

Multichamber intracardiac thrombosis during novel oral anticoagulation reversal with activated prothrombin complex concentrate infusion



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Introduction

While an agent-specific antidote for dabigatran, idarucizumab (Praxbind, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT), is approved for anticoagulation reversal,¹ it is still not universally available, especially in rural hospitals. Therefore, anticoagulation reversal still represents an Achilles' heel for novel oral anticoagulants (NOAC) in some clinical settings. Both vitamin K-dependent clotting factors such as prothrombin complex concentrate (PCC) and activated prothrombin complex concentrate (aPCC; FEIBA, Baxter Healthcare Corporation, Westlake Village, CA) have been studied in this role. However, these studies have mainly been limited to ex vivo or animal studies,² with only a few case reports^{3,4} and 1 small human in vivo study.⁵ Although widely available, aPCC is not FDA-approved to reverse NOAC anticoagulation, and serious adverse effects arising from its use in this scenario have not been previously described. We present a case of multichamber intracardiac thrombosis during aPCC administration for dabigatran reversal.

Case report

A 60-year-old woman with a history of nonischemic cardiomyopathy and persistent atrial fibrillation on dabigatran presented with 4 days of nausea, vomiting, and abdominal pain. The patient was tachycardic into the low 120s with a rhythm of atrial fibrillation with rapid ventricular rate. The blood pressure was low with a systolic blood pressure of 92 mm Hg. She was warm and perfused, but visibly in moderate distress, and her examination was concerning for abdominal

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KEY TEACHING POINTS

- The use of activated prothrombin complex concentrate (aPCC) to reverse novel oral anticoagulant (NOAC) anticoagulation, an unlabeled indication, should be discouraged owing to lack of safety data, and only an agent-specific reversal agent with FDA approval should be used to reverse dabigatran whenever possible.
- This case further supports growing evidence in the literature that suggests abrupt cessation of a NOAC engenders a possible hypercoagulable state.
- Reversal of NOAC anticoagulation in the setting of cardiogenic shock should be done with caution; it may be advisable to start with a conservative dosing approach, such as starting with half the normal dose of a reversal agent and slowly titrating up, with close monitoring.

distention that was exquisitely tender to palpation. A computed tomography study of the abdomen demonstrated a large segment of incarcerated bowel within a ventral hernia. The lactic acid level was 8.1 mmol/L, and arrangements were made for emergent exploratory laparotomy. An arterial blood gas drawn prior to entering the operating suite demonstrated a pH of 7.29, a serum bicarbonate of 15 mmol/L, and a partial pressure of CO₂ of 28 mm Hg. The basic metabolic profile was notable for a serum creatinine of 1.22 mg/dL. A bicarbonate and norepinephrine infusion at 4 µg/min was begun to stabilize the patient perioperatively. Bedside transthoracic echocardiogram (Figure 1, Supplemental Video 1) at that time demonstrated severe global hypokinesis with no intracardiac thrombus. As the patient's last dose of dabigatran had been administered approximately 8 hours prior to

