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Thrombosis & Haemostasis society of Australia and New Zealand

Scientific Workshop

Brisbane Convention & Exhibition Centre
Trade Display: Rooms P1 & P2
Workshop: Room P3 & P4
Brisbane

20th October 2018

Thrombosis and Haemostasis Society of Australia and New Zealand.

Previously named the Australasian Society of Thrombosis and Haemostasis (ASTH) is now the Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ) was established in 1994. The Society represents approximately 200 clinicians, scientists and other health professionals committed to promoting and fostering the acquisition, exchange and diffusion of knowledge and ideas relating to normal and abnormal haemostasis. The Society serves as a forum for bringing together a broad array of disciplines, which relate to bleeding, thrombosis and cognate fields.

The THANZ Mission Statement

Promote excellence in clinical care for people with clotting and bleeding disorders.
To lead education and training of scientists and clinicians in the field;
To foster innovation through research, discovery and clinical trials;
To advocate and develop policies that improve health outcomes.

Membership Privileges

Newsletters (three per year)
Notices, booklets, flyers or brochures of interest to members
Copies of Media releases and letters to members from Council
Invitations to Society presentations and seminars
Attendance to Annual General Meetings
Nomination for a Council position
THANZ Medal competition eligibility at ASM (45 years of age and under)
Voting rights at Council elections, AGMs and subcommittee meetings
Access to the ASTH Website and Member's only area, including Discussion group
Discounted registration fees for ASM and Scientific Workshops

Further information
THANZ Secretariat
Email: info@thanz.org.au

8:00 am Registration and Tea/Coffee

9:00 am Welcome: Grace Gilmore (Chair)

9:10 am Chuen Wen Tan (Sydney – Australia)
Clot wave analysis

9:30 am Vivien Chen (Sydney – Australia)
New Assays for Procoagulant Platelets

9.50 am Sara Ng (Sydney – Australia)
The Coagulopathy of Liver disease assessed by ROTEM and CAT

10.10 am Emma Jones-Perrin (Brisbane –Australia)

Taking a look at routine aPTT data

10:30 am ***MORNING TEA and TRADE***

11:00 am Nora Lee (Melbourne – Australia)
Haemostatic testing in Cancer

11:20 am Hui Yin Lim (Melbourne- Australia)
Global assays in Thrombosis

11:40 am Joanne Beggs (Brisbane – Australia)
Case Study

12:00 pm Poster Session

12:15 pm ***LUNCH and TRADE***

1:15 pm Prof Wolfram Ruf (Mainz – Germany)
Changing Views of TF initiated coagulation; Implication for Haemophilia therapy and Thrombosis

2:05 pm Jiayin Tian (Perth – Australia)
TF and Oestrogen

2:20 pm Paul Ellery (Perth - Australia)
TFPI and FV short

2.40pm Mitchell Bulluss (Perth – Australia)
TFPI and Autoimmunity

3:00 pm ***AFTERNOON TEA and TRADE***

3:30 pm Emma Zadow (Launceston – Australia)
Influence of Travel, Marathon running and Compression socks on Haemostatic Activation

3:50 pm Mark Rane (Brisbane- Australia)
Case Study

4:10 pm Tina Pham (Melbourne – Australia)
Registration for Medical Scientists
4.25pm Closing Remarks/ Poster Prize

4:30 pm SUNDOWNDER and TRADE (until 5:30 pm)
Sponsored by THANZ

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Beyond Clotting Time: Clot Waveform Analysis As A Global Haemostatic Assay

Chuen Wen Tan

Clot waveform analysis (CWA) is an extended evaluation of routine clotting tests (activated partial thromboplastin time and prothrombin time). It is based on the continuous observation of the changes in optical transmittance or absorbance that occur as fibrin is formed in plasma during the performance of these clotting assays. Therefore, the data obtained reflect the global haemostatic function beyond a single clotting time. CWA has been initially investigated in the diagnosis and prognosis of disseminated intravascular coagulation and sepsis. Many studies subsequently followed in the field of bleeding disorders particularly in the diagnosis and management of Haemophilia A. More recently, data are emerging in the area of prothrombotic conditions. With more automated coagulation analysers having the capability to perform CWA and with increasing pre-analytical and clinical information becoming available, CWA could be a potentially rapid, accessible, inexpensive and easily performed tool for the assessment of various thrombotic and haemostatic disorders.


