Beyond Clotting Time – Clot Waveform Analysis (CWA)

DR CHUEN WEN TAN

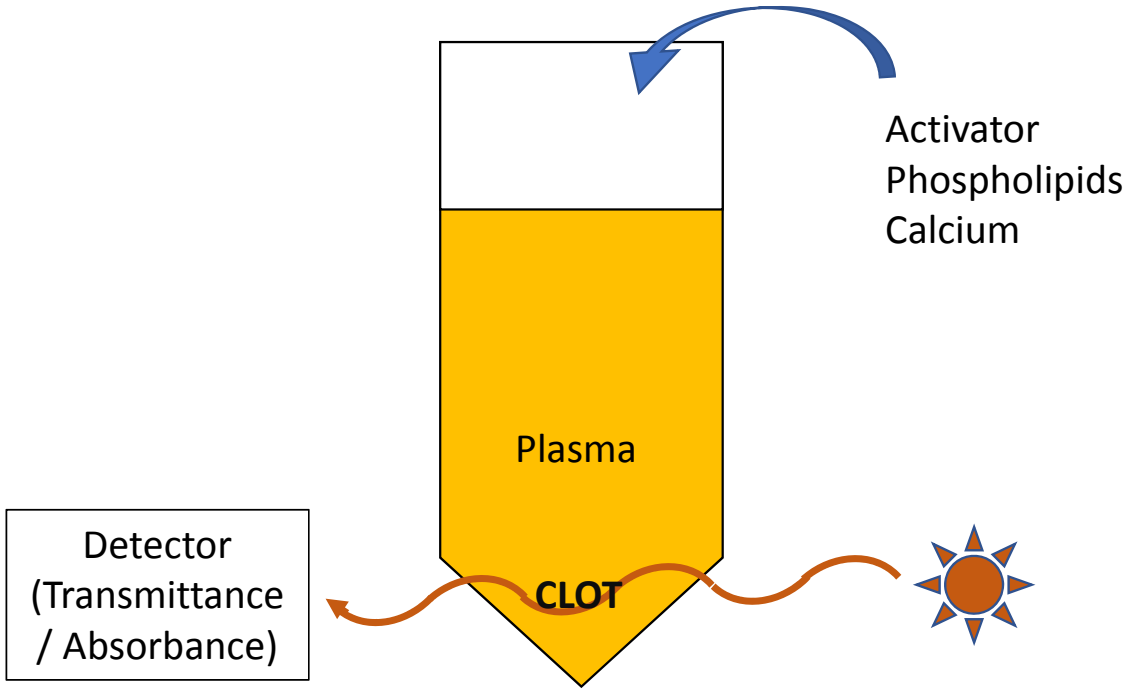
CONSULTANT
DEPARTMENT OF HAEMATOLOGY
SINGAPORE GENERAL HOSPITAL

FELLOW
ANZAC RESEARCH INSTITUTE
