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Evaluation of latest viscoelastic coagulation assays in the transcatheter aortic valve implantation setting

Jonathon Fanning ![ORCID] ,[1,2,3,4] Shaun Roberts,[5] Megan Merza,[2] Chris Anstey,[6] Karl Poon,[2,3] Alexander Incani,[2,3] Sarvesh Natani,[2,4] John Fraser[2,3,4]

[1]Wesley Medical Research Limited, Auchenflower, Queensland, Australia
[2]St Andrew's War Memorial Hospital, Spring Hill, Queensland, Australia
[3]Faculty of Medicine, The University of Queensland, Herston, Queensland, Australia
[4]The Prince Charles Hospital, Chermside, Queensland, Australia
[5]The Princess Alexandra Hospital, Woolloongabba, Queensland, Australia
[6]School of Medicine, Griffith University, Gold Coast, Queensland, Australia

Correspondence to
Dr Jonathon Fanning, Intensive Care Unit, St Andrew's War Memorial Hospital, 457 Wickham Terrace, Brisbane, Queensland, 4001, Australia; jonathon.fanning@uchealth.com.au

ABSTRACT

Background Point of care viscoelastic measures with thromboelastography (TEG; Haemonetics Corporation, Switzerland) and thromboelastometry (ROTEM, Tem Innovations GmbH, Germany) now supersede laboratory assays in the perioperative assessment and management of coagulation. To the best of our knowledge, this sophisticated coagulation assessment has not been performed to characterise thrombotic changes in the transcatheter aortic valve implantation (TAVI) setting, nor have the two latest iteration cartridge-based systems been directly compared in the elective perioperative period.
Methods Patients undergoing TAVI were prospectively recruited. Samples (n=44) were obtained at four timepoints (postinduction of anaesthesia, postheparin (100 IU/kg), postprotamine (1 mg/100 IU heparin) and 6 hours postoperatively). Each sample was concurrently assessed with standard laboratory tests (prothrombin time/international normalised ratio, activated partial thromboplastin time, thrombin clotting time, platelet count and direct fibrinogen, ROTEMSigma and TEG6s).
Results Clot strength showed a statistically significant increase postheparin/TAVI deployment. When considering the subgroup of samples taken following the administration heparin, the heparinase channel of the TEG6s did not yield clotting strength results in 55% of samples and clotting time exceeded the upper limit of normal in 70% of samples. It was retrospectively recognised that the arachidonic acid channel of the TEG6s Platelet Mapping Cartridge had been decommissioned prohibiting assessment of aspirin effect.
Conclusions This study demonstrated a small intraprocedural prothrombotic change of uncertain clinical importance during the transcatheter aortic valve procedure. Further comparison with percutaneous coronary intervention and aortic valve replacement cohorts are needed to assess the merits of current antithrombotic guidelines, which are extrapolated from the PCI setting. The heparin effect was more consistently quantified by ROTEM.

INTRODUCTION

Widespread acceptance of the cell-based model of coagulation and the ease and rapidity of use have increasingly emphasised testing whole blood with point-of-care

Key questions

What is already known about this subject?
► Current intraoperative antithrombotic regimes for patients undergoing transcatheter aortic valve implantation (TAVI) are based on data and strategies extrapolated from percutaneous coronary intervention.

What does this study add?
► This study assesses the prothrombotic changes that occur during the TAVI procedure using whole blood viscoelastic strategies and, to the best of our knowledge, provides the first comparison between the latest iteration viscoelastic haemostatic assays in an elective perioperative setting.

How might this impact on clinical practice?
► A statistically significant intraprocedural prothrombotic signal was identified associated with TAVI. This requires comparison with percutaneous coronary intervention and aortic valve replacement to determine the suitability of current antithrombotic regimens. Findings also mandate further validation of the TEG6s in setting of both heparin and antiplatelet medications.

viscoelastic haemostatic assays.[1] The two most commonly used systems, thromboelastography or TEG (Haemonetics Corporation, Switzerland) and rotational thromboelastometry or ROTEM (Tem International GmbH, Munich, Germany) now supersede laboratory measures for the perioperative assessment of coagulation at many centres.[2] Both devices have experienced recent iterations (TEG6s and ROTEMSigma) composed of preprepared cartridges to which patient blood samples are added and automatically processed. Perioperatively, the information obtained allows for: sophisticated characterisation of coagulation (both coagulopathic and prothrombotic) and managing intraoperative bleeding and clotting issues.[3–6]

