Christchurch Medical Research Society

AGM and Scientific Meeting

Wednesday 16 April 2003

5 pm - 7.15 pm in the Beaven Lecture Theatre

5:00 ANNUAL GENERAL MEETING

5:15 ORAL PRESENTATIONS

5:15 **Azathioprine and 6-Mercaptopurine Adverse Effects and TPMT Genotype in Patients with Inflammatory Bowel Disease**
Richard B. Gearry*, Murray L. Barclay, Michael J. Burt, Judith A. Collett, Rebecca L. Roberts, Martin A. Kennedy

5:30 **Cerebral Haemodynamics and Auto-Regulatory Models of the Circle of Willis**
KT Moorhead, CV Doran, JG Chase, T David

5:45 REFRESHMENTS

There will be no charge for refreshments as this is covered by the $10 subscription which will be gladly accepted at the meeting!!

6:15 ORAL PRESENTATIONS CONT.

6:15 **AT1R Gene Polymorphism Interacts with N-BNP Levels to Predict Prognosis in Heart Failure Patients**
Anna P. Pilbrow*, Barry R. Palmer, Chris M. Frampton, Tim G. Yandle, Richard W. Troughton, Elizabeth Campbell, A. Mark Richards, M. Gary Nicholls, Vicky A. Cameron

6:30 **Models of Clot Dissolution Following Recanalisation**
T. David, C. Pleydell, S. Smye, D. Berridge

6:45 **Can the Oculomotor Control System Compensate for Initial Velocity when Making a Saccade?**
Johnny Tan*, Richard D. Jones, John H. Andreae, Paul R. Davidson, Chris M. Frampton, Harsha R. Sirisena, Tim J. Anderson

7:00 **Quantifying Agitation In Sedated Intensive Care Patients**
J. Geoffrey Chase, ZhuHui Lam, Christina Starfinger, Geoffrey M Shaw, Franck Agogue, Harsha Sirisena

* Contestants for the CMRS Young Researcher Prize

NB The meeting should be finished in time for those who wish to attend the Public Health Series talk on bowel cancer by Professor Frank Frizelle at 7:30 pm in the Rolleston lecture theatre.

Christchurch Medical Research Society

33rd Annual General Meeting, 16 April 2003

Agenda

1. Apologies: Ian Town, Ross Bowie, John Evans, Margaret Currie, Karl Sluis
2. Minutes of the 32nd AGM held on 24 April 2002 (attached)
3. Chairperson's report – Geoff Shaw (attached)
4. Financial statement – Michael MacAskill (attached)
5. Election of Executive

Chairperson	Geoff Shaw – Intensive Care
Secretary/Treasurer	Michael MacAskill – Medicine
Committee	Dru Mason – Zoology, Canterbury University
	David McGregor – Nephrology
	Robyn Niven – Research Office
	Karl Sluis – Biorad Ltd
	Elisabeth Wells – Public Health
	John Fink – Neurology
	Chris Pemberton – Endolab
	Darin O'Keeffe – Medical Physics*

* Nominated Richard Tremewan, seconded David Goode.

6. General business

Thanks to retiring Executive members:
Richard Tremewan.

Minutes of the 32nd Annual General Meeting, 24 April 2002, held in the Rolleston Theatre, Christchurch School of Medicine at 5:02 pm.

Present: Dr Richard Tremewan (in the chair) and 30 members.

Apologies. Don Beaven, Jack Heinemann, David McGregor, Ross Bowie, Gary Nicholls, Evan Begg. (Accepted)

Minutes. The minutes of the 31st AGM held on April 18, 2001 were ratified.

Chairperson's report. Dr Richard Tremewan presented the chairperson's report which was received with acclaim.

Financial statement. The financial statement to 31 March 2001 was presented by the Secretary/Treasurer (Dr Michael MacAskill) and accepted by the meeting. Subscriptions were maintained at $10.00 for 2001/2002.

