiopulmonary bypass: principles and techniques of extracorporeal circulation.* Mora CT. Ed. New York: Springer-Verlag, 1995: 114-46

8 Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M and Newman S. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke* 1994; 24: 1393-9

9 Rogers AT, Newman SP, Stump DA and Prough DS. Neurologic effects of cardiopulmonary bypass. In *Cardiopulmonary bypass: principles and practice*. Gravlee GP, Davis RF and Utley JR. Eds. Baltimore: Williams and Wilkins, 1993: 542-76

10 Treasure T. Interventions to reduce cerebral injury during cardiac surgery-the effect of arterial line filtration. *Perfusion* 1989; 4: 147-52

11 Menkis AH, St. Amand MA, Murkin JM, Baird D and Downey DB. Epiaortic scanning can influence surgical management during cardiac surgery [Abstract]. *Ann Thorac Surg* 1997; 64: 919

12 Rescigno G, Riom H, Nottin R and Arnaud-Crozat E. Doppler analysis of the left venting line: an effective and simple technique to control heart de-airing. *Cardiovasc Surg* 1995; 3: 65-9

13 Webb WR, Harrison LH, Helmcke FR, et al. Carbon dioxide field flooding minimizes residual intracardiac air after open heart operations. *Ann Thorac Surg* 1997; 64: 1489-91

14 Mitchell SJ, Willcox T, McDougall C and Gorman DF. Emboli generation by the Medtronic Maxima hard-shell adult venous reservoir in cardiopulmonary bypass circuits: a preliminary report. *Perfusion* 1996; 11: 145-55

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

16 Todd M. Barbiturate protection and cardiac surgery: a different result. *Anesthesiology* 1991; 74: 402-5

17 Forsman M, Olsnes BT, Semb G and Steen PA. Effects of nimodipine on cerebral blood flow and neuropsychological outcome after cardiac surgery. *Br J Anaesth* 1990; 65: 514-20

18 Legault C, Furberg CD, Wagenknecht LE, et al. Nimodipine neuroprotection in cardiac valve replacement: report of an early terminated trial. *Stroke* 1996; 27: 593-8

19 Evans DE, Catron PW, McDermott JJ, Thomas LB, Kobrine AI and Flynn ET. Effect of lidocaine after experimental cerebral ischemia induced by air embolism. *J Neurosurg* 1989; 70: 97102

20 Shokunbi MT, Gelb AW, Wu XM and Miller DJ. Continuous lidocaine infusion and focal feline cerebral ischemia. *Stroke* 1990; 21: 107-11

21 Rasool N, Faroqui M and Rubenstein EH. Lidocaine accelerates neuroelectrical recovery after incomplete global ischemia in rabbits. *Stroke* 1990; 21: 929-35

22 Nagao S, Murota T, Momma F, Kuyama H and Nishimoto A. The effect of intravenous lidocaine on experimental brain oedema and neural activities. *J Trauma* 1988; 28: 1650-5

23 Fried E, Amorim P, Chambers G, Cottrell JE and Kass IS. The importance of sodium for anoxic transmission damage in rat hippocampal slices: mechanisms of protection by lignocaine. *J Physiol (Lond)* 1995; 489: 557-65

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

25 MacGregor RR, Thorner RE and Wright DM. Lidocaine inhibits granulocyte adherence and prevents granulocyte delivery to inflammatory sites. *Blood* 1980; 56: 203-9

26 Fujitani T, Adachi N, Miyazaki H, et al. Lidocaine protects hippocampal neurons against ischemic damage by preventing increase of extracellular excitatory amino acids: a microdialysis study in Mongolian gerbils. *Neurosci Lett* 1994; 179: 91-4

27 Cogar WB. Intravenous lidocaine as adjunctive therapy in the treatment of decompression illness. *Ann Emerg Med* 1997; 29: 284-6

28 Govier AV. Central nervous system complications after cardiopulmonary bypass. In *Cardiopulmonary bypass: current concepts and controversies*. Tinker JH. Ed. Philadelphia: WB Saunders, 1989: 41-68

29 Lezak MD. *Neuropsychological assessment, 3rd Edition*. New York: Oxford University Press, 1995

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

31 Newman SP. Analysis and interpretation of neuropsychologic tests in cardiac surgery. *Ann Thorac Surg* 1995; 59: 1351-5

