

# Blood Management—Issues: The Panic of Coagulopathic Bleeding—Is There a Rational Approach?

Bruce D. Spiess, MD

Anesthesiology and Emergency Medicine, Virginia Commonwealth University Medical Center, Richmond, Virginia

Presented at Perfusion Downunder, Queenstown, New Zealand, August 5–8, 2010.

**Abstract:** Blood management is an evolving field of reducing transfusions of allogeneic blood by maximizing multi-modality therapy to optimize red cell mass, reduce red cell loss, and harvest red cells that would have otherwise been discarded. These techniques are highly dependent upon teams working together. The programs are not just focused upon red cells but also on coagulation therapy. Coagulopathy is at times a difficult complex pathologic conundrum. In cardiac surgery the complexity is added to because of the inflammatory effects of anticoagulation, air/blood interfaces, and inflammation. Patients respond variably due to their own genetic and environmental factors. There can be a rational approach, thereby avoiding panic (a normal fear response) if

the clinician utilizes not only the available laboratory technologies existing today but also follows published algorithms for treatment. These technologies with their coexisting algorithms have been widely shown to decrease blood usage, yet not to decrease bleeding. That finding suggests that therapy without such guidance wastes expensive pro-coagulant blood products and produces no advantage (a decrease in bleeding). When a therapy produces no advantage all that it leaves the patient with is the side effects or adverse outcomes. Adverse outcomes from coagulation products are real and sobering. **Keywords:** coagulation, coagulopathy, heparin, bleeding, platelets, fresh frozen plasma, monitoring, thromboelastography. *JECT. 2011;43:P58–P64*

People panic because they do not know what to do or feel threatened. When a patient is bleeding after cardiopulmonary bypass (CPB) there are no simple or universal answers. A feeling of helplessness/panic can overwhelm the team if they are not savvy with regards to coagulation. Coagulation is a complex and beautifully maintained homeostasis. It is part of a larger whole body and localized inflammatory system meant to decrease blood loss, isolate bacterial invasion, and heal tissues. When we perform CPB, the coagulation and inflammatory systems dysfunction (1,2). How much they change in any given patient is unpredictable and probably determined by the constellation of gene variability in that particular patient (3,4). Coronary artery bypass graft (CABG) patients are by nature prothrombotic (5,6). However, patients presenting with end stage heart failure, those requiring transplantation, or those with dissected aortas may be far on the other side of the spectrum pushed towards a bleeding diathesis. Perioperative chronic anti-platelet therapy or acute loading of these drugs in the catheterization laboratory may also create pharmacologic reasons for profound suppression of

the platelet membrane recognition system or function. In the end we in the operating rooms have limited options for treatment of coagulopathies. All too often the end result of the confusing bleeding picture is a panic reaction with the team giving a combination of blood products, including fresh frozen plasma (FFP), cryoprecipitate (Cryo), and platelet concentrate (Plts). It is an understandable human reaction to a crisis — seeking any potential means to end the crisis. Along with these blood bank products, all of which carry risks, the team may elect to use some very expensive and prothrombotic drugs such as factor VIIa. There are better ways to respond but they require systems and infra-structure. These methods use already available technologies and existing algorithms for ferreting out potential common coagulopathies. In the CPB world of complexity a rational approach will assist in calming the desire for panic over transfusion. Hypercoagulability may be as dangerous or more so than hypocoagulability.

## THE PATIENT UPON PRESENTATION

Preoperative genetic state is determined for us when the patient presents for surgery (3,4), however, perhaps in the not too distant future, preoperative genetic screening may be available. Some gene polymorphisms exist and

Address correspondence to: Bruce D. Spiess, Anaesthesiology and Emergency Medicine, Virginia Commonwealth University Medical Center, P.O. Box 980662, Richmond, VA 23298-0662. E-mail: [bdspiess@vcu.edu](mailto:bdspiess@vcu.edu)

predispose patients to be prothrombotic. For example, the variants in tissue plasminogen activator (TPA), plasminogen activator inhibitor-1, and pro-thrombin genes all can increase the risk of atherosclerosis as well as perhaps early graft thrombosis (7,8). A polymorphism for an extra sticky portion of the IIb/IIIa platelet surface glycoprotein exists as well as glycoprotein (GP) Ib and variants of Von Willebrand's proteins (9,10). There are almost certainly gene polymorphisms that make some people susceptible to heparin thrombocytopenia whereas others, even if they develop antibodies, do not get the catastrophic thrombosis. We select for prothrombotic patients just by the fact that we do CABG surgery and these variants will be more likely to be expressed in the population coming to heart surgery.