To our knowledge, the latest cartridge-based iterations of the two systems have not
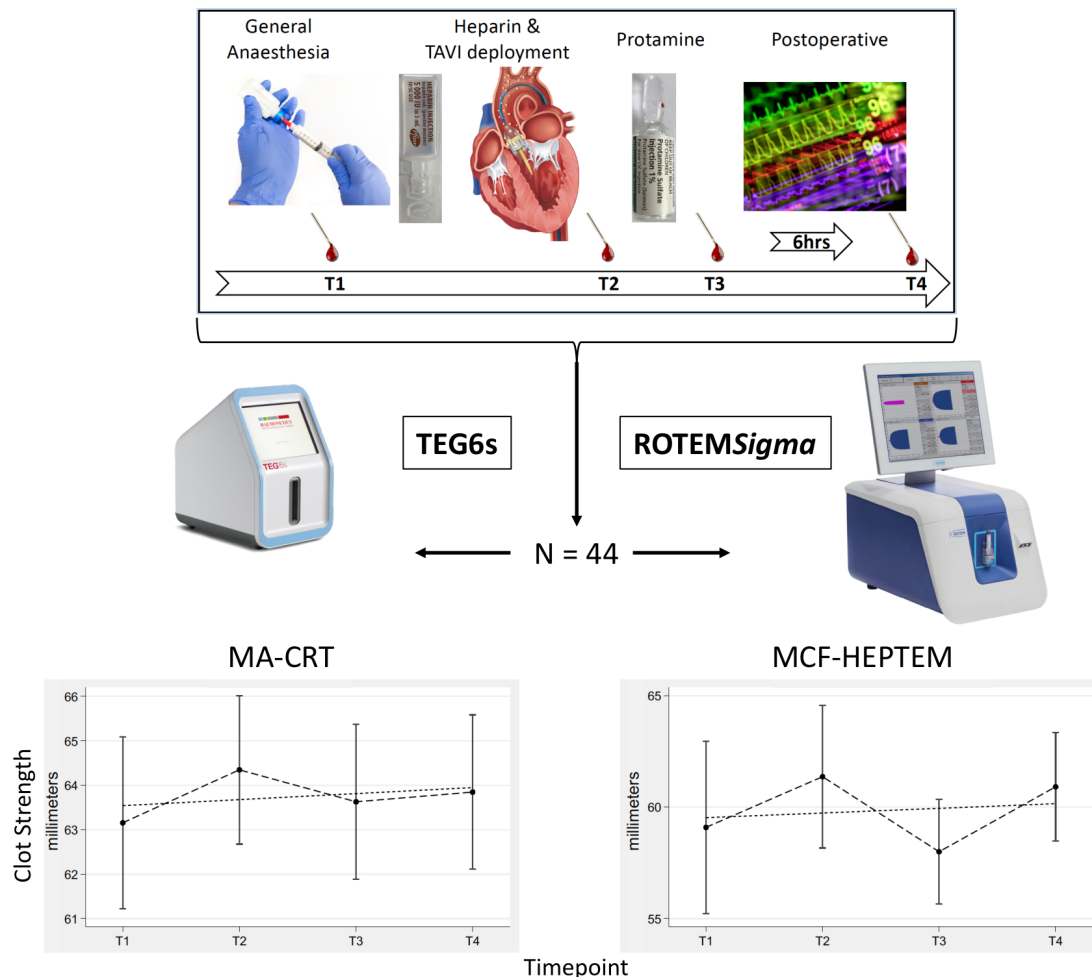
Figure 1 Clot strength measured using maximum amplitude of the citrated rapid TEG (MA-CRT) cartridge (left) and maximum clot firmness of the ROTEMSigma HEPTEM (MCF-HEPTEM) cartridge (right) both demonstrating a statistically significant prothrombotic effect following TAVI deployment, which is of uncertain clinical significance. TAVI, transcatheter aortic valve implantation.

been directly compared in any elective perioperative setting. Additionally, the underlying temporal coagulation changes that occur due to the TAVI procedure itself have not been characterised—a necessary first step to determining the optimal antithrombotic regime.

METHODS

Between March and May 2018, patients undergoing transcatheter aortic valve implantation (TAVI) at St. Andrew's War Memorial Hospital, Australia, were recruited prospectively. Study methods were performed accordingly. Informed written consent was obtained from all eligible patients prior to enrolment.

Patients were consecutively screened for inclusion. All comers were considered, and key exclusion criteria were included: emergency procedures; haemoglobin <100 g/L; platelet count <100×10^9; known/suspected bleeding or clotting disorder (not including dual antiplatelet therapy or intraoperative heparin); ejection fraction <50%; severe liver, renal, respiratory or psychiatric disease; unable/

unwilling to consent; or enrolment in another study with a non-standard therapeutic intervention.