HAEMATOLOGY, CONCORD HOSPITAL

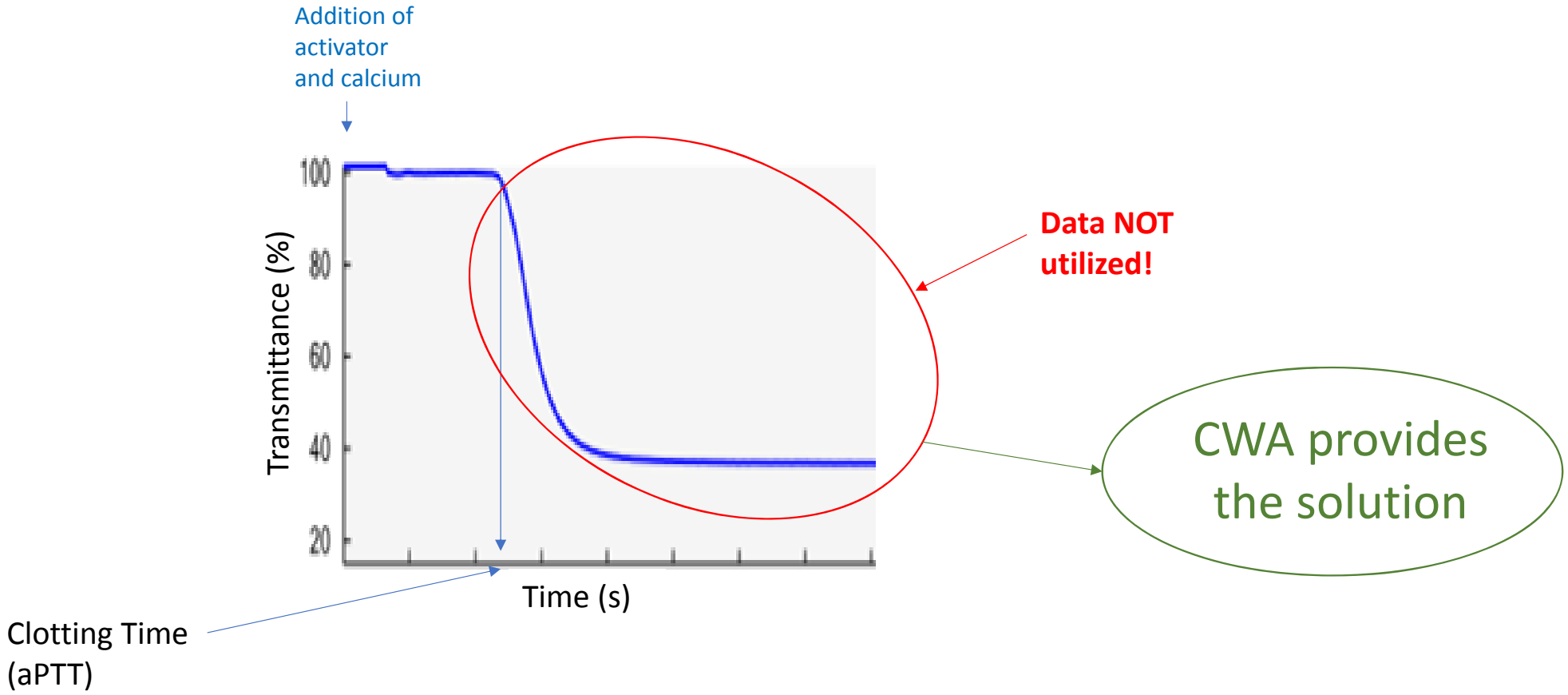
Outline

- Background
- Clinical pplications of CWA

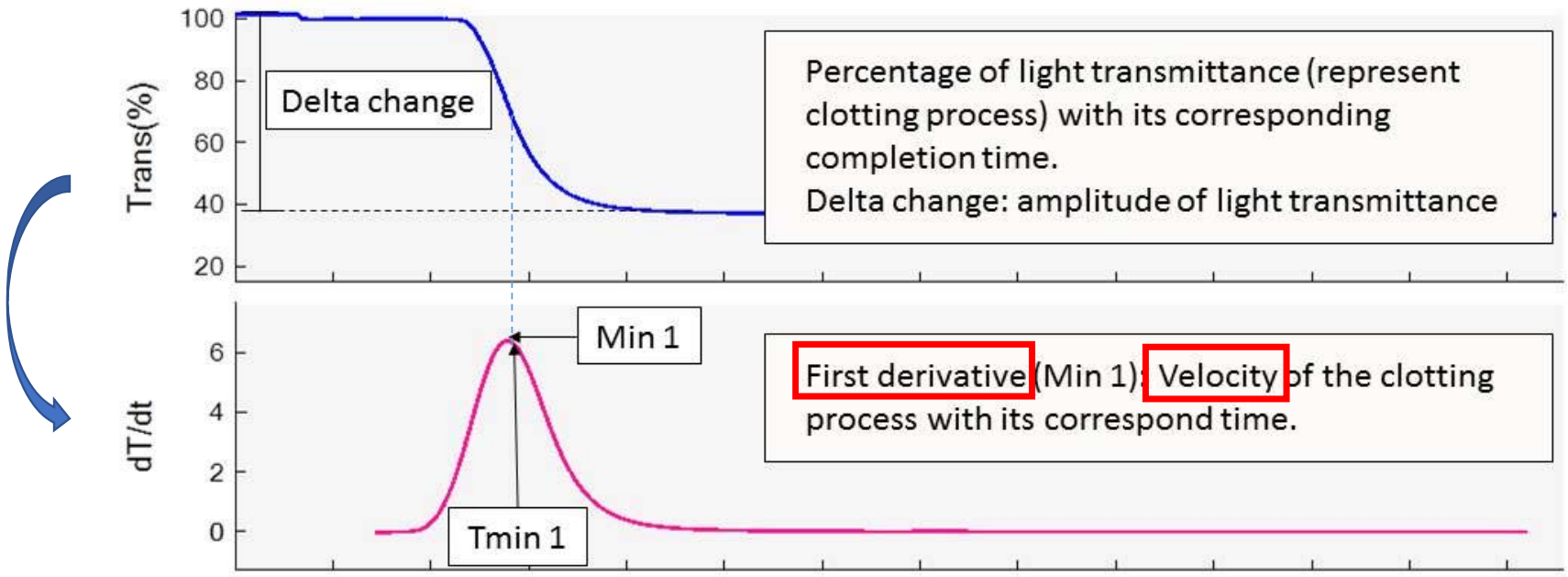
Photo-Optical Method of Clotting Time Measurement