Hypercoagulability has a number of definitions. We suspect it as a causal factor when a patient suffers a thrombotic stroke or occlusion of a coronary graft, but what coagulation screening tests should be used to define and therefore predict an increased thrombotic risk? Thromboelastography (TEG, Haemonetics Corporation, Braintree, MA) is one of the best tests for assessing overall whole blood coagulation interaction. It has been widely used to assess hypercoagulability (11–13). Thromboelastography has demonstrated a higher incidence of a hypercoagulable state in certain populations with atherosclerosis, diabetes, and hypertension, as well as in patients with acute thrombosis. However the preoperative use of TEG has not been shown to be predictive of who will bleed after surgery. To date, there has been no large scale study looking at preoperative hypercoagulability and the prediction of early graft thrombosis, as proven by angiography.

Perioperative use of clopidogrel/PGY12 inhibitors has been widely shown to affect bleeding after heart surgery (13–18). As a pro-drug it must undergo metabolism in the liver to become active leading to its platelet inhibiting effects. Approximately 15–20% of the North American population are deemed to be nonresponders. A new warning has appeared in product labeling suggesting that for the use of clopidogrel, patients should be tested by either genetic testing or through functional testing. The VerifyNow® (Accumetrics Inc., San Diego, CA) is a widely used automated light transmission platelet aggregometer, which has a gathering literature demonstrating its correlation with other “gold standard” testing for platelet aggregometry (19,20). In cardiology it is becoming widely used and it makes sense for us to have it available as a preoperative screening test for cardiac surgery patients on clopidogrel.

Aspirin, as a thromboxane inhibitor, is less likely to be associated with severe bleeding than clopidogrel, although papers showing generally increased oozing are present. The combination of aspirin and clopidogrel as well as high dose clopidogrel are particularly worrisome for us in

perfusion and anesthesia (13–18). Debate arises as to whether it is safe to wait for elective surgery a period of 5–7 days or whether by acute withdrawal of these agents we incur a withdrawal rebound hypercoagulability and unwarranted risk of acute myocardial infarction (21). The discussions of this risk have universally not weighed the increased risk of perioperative transfusion, reoperation for bleeding, infection, prolonged ventilation, and intensive care unit (ICU) stay versus the risk of myocardial infarction. There are no answers but a plethora of passionately held opinions. New PGY12 and anti-IIb/IIIa agents will be introduced within the next few years. Some will be ultra-short acting intravenous agents, which could well be an advance for us in that they would be more easily titrated with the possibility of wearing off during a CPB run.

Pre-operative vitamin K inhibition through warfarin compounds is common prior to valve surgery and particularly re-op valves. Waiting for normalization of the prothrombin time (PT) may be unreasonable while vitamin K works, or the liver function may be partially impaired by cardiac failure such that waiting will take a very long time. Fresh frozen plasma, although potentially effective, will add significant volume expansion. One potential use of Factor VIIa in cardiac surgery is to normalize the PT rapidly with little or no volume. The use of Factor VIIa is highly effective in not just changing the PT test result but in reducing bleeding associated with a prolonged PT.

The routine use of peri-operative PT and activated partial thromboplastin time either alone or in conjunction with a number of coagulation tests are not by themselves predictive of bleeding after heart surgery (22). Therefore, it is a waste of money to routinely order these tests.

## HEPARIN ANTICOAGULATION

The beginning of the potential for bleeding begins with the injection of heparin. Unfractionated heparin (UFH) creates a fascinating pharmacologic conundrum that on injection establishes far reaching biologic changes. This article is limited and cannot fully delve into the effects of heparinization, especially in the dosages used for CPB. UFH is the most widely influencing drug we use. Unfractionated heparin binds to and reacts with 22% of the proteins circulating in blood (23–25). It does not just activate anti-thrombin III thereby leading to the secondary anticoagulant effect that we use for bypass. It activates platelets in many ways and inhibits them in others. It both causes contact activation and inhibits it depending upon the levels of AT-III. Heparin reacts with the surface of endothelial cells causing them to release heparan (their natural barrier to coagulation and inflammation) and through that release unleashes bound tissue factor pathway inhibitor. Tissue factor pathway inhibitor (TFPI) is a dramatic inhibitor of platelet activation, depressing the ability to create a thrombin burst

(26–31). Circulating TFPI is not tested by any routine coagulation testing. Heparin has far reaching effects beyond the blood stream including effects on interstitial water leakage (edema), white cell transmigration, and eventually angiogenesis itself.

Heparin causes platelet factor 4 (PF4) activation/expression. The complex of heparin and PF4 is highly antigenic leading to antibody formation. Fifty percent of patients after heart surgery will test positive for antibodies, 5–7% have antibodies prior to heart surgery. Biology is telling us something and one has to wonder what effect low levels of antibodies may have either in the acute perioperative setting or early in the ICU. Platelet factor 4 antibodies are the most highly prothrombotic stimulus we know of today but if they are present during CPB can they cause a dramatic opposite effect by causing the accelerated destruction/sequestration of platelets?