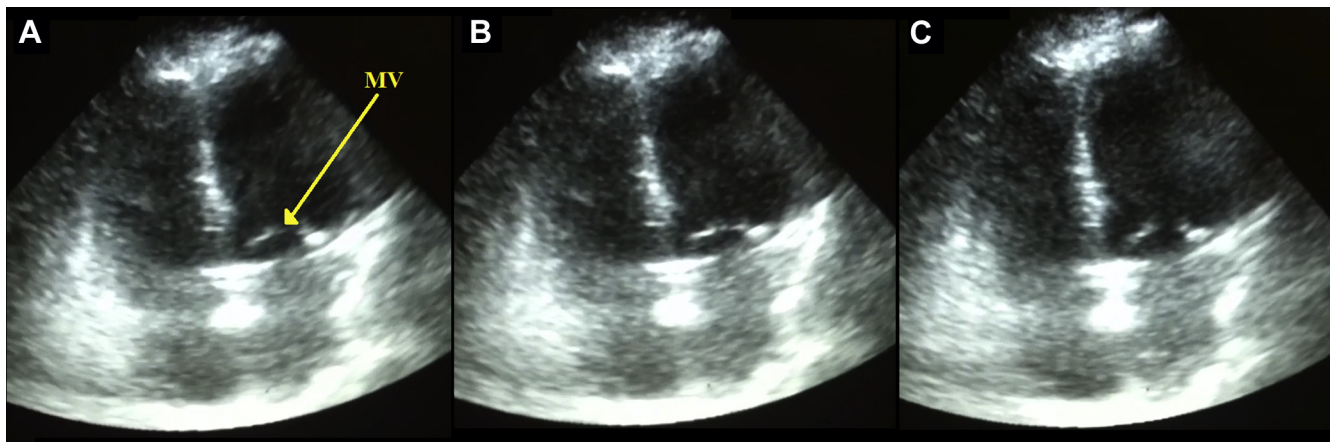


Figure 1 Transthoracic echocardiogram performed on presentation. **A–C:** Video stills from bedside transthoracic echocardiogram in apical 4-chamber view on presentation demonstrating no obvious clot. The mitral valve (MV) is labeled in panel A.

presentation, an infusion of aPCC (100 units/kg) was administered. Within minutes of the start of the infusion, the patient suffered cardiac arrest with an initial rhythm of pulseless electrical activity. Following successful resuscitation, transesophageal echocardiogram ([Figure 2](#), [Supplemental](#)

[Video 2](#)) demonstrated interval development of large, friable-appearing thrombi in multiple cardiac chambers. The patient was admitted to the intensive care unit, where she again experienced cardiac arrest and expired shortly thereafter despite resuscitative efforts.

