Enhanced hemostasis management strategies in cardiac surgery

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English summary

ENGLISH SUMMARY

Cardiac surgery is performed in patients with severe atherosclerosis of the coronary arteries, cardiac valve disease and/or aortic abnormalities. In order to perform most type of surgery on the heart no blood should be flowing through as this would lead to massive blood loss and operating on a beating heart is difficult. For this reason, the blood flow, oxygenation and ventilation are taken over by a heart lung machine (HLM) also known as cardiopulmonary bypass (CPB), shown in figure 1. In order to bypass the heart, blood is removed prior to the heart and pumped into the aorta, which is the major artery suppling blood to the body.

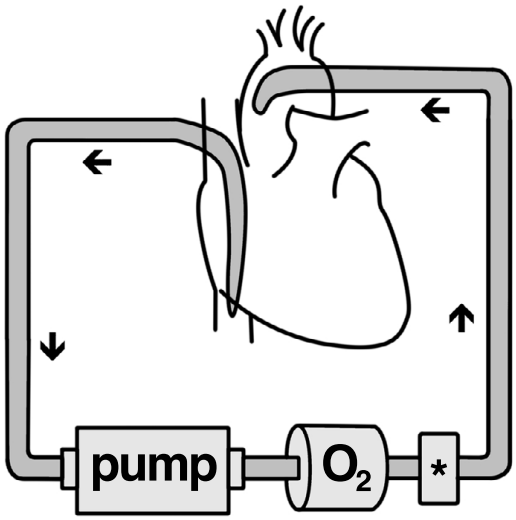

Figure 1. A schematic overview of the heart lung machine. Blood is sucked from the right atrium, oxygenated by an oxygenator and pumped in the aorta, bypassing heart and lungs. (Copyright M.I. Meesters 2017)

When the heart is stopped by the administration of cardioplegia fluid, surgery can safely be performed while oxygen transport is assured by the heart lung machine. In order to prevent clot formation in the heart lung machine, the patients' blood is anticoagulated by administration of heparin. After surgery, the patient is weaned from the heart lung machine, and blood coagulation needs to be restored to prevent blood loss from the surgical wound. This is done by administration of protamine, a drug that binds and inactivates heparin. However, as protamine itself has anticoagulant properties, overdosing of protamine should be avoided. On the other hand, insufficient protamine will lead to residual heparin, which inhibits coagulation. Adequate protamine dosing is required to prevent blood loss due to anticoagulation, as shown in figure 2.

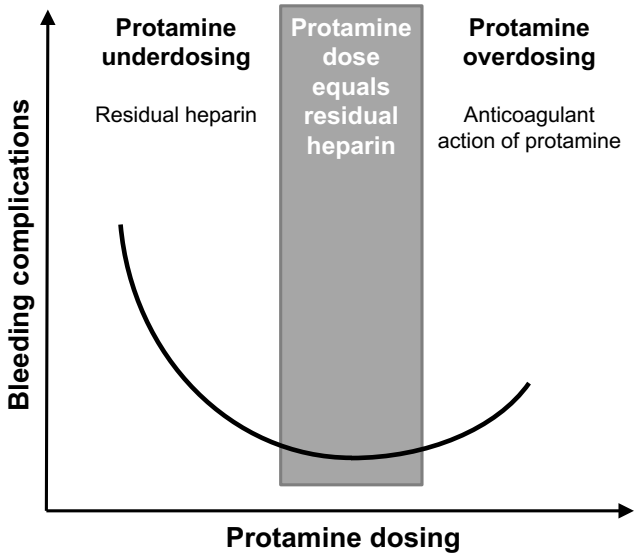

Figure 2. A schematic overview of the importance for adequate protamine dosing.

When the patient is bleeding despite adequate heparine reversal, prompt intervention is necessary as bleeding leads to loss of red blood cells and clotting factors. This might result in blood transfusion and possible reoperation when bleeding does not cease. Bleeding, blood transfusion and reoperation for bleeding are associated with an increased risk of infection and death, highlighting the importance of rapid treatment of coagulation abnormalities.