Reports have demonstrated heparin bound bypass circuits to be effective in conjunction with radically reduced amounts of systemic heparinization (32,33). The technique has not gained wide spread utilization but it is provocative to think that perhaps the most important piece of that work is in showing that by reducing the usage of UFH we can gain on reduction of inflammation as well as bleeding.

Since heparin is, to this author, an uncontrolled and scary drug, then utilizing the lowest dose possible to achieve adequate anticoagulation makes sense. However, there is strong contrary opinion that pushing heparin levels high will further reduce the formation of thrombin during CPB. Lower dose heparin can allow for lower dose protamine (34).

Reversal of heparin with protamine causes a coagulopathy that is little appreciated. Protamine is a mild anti-thrombin. Excess protamine by itself can play into the risk for bleeding. A common practice is to give recipe heparin and 1:1 protamine at the end of bypass. Protamine is so highly poly-cationic that as little as 3% of the protamine is needed to reverse heparin. By using 1:1 ratios, we may well be already using too much protamine. Then, if a patient exhibits a bleeding tendency, most often more protamine is used. Protamine titration by use of automated monitoring system has been shown to decrease bleeding. One less expensive method is to give a lower dose than 1:1, test the ACT, and repeat protamine only in small quantities. If the ACT does not then further reduce after a second small dose of protamine, more protamine will only increase the bleeding, not make it better.

The heparin protamine complex binds to the surface of platelets and causes them to be recognized by the reticuloendothelial system (RES) and leads to inflammation (35,36). This happens very quickly and may be responsible for a great deal of the immediate coagulopathic bleeding after CPB. Often a patient emerges successfully from CPB, is administered protamine, and initially the microvasculature

appears to clot. Then some 10–20 minutes later oozing begins and the response by the surgical team can be to administer FFP, Cryo, Plts, and now even Factor VIIa. What may be occurring is that the platelets, being coated with heparin-protamine complexes and having their glycol-proteins activated, are margined in the pulmonary vasculature. They are therefore sequestered for a period of time by the RES. An acute drop in platelet count is the result. It has been shown that immediately after protamine a 10–90% decrease in platelet count occurs, predicting in which patients this will occur or the severity of such a catastrophic thrombocytopenia is not possible. It is short lived (less than 12 hours) but in the time it occurs, bleeding could be enough that the remaining or recovering platelet count is depressed by hemorrhagic losses. Very few centers get a platelet count at 30 minutes after protamine or on entrance to the ICU, but it does make sense to do so.

### CARDIOPULMONARY BYPASS

The effects of CPB are dramatic upon the coagulation and inflammation system. When CPB was historically young the teaching was that contact activation by the plastic surfaces of the tubing themselves lead to factor XII and XI activation. Today, we know that not to be the primary reason for coagulopathy. Rather there appears to be widespread tissue factor activation and release during CPB. One can debate at length what might be causing such a massive release of tissue factor. Tissue factor is released from endothelial cells, platelets, and tissue (37). All of these factors have reason to be responsible for tissue factor finding its way into circulation. Clearly at surgery there is dramatic tissue destruction in opening the mediastinum and certainly when the mediastinum is suctioned using cardiotomy suction both tissue factor and thrombin are directly pulled into the CPB machine. Platelets when activated express tissue factor and it is the burst of enough critical mass of platelets cross talking and expressing tissue factor and factor VIIa that leads to the critical thrombin burst creating a clot. Remember that heparin activates platelets. Endothelial cells when made ischemic and then reperfused express a dramatic increase in tissue factor.

The bombardment of the plasma with tissue factor leads to factor VII activation and eventually the consumption of serine proteins as well as the production of thrombin (37). Thrombin is a tremendous amplifier of coagulation and inflammation. It has long been known that there is a constant thrombin production during CPB. Unfortunately, heparin AT-III only can bind plasma free thrombin, one molecule at a time. Thrombin does not exist in plasma very often, or for very long. It is instantaneously taken up by platelet and white cell binding proteins, which have a higher affinity and a closer connection to thrombin production than does heparin AT-III. That fact is a major

driver of the consumptive coagulopathy that leads to platelet dysfunction.

Hemodilution is somewhere between 10–40% of circulating volume in CPB. In the last 5 years the use of smaller prime circuits and aggressive retrograde autologous prime (RAP) (both arterial and venous removal of prime) have decreased mean prime volumes. This certainly helps in the coagulopathy of CPB. In our institution the routine usage of RAP has increased the Hgb on entry to the ICU by 1.5 gm/dL. We do not have a measure of how much it has increased platelet count, fibrinogen, and other critical proteins but that must be considerable.