Clinical management and assessment

Suitability for TAVI was determined by a multidisciplinary 'heart team'. All procedures were performed transfemorally using the SAPIEN-3 (Edwards LifeSciences, Irvine, California, USA) prosthesis and under general anaesthesia. All patients received dual antiplatelet loading with 300 mg each of aspirin and clopidogrel within the preceding 24 hours and intravenous heparin (100 IU/kg) prior to valve deployment, which was reversed with protamine (1 mg/100 IU heparin).

A detailed preprocedure questionnaire and in-hospital preprocedure and postprocedure assessments sought to identify risk factors for and clinically apparent complications associated with bleeding and clotting. Bleeding/thrombosis relevant clinical events (including mortality, myocardial infarction, stroke, bleeding complications, vascular complications, conduction disturbances/arrhythmias and requirement for cardiac reintervention)

were adjudicated by medical specialists independent of the treating team using the Valve Academic Research Consortium-2 consensus criteria.[7]

Coagulation assessment

Blood samples were collected at four timepoints: T0: postanaesthesia induction/preheparin; T1: postheparin (100 IU/kg) and TAVI deployment; T2: postprotamine (1 mg/100 IU heparin); and T3: 6 hours postprocedure (see figure 1). At each time point, blood was analysed with the ROTEM*Sigma* analyser using a 'complete+hep' cartridge (with four channels: INTEM, EXTEM, FIBTEM and HEPTEM) and the TEG6s analyser with a citrated cartridge (with four channels: kaolin (CK), RapidTEG (CRT), kaolin/heparinase (CKH) and functional fibrinogen (CFF). Baseline platelet function was assessed using the TEG6s Platelet Mapping Cartridge (with four channels: kaolin/heparinase, reptilase/factorXIIIa/abciximab (ActivatorF or ActF), adenosine-5′-diphsophate/ActivatorF (ADP) and Arachdonic acid/ActivatorF (AA). Key study parameters were: time for clot initiation (clotting time (CT; s) for ROTEM, and reaction time (R; min) for TEG) and clot strength (maximum clot firmness (MCF; mm) for ROTEM, and maximum amplitude (MA; mm) for TEG). Standard laboratory tests of coagulation included prothrombin time (PT)/international normalised ratio, activated partial thromboplastin time (aPTT), thrombin clotting time and direct (Clauss) fibrinogen (Sysmex CS-5100) and full blood count (Sysmex SP-10, Sysmex Corporation, Kobe, Japan). All equipment was used and maintained according to manufacturer recommendations.

Statistical analysis

Summary statistics are reported as: simple percentages (%); group means±SD compared via paired t-tests for normally distributed data; or medians±IQR compared using Wilcoxon paired sign-rank test. For each measure, changes from baseline were plotted over time as a categorical variable. Student's t-tests were performed to identify any statistically significant changes from baseline. Corresponding TEG, ROTEM and laboratory measures were correlated by Pearson's correlation. Highly correlated variables were then assessed for agreement using Bland-Altman plots. Univariate cross-sectional time-based random effects models were developed for each viscoelastic measure using the laboratory clotting indices, in turn, as the dependent variable. Both paired comparisons between timepoints and univariate time series regression were analysed for each variable. Changes over time were compared via paired comparisons between timepoints of each variable with baseline. Times were analysed as regular intervals despite being irregularly spaced. Analyses were performed using STATA V.13 (StataCorp, Texas, USA).

RESULTS AND DISCUSSION

Baseline characteristics

Forty-four samples were obtained from 11 patients undergoing TAVI. Their baseline characteristics are reported in

Table 1 Clinically relevant patient and procedure characteristics

Variable	Measure
Patient baseline characteristics	
Age, year	83.5±8.8
Male sex	7 (64)
BMI, kg/m^2	29.7±5.2
STS mortality, %	4.4±1.8
STS morbidity, %	24.6±11.5
AVA, cm^2	0.9±0.1
Single antiplatelet	2 (18)
Single antiplatelet and anticoagulation	5 (45)
Dual antiplatelet	3 (27)
Dual antiplatelet and anticoagulation	1 (9)
Stroke or TIA	4 (36)
IHD (including stable angina and acute coronary syndromes)	4 (36)
Congestive cardiac failure	0 (0)
Ejection fraction	62±17.8
Pulmonary embolism or DVT	1 (9)
Hypertension	7 (64)
Hyperlipidaemia	4 (36)
Diabetes mellitus	2 (18)
Creatinine >150 µmol/L	1 (9)
Chronic liver disease	0 (0)
Procedural characteristics	
Device success	11 (100)
Average procedure time, min	26±4.5
Duration of rapid ventricular pacing, s	24±5.8

