Haemostasis monitoring

Chapter 9

Valorisation

Chapter 9

Valorisation

The roots of this dissertation originate from one big study in which patients' coagulation state was researched using an extensive interview and panel of laboratory tests, the PANE-study. Soon it was known that the intended laboratory tests had major pitfalls and tweaking of these tests was needed to adequately investigate the haemostatic system. One of the goals of the PANE-study was to simplify the pre-operative coagulation screening process by ruling out those patients who do not have an increased bleeding risk during the operation due to the surgery itself or because of the bleeding diathesis of the patients. In October 2011 the Dutch Heart Foundation gave a course on vascular biology in Papendal, the Netherlands. It was at this course that I was awarded the second prize for the 'Workshop Popular Science Communication'. What follows is the Dutch text that I wrote:

Bloedstollend, maar met een gerust hart, de operatiekamer in

Een operatie ondergaan is voor patiënten een spannende gebeurtenis. Ze worden overgelaten aan de chirurg en 'de man met de hamer', in vakjargon de anesthesioloog. Er wordt geprikt, gesneden, gezaagd en gehecht: bloed! Bloedverlies rondom een operatie wordt zo minimaal mogelijk gehouden door goed samenspel tussen chirurg en anesthesioloog. Maar eigenlijk begint het bloedstelpen al op het spreekuur van de anesthesioloog.

Met een onderzoek onder meer dan 700 patiënten wordt gekeken wat de beste en meest snelle strategie is om patiënten het groene licht te geven voor een operatie. Dit onderzoek in het Maastricht Universitair Medisch Centrum is opgezet vanuit zowel het Hematologisch Laboratorium als de afdeling Anesthesiologie & Pijnbestrijding. Door naar een juiste combinatie te zoeken tussen allerlei vragen over bloedingsproblemen en bloedtesten in het laboratorium, proberen ze een antwoord te krijgen op de vraag of iemand veilig een operatie kan ondergaan.

Patiëntenveiligheid staat voorop bij een operatie. Een operatie wordt dan ook wel vergeleken met de luchtvaart: alles moet tiptop in orde en gecontroleerd zijn. Zo wordt tijdens een operatie bij elke stap een checklijst afgevinkt om bijvoorbeeld verwisseling te voorkomen. Net zoals de kerosine in het vliegtuig, zo moet ook het bloed van de patiënt van goede kwaliteit zijn voordat de operatie begint.

De bloedstolling wordt uiteraard al langer gemeten in het laboratorium, dat is niets nieuws. Wat het nu wezenlijk anders maakt, is dat de technologie steeds beter wordt. Eerder moest lang gewacht worden op de uitslagen van bloedtesten, maar met de apparatuur die bij dit onderzoek worden ingezet kan met één test veel meer informatie verzameld worden in minder tijd. Verder zijn de apparaten veel compacter zodat ze zelfs aan het bed van de patiënt kunnen worden ingezet.

De onderzoekers durven zelfs te stellen dat in de toekomst de technologie nog geavanceerder wordt, zodat slechts met enkele druppels bloed de gehele bloedstolling in kaart kan worden gebracht. Mocht er een aanwijzing zijn uit de vragen dat er een bloe-

dingsprobleem speelt bij de patiënt, dan zal een simpele vingerprik in korte tijd hier uitsluitsel over geven. Maar dit is nog toekomstmuziek. Voorlopig zal er nog veel onderzoek moeten gebeuren, zodat ook u bloedstollend, maar met een gerust hart, de operatiekamer in en weer uit gaat.

Next is a short English summary of the above Dutch text:

Going for surgery in a blood curdling but relieved way

An operation can be frightening for patients. Blood loss is encountered and has to be minimized by the surgeon and the anaesthesiologist. The reduction of blood loss, however, is already initiated on the pre-operative screening clinics of the anaesthesiologist.

In the Maastricht University Medical Centre a study has started to examine the best strategy to give patients green light for going for surgery because of a possible bleeding tendency. Using an extensive interview and panel of laboratory tests, safety for surgery is reviewed.

Protocols of the surgical process are commonly compared to aviation. Checklist are used to assess safety during the operation. Like kerosene in aviation, patients' blood needs to be of good quality.

Technology is ever evolving. The laboratory tests in this study are getting smaller, faster, more precise, and can give the same, or similar results, of multiple tests in one go.

Stated is that in the future this technology is getting even more advanced. A single drop of blood could evaluate the full haemostatic system of a patient in little time.