Fibrinolysis is universal in CPB. Academics argue whether platelet dysfunction or fibrinolysis is the more severe cause of post-CPB coagulopathy (38–41). It really matters not as they both have influences on each other. TPA is released from endothelial cells that are disturbed. Heparin causes the release of a different plasminogen activator but the predominance of affect is carried by the endothelial cell expression of TPA. Plasminogen, when cleaved by serine proteases to plasmin causes destruction of fibrinogen and fibrin. Perhaps more importantly plasmin can attack or bind to platelet surfaces as well as destroy fibrinogen already attached to key glycoprotein binding sites thereby creating a dysfunctional blockade as a competitive inhibition of the platelet surface. Near universal usage of lysine analogues, and previously wide usage of aprotinin was a result of the embracement by our specialties that fibrinolysis should be inhibited. The debate about which lysine analogue to use and or the safety and effectiveness of aprotinin is not the subject of this article. However, since the withdrawal of aprotinin some large series are showing disturbing trends towards more bleeding, worse outcomes, and increased mortality.

A consumptive coagulopathy is set up on CPB, most probably due to platelet activation and thrombin generation (42,43). This has been compared to diffuse intravascular coagulation. Several papers have examined the concentration of key serine protease coagulation proteins during and after CPB. The consumable factors, Factor V, VII, VIII, and fibrinogen are the ones that suffer the greatest (42,43). For the most part, the studies done were on small populations of patients undergoing routine CABG surgery. That may not be our practice today and CABG patients are not the high risk bleeding patients. An observational study of 101 patients in Toronto and Hamilton, Ontario recently examined a number of protein coagulation precursors as well as platelet count and some coagulation testing. The mean drop in platelet count was 52% at one hospital and 43% at another. This may have been due to a difference in anesthesia and perfusion practices (fluid usage and RAP). In these hospitals about a 33% reduction in Hgb was found. Fibrinogen decreased by 41% in Toronto and 31% in Hamilton. Thrombin-anti-thrombin complex

(TAT), AT-III, and soluble fibrin monomer had impressive changes. TAT increased 3000% and fibrin monomer increased 800% (43). These two findings demonstrate the on-going activation of coagulation even in the presence of heparin. The researchers attempted to correlate the quantity of post-operative chest tube output (a surrogate of bleeding) with the changes in measured coagulation proteins and platelets. Of interest they did look at these proteins preoperatively and they did find that there was an inverse correlation in bleeding between F1.2 (prothrombin activation/a measure of on-going hypercoagulable activity) and bleeding. Intraoperatively and postoperatively there was a strong correlation between the amount of thrombin generation, fibrin degradation, and depletion of fibrinogen (43). The degradation of fibrinogen was then correlated to bleeding as was the overall lowering of platelet count. Factor XIII, the stability factor, that cross links and strengthens fibrin was correlated with increased bleeding as well.

The scientific beauty of this study is that it identifies several key factors that can be followed with already existing laboratory testing: platelet count, fibrinogen, and clot strength (TEG). There is no center that will routinely follow multiple factors such as TAT, soluble fibrin monomer, F1.2, and factor XIII, however with some critical knowledge and application of key testing one can make rational decisions.

## TEAM APPROACHES AND COAGULATION MONITORING

Preoperatively there appears to be little benefit in wide-spread coagulation screening testing. However, yet unproven, but tempting is the usage of testing for PGY12 and aspirin effects using the Accumetrix tests. The TEG can provide similar testing of both of these drugs' effects by performing a platelet map. This manipulation of the TEG runs three simultaneous samples with different levels of platelet count as well as activators in platelet mapping. Although very good at detecting the drug effects it is labor intensive and must be performed with an exacting detail for proper handling of the blood as well as centrifugation of blood and platelet count accuracy. Preoperative assessment by history, understanding the nature of the surgery, medication usage, possible consumption (aneurysm), or liver dysfunction (heart failure) is as or more important than routine laboratory testing.

Intraoperative prevention of coagulopathy is paramount and there are no universal truisms here. It appears to this author that heparin titration with a philosophy of least reasonable drug amount for both heparin and protamine makes sense. It is acknowledged that others feel strongly that a great deal of heparin and a high ACT value (>600 seconds) is advantageous. Near universal use of



antifibrinolytics is standard but there is no recent data to show this is the right thing to do. However, in cases where antifibrinolytics have been withheld due to practice changes, bleeding has been remarkable.

