Searching for an Alternate Anticoagulant for Cardiopulmonary Bypass: Does Two Plus Two Equal Two?

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GLOSSARY

ACT = activated clotting time; **AT** = antithrombin; **CPB** = cardiopulmonary bypass; **DTI** = direct thrombin inhibitor; **HIT** = heparin induced thrombocytopenia; **INR** = international normalized ratio; **UFH** = unfractionated heparin; **Va** = activated Factor V; **X** = Factor X; **Xa** = activated Factor X

Unfractionated heparin (hereinafter heparin) has been the mainstay anticoagulant used during cardiopulmonary bypass (CPB) for >6 decades. Its dominance persists despite the limitations of requiring a cofactor (antithrombin), having a variable response in any given individual (hence the need for frequent monitoring) and potentially causing a life- and limb-threatening disease (heparin-induced thrombocytopenia [HIT]). It is notable that the anticoagulant used for the first successful use of extracorporeal circulation—a kidney by Lobel in 1849[1]—had absolutely none of these drawbacks. Of course, ancrod, which Lobel used to defibrinate the blood, also lacked an antidote. The availability of protamine to reverse heparin-induced anticoagulation is undoubtedly the primary reason for heparin's success with CPB and highlights the reason ancrod is only of historical interest to most cardiac anesthesiologists. Having antidotes for anticoagulants for CPB is also the rationale for the work on dabigatran presented by Nadtochiy et al[2] in this issue of the journal.

This is actually the second study conducted by Nadtochiy et al[3] using a dabigatran-based solution for anticoagulation of a simulated CPB circuit. The primary rationale for choosing dabigatran, a direct thrombin inhibitor (DTI) typically given orally, was the availability of a reversal agent—idarucizimab. In their previous work, the same group used dabigatran in concentrations up to 10,000 ng/mL to anticoagulate human blood for a simulated 2-hour CPB run. Fibrin deposition on the CPB filters was then evaluated using electron microscopy, much the same way Young et al[4] did back in 1978 when they assessed the adequacy of heparin-based anticoagulation. Notably, the amount of fibrin deposition during dabigatran anticoagulation was comparable to that of 3 u/mL of heparin anticoagulation, which is commonly utilized as the "floor" for an acceptable heparin level on CPB. Idarucizamab successfully reversed the parenteral dabigatran effects, at least in vitro.[3] Unfortunately, the plasma levels of dabigatran utilized on simulated CPB (5000–10,000 ng/mL) were more than an order of magnitude higher than those reversed by idarucizimab in its initial clinical trial (3–640 ng/mL).[5] Such high levels of dabigatran may not be reliably reversed in vivo and have been associated with hepatic toxicity.[6,7]

These limitations bring us to the current work in which Nadtochiy et al[2] repeated the simulated CPB runs adding a Factor Xa inhibitor, solubilized rivaroxaban, to the dabigatran solution. The plasma level of rivaroxaban chosen, 200 ng/mL, is consistent with peak levels in patients taking a daily 20-mg dose for thromboprophylaxis.[8] The rationale for combining agents was that inhibiting the coagulation cascade at >1 point would lead to the ability to reduce the dose of dabigatran. Perhaps not so coincidentally, this combination of drugs also inhibits the same major targets in the coagulation cascade as heparin and antithrombin (see Figure). By inhibiting coagulation at the Factor Xa level, the downstream thrombin generation can be further reduced. Nadtochiuy et al[2] demonstrated that the addition of the rivaroxaban acted synergistically with the dabigatran, cutting its required dose to about a quarter of that needed in the prior experiments. The

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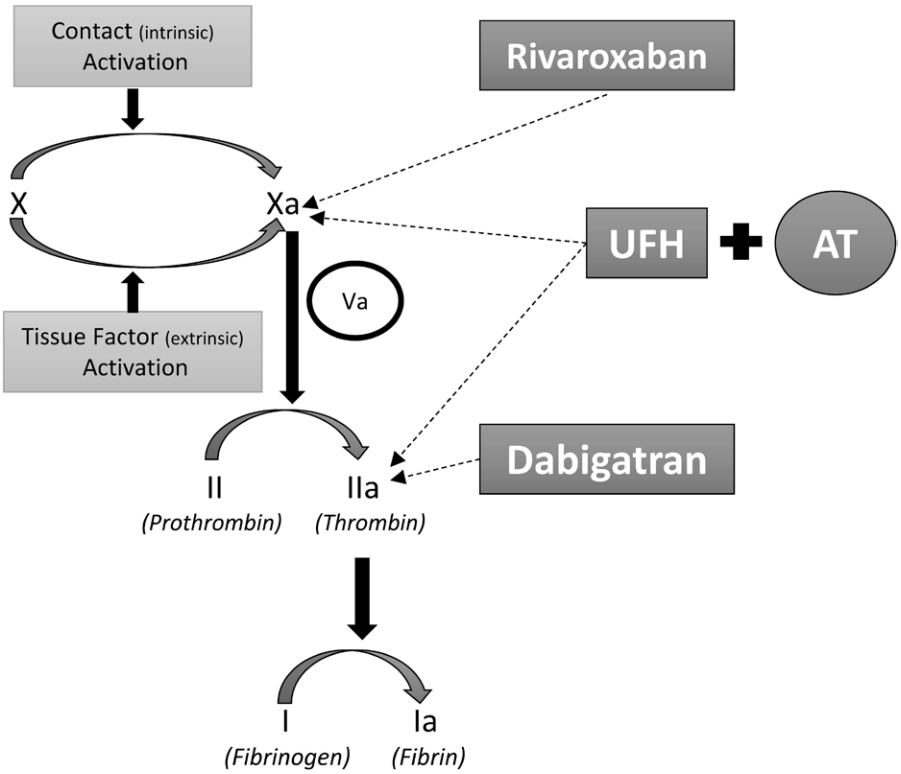

