Rivaroxaban Reduces the Dabigatran Dose Required for Anticoagulation During Simulated Cardiopulmonary Bypass

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BACKGROUND: Heparin is the standard anticoagulant for cardiopulmonary bypass (CPB); however, there are problems with its use that make the development of suitable alternatives desirable. Currently, no ideal alternative exists. We have previously reported that the direct thrombin inhibitor dabigatran can prevent coagulation in simulated CPB at high concentrations. These high concentrations may cause difficulties in achieving the reversal of dabigatran with idarucizumab, given the markedly different pharmacokinetics of the 2 drugs. Herein, we test the hypothesis that the addition of the anti-Xa drug rivaroxaban would provide suitable anticoagulation at a lower concentration of dabigatran given likely synergy between the 2 classes of drugs. The primary goal of the study was to investigate whether the addition of rivaroxaban reduces the concentration of dabigatran necessary to allow 2 hours of simulated CPB.

METHODS: The study was performed in sequential steps. Blood collected from consenting healthy donors was used throughout. First, we added graded concentrations of dabigatran and rivaroxaban alone and in combination and assessed inhibition of anticoagulation using thromboelastometry. Using results from this step, combinations of dabigatran and rivaroxaban were tested in both Chandler loop and simulated CPB circuits. Dabigatran and rivaroxaban were added before recalcification, and the circuits were run for 120 minutes. In both models of CPB, 120 minutes of circulation without visible thrombus was considered successful. In the Chandler loop system, idarucizumab was added to reverse anticoagulant effects. In the CPB circuits, the arterial line filters were examined using scanning electron microscope (SEM) to qualitatively assess for fibrin deposition.

RESULTS: In vitro analysis of blood samples treated with dabigatran and rivaroxaban showed that dabigatran and rivaroxaban individually prolonged clotting time (CT) in a dose-dependent manner. However, when combined, the drugs behaved synergistically. In the Chandler loop system, dabigatran 2400 and 4800 ng/mL plus rivaroxaban (150 ng/mL) effectively prevented clot formation and reduced the dynamics of clot propagation for 120 minutes. Idarucizumab (250–1000 µg/mL) effectively reversed anticoagulation. In the CPB circuits, dabigatran (2500 ng/mL) and rivaroxaban (200 ng/mL) were successful in allowing 120 minutes of simulated CPB and prevented fibrin deposition. Biomarkers of coagulation activation did not increase during simulated CPB. Heparin controls performed similarly to dabigatran and rivaroxaban.

CONCLUSIONS: The dual administration of oral anticoagulant drugs (dabigatran and Rivaroxaban) with different pharmacologic mechanisms of action produced synergistic inhibition of coagulation in vitro and successfully prevented clotting during simulated CPB. (Anesth Analg 2022;135:52–9)

KEY POINTS

- **Question:** Do lower concentrations of dabigatran administered with rivaroxaban prevent clotting during simulated cardiopulmonary bypass (CPB)?
- **Findings:** Dabigatran and rivaroxaban in combination produced synergistic inhibition of coagulation in vitro and effectively prevented clot formation during simulated CPB.
- **Meaning:** The combination of dabigatran and rivaroxaban, which inhibit successive steps in the coagulation cascade, may be considered as a potential anticoagulant strategy in a CPB setting.

GLOSSARY

ACT = activated clotting time; **DMSO** = dimethyl sulfoxide; **ELISA** = enzyme-linked immunosorbent assay; **FDA** = Food and Drug Administration; **HIT** = heparin-induced thrombocytopenia; **Ida** = idarucizumab; **IgG** = immunoglobulin G; **LC-MS/MS** = liquid chromatography/mass spectrometry; **MA** = maximum strength of clot; **ND** = not detected; **PF4** = platelet factor 4; **PVC** = polyvinyl chloride; **R** = reaction time; **RapidTEG** = kaolin/tissue-factor-activated thromboelastography; **Riv** = rivaroxaban; **ROTEM** = rotational thromboelastometry; **RSRB** = Research Subjects Review Board; **SD** = standard deviation; **SEM** = scanning electron microscope; **TAT** = thrombin-antithrombin complex; **TEG** = thromboelastography

Since the initial development of cardiopulmonary bypass (CPB), heparin has been the standard anticoagulant. Heparin inhibits multiple steps of the coagulation cascade, which is bene cial due to the suppression of thrombin generation and consumption of coagulation factors. However, heparin is a less than ideal agent for anticoagulation for CPB for multiple reasons. It requires the intrinsic cofactor antithrombin to achieve anticoagulation, which, in some individuals, is not present in adequate quantity. As a family of large molecules derived from another species, it has signi cant immunogenicity that causes heparin-induced thrombocytopenia (HIT) with disturbing regularity.[1] Currently, no ideal alternative exists for heparin in this setting. The direct thrombin inhibitor bivalirudin is the most studied heparin alternative; however, it inhibits only 1 step in the coagulation cascade[2,3] and has been associated with both thrombotic and bleeding complications.[4] The development of more suitable heparin substitutes would improve the conduct of CPB, particularly in patients for whom heparin is contraindicated.

