

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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The Effects of Cardiopulmonary Bypass on Coagulation



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H&O In what ways does cardiopulmonary bypass (CPB) affect coagulation?

JL Just as a reminder, CPB involves bypassing the heart and the lungs so that the surgeon can operate on them. Most cardiac surgery, including valvular repair and replacement, is performed using CPB. The other option is beating-heart surgery, which can be used for coronary revascularization.

In CPB, blood is interfacing with nonendothelial surfaces. This is also called extracorporeal circulation, meaning “out of body.” When I started in medicine more than 30 years ago, CPB was still done using bubble oxygenators, which were enormously activating to the hemostatic system. In recent years, we have switched to membrane oxygenators, which cause far less blood/surface activation and pathologic activation of coagulation. However, blood is still activated by multiple mechanisms related to tissue and mechanical injury. Whenever large amounts of blood are interacting with nonendothelial surfaces during a procedure, it is critical to anticoagulate the blood. Something I have worked on for many years is our understanding of both anticoagulation and reversal of anticoagulation in this particular setting.

The other important factor in coagulation is all of the surgical interventions that are occurring. That includes sternotomy, and all of the associated injury to tissues that causes additional hemostatic activation. Because CPB patients can bleed, blood needs to be recycled during CPB. As a result, some products of hemostatic activation—including tissue factor and other prohemostatic activation products—are recirculated back into the pump/venous reservoir. Remember that, in addition to the circuit, there is a large 1- to 2-L venous reservoir where the blood pools and then circulates through the oxygenator.

In terms of coagulation, there are a variety of different mechanisms by which hemostatic activation occurs. For example, one of the first things that occurs when we institute CPB is that the patient’s blood is diluted with approximately 1 L of a crystalloid/colloid pump prime. This results in dilutional changes, which may contribute to some of the coagulation issues.

Second, we give massive doses of heparin: the levels range from approximately 300 to 400 U/kg. This is much greater than the standard kind of anticoagulation we would use, such as in the intensive care unit, in a sick patient, or for venous thromboembolic issues.

In addition, we have all of the other surgical injuries that cause hemostatic activation. When blood interacts with a nonendothelial surface, a variety of different types of activation occur, including contact activation and cellular activation. This produces an impressive pathophysiologic response that affects coagulation.

The other interesting point is that the dilution causes patients to develop dilutional thrombocytopenia. This sometimes confuses clinicians when they go to see these patients after surgery, because everyone’s platelet count drops by 40% to 60% after CPB.

H&O What anticoagulants are used in CPB?

JL The main anticoagulant is heparin. Heparin is important for several reasons. First, it can be administered intravenously, and it is not affected by renal dysfunction or other multiorgan dysfunction as many other anticoagulants are. Target values for heparin concentrations are probably 3 to 5 U/mL of heparin. Additionally, it can be reversed readily with a molecule called protamine, which is a cellular histone that is extracted from salmon sperm. Finally, its effects can be readily measured with activated

clotting times. Remember that the partial thromboplastin time (PTT) is only accurate to heparin levels up to about 1 U/mL. After that, it is not an especially accurate test.

Heparin is the mainstay agent that we use, for all of these reasons. It can be measured, monitored, titrated, and reversed. We have an enormous amount of experience with this agent. It inhibits thrombin—through the cofactor antithrombin—as well as multiple other factors, including factor Xa. Unfractionated heparin is thus a mainstay for CPB and cardiac surgery.

H&O Are any other agents used?

JL Yes, other agents are used for patients who either are allergic to heparin or have heparin-induced thrombocytopenia (HIT). Patients with HIT are in a prothrombotic state and may have multiple other issues that can complicate matters. In such cases, the alternate anticoagulant that has been most extensively studied is bivalirudin (Angiomax, The Medicines Company). Bivalirudin is a synthetic direct thrombin inhibitor, and it is a shorter-acting agent than any of the other direct thrombin inhibitors. Two large studies—EVOLUTION ON (A Comparison of Bivalirudin to Heparin With Protamine Reversal in Patients Undergoing Cardiac Surgery With Cardiopulmonary Bypass) and EVOLUTION OFF (Anticoagulation With Bivalirudin for Off-Pump Coronary Artery Bypass Grafting)—have looked at this agent in on- and off-pump cardiac surgery and CPB.

There are some important concerns when we use bivalirudin. But the bottom line is that this is the most extensively studied alternative to heparin, so this is what we use when heparin is not an option. If the surgery is elective, however, an even better approach in an HIT-positive patient would be to wait for the person's antibodies to clear, or to confirm that the serotonin release assay is negative. Heparin still is the best anticoagulant for most patients; only about 1% to 2% of cardiac surgery patients are HIT-positive.

H&O How is the adequacy of anticoagulation determined?

JL The standard measurement is the activated clotting time (ACT). This test was developed in the 1970s because of the higher concentration of heparin that was used, and the inadequacy of the PTT. The typical goal is to have an ACT of approximately 400 to 480 seconds.