Figure. This diagram shows the common pathway for thrombin (factor IIa) formation from prothrombin (factor II) and inhibitory points for UFH and AT, dabigatran, and rivaroxaban. AT indicates antithrombin; UFH, unfractionated heparin; Va, activated Factor V; X, Factor X; Xa, activated Factor X.

amount of fibrin deposition on the arterial filters was once again consistent with that found using 3 u/mL of heparin. Although theoretically possible, reversal of the rivaroxaban with andexanet alpha was not tested in combination with idarucizumab to reverse the effects of the dabigatran.

So can 2 pairs of anticoagulant-antidote combinations do the job of a heparin-protamine duo? It is important to note that a parenteral DTI for CPB anticoagulation already exists. Bivalirudin has been successfully utilized for CPB anticoagulation for more than a decade and a half, albeit with some drawbacks.[9] It is well known that its relatively short 20- to 30-minute elimination half-life can increase by a factor of 5 or more in renally compromised patients, and it of course lacks an antidote.[10] Less appreciated is the fact that bivalirudin inhibits thrombin reversibly, making it less effective at preventing clot propagation and creating the need to avoid blood stasis in the chest or CPB reservoir.[11,12] What the current study from Nadtochiy et al[2] shows us, however, is that by blocking an additional step along the coagulation cascade, the efficacy of a DTI can be increased to that of heparin. This was demonstrated by the similarity between dabigatran plus rivaroxaban anticoagulation and heparin anticoagulation in F1.2 fragment formation over the 2-hour CPB run (found in supplemental Figure 2 of their article). Since F1.2 levels reflect the amount of prothrombin being converted to thrombin, it is a sensitive marker for anticoagulation effectiveness.

Synergism between anticoagulants on CPB was first appreciated when patients on coumadin presented for urgent cardiac surgery. Several decades ago, Dietrich et al[13] noted that patients on phenprocoumon (a coumadin analog) with a prothrombin activity of 47% (equivalent to INR of ~1.5) required only about 2/3 as much heparin for CPB anticoagulation compared to controls. More recently, the combinations of aptamers, which are single-stranded nucleic acids with a high affinity for specific binding sites on molecules, with other anticoagulants have demonstrated synergistic effects strong enough to suppress thrombin formation on CPB.[14] Unfortunately, Nadtochiy et al's current study also shows us the problem when mixing different anticoagulants: the lack of an adequate coagulation test for monitoring multiple agents.

Clotting times, also referred to as "1-stage assays," rely on starting the coagulation cascade at a certain point and measuring the time it takes for fibrin formation. The usefulness of a clotting time for drug monitoring depends on where along the cascade the reaction is started as well as the concentration of reagent used to push the reaction forward. A typical activated clotting time (ACT) uses kaolin, glass, or similar agents to mimic contact activation. The ROTEM EXTEM uses tissue factor to begin the process with the extrinsic pathway, while the rapidTEG uses both kaolin and tissue factor to stimulate both intrinsic and extrinsic pathways simultaneously (see Figure). Unfortunately, even with this "double stimulation"

test, the rapidTEG clotting time, or R-time, averaged 40 to 50 minutes to produce a result.[2] This would significantly limit its value as a point-of-care test. Even if the test could be accelerated, it is sometimes difficult to predict the effects of a particular drug on the assay. Dabigatran, like coumadin, generally has a synergistic effect with heparin on the ACT, but Factor Xa inhibitors can have a "blunting" effect, causing the ACT to increase more gradually for any given heparin amount.[15] Using 2 anticoagulants would necessitate understanding how each agent affected the test result so they could be effectively titrated. Clearly, this is an area in need of further research.

If heparin is to be replaced for CPB anticoagulation, it will definitely require some out-of-the-box thinking. While there are clearly multiple hurdles to a dabigatran and rivaroxaban regimen, we applaud Nadtochiy et al for demonstrating some creativity. Unlike ancrod, at least the required reversal agents are already in existence.

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