

# Monitoring of hemostatic disturbances in cardio-pulmonary bypass patients : pitfalls and prospective solutions

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# VALORIZATION



In cardiac surgical patients the hemostatic condition is preoperatively evaluated by assessment of medical history and routine coagulation tests. However, it is well known that these tests are poor predictors of either a bleeding or a thrombotic tendency. All too often patients having normal test results develop a coagulopathy leading to excessive bleeding. Studies found a mortality rate being four times higher in patients with excessive postoperative blood loss. Avoidance of postoperative hemorrhage may reduce adverse events like sepsis, acute respiratory distress syndrome, renal failure and death. These complications and the risk of re-exploration place a high demand on hospital resources like transfusion needs, ventilatory support, intensive care (ICU) support, and personnel. The associated costs directly related to these adverse events are significant. In 2014 cardio surgical patients in the MUMC<sup>+</sup> consumed ~12% of the total amount of blood products (~€ 560.000). Patients with a high amount of postoperative chest tube drainage have significantly more blood transfusions, but also longer hospital stays than controls. The incremental (extra) cost of excessive postoperative hemorrhage will be significant.

From a clinical perspective, it would be extremely useful to have a test that accurately predicts an individual's coagulation potential. Ideally, such a test should detect the risk for thrombosis, and diagnose, and even predict bleeding in the whole perioperative period. In addition, it should indicate the effect of medical therapy on procoagulant and anticoagulant capacity.

It was already shown in earlier studies that thromboelastography/ thromboelastometry (TEG/ROTEM) may reduce blood product consumption in coronary artery bypass grafting (CABG) patients. This method does also give a good reflection of heparin, used as anticoagulant therapy in cardiac surgery.

Literature suggests that calibrated automated thrombography (CAT) is better at identifying patients at high risk for excessive blood loss or thrombotic complications than simple clotting tests like the activated clotting time (ACT). CAT might improve the timely identification of hemostatic problems underlying a bleeding tendency perioperatively, which may improve timely and tailored transfusion management. In addition, it can be used for assessing substitution and antithrombotic treatment.

CAT is designed to measure thrombin generation in clotting plasma. However, recently CAT is developed into a method that enables the measurement of thrombin in whole blood. Also, CAT measurements including the effect of blood flow on thrombin generation are still under development. It is getting more and more an advanced test coming more closely to the physiological situation.

This thesis underlines the complexity of the disturbances in coagulation in cardiac surgical patients together with the difficulties in monitoring it. However, it can be concluded that the new, more advanced, tests ROTEM and CAT, performed pre-, per- and postoperatively, do have a predictive value for bleeding postoperatively. Measuring

fibrinogen level is a conventional method which equals the predictive value of ROTEM and CAT for blood loss postoperatively, but it is time consuming.

There are still a lot of questions but also a lot of challenges, regarding the topic of hemostasis in cardiac surgery. The first challenge is to organize larger, clinical studies which have more impact. The sample size in our studies was small. Although it allowed us to detect significant differences in the studied parameters, the statistical power is low. In addition, our studies were single-center experiences. Transfusion thresholds, hematologic practice, discontinuation of anticoagulants, and the use of perioperative antifibrinolytics may not reflect worldwide practice, and the generalizability (validity) of our results needs thus to be proven in larger multicenter studies. In addition, intervention studies are needed. Monitoring (anti)coagulation in a correct way and predicting bleeding complications is a good fundament, but knowing what to do in this situation is the ultimate aim. When performed all these studies in a correct way, this can take another 10 years of doing research. Financial resources are required for organizing this. Health foundations should be contacted. Applications for grants are often essential: funds will considerably reducing the time needed to perform those studies, e.g. by investing in personnel and more technical resources. Gradually, we are on the right track in treating patients at risk of excessive bleeding and transfusion.

A very obvious and surprising conclusion from studies described in this thesis is that CAT and ROTEM performed preoperatively are more predictive for blood loss than performed postoperatively at admission on the ICU. Before the most impressive intervention will be done - the surgical procedure with exposure of the patient's blood to the extracorporeal circuit – it is possible to predict whether patients are at risk of bleeding. This means that a patient has already a hemostatic condition prone to hemorrhage, which can be caused by several factors, e.g. exposure to aspirin or oral anti-coagulants preoperatively, renal insufficiency, hepatic disorders, sepsis or other comorbidity leading to hemostatic disturbances. Or are there causes we don't even think about? In fact, we have to deal with the consequences, instead of having to struggle with the cause of the problem as we cannot influence this most of the times. We should have a test, which is suitable for detecting all kinds of hemostatic disturbances. The results of this test should lead to an intervention which reduces the risk of bleeding for the patient without creating adverse events. This test should be available as a point-of-care test in the operating theatre, and could be performed pre- and post-operatively in the ideal situation. The challenge of developing such a test is to implement new technologies in a still more advanced monitoring system, eliminating the limitations of the current tests, reflecting the actual hemostatic condition, and improving (anti)coagulation therapy during CPB. This is not beyond our imagining, because levels of expertise and know-how have been rising constantly. Findings have to be

translated into diagnostic tools, medicines, procedures, policies and education by using a multi-disciplinary, highly collaborative, “bench-to-bedside” approach.