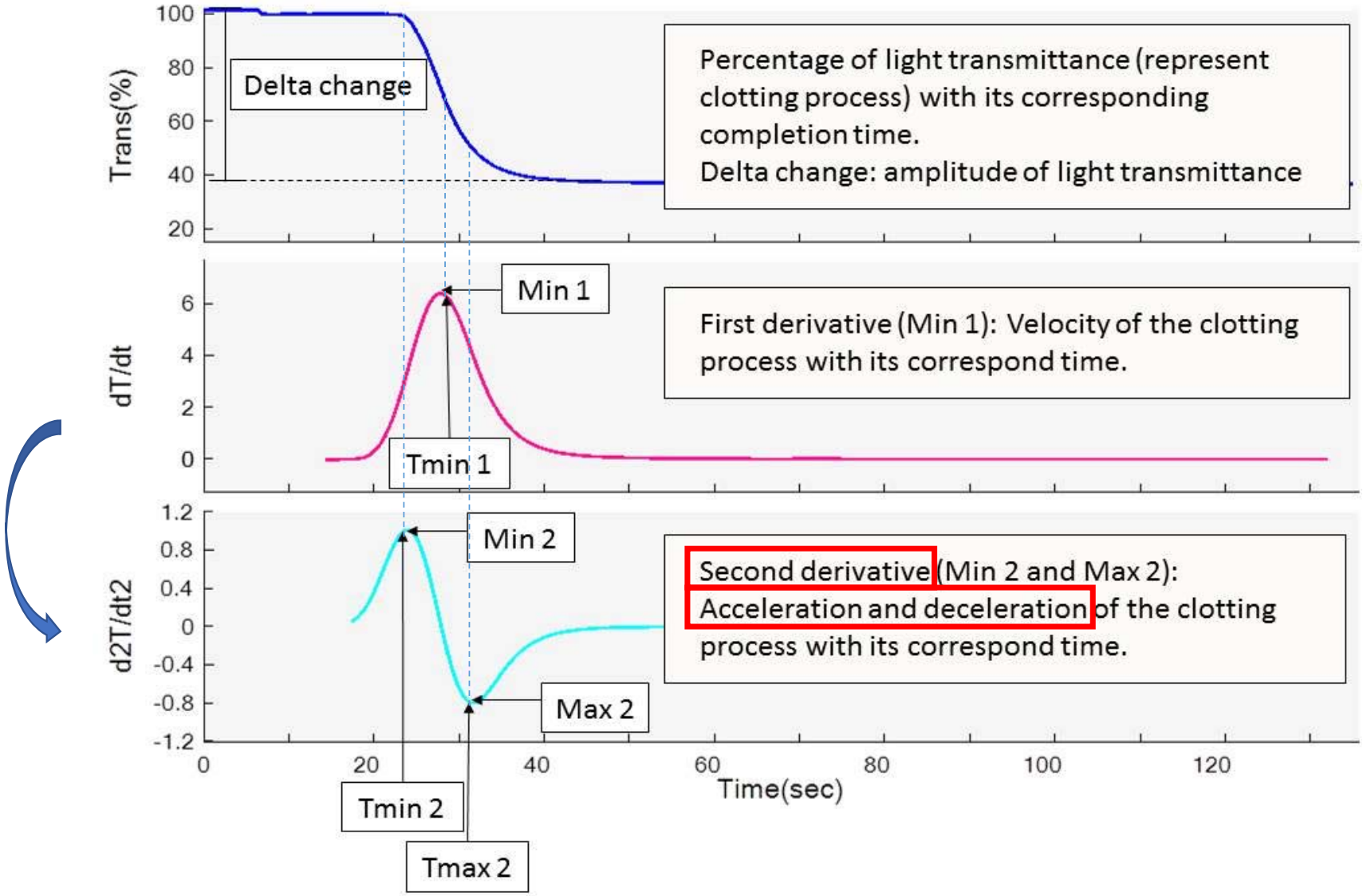


New Utility of An Old Test

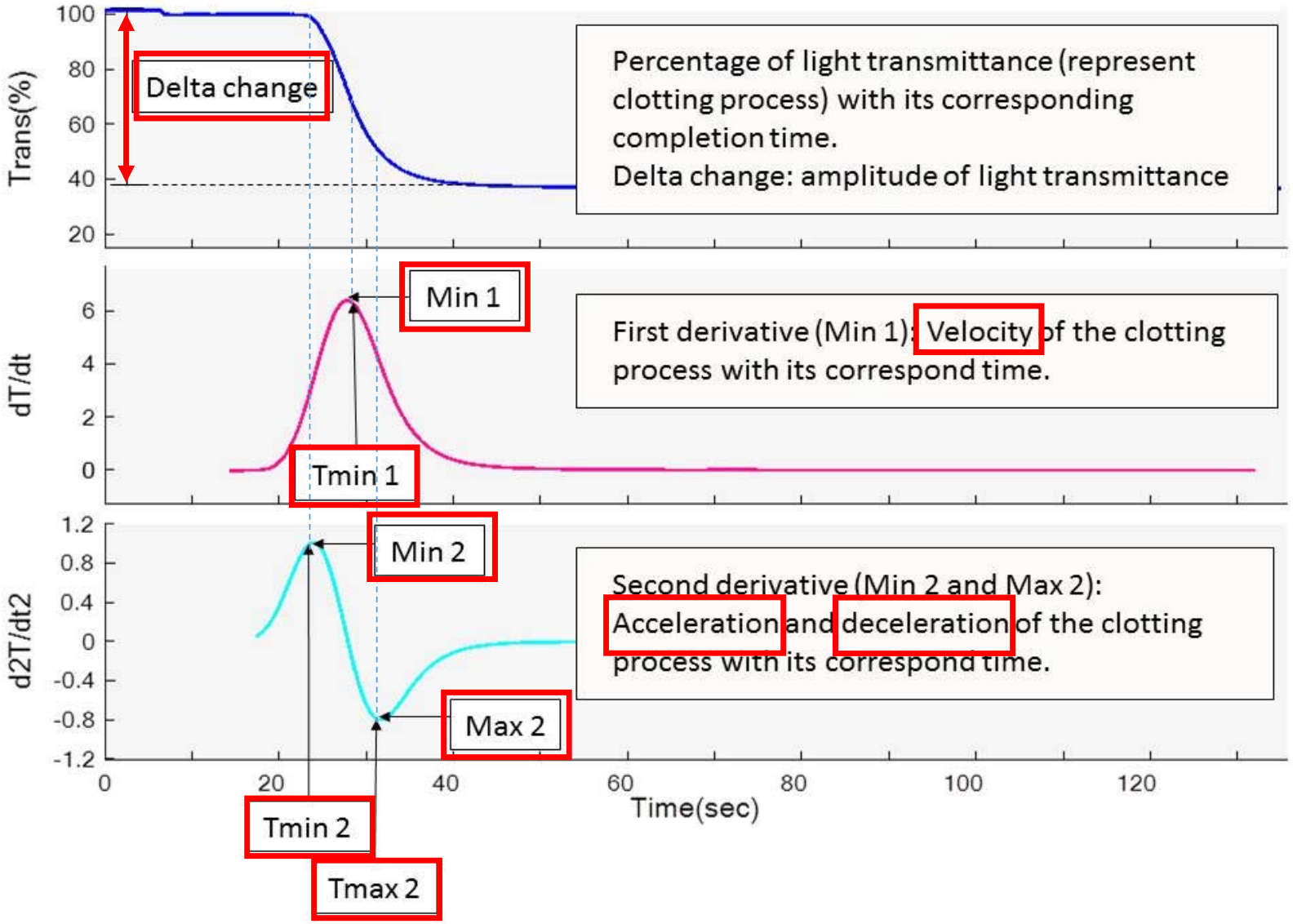


Understanding CWA




Trans(%)
100
80
60
40
20
Delta change
Percentage of light transmittance (represent clotting process) with its corresponding completion time.
Delta change: amplitude of light transmittance
dT/dt
6
4
2
0
Min 1
Tmin 1