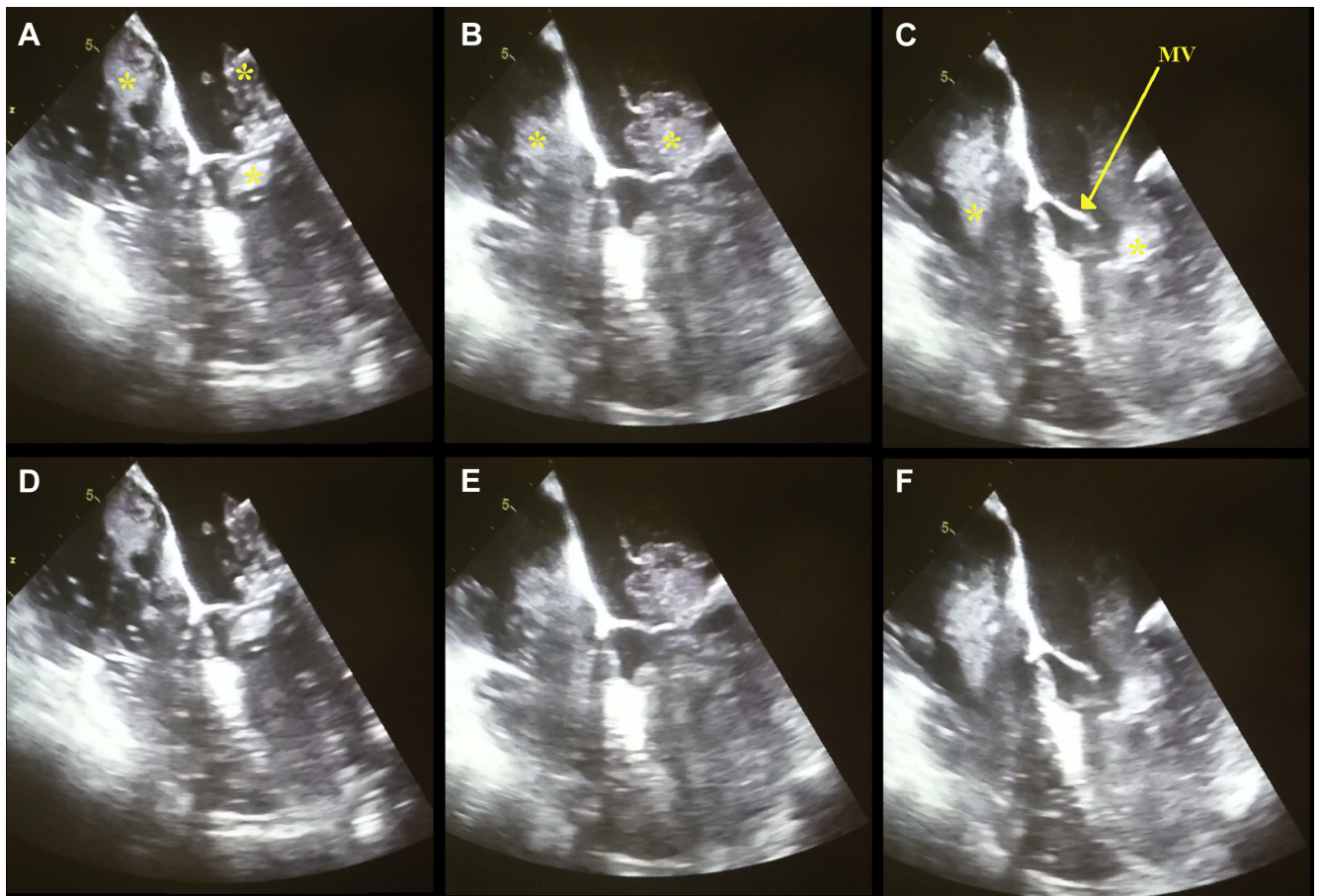


Figure 2 Transesophageal echocardiogram performed post cardiac arrest after activated prothrombin complex administration. **A–C:** Video stills from transesophageal echocardiogram performed in operating room after activated prothrombin complex administration demonstrating copious intracardiac clots (*) in all 4 chambers of heart post cardiac arrest. The mitral valve (MV) is labeled in panel C. **D–F:** Identical video stills corresponding to panels A–C, respectively, without markup.

Table 1 Reversal agents

Agent	Mechanism	Dosing	Half-life elimination
Activated prothrombin complex concentrate (aPCC; FEIBA, Baxter Healthcare Corporation, Westlake Village, CA)	Decreases activated partial thromboplastin time of plasma containing factor VIII inhibitor	50–100 units/kg/dose. Varying dosage and duration depending on bleeding site and extent.	4–7 hours
Prothrombin complex concentrate (PCC; Kcentra, CSL Behring GmbH, Marburg, Germany)	Increases levels of vitamin K–dependent coagulation factors (II, VII, IX, and X) as well as protein C and protein S	0.12 mL/kg/min (~3 units/kg/min); maximum rate of 8.4 mL/min (~210 units/min)	Factor II: 59.7 hours Factor VII: 4.2 hours Factor IX: 16.7 hours Factor X: 30.7 hours Protein C: 47.2 hours Protein S: 49.1 hours
Coagulation factor VIIa (NovoSevenRT, Novo Nordisk A/S, Bagsvaerd, Denmark)	Complexes with tissue factor, activates factor X to Xa and factor IX to IXa, leading to conversion of prothrombin to thrombin	15–30 µg/kg every 4–6 hours for congenital factor VII deficiency Otherwise, 70–90 µg/kg, repeat dosing every 2–6 hours depending on type of hemophilia	2.8–3.1 hours
Idarucizumab (Praxbind, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT)	Humanized monoclonal antibody fragment that binds to dabigatran and metabolites	5 g IV (2 doses of 2.5 g IV, <15 minutes apart)	47 minutes (initial); 10.3 hours (terminal)
Andexanet alfa (Andexxa, Portola Pharmaceuticals, Inc., South San Francisco, CA)	Binding of factor Xa inhibitors and inhibition of tissue factor pathway inhibitor to increase thrombin generation	400 or 800 mg IV bolus at ~30 mg/min, then within 2 minutes an IV infusion of 4 or 8 mg/min for up to 120 minutes, respectively	3–4 hours

IV = intravenous.

Discussion

Well-studied and effective reversal agents for NOACs such as idarucizumab and andexanet alfa, a recently FDA-approved reversal agent for apixaban and rivaroxaban are not widely available at every hospital in the United States.⁶ As a result, other nonspecific reversal agents, including recombinant activated factor VIIa, PCC, and aPCC, have been used to reverse NOACs.² These agents, however, were not developed specifically to reverse the anticoagulant effects of NOACs (Table 1). Furthermore, studies for these agents have primarily been limited to in vivo mouse/rat models, primate models, or human ex vivo blood sample studies. Out of the 3 nonspecific reversal agents, PCC is the only agent that has been studied in a randomized, placebo-controlled, in vivo trial. In that trial, 12 healthy male patients receiving dabigatran for 2.5 days were given either normal saline or PCC.⁵ PCC did not appreciably reverse the anticoagulant effects induced by dabigatran, and no thrombotic events were noted.

