Elevated Factor VIII Levels Associated with Acute Graft Occlusion and Arterial and Venous Thrombosis After Off Pump CABG

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Abstract

Keywords

- coronary artery disease
- post-CABG thrombosis
- factor VIII
- acute arterial thrombosis

Factor VIII is a common acute phase reactant and elevated levels confer an increased risk of thrombosis. Such thrombotic events have been documented in the literature, though to a limited extent. We present the case of a 54-year-old man presenting with a non-Q-wave myocardial infarction who was found to have triple vessel disease and subsequently underwent a 4-vessel coronary artery bypass grafting (CABG). Postoperatively, he was found to have multiple occluded vessels, deep vein thromboses, and a cerebrovascular accident (CVA). A hypercoagulability work-up revealed significantly elevated levels of factor VIII at 377% normal, which likely contributed to these thrombotic events. Further exploration is warranted to elucidate causal mechanisms of these thrombotic events, particularly of multiple graft occlusions, and to guide clinical decision making with regards to anticoagulation and stent management.

The increased risk of atherothrombotic events in patients with elevated factor VIII levels has been sparsely documented in the literature. Overall, 11% of the general adult population has been found to have elevated factor VIII levels, underlining the importance of elucidating this relationship. A limited number of studies have established a causal relationship between elevated factor VIII levels and venous thrombosis, with an especially strong association in younger patients¹; even fewer studies have shown a relationship with arterial thrombosis. One such study found factor VIII to be elevated in 27% of patients with atherothrombotic cardiovascular disease in contrast to only 2% in control patients ($p = 0.001$).²

Case

A 54-year-old man presented with a non-Q-wave myocardial infarction was found on evaluation to have severe triple-vessel disease. He subsequently underwent an uneventful 4-vessel off pump CABG with an anastomosis from the left internal mammary artery (LIMA) to the left anterior descending (LAD), “Y” vein grafts to the diagonal and

obtuse marginal (OM), and a vein graft to the posterior descending artery (PDA). An activated clotting time of over 300 was achieved during surgery. The conduit and target vessels were of good size and quality. The patient received no blood products intra- or postoperatively, and the patient was not on drips postoperatively. He developed transient electrocardiogram changes postoperatively. Aspirin and clopidogrel were started within 12 hours of surgery. An echocardiogram performed the following morning showed a lateral wall motion abnormality. He underwent a repeat cardiac catheterization, which demonstrated that the LIMA to LAD graft was intact. There was a proximal clot in the diagonal and OM grafts with flow through the Y graft and distal anastomoses. The PDA graft and distal RCA were thrombosed and there was 95% stenosis of the OM vessel with clot. This was successfully angioplastied and stented. P2Y12 levels were checked to evaluate clopidogrel efficacy with the VerifyNow system (Accumetrics, San Diego, CA) and the patient was found to be a nonresponder. He was then treated with ticagrelor. The patient was also found to be thrombocytopenic; he was thus treated with argatroban

until heparin-induced thrombocytopenia was ruled out. Partial prothrombin time was maintained between 40 and 60 seconds. He developed noncardiogenic acute respiratory distress syndrome (ARDS), bilateral deep vein thromboses, and an occipital cerebrovascular accident (CVA) despite treatment with aspirin, ticagrelor, and argatroban. A hypercoagulability work-up was significant for a factor VIII level of 377% of normal (75–125% reference value). Full-strength enoxaparin was then used to transition to warfarin. The patient was discharged home without further sequelae. Follow-up revealed that the patient's factor VIII levels returned to normal 9 months' postoperatively.

Discussion

Clinicians should follow an orderly algorithm when faced with thrombotic events after coronary artery bypass grafting (CABG). The most common causes of acute bypass graft occlusion after CABG include technical issues of the anastomosis, vessel size and quality, graft kinking, competitive flow, and damage to the intima of the conduit.³ Once these factors have been explored further attention must be given to the evaluation of less common causes of occlusion after CABG, such as hypercoagulability.⁴ Although technical issues can never be definitively ruled out our patient's postoperative thromboembolism complications such as deep vein thrombosis and CVA in addition to the graft closures are more indicative of a systemic hypercoagulable state.