First derivative (Min 1): Velocity of the clotting process with its correspond time.
d2T/dt2
1.2
0.8
0.4
0
-0.4
-0.8
-1.2
Min 2
Max 2
Second derivative (Min 2 and Max 2): Acceleration and deceleration of the clotting process with its correspond time.
0
20
40
60
80
100
120
Time(sec)
Tmin 2
Tmax 2

CWA Parameters



CWA Parameters

Coagulability

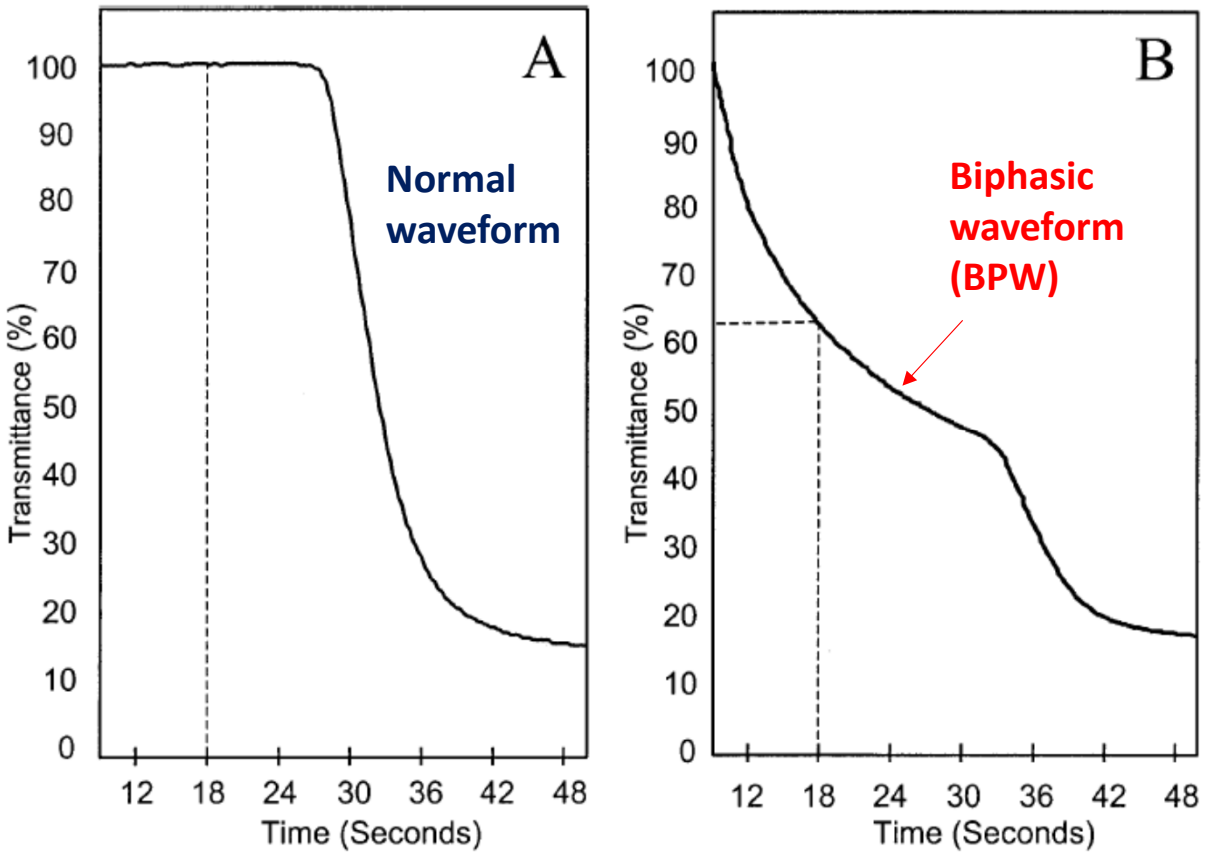
Growing List of Analyzers with CWA Function