aPCC is similar to PCC except its factors have already been activated in vitro.⁴ Ex vivo plasma and animal studies demonstrated that aPCC enhanced thrombin generation and reduced bleeding time in mice.² Kiraly and colleagues⁴ reported a case of a patient on dabigatran who developed subarachnoid hemorrhage and required emergent anticoagulation reversal, which was successfully reversed with aPCC at a dose of 100 units/kg.⁴ This was the same dose given to our patient, and there was no adverse drug effect or thrombosis reported in that case report. Another case report of a

patient who developed cardiac tamponade secondary to intracardiac perforation during an elective atrial fibrillation ablation reported that aPCC at a dose of 26 units/kg infused over 15 minutes was successful in achieving hemostasis with no thrombotic events.³

Currently, there are no reports in the literature of adverse thrombotic events occurring after the use of PCC to reverse anticoagulation induced by NOAC. However, available evidence shows that acute discontinuation of NOACs may engender a hypercoagulable state. Over the past several years, multiple case reports have described clinically significant acute thrombosis following abrupt cessation of NOACs. Adams and colleagues⁷ report a case of superior mesenteric artery thrombosis after holding rivaroxaban in anticipation of an elective atrial flutter ablation procedure in a 59-year-old man.⁷ Another case report details the occurrence of a large, ischemic middle cerebral artery stroke 5 days after an 80-year-old man haphazardly discontinued his rivaroxaban.⁸ Finally, Weiler and colleagues⁹ describe a case of left ventricular thrombus seen in an 84-year-old man after he had stopped his dabigatran for 2 days.⁹ There is also in vitro evidence suggesting that a rebound prothrombotic effect occurs after stopping rivaroxaban.¹⁰

Data from large, randomized clinical trials have also suggested an increased prothrombotic effect following NOAC cessation. There was a greater incidence of thrombosis following rivaroxaban cessation in the ROCKET-AF trial, although this was later thought to be due to suboptimal management of anticoagulation after the rivaroxaban arm was

transitioned onto warfarin.^{11,12} However, similar events were also noted during the end of the ARISTOTLE trial when patients on apixaban were switched to warfarin.¹³ Furthermore, in RE-VERSE AD, a phase 3 trial where idarucizumab was used to reverse the anticoagulation of dabigatran in 91 patients who urgently required reversal, 5 patients experienced thrombotic events in the form of 3 deep vein thrombi, 2 pulmonary emboli, 1 ischemic stroke, and 1 myocardial infarction.¹ Additionally, abrupt reversal of NOAC using andexanet alfa, a recombinant modified human factor Xa decoy protein, resulted in significant thrombotic events in almost 10% of study patients (34/352) within 30 days of andexanet alfa administration. These events included 7 myocardial infarctions, 14 ischemic strokes, 1 transient ischemic attack, 13 deep vein thromboses, and 5 pulmonary embolisms; one-third of these events occurred within 5 days of andexanet alfa administration.^{14,15}

In our patient, we suspect the aforementioned hypercoagulable state and blood flow stasis owing to cardiogenic shock, which embody 2 of the 3 tenets of Virchow's triad, resulted in the formation of extensive intracardiac thrombi. In fact, there were prominent similarities between our patient and the case reported by Weiler and colleagues.⁹ Both cases involved patients presenting with evidence of small bowel obstruction or ischemia, a depressed ejection fraction on echocardiogram, and finally, evidence of clinically significant intracardiac thrombosis after abrupt cessation of anticoagulation, which in our case was perpetrated by aPCC administration. Given the striking parallels in these 2 cases, we suspect abrupt reversal of NOAC anticoagulation in the setting of a low-flow state, which contributes to blood flow stasis, may increase the risk of clinically significant thrombosis.

Conclusions

We report a fatal thrombotic event associated with aPCC administration to reverse dabigatran in a patient with cardiogenic shock. In light of evidence that suggests a hypercoagulable state may be present after abrupt cessation of NOACs, it is prudent to avoid reversal unless in dire situations where bleeding is life-threatening, especially in low-flow states such as severe heart failure. It is also possible that an acidotic state further potentiates this effect. In the event dabigatran reversal is absolutely required, nonspecific reversal agents such as PCC or aPCC should be avoided, as they have not been studied in large clinical trials for NOAC reversal, and their risk for adverse thrombotic events, which is currently unknown, may be prohibitively high. Additionally, when reversal is required, dose reduction of the agent-specific

reversal antidote should be considered, or at the very least, the antidote should be given in divided doses over an interval wherein the patient can be carefully monitored for catastrophic thrombosis development. In some instances where the risk of bleeding postoperatively is low, bridging should be considered in these patients who have had NOAC anticoagulation acutely reversed.

Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrcr.2019.11.010>.

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