32 Stockard JJ, Bickford RG and Schauble JF. Pressure dependent cerebral ischemia during cardiopulmonary bypass. *Neurology* 1973; 23: 521-9

33 Myers JL and Well AD. *Research design and statistical analysis*. New York: HarperCollins, 1991: 256 8

34 Brandt PWT, Partridge JB and Wattie WJ. Coronary arteriography: a method of presentation of the

arteriogram report and a scoring system. *Clin Radiol* 1977; 28: 361-8
35 Nussmeier NA. Adverse neurological events: risks of intracardiac versus extracardiac surgery. *J Cardiothorac Vasc Anesth* 1996; 10: 31-7
36 Aberg T and Kihlgren M. Cerebral protection during open-heart surgery. *Thorax* 1977; 32: 525-33
37 Townes BD, Bashein G, Hornbein TF, et al. Neurobehavioural outcomes in cardiac operations: a prospective controlled study. *J Thorac Cardiovasc Surg* 1989; 98: 774-82
38 Wolman RL, Kanchuger MS, Newman ME Roach GW and Nussmeier NA. Adverse neurologic outcome following intracardiac versus extracardiac surgery [Abstract]. *Perfusion* 1994; 9: 406
39 Murkin JM. Neurological dysfunction after CAB or valvular surgery: is the medium the miscreant? *Anesth Analg* 1993; 76: 213-4
40 Shaw PJ, Bates D, Cartlidge NEF, et al. Early intellectual dysfunction following coronary bypass surgery. *Q J Med* 1986; 58: 59-68
41 Aberg T, Ronquist G, Tyden H, et al. Adverse effects on the brain in cardiac operations as assessed by biochemical, psychometric, and radiologic methods. *J Thorac Cardiovasc Surg* 1984; 87: 99-105

*An earlier version of this paper was presented by Dr Gorman at the SPUMS Annual Scientific Meeting 1998 in Palau.*

*Dr Simon Mitchell, MB ChB, Dip DHM, who is the Vice-President of the Underwater and Hyperbaric Medical Society, was Director of the Slark Hyperbaric Unit at the Royal New Zealand Navy Hospital, Naval Base, Auckland, New Zealand. This work was part of his PhD research program. He is now Medical Director of the Wesley Centre for Hyperbaric Medicine, Sandford Jackson Building, Chasely Street, Auchenflower, Queensland 4066, Australia. Telephone + 61-7-3371-6033. Fax 61-7-3371-1566. E-mail smitchell@wesley.com.au .*

*Ora Pellett, MSc, is a research psychologist at the University of Auckland, New Zealand. She is completing a PhD in Psychology in which she is studying the neurocognitive effects of cardiac surgery and their modification by protective strategies.*

*Professor D F Gorman FAFOM, PhD, is Head, Occupational Medicine, Faculty of Medicine and Health Sciences, University of Auckland, New Zealand. He is a Past-President of SPUMS. His address is 52 Albert Road, Devonport, Auckland 9, New Zealand. Telephone + 64-9-373-7599. Fax + 64-9-308-2379. E-mail d.gorman@auckland.ac.nz .*



# SPUMS ANNUAL SCIENTIFIC MEETING 1999

## THE EFFECT OF BUBBLES ON THE LIVING BODY

Alf Brubakk

**Key Words**
Bubbles, decompression illness, physiology.

### Introduction

There is general agreement that the basic problem in decompression is gas coming out of solution and forming a gas phase. However, it is also well known that a considerable number of bubbles can be formed without any acute signs or symptoms. Such bubbles have been called "silent" bubbles[1] and have, in particular, been observed in the pulmonary artery.[2] One conclusion that can be drawn from this observation is that acute clinical symptoms are critical dependent upon the location of the bubbles. Bubbles in the brain, for instance, could give few symptoms, as large areas of the brain are clinically silent. Bubbles in joints, on the other hand, would give symptoms, because of the rich innervation by pain receptors in these areas. One effect of this would be that we have to distinguish between primary and secondary effects of bubbles. The primary effects are related to the mechanical effect of the bubbles, which may be blockage of the circulation or distortion of tissue. The secondary effects are related to the numerous effects of the bubble surface, with activation of a large number of biochemical and cellular mechanisms. It seems obvious that this secondary effect can occur without any acute signs or symptoms.

### When do bubbles form ?

Most, if not all, practical decompressions will lead to some degree of gas bubble formation in the organism