Table S 1 Coagulation analyzers and APTT reagents for Clot Waveform Analysis		
Coagulation analyzer		
	CA-7000	Sysmex
	CS-5100	Sysmex
	CS-2000i, CS-2100i	Sysmex
	CA-1500	Sysmex
	BCS	Siemens
	BCT	Siemens
	ACL-Top 700	IL
	ACL-Top 500 CTS	IL
	ACL-Top 300 CTS	IL
	ACL-Advance	IL
	ACL-FUTURA	IL
	ACL-ELITE pro	IL
	ACL-7000	IL
	CD-X	Dia Med
	MDA-II	Trinity
	Coapresta2000	Shimazu

Shima et al 2013

Applications of CWA

Early Disseminated Intravascular Coagulation (DIC) marker – Biphasic Waveform



- 1187 patients admitted to ICU
- BPW preceded DIC diagnosis by 18hours
- BPW is due to formation of a precipitate containing VLDL and CRP in the presence of Ca++ → changes turbidity on recalcification of plasma

Toh et al (Blood 2002)

APTT-BASED CLOT WAVEFORM ANALYSIS IN VARIOUS INFECTIONS

- Retrospective study

- Subjects:
  - **Controls subject**: Patients admitted for elective orthopedic, urology surgery with pre-operative screening aPTT

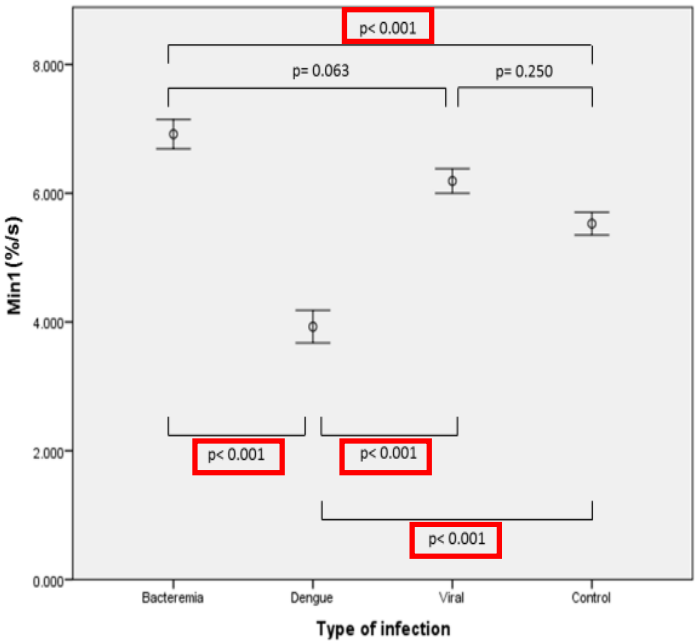
  - **Infection subject**: Patients admitted with various infection (proven by cultures/molecular tests) who had aPTT done within 48 hours of admission:
    1. Patients with bacterial infection
    2. Patients with dengue infection
    3. Patients with viral respiratory tract infection

- Exclusion criteria: Subjects on anticoagulant, with active thrombosis and cancer, DIC

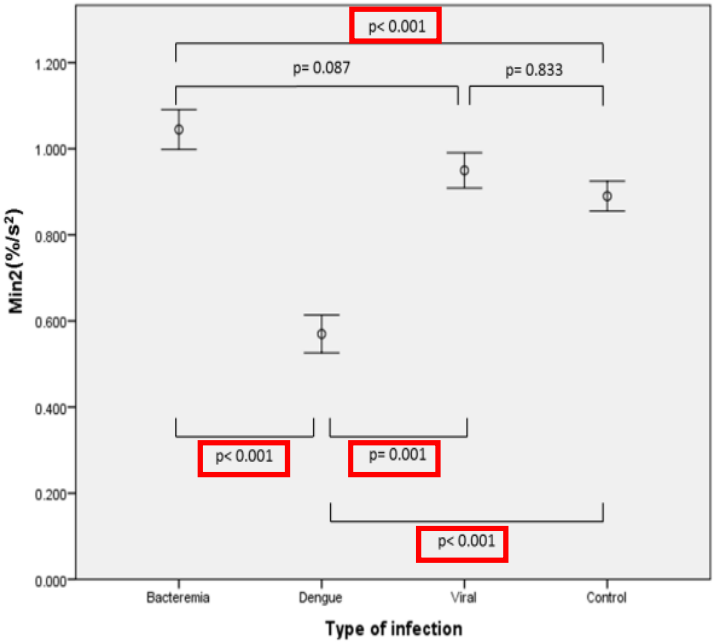
Different infections, different CWA parameters: Increased CWA results in bacterial infection and reduced CWA results in dengue infection