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New Assays for Procoagulant Platelet

Vivien Chen


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The Coagulopathy of Liver Disease assessed by ROTEM and CAT

Sara Ng

Background and Aims
Coagulopathy in liver disease represents a complex spectrum of clinical bleeding and thrombosis due to its effect on both pro-coagulant and anticoagulant factors. Global coagulation assays such as rotational thromboelastometry (ROTEM) and thrombin generation assays such as Calibrated Automated Thrombogram (CAT) are promising tools with utility and differential strengths in predicting acute haemorrhagic and thrombotic risks. There is limited data on their relationship and how they can be used in complement in the clinical setting. We aim to study the relationship between these assays in patients with coagulopathic liver disease and to identify parameters which may be predictive of bleeding risks in this patient cohort.

Methods
Twenty cirrhotic liver patients with significant coagulopathy (defined as INR$\geq$ 1.8 and/or platelets $\leq 50x10^9$/L) were studied. Conventional coagulation, ROTEM and CAT parameters were analysed for concordance.

Results
The following relationships were found between conventional coagulation, ROTEM and CAT parameters:

- There was a positive correlation between PT with CT_{EXTEM} (r 0.71, p=0.0004) and APTT with CT_{INTEM} (r 0.58, p=0.0104).
- An inverse correlation with PT and APTT with peak thrombin (r -0.79, p=0.0007) and endogenous thrombin potential (ETP) (r -0.79, p=0.0007).
- Fibrinogen levels correlated strongly with MCF_{FIBTEM} (r 0.90, p<0.0001)
- $MCF_{EXTEM, INTEM, FIBTEM}$ showed strong correlation with peak thrombin and α-angle with ETP (r 0.70, p=0.0045).

A shorter MCF, longer CT and longer CFT were observed in the patients with a bleeding history. The CAT demonstrated a shorter lag time and ttPeak, a higher thrombin peak and a smaller ETP in the patients with a bleeding history compared to those with a thrombotic history

Conclusion
There is strong correlation between conventional coagulation tests and global coagulation assays in the coagulopathy of liver disease. ROTEM parameters appear to be more predictive of bleeding phenotype compared to CAT in this patient cohort.
APTT and fibrinogen. In the user experience survey, CP3000 scored significantly higher for instrument size, QC monitoring, weekly maintenance and troubleshooting, but lower for calibration, QC processing, start-up, and noise.


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Taking a look at Routine aPTT Data.

Emma Jones-Perrin,
Senior Scientist, Pathology Queensland, Princess Alexandra Hospital

Too many organisations are data rich but information poor. Many organisations make limited use of their data for many reasons. It may be scattered across many systems rather than centralized in one readily accessible integrated data store. In pathology we have access to much data about a patient but often lack the time to fully take advantage of the power it holds to maybe improve patient outcomes, processes or even decisions. Because we are so time poor we only ever seem to be able to quote turn around time with any consistency. Imagine what we could do if we could combine the pathology data with the vast data out there attached to each patient and patient episode.
I have had a more than average interest in statistics compared to most scientists working in a hospital-based pathology laboratory for some years. I even began a Biostats course in the mid-2000's, only to discontinue after completing 2 subjects. Just over a year ago I started studying data science and I wanted to try to give a short presentation about something in coags that has bugged me for some time. Do we really get more critical high APTT's on patients on IV heparin after hours compared to during the day?


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Thrombin generation assays: stratifying thromboembolic risk in patients with NSCLC – a further analysis from the BIOTEL study

Authors: Nora Lee[1], Marliese Alexander[1], Ray Dauer[2], Cindy O'Malley[3], Dimitra Savva[1], David Ball[1] , Ben Solomon[1], Kate Burbury[1]

1 Peter MacCallum Cancer Centre, Melbourne, Victoria; 2 Eastern Health, Melbourne, Victoria; 3 RMIT, Melbourne, Victoria

Background and aim

Thromboembolism (TE) remains a frequent and preventable complication in patients with cancer, with significant clinical and economic consequences. Risk-stratified pharmacological thromboprophylaxis (P-TP) is safe and highly effective, albeit complicated by the heterogeneous and dynamic nature of TE. Published predictive models (CONKO, Khorana, CATS, PROTECHT) have variable and largely suboptimal sensitivity. This study extends the BIOTEL high-risk model (BHRM)*, assessing the role of global assays (thromboelastography, thrombin generation) and additional thrombogenic biomarkers in patients with NSCLC.

Methods

Stored venous blood samples from BIOTEL were tested for PF1+2, TAT, FM, procoagulant phospholipids (PPL), and ETP. Longitudinal changes from commencement of anti-cancer treatment (baseline, Months 1,3,6,9,12) were mapped with clinical progress, fibrinogen, d-dimer, vWF-Ag, FVIII and thromboelastography. Median differences were compared at each time point, and between patients with/without TE. Multivariate analysis of biomarkers and global assay for TE incidence, risk prediction and overall survival (OS) were explored #.