In case of bleeding due to coagulation abnormalities, adequate supplementations of the deficient coagulation factors is necessary. This can be guided by rapid coagulation tests, such as thromboelastometry or other point of care coagulation assays. Another approach is transfusion based on patient and surgical characteristics guided by the experience of the attending anesthesiologist.

Chapter 1 describes the complexity of all possible modalities to *prevent*, *predict, monitor* and *treat* bleeding in cardiac surgery. These components are usually referred to as 'patient blood management'. There are several ways to prevent bleeding after cardiac surgery including: cessation of drugs that inhibit coagulation before surgery, administration of medication to optimize patients clotting capacity and anemic patients can be treated to improve their red blood cell concentration. The patient at risk for bleeding can be identified by the use of risk scores based on patients and surgical characteristics and advanced clotting tests. In the case of ongoing hemorrhage there are several drugs that can be used to prevent further bleeding, which drug should be used can be guided by the use of rapid clotting monitors.

The thesis starts with methods to *prevent* bleeding, including optimization of protamine dosing. As mentioned before, protamine is used to reverse the anticoagulant properties of heparin after cardiac surgery. However, in laboratory studies it has been found that protamine acts as an anticoagulant in the absence of heparin. **Chapter 2** summarizes what is known about protamine starting from its origin and the discovery of the heparin neutralizing effect. The pharmacological properties and well-known side effects are reviewed, including anaphylaxis and the effect on heart and blood vessels. However, the emphasis is on the negative effect of protamine on coagulation including blood platelets, coagulation factors and clot breakdown. Moreover, the effect of protamine on several coagulation testing methods is discussed. Finally, methods for protamine dosing and alternatives to protamine are reviewed.

In **chapter 3** we investigated if the anticoagulant effect of protamine is clinically significant and influences the amount of blood loss and coagulation status in patients undergoing cardiac surgery. We therefore randomized patients to low or high protamine dosing, all within the spectrum of clinically used dosages. We found that the high dosing group had significantly more blood loss and needed more blood transfusion compared to the low dosing group. This can be explained by the anticoagulant effect of protamine as clotting tests were worse in the high dosing group. This is the first study to prove that too much protamine in patients impairs the coagulation system and has a clinical significant effect on bleeding.

In order to further improve protamine dosing, we investigated a novel dosing regime in **chapter 4**. The method estimates the amount of heparin at the moment that protamine is planned to be administrated. This is realized by a complex pharmacological model that estimates the patient blood volume and takes the administrated dose of heparin and loss of heparin due to its breakdown into account. When the amount of heparin is known, the amount of protamine needed can easily be calculated. We compared the clotting capacity and need for blood transfusion before and after the implementation of the novel dosing strategy. We found that the new protamine dosing method reduced the need for blood transfusion and improved clotting when compared to regular protamine dosing.

Next, the thesis focusses on the *prediction* of bleeding. In **chapter 5** we systematically reviewed the literature on the predictive value of the advanced coagulation monitoring device rotational thromboelastometry (figure 3). This device has been developed for the rapid detection and guidance of coagulation abnormalities at the point of care for the patient in the case of (severe) bleeding. Although rotational thromboelastometry was developed to guide coagulation treatment it remained unclear if abnormal thromboelastometry test results risk

patients for bleeding. Therefore, we performed an analysis of the predictive value of thromboelastometry in our center and additionally performed a systematic literature search which resulted in 1311 publications of which 10 regarded the predictive value of rotational thromboelastometry in cardiac surgery patients. We combined the results of our study with the results of the 10 publications and concluded that rotational thromboelastometry does not predict which patients are at risk for bleeding.