Bacterial infection (n= 52)	Dengue infection (n= 36)	Other viral infection (n= 13)	Control (n= 112)

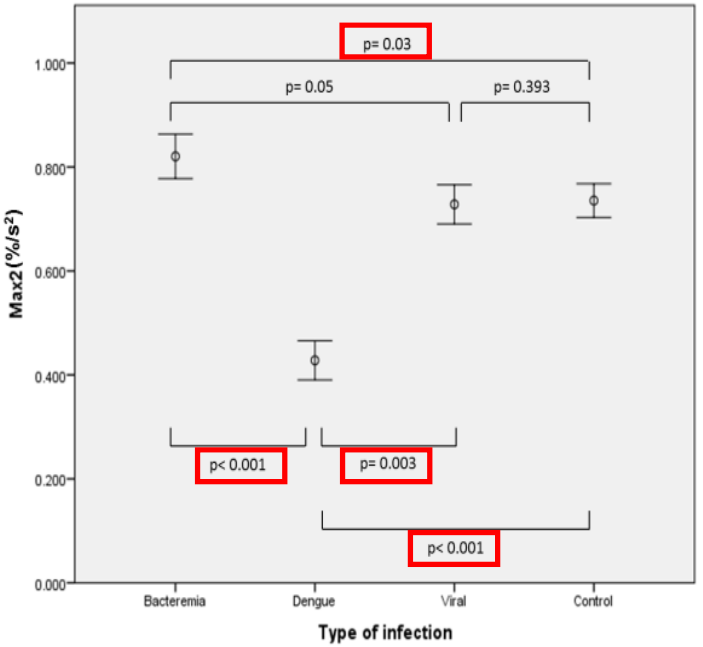
A

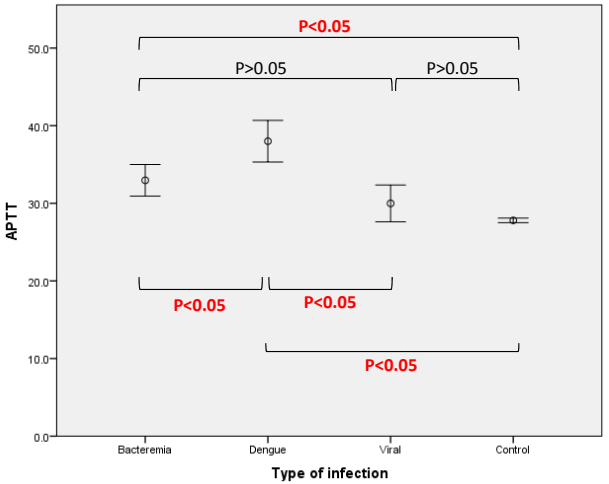


B



C





1-way Anova with Bonferoni correction
Adjusted for age/gender/race

EHA 2018

Application of CWA in Bleeding Disorders

Application of CWA in Bleeding Disorders

Journal of Thrombosis and Haemostasis, **16**: 1078–1088 DOI: 10.1111/jth.14022

ORIGINAL ARTICLE

Modified clot waveform analysis to measure plasma coagulation potential in the presence of the anti-factor IXa/factor X bispecific antibody emicizumab

K. NOGAMI,* T. MATSUMOTO,*† Y. TABUCHI,‡ T. SOEDA,§ N. ARAI,‡ T. KITAZAWA§ and M. SHIMA*†

Usefulness of the second-derivative curve of activated partial thromboplastin time on the ACL-TOP coagulation analyzer for detecting factor deficiencies

Naoki Tokunaga[a], Chihiro Inoue[a], Toshiyuki Sakata[b], Kumiko Kagawa[c], Masahiro Abe[c], Norimichi Takamatsu[a], Takayuki Nakao[a] and Toshio Doi[d]

[a]Division of Medical Technology, Tokushima University Hospital, Tokushima, [b]IL Japan Co., Ltd., Tokyo, [c]Department of Hematology, Tokushima University Hospital, Tokushima and [d]Clinical Laboratory Tokushima, University Hospital, Tokushima, Japan

ORIGINAL ARTICLE *Laboratory science*

New quantitative aPTT waveform analysis and its application in laboratory management of haemophilia A patients

M. MILOS,* D. COEN HERAK,* S. ZUPANCIC-SALEK† and R. ZADRO‡

*Department of Laboratory Diagnostics; †Department of Medicine University Hospital Centre Zagreb; and ‡Department of Laboratory Diagnostics University Hospital Centre Zagreb and Faculty of Pharmacy and Biochemistry, Zagreb, Croatia