Dabigatran (Dab) is a direct-acting thrombin inhibitor currently US Food and Drug Administration (FDA)–approved as an oral formulation for thromboprophylaxis in atrial brillation and for patients with deep vein thrombosis. Dab is an attractive heparin alternative given the existence of idarucizumab, an effective and speci c reversal agent. We have previously shown that Dab can be formulated in a solution suitable for parenteral use and, at high concentrations (≥7500 ng / ml), is an effective and reversible anticoagulant in simulated CPB with human blood.[5] However, at such high concentrations, the reversal of Dab may be problematic in vivo, given the markedly different volumes of distribution of the 2 drugs.[6]

It has been previously shown that direct thrombin inhibitors and anti-Xa agents are synergistic,[7] likely due to inhibition of sequential steps in the coagulation cascade. These synergistic effects between anti-Xa agents and direct thrombin inhibitors may be useful as an anticoagulant paradigm for CPB, providing acceptable anticoagulation at lower (clinically applicable) concentrations of individual drugs, thereby decreasing potential adverse effects. Rivaroxaban

platform to measure the anticoagulant effect of high Dab doses used in the Chandler loop and simulated CPB models.

Chandler Loop

The addition of Riv (150 ng / mL) to Dab (2400 ng / mL) prevented clot formation in 5 out of 6 volunteers (Table 3), while Dab alone (at 2400 ng / mL) did not prevent clot formation for 120 minutes. The combination of Dab and Riv signi cantly reduced the clot strength (MA) and the dynamics of clot propagation (Angle; Table 2 and Figure 2A). Interestingly, the anticoagulant effects of the drugs gradually declined toward the end of 120 minutes, despite the fact that the drug concentrations remained stable throughout the whole run (Table 2).

Idarucizumab added after 120 minutes in up to four 250-µg / mL stepwise (250 µg / mL every 5 minutes) reversed anticoagulation, initiating clot formation in the loops (the earliest at 4 minutes, the latest at 20 minutes; Figure 2B). Importantly, Riv reversal was not required to block anticoagulation.

CPB Simulation

To achieve full anticoagulant ef cacy (in 6 out of 6 volunteers) for the CPB settings, Dab and Riv concentrations were increased up to 2500 and 200 ng / mL accordingly. Although Dab alone at this concentration showed extensive brin deposition (Figure 3A), in combination with Riv, all simulated CPB runs were completed with no evidence of gross thrombus for 120 minutes. No brin deposition on the lters was seen on the electron micrographs (Figure 3B). The values of R, measured by TEG, were signi cantly elevated after the addition of the drugs, while Angle and MA were depressed, indicating reduced clot propagation and strength (Supplemental Digital Content, Table S1, http://links.lww.com/AA/D924). Blood gases and electrolytes were stable during 120 minutes of the CPB experiment (Supplemental Digital Content, Table S1, http://links.lww.com/AA/D924). Concentrations of plasma F1 + 2, brinogen, and thrombin / antithrombin during CPB (at 1, 30, 60, and 120 minutes) were not different compared to baseline (no drugs; Supplemental Digital Content, Figure S2, http://links.lww.com/AA/D924). Fibrinogen degradation products were undetectable.

Heparin (3 U / mL), used as a positive control, prevented clot formation and brin deposition in all 6 volunteers (Figure 3C). Plasma levels of F1 + 2 and brinogen were not different from baseline (Supplemental Digital Content, Figure S2, http://links.lww.com/AA/D924), exhibiting similar trends observed in the Dab / Riv-treated groups. However, in the Heparin-treated group, the levels of thrombin / antithrombin signi cantly declined at 1, 30, 60, and 120 minutes versus baseline.

DISCUSSION

This study demonstrates that Riv and Dab have supraadditive (synergistic) effects on coagulation as measured by thromboelastometry and that this synergy may be used to reduce the concentration of Dab

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