Values are expressed as median±IQR or as n (%).
AVA, aortic valve area; BMI, body mass index; DVT, deep vein thrombosis; IHD, ischaemic heart disease; STS, Society of Thoracic Surgeons; TIA, transient ischaemic attack.

table 1. Patients were a mean 84±5.9 years old, predominantly male (66%) and all had severe aortic stenosis (aortic valve area of 0.9±0.1 with mean aortic valve gradient of 36±8.5). The average TAVI procedure time was 26.6±3.9 min; no procedure required postimplantation manoeuvres. Serial clinical assessments revealed no clinically apparent bleeding or thrombotic events.

Binary comparisons between assays

Direct comparisons between complementary laboratory and viscoelastic clotting indices are summarised in table 2. Regarding clotting time, both PT and aPTT showed significant associations with the independent variables CT-activation of intrinsic pathway (INTEM) and R-CRT and an association was significant for CT-activation of extrinsic pathway (EXTEM) versus R-CRT. Regarding clot strength, significant associations with at least moderate correlations was evident for MCF-INTEM versus MA-CK, MCF-EXTEM versus MA-CRT and MCF-activation of extrinsic pathway and in vitro blocking of

Table 2 Binary comparisons between corresponding assays

Variable	Regression slope (β)	95% CI	P value	R^2
Clotting time				
Prothrombin time with				
CT-INTEM	+0.013	+0.008 to +0.018	<0.001	0.30
CT-EXTEM	+0.037	−0.027 to +0.101	0.260	
R-CK	−0.043	−0.434 to +0.348	0.83	
R-CRT	+5.355	+4.197 to +6.513	<0.001	0.62
Activated partial thromboplastin time with				
CT-INTEM	+0.169	+0.121 to +0.218	<0.001	0.53
CT-EXTEM	+0.468	−0.202 to +1.138	0.17	
R-CK	−5.939	−13.180 to +1.302	0.11	
R-CRT	+52.6	+37.5 to +67.8	<0.001	0.52
CT-INTEM with R-CK	−1.55		0.904	
CT-EXTEM with R-CRT	+9.87		0.041	0.092
CT-FIBTEM with R-CFF	−0.23		0.834	
Clot strength				
MCF-INTEM with MA-CK	+0.822	+0.664 to +0.980	<0.001	0.78
MCF-EXTEM with MA-CRT	+1.347	+0.728 to +0.966	<0.001	0.47
MCF-FIBTEM with MA-CFF	+0.625	+0.392 to +0.859	<0.001	0.69
ΔMCF with ΔMA	+0.452	−0.171 to +1.075	0.16	

CFF, citrated functional fibrinogen; CK, citrated kaolin; CKH, citrated kaolin with heparinase; CRT, citrated rapid thromboelastogram; CT, clotting time; EXTEM, activation of extrinsic pathway; FIBTEM, activation of extrinsic pathway and in vitro blocking of thrombocytes; HEPTEM, activation of intrinsic pathway and in vitro blocking of heparin; INTEM, activation of intrinsic pathway; MA, maximum amplitude; MCF, maximum clot firmness; R, reaction time.

thrombocytes (FIBTEM) versus MA-CFF but not for the platelet function surrogate measure ΔMCF (MCF-EXTEM − MCF-FIBTEM) versus ΔMA (MA-CRT − MA-CFF).

Platelet inhibition

Analysis of the ADP channel of the TEG6s Platelet Mapping Cartridge demonstrated that clopidogrel resulted in 32.2%±8.5% platelet inhibition with one non-responder (<10%) and three semiresponders (10%–30%). Over the course of the study, it became apparent that the AA channel was non-functional; consequently, results regarding the aspirin component of platelet inhibition are unavailable. Other assays of aspirin inhibition of platelet function, such as optical aggregometry (considered the gold standard assessment), electrode impedance aggregometry and flow cytometry also have well-recognised limitations for measuring the antiplatelet effects of aspirin. Alternative point of care testing systems were not logistically feasible at the time of recruitment.[8–10]

Characterising the changes that occur during TAVR

Temporal changes for each of the indices are summarised in table 3, and for clot strength, this is also demonstrated in the figure 1. As expected, CT was prolonged at T1 versus baseline and normalised by T2 for all measures. Fibrinogen was significantly lower than baseline at T1 but significantly higher at T3. MA-CRT showed a statistically-significant increase at T1, providing evidence of a prothrombotic change.