Results

The cohort of 83 patients had 16 (19.2%) TE events within 6 months of study entry (median 44.2 days [0.99-149]). 60-70% of patients displayed hypercoagulable characteristics (elevated FVIII, vWF-Ag, d-dimer, fibrinogen, TEG-MA) most evident at baseline and/or Month 1 with a progressive reduction by Month 12. The additional biomarkers had no significant longitudinal risk stratification trends. Median PF1+2, FVIII and VWF-Ag levels were persistently elevated without statistical associations with TE, death or OS. Baseline (i) ETP, (ii) ETP peak, (iii) velocity index, (iv) alpha-2-macroglobulin (α2m) and (v) Month 1 TAT were predictive for TE. ETP alone (i-iv) or with BHRM improved prediction specificity (**Table 1**) without additive predictive power for OS. Importantly, ETP and BHRM low risk stratified patients was concordant.

Table 1

TE Risk factor	Baseline Biomarkers						
	Sensitivity	Specificity	PPV	NPV	sHR[a]	95%CI	P
BIOMARKERS	31 patients, 8 TE						
ETP Peak >=260	87.5%	65.2%	46.7%	93.8%	9.39	1.16-76.24	0.036
ETP >=1930	87.5%	65.2%	46.7%	93.8%	9.39	1.16-76.24	0.036
Alpha 2M >=15	75.0%	82.6%	60.0%	90.5%	9.53	2.07-43.80	0.004
Velocity Index >=69	87.5%	65.2%	46.7%	6.3%	9.39	1.16-76.24	0.036
ETP Peak >=260 and ETP>1930	87.5%	73.9%	53.8%	94.4%	12.87	1.58-104.64	0.017
ETP Peak >=260 and BHRM	87.5%	69.6%	50.0%	94.1%	10.96	1.35-89.04	0.025
ETP Peak >=260 or BHRM	100.0%	30.4%	33.3%	100.0%	All events predicted		
ETP Peak >=260 and ETP>1930 and Vel Index >=69	87.5%	78.3%	58.3%	94.7%	15.25	1.87-124.13	0.011

Conclusion

The BHRM is a simple and robust risk prediction tool with real-time applicability. The derivation model established in NSCLC was validated in gastrointestinal cancer. This decision-making algorithm is currently being tested in a phase 3 RCT (TARGET-TP). Whilst ETP is not routinely available, our findings support the biological validity of BHRM, and incorporating ETP potentially strengthens TE risk prediction, achieving higher specificity with minimal loss in sensitivity

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Global Assays in Thrombosis

Hui Yin Lim

Global coagulation assays such as thromboelastography, fibrin and thrombin generation have been used to assess bleeding risks and guide blood product replacement in trauma and massive transfusion settings. However, the role of these assays in thrombosis is less clear and this is important to ascertain as predicting the risk of cardiovascular and thrombotic complications remains an unmet need. Various small studies have explored the use of individual assays in predicting cardiovascular and thrombotic risks. Interestingly, some studies have paradoxically demonstrated reduced thrombin generation and higher Protein C and S levels in patients with cardiovascular disease. Conversely, we have previously reported that global coagulation assays such as thromboelastography and thrombin generation can show subtle differences in age, gender and race, not seen on standard coagulation assays. Hence, these global coagulation assays, particularly when used in combination, may provide a better assessment of an individual's cardiovascular and thrombosis risk.

We provide a review of the literature of the role of these assays in thrombosis, including presenting the data we have collected in normal controls, patients with cardiovascular disease, venous thrombosis and myeloproliferative disorder. Specifically, to the best of our knowledge, we are the only investigators who have used all 3 assays (thromboelastography, fibrin and thrombin generation) in combination in each of these conditions, with unique differences and contradictions seen with each assay and disease process, highlighting the complexities of the coagulation system.


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Lupus Anticoagulant or Haemophilia B.

Dr M Harwood and Joanne Beggs (Senior Scientist)

The diagnostic dilemma when a high APTT requires investigation and the laboratory is faced with different possibilities with each one affecting the other. In this case the clinical picture gives us some clues but ultimately the treating team needs to decide the patient's treatment. This presentation highlights the need for both the laboratory and the Haematologist to work with each other to put together the best treatment.

