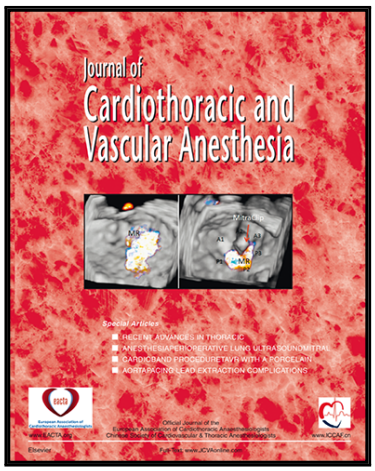

Perioperative Management of Mild Hemophilia B during and after Coronary Artery Bypass Grafting: challenges and solutions

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PII: S1053-0770(18)30392-6
DOI: 10.1053/j.jvca.2018.06.005
Reference: YJCAN 4753

To appear in: *Journal of Cardiothoracic and Vascular Anesthesia*

Received date: 4 June 2018

Please cite this article as: Rohesh J. Fernando MD , Blaine E. Farmer MD , John G. Augoustides MD, FASE, FAHA , Jeffrey C. Gardner MD , Sean D. Johnson MD , Bao Ha MD , Jan-Oliver Friess MD , Markus M. Luedi MD , Gabor Erdoes MD , Peter J. Miller MD , Caroline Ripat MD, MSPHc , Michael Fabbro II DO , Perioperative Management of Mild Hemophilia B during and after Coronary Artery Bypass Grafting: challenges and solutions, *Journal of Cardiothoracic and Vascular Anesthesia* (2018), doi: 10.1053/j.jvca.2018.06.005

Perioperative Management of Mild Hemophilia B during and after Coronary Artery Bypass Grafting: challenges and solutions

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Disclosure of funding: Institutional - no commercial or research funding to disclose.

Acknowledgments: None

Conflicts of interest: None

Key words: hemophilia B; coronary artery bypass grafting; bleeding; factor IX; prothrombin complex concentrate; recombinant factor VIIa; inhibitors; World Federation of Hemophilia

Introduction

Hemophilia B is a rare X-linked recessive condition with an incidence of 1 in 30,000 male births that results in factor IX deficiency.[1] Recent reports have demonstrated that cardiac surgery can be safely performed in hemophiliacs, although patients with known hemophilia generally receive prophylactic doses of factor replacement.[2-4] This case conference presents and discusses an unusual case of coronary artery bypass grafting (CABG) in a patient with unknown hemophilia B wherein no prophylaxis was administered due to the lack of a comprehensive diagnosis.

Case Presentation

A 68-year-old man with a history of hypertension and hyperlipidemia presented to the hospital with an acute coronary syndrome. He was medically managed and referred for left-heart catheterization that showed severe 3-vessel coronary artery disease. The patient was referred for elective CABG. The remaining history and physical exam were unremarkable. There was no history of a bleeding disorder. On the day of surgery, the complete blood count and coagulation tests were within normal limits, except for a partial thromboplastin time in the high normal range.

After placement of an arterial line, general endotracheal anesthesia was induced uneventfully. A pulmonary artery catheter and transesophageal echocardiography probe were subsequently placed without difficulty. The echocardiographic exam showed normal left ventricular function, mildly reduced right ventricular systolic function, and no significant valvular abnormalities. The baseline activated clotting time was 131 seconds.

After surgical incision, the surgeons noted more bleeding than usual, but this was attributed to recent clopidogrel therapy with residual intraoperative effects. After

dissection of both internal mammary arteries and harvesting of saphenous vein, systemic heparinization proceeded with a resultant activated clotting time greater than 1000 seconds. Cardiopulmonary bypass was initiated uneventfully. The patient underwent CABG with a pump time of 70 minutes. The separation from cardiopulmonary bypass was without difficulty. The echocardiographic examination revealed no new findings. Protamine reversal proceeded with prompt return of the activated clotting time to baseline.