More advanced self-tests, are already under development, so patients can test the coagulability of their blood at home. Continuously adjusting hemostatic therapy could be quite simple having such a self-test, as a result of which bleeding risks could be minimized preoperatively.

In addition, it would be superior to develop this method into a test which can be used also intraoperatively, e.g. in case of emergency when there is no time to care about monitoring hemostatic conditions preoperatively. A refined hemostatic assay should elucidate this during surgery. Imagine, the patient is anticoagulated and connected to the extracorporeal circuit without knowing the level of anticoagulation. Neither there is a reliable anamnesis or medical history. Especially, in this situation it is desirable to have information about the coagulation status intraoperatively.

However, a new developed method should be useful also in elective cases, simply because of the great need for such a test to classify patients with increased risk of thrombosis or bleeding. New techniques should be created considering the experience in the field of cardiopulmonary bypass we got used to and what kind of monitoring we prefer. We are familiar with continuous monitoring of blood gasses in-line in the extracorporeal circuit. That is fast and easy. Wouldn't it be innovative to monitor (anti)coagulation status in-line during cardiopulmonary bypass? Then it would approach the physiologic system rather close by measuring also flow rates. How can we develop this insight into a monitoring technique which is user-friendly: fast, cheap and easy to perform. A good collaboration between clinical perfusionists, hematologists, technicians, and companies is required to start an industrial process. Financial resources should be secured before contacting companies. Investing money is an essential thing in developing new assays. Companies are needed which have experience in the field of monitoring hemostasis and which are also close to the (cardiac surgical) clinic. They have to develop advanced hemostatic assays specific for our cardiac surgical patients. If it is possible to make a self-test, then the next step should be to convert such a small device into the extracorporeal circuit, to implement it as an in-line system for continuously monitoring intraoperatively. This can be a diagnostic tool connected to a sample line in the extra-corporeal circuit. It should be able to monitor the anticoagulation status of the patient at a specific moment, but also to give information about the underlying coagulation status when heparin would be neutralized.

Developing a new diagnostic coagulation monitoring system will be a challenge which brings a solution with a great impact on future cardiac surgical patients worldwide.

# VALORIZATION

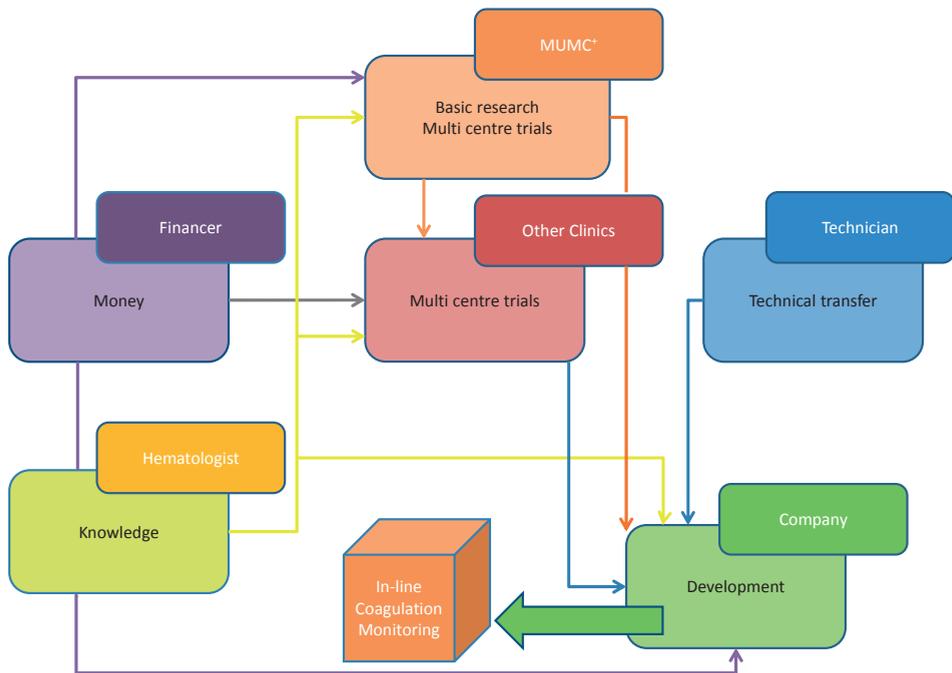


Figure 1: schematic overview of a translational approach to produce a hemostatic monitoring application that can be used point-of-care.