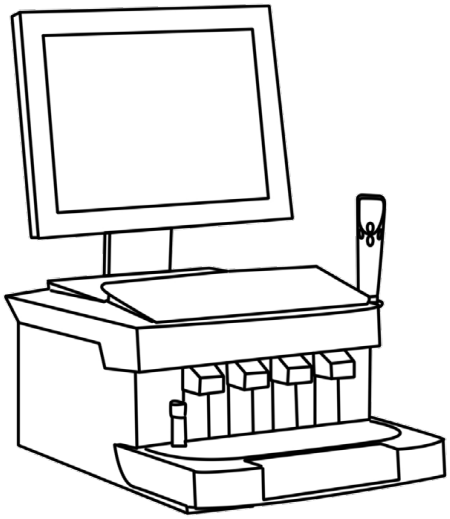

Figure 3. The rotational thromboelastometry test device. (Copyright M.I. Meesters 2017)

During cardiac surgery patients frequently develop coagulopathy (e.g. coagulation abnormalities) due to blood loss, the surgical wound and the use of the cardiopulmonary bypass system. Several hemostasis monitors have been developed to measure patients' hemostatic capacity and guide hemostatic treatment. We investigated the adequacy of different devices to *monitor* coagulation abnormalities during cardiac surgery.

Thromboelastometry includes several tests to investigate different aspects of the coagulation cascade. These tests measure the coagulation capacity and include assays with (EXTEM and INTEM) and without (NATEM) artificial coagulation activators. Another test focuses on a specific important coagulation factor (fibrinogen), the FIBTEM test. The HEPTEM test is same as the INTEM test with the addition of heparinase. Heparinase is an enzyme that breaks down heparin and thereby investigates the coagulation capacity without the effect of heparin. Heparin prolongs the INTEM test results. The HEPTEM test, without a heparin effect, should only show equal or shorter clotting test results compared

to the INTEM test. However, in clinical practice we found that the HEPTEM test is frequently longer than the INTEM test. Furthermore, we recurrently found a difference in HEPTEM and INTEM test results before the administration of heparin before surgery. In **chapter 6** we investigated the incidence of these abnormal results in cardiac surgery patients of two university hospitals. We found that 15 – 36% of the HEPTEM-INTEM assays in routine cardiac surgery showed abnormal test results. Furthermore, our results suggested these aberrant HEPTEM results might be caused by protamine (over)dosing. However, further studies should elaborate on this hypothesis.

Besides the HEPTEM assay we investigated the accuracy of the thromboelastometric NATEM test. The non-activated rotational thromboelastometric assay (NATEM) does not use any artificial activators and is therefore very sensitive to changes in patients' coagulation status. The test is increasingly used in research due to its high sensitivity. In **chapter 7** we investigated if the storage time of the patients' blood before the start of the test influences NATEM test results. We drew blood in healthy volunteers and intensive care patients and directly performed the NATEM test. We repeated the test after 45 and 90 minutes and evaluated if the test results changed after storage. We found that over storage time the blood clotted quicker as measured by the NATEM test. This suggests that the coagulation cascade gets activated within the blood sample over time. The regular thromboelastometry tests used for clinical practice have previously shown that blood storage does not affect the test results up to 6 hours after blood withdrawal. However, we found that the NATEM test is so sensitive to notice this change. Unfortunately, we could not identify the factor that changed the test results over time. We advise to start the test as soon as possible after blood withdrawal in order to prevent biased test results due to the storage time. Future, research should evaluate the factor(s) responsible for the activation of clotting over time in the stored blood sample.

Besides, thromboelastometry there are other devices which rapidly investigate the coagulation capacity of a patient, an example is the point-of-care (POC) prothrombin time (PT) as shown in figure 4. The PT is a conventional laboratory coagulation assay, however as mentioned before these tests require much time. To overcome this limitation the POC-PT was developed where the test is modified to obtain the test results more rapidly and near the patient, at the 'point-of-care'. As the test was developed for patients on anticoagulation medication the device was not validated for the use in cardiac surgery. Therefore, we investigated the accuracy of the POC-PT in cardiac surgery as described in **chapter 8**. Before and after cardiac surgery we drew a blood sample and investigated if the POC-PT corresponded with the laboratory PT. Before cardiac surgery there was a good

agreement between the rapid POC-PT and the laboratory, however 3 minutes after protamine administration after cardiac surgery the test results were very different. In order to investigate if after 6 or 10 minutes after protamine administration the test results would agree we performed another investigation, as described in **chapter 9**. However, also 6 and 10 minutes after protamine administration the results remained much shorter in the POC-PT assay. Therefore, we concluded that the POC-PT is not applicable in cardiac surgery.