Finding the ideal ACT is a bit of a complex story because this has been part of our clinical practice guidelines for many years. We have performed 2 big surveys—one that was published in *Anesthesiology* in 1999 and one that was published in the *Journal of Thoracic and Cardiovascular Surgery* in 2010—where we looked at what is used in clinical practice.

Although ACT is the gold standard, we have additional assays that can be used to monitor the level of heparin concentrations during cardiac surgery. In one test, incremental doses of protamine are used to determine the circulating heparin levels. Somewhere between one-quarter to one-third of institutions use a protamine test in addition to using ACT during CPB.

H&O Is altered heparin response always detectable before surgery?

JL In altered heparin response, the patient's responsiveness to heparin—the slope of the anticoagulation curve—is attenuated. Some refer to this as heparin resistance, but that is not accurate because the patient is not actually resistant.

Multiple factors can cause altered heparin response. The problem is that it can be tricky to detect before surgery. There are tests that can help determine whether a patient has altered heparin response, but the tests use small concentrations of heparin. This does not reflect what happens in clinical practice, which involves much higher doses. The standard dose of heparin for CPB at most institutions is 300 to 400 U/kg. An additional 5000 to 10,000 U of heparin are used in the pump prime. These amounts far exceed those that tend to be used in the *in vitro* tests. As a result, the tests are not always accurate.

H&O What factors can affect activated clotting time values?

JL The ACT is an interesting test. Basically, it is a whole-blood coagulation assay that looks at the intrinsic hemostatic activation system, which is affected by many of the same things that affect the PTT. The PTT test involves taking a sample of plasma, isolating it, and using ellagic acid as an activator. A whole-blood ACT test involves putting blood in a cartridge and using the platelet as a phospholipid surface. The platelets serve as a phospholipid surface for the ACT. If a patient has dysfunctional platelets or is on a platelet inhibitor such as a IIa/IIIb inhibitor, this may greatly increase the ACT.

The point is that dilutional changes, low fibrinogen levels, and other factors may affect the ACT. Despite this, ACT is still the test of choice to monitor anticoagulation during CPB.

H&O Is there a role for antithrombins to improve responsiveness to heparin?

JL I think there is, and I have published several studies looking at the role of antithrombin and acquired altered heparin dose responsiveness. Antithrombin is the cofactor that is needed in order for heparin to work. A lot of interesting studies exist that

show that heparin can deplete a patient's antithrombin level by approximately 30% in as little as 12 hours.

The other factor that is important is that a patient's antithrombin level is diluted by about 50% from baseline to the end of CPB. The patient may be starting low because of heparin exposure, and then going lower. We have looked at both purified antithrombin from human donors and recombinant thrombin as they relate to cardiac surgery, CPB, and alterations in heparin dose responsiveness.

One of the consistent findings is that we can restore heparin responsiveness with antithrombin. We have found this to be true with both purified human antithrombin and recombinant thrombin.

There has been a little bit of confusion over how to define heparin resistance—or alterations to heparin dose responsiveness—but the standard definition is an ACT of less than 480 seconds after 500 U/kg of heparin.

As discussed, antithrombin is depleted with heparin, and it has been measured at as low as 20% to 30% during CPB. Why is this important? If you or I have an antithrombin level of 50%, we are heterozygous for antithrombin deficiency and we are prothrombotic. The point is that nature designed an interesting hemostatic system based on circulating levels of different serine protease inhibitors and activators. The bottom line is that a normal antithrombin level is between 80% and approximately 120%.

With that in mind, we have shown that if you normalize antithrombin at the end of CPB, as George Despotis and I did in a study that was published in *Anesthesiology* in 2002, you can prevent hemostatic activation.

On the other hand, finding connections between molecular endpoints and clinical endpoints is difficult, especially given all the complexities of cardiac surgery.

I believe that there is a role for antithrombin in improving heparin responsiveness, and I have spent lots of years working on this and trying to develop ways to find the clinical parameters. On a molecular level and as measured by ACT responsiveness, you can clearly demonstrate the critical role that antithrombin plays in this particular perspective. There are also studies reporting that low antithrombin levels after surgery and in the ICU are associated with adverse outcomes. But we continue to work on finding the clinical relevance and outcomes associated with antithrombin repletion.

H&O What can physicians do to better manage the coagulation effects of CPB?

JL It is important to remember the important link between coagulation and inflammation. In my opinion, modulating thrombin generation during CPB is akin to modulating the proinflammatory effects of CPB, including all the cellular

and humoral amplification that occurs. We have worked on multiple serine protease inhibitors that inhibit elements of contact activation, and a multitude of other agents.

It is important to take a multimodal approach, and better modulate thrombin, inhibit plasmin and fibrinolysis, and modulate contact activation. One of the interesting things about CPB is that we have the opportunity to prophylactically treat the patient; we can administer the medications before all these pathologic stimuli come into play. This is all part of the ongoing work of looking at novel molecules that inhibit activation of hemostatic coagulation, inflammation, and fibrinolysis.

Suggested Readings

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