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Changing Views of TF Initiated Coagulation: Implications for Haemophilia Therapy and Thrombosis

Prof Wolfram Ruf

Recent insights into the biochemistry of tissue factor (TF) initiated coagulation and its regulation indicated distinct pathways by which TF contributes to hemostasis versus thrombosis. In the traditional view TF serves as a trigger, which provides limited amounts of thrombin activating the plasmatic cofactors V and VIII and thereby enabling coagulation amplification by FIXa generated by either TF-FVIIa, the FXII contact pathway or thrombin-activated FXIa. These reactions play a dominant role in standard coagulation assays in which thrombin rapidly accumulates and readily escapes dilution by blood flow and physiological neutralization by fibrinogen and the vessel wall. These regulatory processes are highly relevant for thrombosis and hemostasis and standard coagulation assays underappreciated roles of FXa in cofactor activation and its regulation. The relevance of thrombin-independent FV activation in coagulation initiation was shown with a tick-derived inhibitor that specifically blocks FXa-mediated FV activation and thus prevents formation of an active prothrombinase complex in whole blood. In line with this finding, evidence is accumulating that platelet- and plasma-derived TF pathway inhibitor α (TFPIα) is a physiological inhibitor of FXa-mediated activation of FV. Surprisingly, TFPIα does not interfere with activation of the anti-hemophilic cofactor VIII by the nascent product FXa generated by TF-FVIIa. Mutants of FVIIa capable of activating FX, but defective in releasing the newly formed product FXa, showed that the TF-FVIIa-FXa coagulation initiation complex directly activates both, cofactor VIII and enzyme FIX, leading to thrombin generation and FVIII-dependent fibrin formation in flowing blood. Thus, the hemostatic function of TF is triggered early and prior to amplified thrombin generation. These distinct biochemical routes of TF initiation of the hemostatic FVIII pathway and the generation of prothrombotic prothrombinase and the regulatory roles of TFPI in these pathways have important implications for the diagnostic assessment of new hemostatic agents and anticoagulant drugs.


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TF and Oestrogen

Jiayin Tian

[1]Western Australian Centre for Thrombosis and Haemostasis, Murdoch University, Perth, Western Australia, [2]Perth Blood Institute, Perth, Western Australia, [3]School of Veterinary and Life Science, Murdoch University, Perth, Western Australia

Aim: High oestrogen (E_2) can influence the levels of various coagulation factors, including tissue factor (TF), which may contribute to hypercoagulability and an increased risk of venous thromboembolism (VTE). However, the underlying molecular mechanism(s) remains unclear. We have previously found that an E_2-responsive microRNA (miRNA), miR-494-3p, directly inhibits Protein S expression in HuH-7 liver carcinoma cells. Therefore, the aim of this study was to identify additional E_2-responsive miRNA candidates, with a focus on investigating their potential effects on TF expression.

Method: HuH-7 cells were treated with -/+10nM E_2 for 12h and E_2-responsive miRNAs were identified using NanoString® nCounter array and reverse transcription - quantitative PCR (RT-qPCR). The *in silico* miRNA:*F3* interaction were confirmed *in vitro* by dual-luciferase assays. HuH-7 cells were then transfected with 50nM miRNA precursors (negative control or candidate miRNAs) for 48h and 72h, and assessed for post-transfection effects of TF mRNA and protein in RT-qPCR and Western Blot, respectively. Student's t-test was used for statistical analysis.

Result: During E_2 treatment, six miRNAs demonstrated consistent E_2-downregulation in NanoString® and RT-qPCR expression analyses. An upregulation of *F3* expression was also observed in E_2-treated samples ($P<0.05$, $n=2$). Candidate E_2-responsive miRNAs were each predicted to bind to the *F3*-3'UTR, however only miR-365a-3p induced a ~23% reduction of *F3*-3'UTR activity in luciferase reporter assays ($P<0.05$, $n=3$). After miR-365a-3p transfection, levels of TF transcript and protein significantly reduced by ~50% and ~30%, respectively ($P<0.05$, $n=3$).

Conclusion: In the presence of high E_2 levels, expression of miR-365a-3p and *F3* were down-regulated and up-regulated, respectively. Furthermore, miR-365a-3p was confirmed to have a direct binding site on the *F3*-3'UTR. The interaction of miR-365a-3p:*F3* could result in the decrease of TF transcript and protein levels. These findings strongly suggest that E_2 may indirectly regulate TF via the modulation of E_2-responsive miRNAs. Characterisation of further E_2-responsive miRNAs may help in the identification of diagnostic biomarkers and/or development of miRNA-targeted therapeutics.