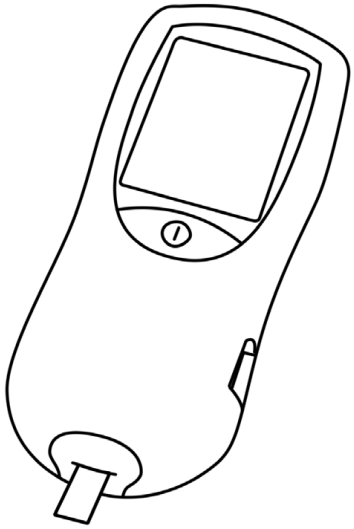

Figure 4. The point-of-care prothrombin time device. (Copyright M.I. Meesters 2017)

Hereafter we focused on *treatment* options for hemostatic abnormalities. In the case of coagulopathy patients might require transfusion of coagulation factors and/or blood platelets. It remains difficult to determine the need for transfusion of coagulation factors, i.e. fresh frozen blood plasma composed from donated blood. Conventional coagulation tests can indicate a deficiency in coagulation factors, however these tests are time consuming and in the bleeding patient the time to wait for the test results is lacking. Therefore, the decision to transfuse coagulation factors is frequently based on clinical signs of bleeding. These signs usually include oozing of blood from the surgical field, long time connection to cardiopulmonary bypass and complex surgery. However, thromboelastometry can help to guide the need for coagulation factor supplementation as test results are rapidly available. In **chapter 10** we investigated if the clinical decision to transfuse blood plasma is confirmed by the findings of thromboelastometry. We found that the clinical decision of the (experienced) cardiac anesthesiologist to transfuse plasma is accurate in 95% of the cases when compared to thromboelastometric

test results.
Another method to treat coagulopathy is the administration of pharmaceutically produced coagulation factor concentrates instead of plasma transfusion. A recent study by Bilecen and colleagues investigated if the administration of fibrinogen concentrate (a specific coagulation factor concentrate) reduced bleeding after cardiac surgery. (*Effect of Fibrinogen Concentrate on Intraoperative Blood Loss Among Patients With Intraoperative Bleeding During High-Risk Cardiac Surgery: A Randomized Clinical Trial. JAMA, 2017 317(7), 738–747*) They concluded that fibrinogen concentrate did not reduce bleeding during cardiac surgery. In our letter to the editor (**chapter 11)** we noted that blood loss during surgery is not a relevant endpoint as most bleeding occurs after surgery and their study showed that fibrinogen concentrate did reduce this amount of blood loss. Furthermore, fibrinogen was administrated to patients who were not deficient in fibrinogen. These notes tone down the strong conclusion drawn by the authors.
In **chapter 12** we describe the limitations of the studies of this thesis. Furthermore, the results from the individual chapters are combined and placed in perspective. First, the results of the protamine dosing studies and directions for future studies are given. Hereafter, predictors for bleeding after cardiac surgery are discussed. Then the implementation of thromboelastometry and the current evidence for its use is elaborated. It is highlighted that most studies on thromboelastometry guided coagulation therapy are limited by the implementation of the device *and* the use of coagulation factor concentrate *and* a transfusion algorithm, making it difficult to determine the additive value of each individual component. Also, the evidence and risks of the use of fibrinogen concentrate are discussed. Next, the disturbing factors in thromboelastometry testing are highlighted in addition to the storage time and use of heparinase. The clinical applicability and validation of point of care coagulation testing is shortly reviewed. Finally, the possible 'dark side' of active patient blood management: thrombosis (excessive coagulation) is examined.