Thromb Haemost 2002; 87: 436–41

Haemophilia

Utility of global hemostatic assays in haemophilia patient

I. Q. Wu □, C. W. Tan, W. H. Wong, H. J. Ng

Clot waveform analysis in patients with haemophilia A

T. Siegemund[1]; U. Scholz[2]; R. Schobess[2]; A. Siegemund[2]

[1]The Scripps Research Institute, Department of Molecular and Experimental Medicine, Roon Research Center for Arteriosclerosis and Thrombosis, La Jolla, California, USA; [2]MVZ Lab Dr. Reising-Ackermann and Colleagues, Center of Coagulation Disorders, Leipzig, Germany

The Utility of activated Partial Thromboplastin Time (aPTT) Clot Waveform Analysis in the Investigation of Hemophilia A Patients with very Low Levels of Factor VIII Activity (FVIII:C)

Midori Shima[1], Tomoko Matsumoto[1], Kazuyoshi Fukuda[1], Youko Kubota[1], Ichiro Tanaka[1], Katumi Nishiya[1], Alan R. Giles[2], Akira Yoshioka[1]

Journal of Thrombosis and Haemostasis, **4**: 377–384

ORIGINAL ARTICLE
Laboratory science

Clot waveform analysis using CS-2000i™ distinguishes between very low and absent levels of factor VIII activity in patients with severe haemophilia A

T. Matsumoto[1,2] | K. Nogami[1] | Y. Tabuchi[3] | K. Yada[1] | K. Ogiwara[1] | H. Kurono[3] | N. Arai[3] | M. Shima[1]

WILEY Haemophilia

ORIGINAL ARTICLE

The measurement of low levels of factor VIII or factor IX in hemophilia A and hemophilia B plasma by clot waveform analysis and thrombin generation assay

T. MATSUMOTO,* M. SHIMA,* M. TAKEYAMA,* K. YOSHIDA,* I. TANAKA,* Y. SAKURAI,* A. R. GILES† and A. YOSHIOKA*

Application in Bleeding Disorders

- Detection of low levels of factor VIII and IX activities
- Management of haemophilia
  - Factor replacement
  - Bypassing agents including emicizumab

Application of CWA in Thrombotic Disorders

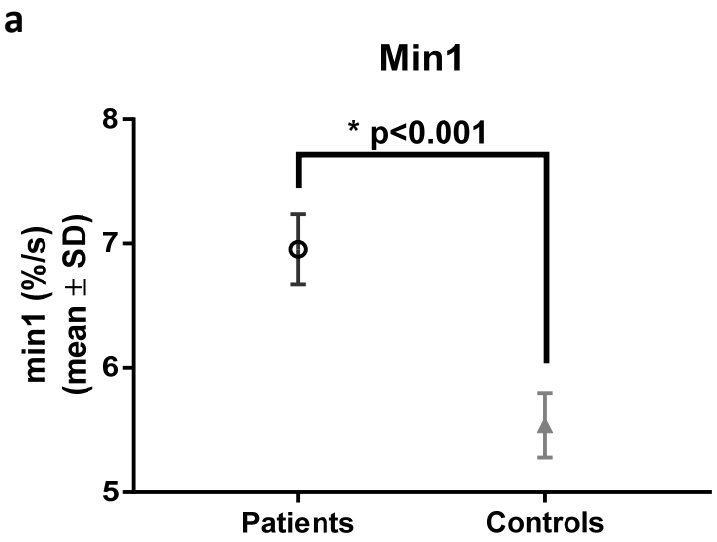
THE ASSOCIATION OF CWA PARAMETERS WITH ACUTE VENOUS THROMBOEMOBLISM (VTE)