Election of officers. The Committee for 2002/2003 will be as follows:

Chairperson	Geoff Shaw – Intensive Care
Secretary/Treasurer	Michael MacAskill – Medicine
Committee	Dru Mason – Zoology, Canterbury University
	David McGregor – Nephrology
	Robyn Niven – Research Office
	Karl Sluis – Biorad Ltd
	Richard Tremewan – Medical Physics
	Elisabeth Wells – Public Health
	John Fink – Neurology*
	Chris Pemberton – Endolab**

* Nominated Tim Anderson, seconded Michael MacAskill

** Nominated Chris Charles, seconded Michael MacAskill

General business.
Thanks to retiring Executive members

Barbara Peddie, Chris Charles, Tim Anderson, John Elliott, and Steven Gieseg retired from the Executive Committee and were thanked for their efforts over the years.

Discussion

1. Richard Jones queried the continued need for the Society to levy subs. The Secretary noted that although the costs of running the Society's affairs had decreased markedly (as a result of both the administrative assistance provided by the Research Office and the catering of two of the meetings as part of the normal Friday lunchtime clinical meeting), there were still costs to be covered, such as catering the evening meeting and providing a second prize for the Young Researcher contest.
2. Christine Winterbourne noted that the presentations had increasingly become the preserve of junior researchers and that there was a need for more of the senior researchers to present. Tim Anderson suggested this could be addressed by senior researchers presenting their posters from other meetings. It was also suggested that one evening could be held as a more informal social gathering, combined with poster presentations.
3. Martin Kennedy suggested that the Society could attempt to tie in with the Royal Society meetings, which are held monthly.
4. Geoff Shaw suggested that the meeting format could be changed to one with shorter presentations.
5. Robin Fraser stressed the importance of the abstracts of the meetings being published in the New Zealand Medical Journal.

Closure

There being no further business, the AGM closed at 5.15 pm.

CMRS Chair's 2002/03 Annual Report

This is the 33rd AGM of the society and the CMRS continues to remain in good health. The CMRS was set up to allow young and sometimes not-so-young researchers to stand up and present their stuff at a multi-disciplinary forum. To this end the CMRS as been highly successful in running 14 presentations in 2002 which have been of a very high standard.

For the last two years 3M have sponsored a prize of $300 for the best presentation. The Society would like to thank the continued support of 3M and congratulate last year's recipients:

1st. Margaret Currie
"VEGF-D expression is associated with lymph node status in primary human breast carcinomas and regulated by estrogen in breast carcinoma cell lines".

2nd Stephen Hoskin
"Oxidation of β_2-agonists by Peroxidases and its Relevance to Asthma Control"

My thanks to Robyn Niven and Michael MacAskill for their unfailing support in pulling together the scientific sessions. I would particularly like to thank Dr Richard Tremewan whose mentorship and support as a committee member and previous chairman has been much appreciated. Richard is retiring from the Committee this year.

Finally a huge vote of thanks goes to the presenters, their supporters, and to the members who continue to infuse the Society with their knowledge, wits, and skills. This is what creates the sense of community amongst researchers. This year we can again look forward to a fascinating mix of presentations from molecular biology and basic science through to bioengineering, clinical science.

Geoffrey M Shaw
Chair
16 April 2002

Christchurch Medical Research Society

Annual Financial Statement to 31 March 2002

Balance brought forward (as at 31.03.02) $2996.15

Income	**2002 (error)**	**2002 (correct)**	**2003**
Subscriptions	425.00	425.00	760.00
Sponsorship: 3M	300.00	300.00	220.00
Interest	34.05	34.05	0.00
PAYE Refund	6.63	8.61	0.00
Total	765.68	767.66	980.00
Expenditure			
Meals (including drinks)	344.65	344.65	280.00
PAYE	6.63	6.63	0.00
Prizes	600.00	400.00	400.00
Total	951.28	751.28	680.00
Income over expenditure	**($185.60)**	**$16.38**	**$300.00**