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TFPI and FV Short

Paul Ellery PhD

School of Pharmacy and Biomedical Sciences, Curtin University, Perth, Western Australia, Australia

Tissue Factor Pathway Inhibitor (TFPI) is the major regulator of Tissue Factor (TF) - induced coagulation. Two major TFPI isoforms, TFPIα and TFPIβ, are produced *in vivo*. Their inhibition of activated factor VII (fVIIa) in the TF-fVIIa complex, and of activated factor X (fXa), is well characterised. In recent years, studies have demonstrated an important interaction between the basic C-terminus of TFPIα and forms of activated fV (fVa) that retain an acidic region (AR) within its B-domain. This binding allows TFPIα to inhibit forms of prothrombinase produced before thrombin generation, termed "early" prothrombinase. The clinical importance of this interaction is highlighted in the bleeding disorders FV East Texas and FV Amsterdam, in which mutations within the FV B-domain result in elevated levels of plasma FV retaining the AR. This, in turn, leads to elevated plasma TFPIα. There is also evidence to suggest that the TFPIα-FV interaction plays a role in the thrombotic disorders FV Leiden and the FV R2 haplotype. This presentation will summarise key findings describing the mechanism of the TFPIα-FV interaction and its clinical importance in bleeding and thrombotic disorders.


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TFPI and Autoimmunity

Mitchell Bulluss

Honours Student, WACTH, Murdoch University, WA

Haemostatic abnormalities, especially thrombosis are characteristic manifestations of many systemic autoimmune diseases. Tissue factor (TF) pathway inhibitor (TFPI), the primary inhibitor of TF-pathway coagulation, has been shown to have impaired function in patients with autoimmune disorders. The underlying mechanisms behind this impaired TFPI activity have yet to be fully elucidated. Our laboratory has an ongoing interest in investigating the haemostatic abnormalities in autoimmune diseases. This presentation will describe the relationship between TFPI activity and biomarkers of inflammation and coagulation. Furthermore, it will describe the effects of patient-derived IgG antibodies on TFPI function. The results from this study may determine whether inflammation in autoimmune diseases correlates with TFPI impairment and may implicate TFPI activity as a useful prognostic biomarker for thrombosis in at-risk patients. Additionally, our anti-TFPI activity characterisation methods may be useful in determining the underlying mechanisms behind TFPI impairment.

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Influence of Travel, marathon running and compression socks on Haemostatic activation

Emma Zadow

Emma K. Zadow[1], Murray J. Adams[1,2], Sam S.X. Wu[1,3], Cecilia M. Kitic[1], Indu Singh[4], Avinash Kundur[4], Nerolie Bost[5,6], Amy N.B. Johnston[5,6], Julia Crilly[5,6], Andrew C. Bulmer[4], Shona L. Halson[7] and James W. Fell[1]

1. Sport Performance Optimisation Research Team, University of Tasmania, Launceston, Tasmania, Australia
2. Murdoch University, Perth, Western Australia
3. Swinburne University of Technology, Melbourne, Victoria
4. Menzies Health Institute Queensland and Griffith University, Gold Coast, Queensland
5. Griffith University, Gold Coast, Queensland
6. Department of Emergency Medicine, Gold Coast Health, Queensland
7. Australian Institute of Sport, Belconnen, ACT

Introduction & Aims: Travel and exercise are associated with increased thrombotic risk. Compression socks (CS) may reduce haemostatic activation during exercise. We investigated the effect of pre-marathon travel on haemostatic markers and influence of CS on coagulation following a marathon.

Methods: 42 runners travelling domestically (DOM) and 25 runners travelling internationally (INT were recruited. Both DOM and INT runners were allocated to wear CS (SOCK: DOM (n=19), SOCK: INT (n=15)) or no CS (CONTROL: DOM (n=23), CONTROL: INT (n=10)). Venous blood samples were obtained 24h prior-to and immediately post-marathon and analysed for thrombin anti-thrombin (TAT) complexes, tissue factor (TF), tissue factor pathway inhibitor (TFPI) and D-Dimer.

Results: Pre-exercise concentrations of D-Dimer were higher in INT travellers compared to DOM travellers ($p<0.0001$). A main effect for magnitude of change (PRE-POST) for TF ($p=0.02$) and D-Dimer ($p=0.002$) was observed, with the magnitude of change for D-Dimer significantly greater in the CONTROL:DOM group compared to SOCK:DOM and SOCK:INT groups ($p<0.02$).

Conclusion: Greater pre-exercise coagulation activation occurred in runners travelling internationally versus domestically. CS reduced the magnitude of change in D-Dimer only. Therefore, CS worn during a marathon have the potential to reduce overall haemostatic activation and blood clot risk.

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Case Study

Mark Rane


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Registration for Medical Scientists

Tina Pham

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