One underappreciated behavior is to reduce the use of unnecessary red cell transfusions (44). Red cell transfusions are widely associated with worse outcomes and bleeding. One can argue this is a result of bleeding but there are new research findings suggesting that micro-particles of erythrocyte membrane themselves have pro-inflammatory effects and platelet inhibiting effects which make sense as relating to bleeding (45,46). Of interest, series of Jehovah's Witness patients seem to have less bleeding than do other patients. That could be due to the fact that surgeons are more meticulous during surgery in these patients but it could also have relationships to the lack of transfusion.

During the CPB run and after protamine the application of selected coagulation monitoring can be extremely useful. Thromboelastography and Rotem (Tem International GmbH, Munich, Germany) are tests of whole blood viscoelastic properties (47–51). Coagulation is a whole blood phenomenon, it is not an isolated plasma event. Indeed today we do understand that red cells play roles in coagulation as do white cells. Both the TEG<sup>®</sup> and Rotem<sup>®</sup> are adequately described elsewhere. There are few differences between them in terms of how the two tests interrogate clot strength over time. That one measurement, clot strength, is key to understanding the potential for bleeding.

Clot strength is a function of the interaction of platelet surface GPIIb/IIIa interaction with fibrinogen and then fibrin cross linking with factor XIII. As a whole blood test, TEG<sup>®</sup> examines not only platelet functions and interactions with fibrinogen, but all the complex interactions of all the proteins and cell lines together. Work has shown that TEG<sup>®</sup> has the best sensitivity and specificity for bleeding of any coagulation test available with regards to heart surgery, and is the best predictive in a number of other settings including renal biopsy, liver transplantation, and trauma.

Thromboelastography, however, is not magic. It is limited in that it can only tell us whether a clot forms normally, proceeds to normal strength, holds together, or is prematurely lysed. Thromboelastography without special handling is not sensitive to aspirin and P2Y12 inhibitors. The TEG<sup>®</sup> can be run during the fully heparinized bypass run (52). By using heparinase added to the cup of the machine heparin can be neutralized. If one runs a TEG<sup>®</sup> test side by side with a native (or Kaolin activated test) and a heparinase test it is very easy to test for residual small amounts or rebound heparin. In a number of publications wherein TEG<sup>®</sup> has been used along with other coagulation testing, bleeding, blood product usage, and reoperation for bleeding have been reduced.

The use of several key tests and the application of a coagulation algorithm make sense. The ACT and/or

heparin protamine titration will ferret out the presence of residual heparin. The post protamine ACT should be a few seconds shorter than the preoperative one due to the presence of more tissue factor. Other tests that we use are the fibrinogen, platelet count, and the TEG (kaolin activated or heparinase treated). The PT although often ordered can be misleading due to the fact that there is an interaction between the heparin protamine complexes and the activator in the PT. An international normalized ratio of less than 2 after protamine cannot be considered prolonged. If one treats such international normalized ratios with FFP one will end up over treating. The algorithm we use is similar to the one developed by Shore-Lesserson et al. (53,54). Others have perfected other algorithms and the Society of Thoracic Surgeons/Society of Cardiovascular Anesthesiologists Guidelines for Transfusion after heart surgery do recommend the use of coagulation driven algorithm therapy (55).

Both D-8-amino arginine vasopressin (DDAVP) and Factor VIIa are frequently used in bleeding management. D-8-amino arginine vasopressin is an analogue of the vasoconstrictive agent but rather than constrict, it causes vasodilatation. It also has an enhanced release of von Willebrand's factor from the endothelial cells. Early work had shown this to not be a panacea for coagulopathic bleeding. Despite this, DDAVP has gained some popularity recently in trauma and in Europe with a literature to support its use in heart surgery (56,57). It has been shown effective in patients with proven platelet dysfunction (as demonstrated by TEG<sup>®</sup>) when administered only in those patients with a mild to moderate amount of platelet dysfunction (58). Factor VIIa is an expensive recombinant protein that has rapidly gained "off-label" usage for bleeding in heart surgery. It is indicated for hemophilia and acquired factor VIIa deficiencies. There is no doubt in series where it has been used that it can dramatically decrease the flow of chest tube bleeding and it has probably been life saving. However, it is prothrombotic and debate rages as to when it should be used. Some view it as a first line drug, in other words, it offers advantages to apply it early on before a bleeding diathesis is complicated with massive usages of FFP, Cryo, and Plts. Others have suggested it should only be used as a last resort. There are emerging data that are sobering in terms of potential thrombotic risks. With the withdrawal of aprotinin, factor VIIa's usage has increased and one cannot say this is a good thing (59).