When hemostasis was thought to be reasonable, the chest was closed with sternal wires. After chest closure, however, the rate of bleeding appeared to increase with an extrapolated rate of 600mL per hour. Given the high rate of bleeding, the chest was reopened, but no surgical source of bleeding was found. Shortly thereafter, the results of laboratory testing revealed a significantly elevated partial thromboplastin time, and thrombocytopenia. Despite additional protamine, and ongoing titrated transfusion of platelets, fresh frozen plasma and cryoprecipitate, there was limited resolution of the coagulopathy. While the resuscitation continued, the family was updated about the progress of the case – at this time, the family reported a history of factor IX deficiency. Factor IX levels were immediately drawn to confirm the diagnosis, and hematology was consulted for further evaluation and recommendations for management.

While awaiting both the factor IX level and recombinant factor IX therapy, an additional titrated transfusion of fresh frozen plasma was continued to treat the coagulopathy. By the time the recombinant factor IX was ready, the bleeding had slowed down and the factor IX level was still pending. The team decision was then reached to continue resuscitation in the intensive care unit, given that there were no sources of

bleeding that required surgical intervention. Shortly after admission to the intensive care unit, the intraoperative factor IX level was reported at 24% of normal. Since the mediastinal bleeding had begun to worsen, recombinant factor IX was then administered as recommended by the hematology team. The hematology consultation was continued to guide the daily infusions of factor IX during the postoperative course (refer to Figure 1). The mediastinal coagulopathy resolved and surgical exploration was not required.

After tracheal extubation, the patient was questioned about prior bleeding episodes. He denied any previous problems with bleeding. Although he was aware of a family history of hemophilia, he had previously undergone dental extractions and nasal septoplastly without bleeding complications. He was eventually discharged home on a course of intravenous recombinant factor IX. A follow-up factor IX level after completion of therapy was 15%, consistent with mild hemophilia B (refer to Figure 1).

Case Discussion

Hemophilia B is a rare hematologic disorder with varying deficiencies in factor IX. Its severity is classified according to factor IX plasma levels as a percentage of normal in the following 3 clinical categories: mild (5% – 40% of normal); moderate (1% - 5% of normal); and, severe (< 1% of normal).[5] The severity of the disease often dictates its clinical presentation and course. Patients with severe hemophilia are prone to spontaneous hemorrhage, most typically hemarthosis in the knees, ankles, and elbows. In contrast, those with mild hemophilia may only bleed in response to significant tissue injury, such as in trauma or surgery.[5-6] This phenotypic presentation of mild hemophilia B explains why the presented patient remained asymptomatic till his index cardiac surgery, despite previous minor surgeries. This subclinical Factor IX deficiency remained

undiagnosed due to his lack of bleeding symptoms and barely noticeable elevation in the partial thromboplastin time, reflecting a mild Factor IX deficiency.[4-6]

In patients with known hemophilia, the timing of surgery is an important consideration. Some authors have suggested that elective surgery should be performed at the beginning of the work day and work week.[6-7] This strategy helps to ensure the availability of all staff, an important consideration given that a multidisciplinary team has been identified as a key component to ensuring successful outcomes in these patients.[6-8] The cornerstone of successful perioperative management for hemophilia B is adequate timely replacement of factor IX.[4-5] Preoperative factor replacement has typically been recommended prior to surgery, regardless of whether the patient has mild or severe hemophilia B.[7-8] The recommended target ranges for factor IX during preoperative replacement have been designated as 30% - 80% of normal for minor surgery and 50% - 100% of normal for major surgery.[8-9]

During the intraoperative period, the monitoring of Factor IX levels is not typically required in the setting of known hemophilia B. A prophylactic intraoperative dose based upon recent factor levels has been recommended; the precise dose can be calculated with timely hematology consultation.[8-9] The intraoperative regimen can consist of a bolus dose with additional smaller doses depending on the degree of blood loss.[9] During the postoperative period, experts have recommended targeting factor IX trough levels of 80% - 100% for days 1-3, 60% - 80% on days 4-6, and 40-60% thereafter as needed. Furthermore, trough levels should be monitored twice daily during the first postoperative week, and thereafter daily as needed.