As with all interventions, the efficacy of these medications must be verified and adjusted for each patient as necessary. This patient experienced multiple thrombotic events, including multiple graft occlusions, despite modifications in his anticoagulation regimen. He was later found to have an elevated level of factor VIII, which significantly increased his risk of thrombosis. This transient increase in factor VIII is a possible etiology of postoperative hypercoagulable states.⁵ Although such thrombotic events due to elevated factor VIII are rare; however, it is not necessary for patients with off-pump coronary artery bypass (OPCAB), or the general population, to be tested for baseline factor VIII excess or to be anticoagulated without other clinical indications. Factor VIII excess is simply a possible explanation of postoperative hypercoagulability that is commonly seen.

Some patients with elevated factor VIII levels have been found to be heparin and argatroban resistant.⁶ Recent literature has shown that elevated factor VIII levels decrease the activated partial thromboplastin time levels without directly disturbing heparin activity, resulting in an apparent heparin-resistant state rather than a true resistance.⁷ Given the increased risk of thrombosis in patients with elevated factor VIII levels and the need for antithrombotic management, it is worthwhile to explore this relationship further.

It is interesting to note that all vein grafts were occluded in this patient, while the LIMA–LAD was spared. This may be because of the known differences in histology between the internal mammary artery and the vein grafts. The internal elastic lamina is nonfenestrated and well developed in the internal mammary artery, which shields it from laminal

stress. While this is known to prevent intimal hyperplasia, ultimately resulting in a greater than 90% patency rate in CABG, it may also protect against acute thrombosis.⁸ Vein grafts lack this beneficial histology and are thus associated with a fourfold and threefold increased risk of functional graft occlusion when compared with the right internal mammary artery and radial artery, respectively.⁹

Clinical manifestations such as myocardial infarction and stroke are of particular interest given the implications for management of acute coronary syndrome with oral anti-coagulants. Costa et al recently reported a case of a 36-year-old man with a history of ST-elevation myocardial infarction at the age of 26 years, who was found to have elevated levels of factor VIII.¹⁰ The case of a healthy 48-year-old woman who suffered cerebral venous thrombosis with no identifiable risk factors other than an elevated factor VIII level has also been reported.¹¹ Another study found that in patients who had suffered a stroke, those with elevated factor VIII levels were more likely to show evidence of a carotid or cerebral thrombus and presented with more disability when compared with those patients with normal levels of factor VIII.¹² Our case is unique among those in the literature, as the patient was significantly older than what has been documented thus far. We postulate that changes in the coagulation cascade after surgery precipitated these events.

Conclusion

The existing literature supports a correlation between elevated levels of factor VIII and various thrombotic episodes, including CVA, deep vein thrombosis (DVT), and myocardial infarction (MI). No studies have thus far proven a causative relationship, however. We presented a case of a previously healthy 54-year-old man who presented with an MI and after an extensive work-up and surgical intervention, developed a CVA, bilateral DVT, and a pulmonary embolus resulting in ARDS, while being anticoagulated. He also failed argatroban, highlighting the importance of determining clinical recommendations for anticoagulation in patients with elevated factor VIII levels.

The coagulation cascade is a complex system in which microscopic thrombosis and thrombolysis are constantly occurring. A disruption of this homeostasis causes a clinical hypo- or hypercoagulable state, leading to hemorrhage or thrombosis, respectively. Coronary artery bypass surgery involves abrupt changes in the coagulation system, upsetting this hemostasis. Heparin is given in large doses to achieve an activated clotting time greater than 250 seconds to prevent thrombosis and clot formation while anastomoses are being performed. Protamine is subsequently given after surgery to reverse these effects and to prevent hemorrhagic complications postoperatively. These significant changes in hemostatic homeostasis can be precarious for some patients.

As discussed, increased levels of factor VIII are associated with increased thrombotic events. Factor VIII is a glycoprotein pro-factor and cofactor of factor IXa; both work together as procoagulants. Factor VIII is also an acute phase protein and is known to increase in the acute setting, as exemplified by the postoperative

state. A hypercoagulability work-up in our patient was negative except for elevated factor VIII levels. It is possible that this was a result of a positive feedback loop, initiated in the prothrombotic state post-OPCAB, which led to numerous arterial and venous thrombotic events. Further research into the mechanism by which elevated levels of factor VIII increase thrombotic risk may elucidate pharmacological interventions to prevent such catastrophic thromboses in these patients.

Author Contributions

All authors contributed to this work. F. M. was involved in the acquisition of data, drafting, revision, and final approval. C. K. contributed supporting data, drafted, and revised the work. P. Y. revised and approved the work.

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