Dosing of factor VIIa is also unclear. The initial papers had suggested that 90 ug/kg was appropriate and effective. Today papers are being presented saying that as little as 20 ug/kg can be very effective and if not repeat dosing can be quickly carried out (60). There is no resolution or recommendation as to what dose to give. The 90 ug/kg dose was arrived at much the same way as the "Hammersmith" dose of aprotinin—experts' best guess.

## SUMMARY

Today we have not progressed a great deal further than where we were years ago in terms of an industry approach to bleeding after heart surgery. Practitioners continue to hope for a single treatment option to stop bleeding. Stopping bleeding will almost certainly confer a risk of thrombosis. Understanding coagulopathy from CPB is highly complex and our treatment options are limited. Indiscriminate use of FFP, Plts, and Cryo, as well as unnecessary use of red cell products have major consequences that probably worsen coagulopathy rather than fix them. Some good coagulation monitors do exist. However, to make effective use of them human systems must be in place for timely results. It is most often a problem that a hospital has not solved — how to get test results to the practitioners fast enough for them to make essentially real time decisions. No doubt new anti-coagulant, anti-platelet agents and more difficult patients will forever challenge our CPB case load. A rational, monitored, and metered approach to coagulopathies will be met with more success than failure.

## REFERENCES

- Spieß BD, Harrow J, Kaplan JA. Transfusion medicine and coagulation disorders. In: Kaplan JA, Reich DL, Lake CL, Konstadt SN, eds. Kaplan's Cardiac Anesthesia, 5th Ed. Philadelphia, PA: Saunders Elsevier; 2006:937–84.
- Ferraris VA, Ferraris SP, Saha SP, et al. Perioperative blood transfusion and blood conservation in cardiac surgery. The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg.* 2007;83(Suppl):S27–86. Review.
- Duggan E, O'Dwyer MJ, Caraher E, et al. Coagulopathy after cardiac surgery may be influenced by a functional plasminogen activator inhibitor polymorphism. *Anesth Analg.* 2007;104:1343–7.
- Welsby IJ, Padgoreanu MV, Phillips-Bute B, et al. Genetic factors contribute to bleeding after cardiac surgery. *J Thromb Haemost.* 2005;3:1206–12.
- Tantry US, Bliden KP, Suarez TA, Kreutz RP, Kichiara J, Gurbel PA. Hypercoagulability, platelet function, inflammation and coronary artery disease acuity: Results of the Thrombotic Risk Progression (TRIP) study. *Platelets.* 2010;21:360–7.
- Pineda J, Marin F, Marco P, et al. Premature coronary artery disease in young age (<45) subjects: Interactions of lipid profile, thrombophilic and hemostatic markers. *Int J Cardiol.* 2009;136:222–5.
- Zorio E, Gilabert-Estelles J, Espana F, Ramon LA, Cosin R, Estelles A. Fibrinolysis: The key to new pathogenic mechanisms. *Curr Med Chem.* 2008;15:923–9.
- Benza RL, Grennett HE, Bouge RC, et al. Gene polymorphisms for plasminogen activator inhibitor-1/tissue plasminogen activator and development of allograft coronary artery disease. *Circulation.* 1998;98:2248–54.
- Boekholdt SM, Peters RJ, de Maat MP, et al. Interaction between a genetic variant of the platelet fibrinogen receptor and fibrinogen levels in determining the risk of cardiovascular events. *Am Heart J.* 2004;14:181–6.
- Zotz RB, Winkelmann BR, Muller C, Boehm BO, Marz W, Scharf RE. Association of polymorphisms of platelet membrane integrins alpha IIb(beta)3 (HPA-1bPI) and alpha 2 (beta)1(alpha8077TT) with premature myocardial infarction. *J Thromb Haemost.* 2005;3:1522–9.
- Pivalizza EG. TEG and perioperative hypercoagulability. *Anesth Analg.* 2006;102:334–5.
- Akay OM, Ustuner Z, Canturk Z, Mutlu FS, Gulbas Z. Laboratory investigation of hypercoagulability in cancer patients rotation thromboelastography. *Med Oncol.* 2009;26:358–64.