However, this seems to be science fiction, as for now lots of research has to be performed before patients can proceed blood curdling, but relieved, for surgery.

This short assay was envisioning the essence of this thesis back then in 2011 and now emphasizes the bigger picture of this valorisation chapter.

So how can the acquired knowledge from this thesis be of any use?

The gathered knowledge from this dissertation is of great value for patients, hospitals, medical healthcare personnel (e.g. surgeons, anaesthesiologists, perfusionists, blood bankers, et cetera), blood donors, and healthcare technology companies (of ROTEM, MultiPlate, PFA-100, TEG, et cetera) alike.

Although the monitoring principles date back to the 1940's for the viscoelastic measuring devices, the amount of clinical research in haemostasis monitoring has exploded after the rebirth of ROTEM and TEG in the mid-eighties. One of the first publications of viscoelastic monitoring of haemostasis in liver transplant surgery,[1] showed at that time that these devices are beneficial in many ways: to summarize, potential added value for patients is because of improved safety (**chapter 7**), less need for blood testing (**chapter 4**), earlier and more precise

diagnosis of coagulation abnormalities (**chapters 3, 5, and 6**), and shorter length of stay on the ICU and in the hospital (**chapter 7**). While for hospitals, there is benefit because of similar reasons as for patients. On top of that, overall costs are reduced (**chapters 4 and 7**).

The improvements in patient safety and lower costs for hospitals are the resultant of earlier and more precise diagnosis of coagulation disturbance and the subsequent initiation of adequate therapy by physicians. Other healthcare workers, like those working on laboratories have less workload because of the need for less laboratory tests, the need for less samples which need to be investigated, and the potential to incorporate our measurements in a fully automatic process. Blood bankers might need less allogeneic transfusion products in their stock (**chapter 7**). In 2016 the WHO released their 'Global Status Report on Blood Safety and Availability'[2], which reported that around 6% of all blood products have to be discarded in the high income countries and that in these countries 2.7% is discarded because of expiry, making expiry the biggest reason for discarding blood products worldwide. In 2012 more than half a million of red blood cell concentrates were transfused in the Netherlands. That would mean that around 37 of these red blood cell concentrates were discarded daily in the Netherlands. Reductions in the use of allogeneic transfusion products in expense of enlargements of allogeneic transfusion products results in less wastage of transfusion products. In the end, less blood donors are needed to supply the demand of transfusion products.

The newly developed fibrinolysis assay and the correction of both platelet function testing device, can be nice opportunities for the manufacturers of these devices to improve their tests or for us to hop along the bandwagon (**chapters 3 and 5**). Fast and easy whole blood point-of-care fibrinolysis testing is so far a niche market and seems to have great growing potential (**chapter 8**). Not so long ago, thromboelastometry and multiple electrode aggregometry were two separate whole blood point-of-care devices. Nowadays, both techniques have been merged into one machine, the ROTEM *platelet*. Manual pipetting is still needed in this all-in-one machine, but the most recent addition as of now, the ROTEM sigma, is a fully automated viscoelastic haemostasis monitoring device

in which little to no user input is needed to perform a complete coagulation check. Platelet function assessment is not present on the ROTEM sigma. Haemonetics, the ROTEM competitor, also has improved their TEG5000 coagulation monitor into an all-in-one solution using microfluid cartridges. The TEG 6s includes both viscoelastic analysis as well as platelet function measurements without the need for manual pipetting. The technique of the TEG 6s differs from the traditional viscoelastic properties analysis, as now the effect of various radiofrequencies thrown at the blood sample on the motion of the forming clot during the formation and breakdown is analysed: 'Stronger clots have higher resonant frequencies and higher TEG readouts'.[3] According to Haemonetics[4] the total coagulation testing market potential in 2014 was estimated at 1.5 billion US dollars, of which 1/6th derives from advanced coagulation testing (i.e. viscoelastic and platelet function testing). Haemonetics stated it holds an 86% market share (in disposable units) of this division. Werfenlife, the healthcare technology corporation specialized in in vitro diagnostics and medical devices which acquired ROTEM in 2016, reports that in vitro diagnostics represent 84% of their total revenue with almost one billion US dollars in sales.[5] Their haemostasis portfolio has a constant currency growth of +6.2%, with a global market share of 28%, ranking it at number one in the world. Our new fibrinolysis assay has the potential to be implemented in the current ROTEM portfolio of tests, specifically targeting the fibrinolytical pathway of haemostasis. Haemonetics, the other partner with whom cooperation can be achieved, has to validate our method on their new resonance based TEG 6s system in order to further develop our tPA induced viscoelastic assay principle.