In this case conference, the diagnosis of hemophilia B was Factor IX monitoring and targeted therapy were commenced late in the intraoperative period due to the delayed diagnosis as outlined. After the diagnosis was made, factor IX replacement was promptly titrated to clinical effect, and measured levels as recommended by hematology consultation.

A rare but important challenge in hemophilia B patients is the development of neutralizing antibodies to recombinant Factor IX that are known as inhibitors.[8-12] In a large database (N = 1172 patients with hemophilia B), only 12 patients (1%) were found to develop inhibitors.[10] Of note, only 86.7% of these patients were confirmed to have received treatment for hemophilia.[10] The incidence of these inhibitors has been reported to be in the range of (1-5)%.[11-12] If these inhibitors are detected, their levels can be measured in Bethesda units to stratify clinical risk as follows: low-risk (defined as inhibitor levels < 5 Bethesda units/mL); and, high-risk (defined as inhibitor levels > 5 Bethesda units/mL).[13] While low-risk patients typically require higher doses of recombinant factor IX for effective hemostasis, high-risk patients may require additional therapies such as recombinant factor VIIa or prothrombin complex concentrates due to their higher resistance to standard therapy.[14-15]

In 1999 recombinant factor VIIa was approved in the United States for hemophiliacs with significant inhibitor levels.[14] Administration of factor VIIa leads to activation of factor X and subsequent thrombin generation.[13] In a population of 395 patients with hemophilia (261 surgical patients, 89 dental patients, 45 patients with miscellaneous procedures), factor VIIa had an overall efficacy of 84% with only 0.4% experiencing thrombotic complications.[14]

Prothrombin complex concentrates were originally developed for bypassing factor VIII or factor IX in hemophilic patients with inhibitors. [15] The 4-factor versions contain factors II, VII, IX, and X, along with proteins C and S.[15-17] Thromboembolic complications may complicate this therapeutic intervention.[15-17] In a large meta-analysis with 1,032 patients who received PCCs for warfarin reversal, however, the incidence of thromboembolic complications was only 1.4%.[16]

While not a mainstay therapy for hemophilia, antifibrinolytics such as tranexamic acid or aminocaproic acid have been suggested as possible adjuncts.[7, 13] A recent systematic review recently examined the use of antifibrinolytics in oral surgery, but no definitive conclusions were drawn due to the limited amount of randomized controlled trials.[18] However, several trials suggested beneficial effects regarding the amount of blood loss, number of bleeding episodes, and the requirements for factor concentrates.[18]

In summary, we highlight a case wherein patient with previously undiagnosed mild hemophilia B underwent CABG. While patients with severe forms of hemophilia are likely to have spontaneous bleeding prompting earlier diagnosis, patients with milder forms may not manifest until they undergo major surgery. Although this patient successfully underwent minor surgeries in the past without complication, his hemophilia manifested with severe bleeding during major surgery. His family history was critical in raising suspicion for the condition and subsequent factor IX levels confirmed the diagnosis. Ultimately, he had a successful outcome due to integrated multidisciplinary management.

First Expert Commentary - The Diagnostic Perspective

(Drs Friess, Lued and Erdoes)

The authors in this case conference present a case of hemophilia B which was initially unrecognized, leading to severe postoperative bleeding in a patient who had undergone on-pump CABG. The medical history and the preoperative coagulation profile were unremarkable for hemophilia. Due to severe bleeding after weaning from cardiopulmonary bypass and heparin reversal with protamine, mediastinal exploration was required immediately after initial chest closure. However, no obvious cause for bleeding could be found at that time. It wasn't until contact with the patient's relatives in that a hereditary cause for the significant bleeding was suggested. Focused laboratory testing subsequently confirmed the presence of mild hemophilia B, and treatment with recombinant factor IX was initiated.