- Kashuk JL, Moore EE, Sable A, et al. Rapid thromboelastography (r-TEG) identifies hypercoagulability and predicts thromboembolic events in surgical patients. *Surgery.* 2009;146:764–72.
- Ascione R, Ghosh A, Rogers CA, Cohen A, Monk C, Angelini GD. In-hospital patients exposed to clopidogrel before coronary artery bypass graft surgery: A word of caution. *Ann Thorac Surg.* 2005;79:1210–6.
- Chen L, Bracey AW, Radovancevic R, et al. Clopidogrel and bleeding in patients undergoing elective coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2004;128:425–31.
- Chu MW, Wilson SR, Novick RJ, Stitt LW, Quantz MA. Does clopidogrel increase blood loss following coronary artery bypass surgery? *Ann Thorac Surg.* 2004;78:1536–41.
- Kapetanakis EI, Medlam DA, Boyce SW, et al. Clopidogrel administration prior to coronary artery bypass grafting surgery: The cardiologist's panacea or the surgeon's headache? *Eur Heart J.* 2005;26:576–83.
- Ray JG, Deniz S, Olivieri A, et al. Increased blood product use among coronary artery bypass patients prescribed preoperative aspirin and clopidogrel. *BMC Cardiovasc Disord.* 2003;3:3.
- Godino C, Mednolicchio L, Figini F, et al. Comparison of VerifyNow-P2Y12 test and Flow Cytometry for monitoring individual platelet response to clopidogrel. What is the cut-off value for identifying patients who are low responders to clopidogrel? *Thromb J* 2009; 7:4.
- Dyszkiewicz-Korpanty AM, Kim A, Burner JD, Frenkel EP, Sarode R. Comparison of a rapid platelet function assay—Verify Now Aspirin—with whole blood impedance aggregometry for the detection of aspirin resistance. *Thromb Res.* 2007;120:485–8.
- Spieß BD. Con: Continuation of aspirin/clopidogrel for cardiac surgery. *J Cardiothorac Anesth.* 2007;21:606–9.
- Gravlee GP, Arora S, Lavender SW, et al. Predictive value of blood clotting tests in cardiac surgical patients. *Ann Thorac Surg.* 1994;58:216–21.
- Spieß BD. A little coagulation knowledge can be dangerous. *Can J Anaesth.* 2009;56:478–82.
- Borsig L. Antimetastatic activities of heparin and modified heparins. Experimental evidence. *Thromb Res.* 2010;125:S66–71.
- Casu B, Naggi A, Torri G. Heparin-derived heparan sulfate mimics to modulate heparin sulfate-protein interactions in inflammation and cancer. *Matrix Biol.* 2010;29:442–52.
- Lever R, Smailbegovic R, Page CP. Locally available heparin modulates inflammatory-cell recruitment in a manner independent of anticoagulant activity. *Eur J Pharmacol.* 2010;630:137–44.
- Li JP, Vlodavsky I. Heparin, heparin sulfate and heparanase in inflammatory reactions. *Thromb Haemost.* 2009;102:823–8.
- Taylor KR, Gallo RL. Glycosaminoglycans and their proteoglycans: Host associated molecular patterns for initiation and modulation of inflammation. *FASEB.* 2006;20:9–22.
- Vlodavsky I, Ilan N, Naggi A, Casu B. Heparanase: Structure, biological functions and inhibition by heparin-derived mimetics of heparin sulfate. *Curr Pharm Des.* 2007;13:2057–73.
- Borawski J, Gozdziakiewicz J, Dubowski M, Pawalak K, Mysliwiec M. Tissue factor pathway inhibitor release and depletion of sulodexide in humans. *Adv Med Sci.* 2009;54:32–6.
- Ilhrcke NS, Platt JL. Shedding of heparin sulfate proteoglycan by stimulated endothelial cells: Evidence for proteolysis of cell-surface molecules. *J Cell Physiol.* 1996;168:625–37.
- Eisses MJ, Velan T, Aldea GS, Chandler WL. Strategies to reduce hemostatic activation during cardiopulmonary bypass. *Thromb Res.* 2006;117:689–703.
- O'Gara PJ, Aldea GS, Shemin RJ, Shapira OM. Heparin-bonded circuit with low systemic anticoagulation in a patient with heparin-induced thrombocytopenia: A case report. *J Extra Corpor Technol.* 1999;31:142–4.
- Paparella D, Al Radi OO, Meng QH, Venner T, Teoh K, Young E. The effects of high-dose heparin on inflammatory and coagulation parameters following cardiopulmonary bypass. *Blood Coagul Fibrinolysis.* 2005;16:323–8.