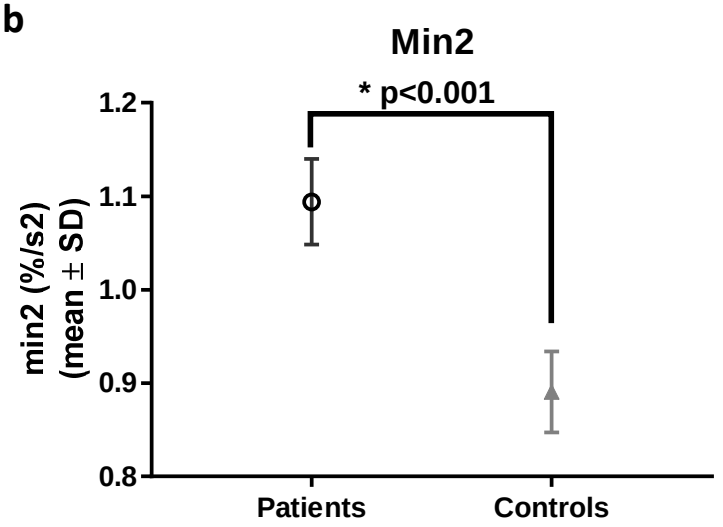
- Retrospective study

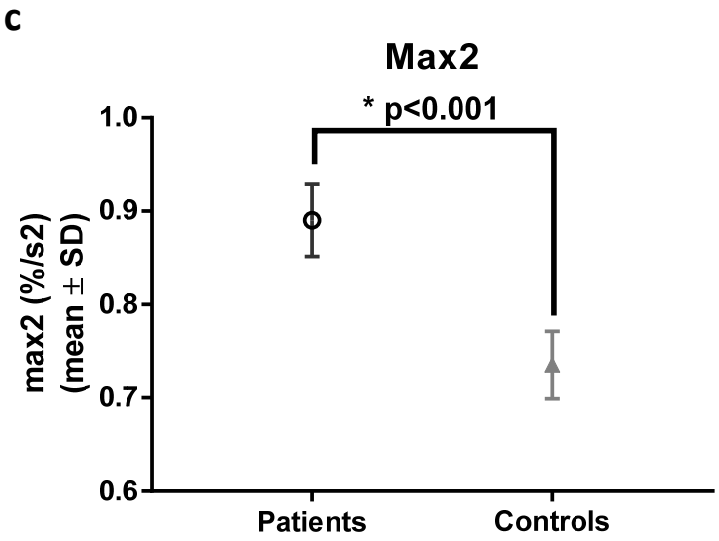
- Subjects:
  - **Controls subject**: Patients admitted for elective orthopedic, urology surgery with pre-operative screening aPTT

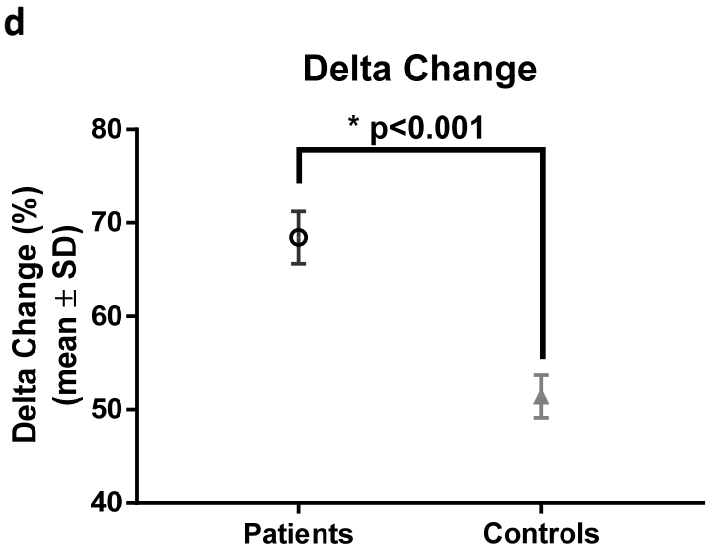
  - **Patients with acute VTE:** Patients with acute VTE prior to initiation of anticoagulants

CWA parameters are significantly elevated in acute venous thromboembolism









Patients (n) = 45

Controls (n) =111

aPTT results similar between the groups

2-sample independent T-test
Adjusted for age/gender/race

EHA 2018

Elevated CWA are strongly associated with venous thromboembolism

Parameter	Unadjusted			Adjusted (for age, gender, ethnicity)		
	Odds ratio	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
APTT ratio ≤0.9	1.790	0.76 - 4.20	0.182	2.03	0.83 - 4.95	0.119
Min1 >reference interval	**8.00**	**3.59 - 17.83**	*** <0.001**	**8.37**	**3.63 - 19.26**	*** <0.001**
Min2 >reference interval	**5.24**	**2.48 - 11.07**	*** <0.001**	**5.93**	**2.68 - 13.11**	*** <0.001**
Max2 >reference interval	**4.75**	**2.15 - 10.48**	*** <0.001**	**4.99**	**2.20 - 11.34**	*** <0.001**
Delta change >reference interval	**18.55**	**6.36 - 54.15**	*** <0.001**	**19.09**	**6.31 - 57.69**	*** <0.001**

EHA 2018

CWA as potential markers for hypercoagulability

Ruberto et al (2018)

Comparability of CWA Results

Multicentre Study of Normal Controls

- 6 centres (at least 40 samples from each centre)
- 3 reagents: Actin FS, Actin FSL, Pathromtin SL (approximately 200 samples for each reagent)
- Analyzer: Sysmex CS2100i

ACTIN FS:
Normal ranges of CWA comparable across the labs

ACTIN FSL:
Normal ranges of CWA parameters are comparable between the labs

Different aPTT Reagents: CWA data are dissimilar

Possibility of combining CWA data and future multicentre studies

- Combine CWA data from different labs
  - Coagulation analyser
  - aPTT reagents

Standardised

CWA: Advantages vs Disadvantages

Advantages

- Easily performed/automated
- Widely available
- Routine reagents
- Low cost

Disadvantages

- Whole blood/platelet rich plasma samples not suitable
- Data on influence of preanalytical variables lacking

Conclusions

- Global haemostatic assay
  - Wide availability
  - Automated
  - Cheap

- Potential applications in:
  - Bleeding disorders
  - Thrombotic disorders
  - Infection/Sepsis

Acknowledgement

- Singapore General Hospital
  - Department of Haematology
    - **Dr Heng Joo Ng**
    - Dr Lai Heng Lee
  - Haematology Laboratory
    - **Dr Wan Hui Wong**

- All the patients and blood donors

Thank You

Singapore General Hospital