Current balance as at 31.03.03 $3296.15

Recommendations:
1 – that the report be received
2 – that this report supersedes last year's erroneous one
3 – that the annual subscription remain at $10 for 2003-2004
4 – that alternative banking arrangements be investigated

Michael R. MacAskill (Secretary/Treasurer)

Azathioprine and 6-Mercaptopurine Adverse Effects and TPMT Genotype in Patients with Inflammatory Bowel Disease

Richard B. Gearry[1], Murray L. Barclay [1, 2], Michael J. Burt[1], Judith A. Collett[1], Rebecca L. Roberts[3], Martin A. Kennedy[3]

[1] Department of Gastroenterology, Christchurch Hospital

[2] Department of Clinical Pharmacology, Christchurch Hospital

[3] Department of Pathology, Christchurch School of Medicine and Health Sciences

The thiopurine drugs (azathioprine and 6-mercaptopurine) are well-established treatments for inflammatory bowel disease (IBD) but have severe adverse effects in some patients. We suspected adverse effects were more common in Canterbury than reported elsewhere and that the likelihood and type of adverse effect may relate to thiopurine methyltransferase (TPMT) enzyme activity and genotype.

We aimed to (1) determine the types and frequency of adverse effects to thiopurine drugs in the Canterbury IBD population and (2) compare TPMT genotypes in patients who had reacted to and those who tolerate thiopurine drugs.

IBD patients treated with thiopurine drugs were identified using a computerised word search of letters from the Department of Gastroenterology, Christchurch Hospital. Patient records were screened for information relating to adverse effects. TPMT genotyping was performed on peripheral blood samples from patients who had reacted to a thiopurine drug and those who had tolerated these drugs (controls). Genotype frequencies were compared.

25.9% (56 of 216) of patients taking thiopurine drugs had reactions compared with 9% in a large reported study. The spectrum of adverse effects was similar to previous reports. 44 patients with reactions had a normal TPMT genotype (*1/*1), five were heterozygotes (*1/*3) and one patient with severe myelotoxicity was a homozygote poor metaboliser (*3/*3). Six patients were not available for genotyping. Only three of fifty randomly-chosen control patients had variant alleles (*1/*3).

In Canterbury there is a higher rate of severe adverse effects from thiopurine drugs than reported elsewhere. While a slight trend was seen for more frequent TPMT mutations in patients with reactions, this was not significant.

Cerebral Haemodynamics and Auto-Regulatory Models of the Circle of Willis

KT Moorhead[1], CV Doran[1], JG Chase[1], T David[1]

[1]University of Canterbury, Christchurch, New Zealand

The Circle of Willis (CoW) is a ring-like structure of blood vessels found beneath the hypothalamus at the base of the brain distributing blood to the cerebral hemispheres. A one-dimensional computational fluid dynamic [1-D CFD] model is developed to capture the auto-regulation dynamics that maintain blood perfusion pressure with a goal of developing diagnostic tools for stroke prediction.

The afferent and circulus arteries have constant resistances, and the efferent arteries have variable resistors limited to changes in radius of up to 40% to capture auto-regulatory behaviour. Auto-regulation is modelled by feedback control coupled with peripheral resistance dynamics to create a non-linear system. Solutions are obtained far more quickly than higher dimensional CFD models via a unique non-linear solution method. The overall model enables simulation of different CoW geometries for different patient conditions.

The CoW is simulated with a 20mmHg arterial pressure drop in the right internal carotid artery for the balanced configuration and each case where a single circulus vessel is omitted. Results match the 20% drop in flowrate, and 20 second response time from published clinical data and prior research. No single omission leads to failure in reaching the required efferent flowrates, highlighting the overall robustness of this arterial structure. A high stroke risk case, however, fails to achieve the required flowrate in the left posterior communicating artery ($LPCA_2$), representing a potential stroke. All of these results agree well with known clinical results, indicating the potential of this model for pre-determining potential outcomes of surgical or other procedures.