35. Warkentin TE, Crowthen MA. Reversing anticoagulants both old and new. *Can J Anaesth*. 2002;49:811–25.
36. Bruins P, te Velthuis H, Eerenberg-Belmer AJ, et al. Heparin-protamine complexes and C-reactive protein induced activation of the classical complement pathway: Studies in patients undergoing cardiac surgery and in vitro. *Thromb Haemost*. 2000;84:237–43.
37. Shibamiya A, Tabuchi N, Chung J, Suanori M, Koyama T. Formation of tissue factor-bearing leukocytes during and after cardiopulmonary bypass. *Thromb Haemost*. 2004;92:124–31.
38. Chandler WL, Velan T. Secretion of tissue plasminogen activator and plasminogen activator inhibitor 1 during cardiopulmonary bypass. *Thromb Res*. 2003;112:185–92.
39. Yavari M, Becker RC. Coagulation and fibrinolytic protein kinetics in cardiopulmonary bypass. *J Thromb Thrombolysis*. 2009;27:95–104.
40. Chandler WL, Velan T. Plasmin generation and D-dimer formation during cardiopulmonary bypass. *Blood Coagul Fibrinolysis*. 2004;15:583–91.
41. Chandler WL, Fitch JCK, Wall MH, et al. Individual variations in the fibrinolytic response during and after cardiopulmonary bypass. *Thromb Haemost*. 1995;74:1293–7.
42. Despotis GJ, Avidan MS, Hogue CW. Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. *Ann Thorac Surg*. 2001;72:S1821–31.
43. Karkouti K, McClusky S, Syed S, Pazaratz C, Poonawala H, Crowther M. The influence of perioperative coagulation status on postoperative blood loss in complex cardiac surgery: A prospective observational study. *Anesth Analg*. 2010;110:1533–40.
44. Beckman SR, Carlile D, Bissinger RC, Burrell M, Winkler T, Shely WW. Improved coagulation and blood conservation in the golden hours after cardiopulmonary bypass. *J Extra Corpor Technol*. 2007;39:103–8.
45. Diamanti M, Tushuizen ME, Sturk A, Niwland R. Cellular microparticles: New players in the field of vascular disease? *Eur J Clin Invest*. 2004;34:392–401.
46. Khan SY, Kelher MR, Heal JM, et al. Soluble CD40 ligand accumulates in stored blood components, primes neutrophils through CD40 and is a potential cofactor in the development of transfusion-related acute lung injury. *Blood*. 2006;108:2455–62.
47. Moganansundram S, Hunt BJ, Sykes K, et al. The relationship among thromboelastography, hemostatic variables, and bleeding after cardiopulmonary bypass surgery in children. *Anesth Analg*. 2010;110:995–1002.
48. Hertfeldt HJ, Bos M, Weber D, Winkler K, Hanfland P, Preusse CJ. Perioperative monitoring of primary and secondary hemostasis in coronary artery bypass grafting. *Semin Thromb Hemost*. 2005;31:426–40.
49. Cherng YG, Chao A, Shih RL, et al. Preoperative evaluation and postoperative prediction of hemostatic function with thromboelastography in patients undergoing redo cardiac surgery. *Acta Anaesthesiol Sin*. 1998;36:179–89.
50. Kettner SC, Kozick SA, Groetzner JP, et al. Effects of hypothermia on thromboelastography in patients undergoing cardiopulmonary bypass. *Br J Anaesth*. 1998;80:313–7.
51. Cammerer U, Dietrich W, Rampf T, Braun SL, Richter JA. The predictive value of modified computerized thromboelastography and platelet function analysis for postoperative blood loss in routine cardiac surgery. *Anesth Analg*. 2003;96:51–7.
52. Preisman S, Kogan A, Itzkovsky K, Leikin G, Raanani E. Modified thromboelastography evaluation of platelet dysfunction in patients undergoing coronary artery surgery. *Eur J Cardiothorac Surg*. 2010;37:1367–74.
53. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA. Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg*. 1999;88:312–9.
54. Enriquez LJ, Shore-Lesserson L. Point-of-care coagulation testing and transfusion algorithms. *Br J Anaesth*. 2009;103:114–22.
55. Despotis GJ, Skubas NJ, Goodnough LT. Optimal management of bleeding and transfusion in patients undergoing cardiac surgery. *Semin Thorac Cardiovasc Surg*. 1999;11:84–104.
56. Cattaneo M. The use of desmopressin in open heart surgery. *Haemophilia*. 2008;14:S40–7.
57. Weber CF, Dietrich W, Spannagl M, Hofstetter C, Jambor C. A point-of-care assessment of the effects of desmopressin on impaired platelet function using multiple electrode whole blood aggregometry in patients after cardiac surgery. *Anesth Analg*. 2010;110:702–7.
58. Mongan PD, Hosking MP. The role of desmopressin acetate in patients undergoing coronary artery bypass surgery. A controlled clinical trial with thromboelastographic risk stratification. *Anesthesiology*. 1992;77:38–46.
59. Wang X, Zheng Z, Ao H, et al. A comparison before and after aprotinin was suspended in cardiac surgery: Different results in the real world from a single cardiac center in China. *J Thorac Cardiovasc Surg*. 2009;138:897–903.
60. Willis CD, Cameron PA, Phillips LE. Clinical guidelines and off-license recombinant activated factor VII: Content, use and association with patient outcomes. *J Thromb Haemost*. 2009;7:2016–22.