Quantifying and neutralising the heparin effect

When considering those samples taken at T1, TEG6s MA-CKH yielded no results in 55% of samples and R-CKH exceeded the upper limit of normal in 8/11 heparinised samples (median: 588s; IQR 366–738) versus ROTEM *Sigma*, where MCF-HEPTEM was determined in 100% of samples and both CT-HEPTEM (223s; 212–229) and MCF-HEPTEM (60mm; 58–66) were within the normal range for all samples. Thus, in our cohort, the CKH appeared insufficient to reverse the heparin effect. This occurred despite maximum activated clotting times (ACTs) <450s, equivalent to heparin levels of <2IU/mL, far below the 6IU/mL capacity purported for the CKH channel.

CONCLUSIONS

This study demonstrated a small intraprocedural prothrombotic change of uncertain clinical importance during the TAVI procedure, and further comparison with PCI and AVR cohorts are needed to assess the merits of current antithrombotic guidelines, which are extrapolated from the PCI setting and based on expert consensus.[11 12] Baseline platelet mapping revealed that the aspirin contribution currently cannot be assessed with the TEG6s Platelet Mapping Cartridge, and alternative platelet function testing should be employed until manufacturing issues are sorted. Similarly, the TEG6s

Table 3 Temporal changes in coagulation assays over time

Variable	T0	T1	T2	T3
Laboratory				
PT				
Median (IQR)	13 (12–14)	22 (20–26)	13 (13–15)	12 (12–13)
P value	–	0.003	0.415	0.191
APTT				
Median (IQR)	27 (26–32)	180 (180–180)	28 (28–31)	27 (26–31)
P value	–	0.001	0.870	0.976
TCT				
Median (IQR)	16 (14–18)	180 (180–180)	17 (16–24)	15 (14–17)
P value	–	0.020	0.054	0.256
Fibrinogen				
Median (IQR)	2.87 (2.61–3.01)	2.65 (2.19–2.78)	2.69 (2.65–2.91)	3.16 (2.91–3.37)
P value	–	0.016	0.858	0.007
ROTEM*Sigma*				
MCF FIBTEM				
Median (IQR)	18 (12–19)	15 (12–19)	17 (13–18)	17 (12–20)
P value	–	0.299	0.494	0.928
CT HEPTEM				
Median (IQR)	178 (169–181)	223 (212–229)	181 (175–187)	177 (162–183)
P value	–	0.004	0.126	0.755
MCF HEPTEM				
Median (IQR)	60 (52–66)	60 (58–66)	58 (57–59)	61 (58–63)
P value	–	0.211	0.878	0.097
TEG6s				
MA CRT				
Mean (SD)	63.2 (3.3)	64.3 (2.6)	63.6 (2.9)	63.8 (2.9)
P value		0.005	0.272	0.164
R CRT				
Mean (SD)	0.44 (0.13)	2.27 (1.00)	0.59 (0.24)	0.40 (0.13)
P value		<0.001	0.057	0.459
MA CKH				
Median (IQR)	60.9 (58.2–63.5)	60.8 (33.1–62.0)	60.7 (57.3–61.2)	62.0 (59.2–66.1)
P value	–	0.500	0.998	0.018
R CKH				
Median (IQR)	7.2 (6.9–8.0)	9.8 (6.1–12.3)	8.9 (7.1–9.5)	8.1 (7.2–8.8)
P value	–	0.286	0.083	0.062
MA CFF				
Median (IQR)	23.6 (20.5–26.6)	22.1 (19.2–24.9)	23.5 (21.1–26.5)	22.9 (20.3–29.6)
P value	–	0.655	0.306	0.247
TEG-ACT				
Median (IQR)	97 (79–97)	219 (182–303)	97 (88–116)	88 (79–97)
P value	–	0.003	0.058	0.582

aPTT, activated partial thromboplastin time; CFF, citrated functional fibrinogen; CK, citrated kaolin; CKH, citrated kaolin with heparinase; CRT, RapidTEG; CT, clotting time; EXTEM, activation of extrinsic pathway; FIBTEM, activation of extrinsic pathway and in vitro blocking of thrombocytes; HEPTEM, activation of intrinsic pathway and in vitro blocking of heparin; INTEM, activation of intrinsic pathway; MA, maximum amplitude; MCF, maximum clot firmness; PT, prothrombin time; R, reaction time; T0, baseline post induction of anaesthesia; T1, postheparin and TAVI deployment; T2, post protamine; T3, 6 hours postprocedure; TCT, total clotting time.

heparinase channel appeared unable to reverse the heparin effect despite modest ACTs, and this channel should not be relied on in any setting involving heparin until further investigated/validated.

ORCID iD
Jonathon Fanning http://orcid.org/0000-0002-1675-0522

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