On the other hand, our established reference intervals for the platelet function measuring devices might be of less interest to the manufacturers of both MEA and PFA-100, because the tests themselves remain untouched. It is only the calculation algorithm of the new reference ranges which need to be incorporated in their existing devices. However, our findings could mean a boost in sales for PFA-100 and MEA, because researchers and clinicians gain new interest after publication of our research paper on how to correctly interpret platelet function in anaemia and thrombocytopenia conditions.

As of now, around ten mL of whole blood is needed to globally assess the coagulation status of patients. Whether the panel of blood tests and the results of the interviews can pinpoint the cause of the possible bleeding remains to be seen, as the research on this topic is still on-going. If reduction of the amounts of mL of blood to just a drop can be achieved, like I speculated in my Dutch assay, also remains to be seen. However, whole blood thrombin generation testing using the calibrated automated thrombogram (CAT), pioneered by Hemker et al,[6] has already made this step from mL to drops.[7] Monitoring of anticoagulant medication might emerge to be the unique selling point (USP) of whole blood thrombin generation testing using CAT.

When we think about investments of the future, we see other start-ups emerge from everywhere (e.g. Stasys Medical Corp[8] has developed a patented microfluid platelet aggregation and contractility method under shear stress; Emulate Inc.[9] pioneered the Organs-on-Chips technology; et cetera) which all present 'new technology' to investigate haemostasis using drops of blood. Seeing how far TEG and ROTEM have become, these start-ups might be wandering in a snake pit. Their USP should gravely outweigh those of TEG and ROTEM, as well as the field of antiplatelet and anticoagulant medication monitoring. In my opinion implemented point-of-care whole blood haemostasis monitoring technology should address the full range of haemostasis: from start of coagulation to breakdown of the clot. It should give an answer to the most essential question: if a patient is bleeding, is it because of a disturbed haemostasis balance or not. It should point clinicians to the cause or to the potential culprit would haemostasis be deranged. It should help clinicians decide which treatment strategy to initiate: focus on platelets, coagulation factors, or fibrinolysis. Foremost, it should be fast, compact, and easy to use and maintain. The viscoelastic methods of TEG and ROTEM seem to embody this whole concept the best and will probably remain the most important players on this point-of-care market. On the other hand, for start-ups to become successful they sometimes need to think outside the box and might have to introduce something which creates demand instead of fulfilling current ones.

References

1. Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw BW Jr, Starzl TE, Winter PM. *Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation.* Anesth Analg. 1985 Sep;64(9):888-96.
2. World Health Organization. *Global Status Report on Blood Safety and Availability 2016.* 2017. ISBN 978-92-4-156543-1. File: 'WHO.2016-9789241565431-eng.pdf'. Available from: http://apps.who.int/iris/bitstream/10665/254987/1/9789241565431-eng.pdf
3. Gurbel PA, Bliden KP, Tantry US, Monroe AL, Muresan AA, Brunner NE, Lopez-Espina CG, Delmenico PR, Cohen E, Raviv G, Haugen DL, Ereth MH. *First report of the point-of-care TEG: A technical validation study of the TEG-6S system.* Platelets. 2016 Nov;27(7):642-649.
4. Gould G. *Innovation and Automation for Blood Management.* November 20th, 2014. File: 'TH 0840 3 Haemonetics FINAL.pdf'. Available from: http://www.jefferies.com/CMSFiles/Jefferies.com/files/TH%200840%203%20Haemonetics%20FINAL.pdf
5. Werfenlife. *Annual Report 2016.* File: 'annualReport_2016_v5.pdf'. Available from: http://www.werfenlife.com/werfenlife/flipbook/annualReport_2016_v5.pdf
6. Hemker HC, Giesen P, AlDieri R, Regnault V, de Smed E, Wagenvoord R, Lecompte T, Béguin S. *The calibrated automated thrombogram (CAT): a universal routine test for hyper- and hypocoagulability.* Pathophysiol Haemost Thromb. 2002 Sep-Dec;32(5-6):249-53.
7. Ninivaggi M, Apitz-Castro R, Dargaud Y, de Laat B, Hemker HC, Lindhout T. *Whole-blood thrombin generation monitored with a calibrated automated thrombogram-based assay.* Clin Chem. 2012 Aug;58(8):1252-9.
8. Stasys Medical Corp. 2017. Webpage: https://www.stasysmedical.com
9. Emulate, Inc. 2017. Webpage: https://emulatebio.com