AT1R Gene Polymorphism Interacts with N-BNP Levels to Predict Prognosis in Heart Failure Patients

Anna P. Pilbrow, Barry R. Palmer, Chris M. Frampton, Tim G. Yandle, Richard W. Troughton, Elizabeth Campbell, A. Mark Richards, M. Gary Nicholls and Vicky A. Cameron.

Christchurch Cardioendocrine Research Group, Department of Medicine, Christchurch School of Medicine and Health Sciences.

The angiotensin-converting enzyme gene insertion/deletion (ACE I/D) polymorphism and a single nucleotide polymorphism in the angiotensin II type I receptor gene (AT1R A1166C) have been associated with increased risk and poor prognosis in myocardial infarction and heart failure patients, and have been reported to have a synergistic effect. This study investigates interactions between hormonal prognostic markers and genotype, in 426 heart failure patients genotyped for ACE I/D and AT1R A1166C polymorphisms.

The mean age on admission was 74.7 years, 51% of patients were male, and median patient follow-up was 1.4 years. Genotype frequencies for the ACE I/D polymorphism were 24% II, 50% ID and 26% DD and for the AT1R A1166C polymorphism were 46% AA, 46% AC and 8% CC. Univariate analyses showed patients with an AT1R CC genotype tended to have lower levels of N-BNP, elevated levels being an established marker for severity of heart failure. Despite this, nearly 70% of patients with a C allele died or were readmitted to hospital with heart failure compared with 58% for patients with an AA genotype over the follow-up period ($p<0.05$). Multivariate analyses showed the interaction between AT1R genotype and plasma N-BNP levels was the strongest independent predictor of death ($p<0.001$). Previously unreported associations between the AT1R genotype and plasma levels of interleukin-2 ($p<0.001$), endothelin-1 ($p<0.01$), angiotensin II ($p<0.01$), adrenomedullin ($p<0.05$) and atrial natriuretic peptide ($p<0.01$) were observed.

In summary, our data suggest that AT1R genotype may provide prognostic information in heart failure patients in combination with plasma N-BNP measurements.

Models of Clot Dissolution Following Recanalisation.

David.T [1], Pleydell. C. [2], Smye. S. [2] and Berridge.D[2]

[1] Department of Mechanical Engineering University of Canterbury, N.Z

[2] St James' Teaching Hospital Leeds, U.K.

A blood (fibrin) clot is a porous material. Plasma will flow through the pores in the fibrin matrix when subjected to pressure gradients as found across occlusive arterial thrombi. Previous modelling of local therapeutic thrombolysis in the porous solid has shown that the reaction front degrades into small 'fingers' which eventually lead to a recanalisation of the clot. There is a corresponding increase in flux of thrombolytic agent and a totally different process, parametrised by convection and diffusion of clot lysis takes place. If a residue of clot is left then re-occlusion occurs.

The presented work, using a similarity solution algorithm to solve a set of coupled ordinary differential equations, models the flow and reaction of the thrombolytic agent through the canal. Results show that as the canal radius increases due to the lysing of the clot the flux of unreacted thrombolytic agent increases significantly without increasing the rate of lysis. This has the potential to produce excessive concentrations of thrombolytic agent in the systemic blood stream which can react with fibrinogen and deplete important proteins in the blood plasma. However an increase in the diffusion coefficient of the clot reaction products increases the amount of lysed clot. On the basis of these results variations in thrombolytic agent concentration, would have little clinical effect.

Can the Oculomotor Control System Compensate for Initial Velocity when Making a Saccade?

Johnny Tan[1,2], Richard D. Jones[1,2,3], John H. Andreae[2], Paul R. Davidson[1,4], Chris M. Frampton[3], Harsha R. Sirisena[2], Tim J. Anderson[3]

[1]Department of Medical Physics and Bioengineering, Christchurch Hospital, Christchurch

[2]Department of Electrical and Computer Engineering, University of Canterbury, Christchurch

[3]Department of Medicine, Christchurch School of Medicine and Health Sciences, Christchurch

[4]Sobell Department of Motor Neuroscience, Institute of Neurology, London, United Kingdom

Although unproven, it is generally considered that the oculomotor control system takes initial velocity immediately preceding saccades (fast eye movement to bring objects of interest onto the fovea) into account when planning and executing saccadic eye movements. This is probably so that degradation of vision during a saccade can be minimized by achieving an optimal velocity profile which balances conflicting requirements of getting to a target as quickly as possible while minimizing under- and over-shoot.

Simulations, based on a linear biomechanical model of the eyeball and its musculature, showed that the peak velocity of a saccade is strongly dependent on the velocity of the eye just prior to the saccade. An experiment involving 4 normal adult subjects (3M/1F, 20-24 yr) was subsequently undertaken in which each subject was asked to visually track either a stationary or a sinusoidal target. At unexpected times during this smooth oculomotor pursuit, and while the subject's eyes were stationary or moving at various velocities up to $\pm 40^{o}$/s, the target switched to a step to induce a saccade. The target steps were in both the same and opposite directions to that of the pre-saccade smooth pursuit velocities.

ANCOVA analysis showed that the regression coefficient of the peak-velocity—saccade-amplitude relationship is dependent on initial velocity of the eye ($p=0.002$). Specifically, for forward saccades, the brain is only able to partially compensate for initial velocity of the eye relative to that expected for a purely biomechanical model. In contrast, for reverse saccades, the brain over-compensates for the initial velocity; that is, rather than the initial negative velocity causing a reduced peak velocity (as would be expected for partial compensation), or zero change in peak velocity (perfect compensation), the peak saccadic velocity is actually higher than that seen for zero initial velocity.

This is the first study to demonstrate experimentally that the oculomotor control system is able to compensate – but only partially – for initial eye velocity when planning and executing saccades.

Quantifying Agitation In Sedated Intensive Care Patients

J. Geoffrey Chase[1], ZhuHui Lam[1], Christina Starfinger[1], Geoffrey M Shaw[2], Franck Agogue[3], and Harsha Sirisena[3]

[1] Dept of Mechanical Engineering, University of Canterbury

[2] Department of Intensive Care Medicine, Christchurch Hospital

[3] Department of Electrical and Computer Engineering, University of Canterbury

Agitation in intensive care patients is poorly understood and subjectively measured making sedation and agitation management complex, increasing length of stay, and increasing cost. Current methods are entirely subjective and based primarily on patient motion. This research presents an automated, quantifiable method of measuring agitation. Objective measurement of agitation will enable more consistent agitation and sedation management, and create a platform for understanding the effects of different sedative therapeutics.

Observations of intensive care patients show that biomedical signals such as blood pressure, heart rate and respiratory rate all change as patients undergo agitation. This research quantifies agitation by applying signal processing to biomedical signals to correlate variation in these signals with assessed agitation. More specifically, the correlation of sympathetic response seen in heart rate variability (HRV), blood pressure magnitude, blood pressure variability (BPV) and respiratory rate, to current measurements of agitation was determined. Image processing of patient motion was also examined as an automated patient agitation detection method.

Proof of concept clinical trials were performed on 13 normal and 5 intensive care patients. Normal patients underwent testing designed to induce agitation responses from the sympathetic nervous system. Initial results show that during periods of agitation the ratio of very low frequency to high frequency components in HRV analysis increase, whereas in BPV analysis this ratio is decreased. Respiratory rates and quantified movement also visibly increased with agitation. A fuzzy quantification system was introduced to provide a final index of agitation. Results correlated well with subjective assessments, provided by medical staff, using the Riker SAS scale including measurments during calm periods.