Few cases of preoperatively diagnosed hemophilia B have been published. Recent reports demonstrate a good clinical outcome for patients with hemophilia B if the diagnosis has been established prior to a severe bleeding episode and a proactive diagnostic and substitution strategy with recombinant factor IX has been followed.[19-21] The World Federation of Hemophilia has produced evidence-based guidelines on the management of hemophilia B, and a chapter is dedicated to proactive perioperative measures.[5]

In the setting of cardiac surgery, cardiac anesthesiologists are often have the responsibility for the evaluation of hereditary and acquired bleeding disorders. A thorough preoperative assessment may detect a suspicious history of bleeding phenomena.[22] As mild hemophilia B may remain undetected by routine coagulation

testing, affected patients lacking obvious bleeding phenomena can be cleared for cardiac surgery.[23] This dilemma underlines the importance of a careful and detailed preoperative investigation of the medical history, especially if clinical coagulation is significantly impaired in the perioperative course.

In retrospect, the slightly prolonged baseline activated clotting time of 131 seconds in this patient, and the surgeon's remark that bleeding after skin incision was abnormal, might have hinted at the presence of an underlying bleeding disorder. Nevertheless, these clues were confounded by the presence of recent therapy with clopidogrel, as outlined in the case presentation.

After uneventful CABG and weaning from cardiopulmonary bypass, severe bleeding developed without obvious surgical etiologies. The heart team examined the possibilities, followed up on all the leads, tested their hypotheses, and initiated respective therapies. Goal-directed therapy and targeted resuscitation were possible when the etiology had been satisfactorily identified. Finding the causative diagnosis, however, required sufficient time, which was not readily available in the presented patient given the risk of further deterioration due to ongoing bleeding.

Apart from obtaining the routine laboratory values as stated in the case presentation, point-of-care testing such as viscoelastic hemostatic assays and platelet function tests may also be valuable in evaluating unexpected bleeding after cardiopulmonary bypass (refer to Figure 2).[24] Furthermore, if available in the operating room after cardiopulmonary bypass, an estimation of the residual heparin level or complete neutralization with protamine should be assessed with a point-of-care test. Frequently, remaining heparin in the patient's plasma – after incomplete heparin reversal

with protamine or as a consequence of heparin rebound – can lead to a prolonged activated clotting time with aggravated bleeding.[25] In these scenarios, directed point-of-care testing can distinguish the common causes of prolongations in the activated clotting time and unexpected bleeding. During this evaluation process of disordered hemostasis, the patient's temperature, acid-base status, and plasma calcium level should be kept in the normal range, as these variables also contribute to an abnormal clotting cascade.

The result of the activated clotting time is typically available within minutes. Further viscoelastic testing may provide 'on-line' diagnostic evaluation of the coagulation process to guide targeted therapy.[24] Unfortunately, current viscoelastic testing such as thromboelastography cannot detect mild hemophilia B specifically, although many differential diagnoses of severe bleeding are detected readily.[24-27] Platelet function testing also offer an 'on-line' analysis and detect pharmacologically impaired platelet function. In this presented case, this directed testing could have excluded or weakened clopidogrel as the cause for early bleeding, as noticed by the surgeon. Laboratory testing, including point-of-care tests, can be ordered and evaluated if severe bleeding is expected or encountered. This sophisticated testing can be conducted towards the end of cardiopulmonary bypass to facilitate prediction and management of coagulopathy after separation from cardiopulmonary bypass and reversal of heparin.[28-30]

The goal of hemostatic testing and management is to diagnose and manage the coagulopathy with directed therapy based on test results where possible. Although hemophilia B cannot be diagnosed with point-of-care testing alone, many severe abnormalities can be revealed and treated in case of ongoing bleeding e.g. hypofibrinogenemia and platelet deficiency. In case of hemophilia B – especially if

associated with severe perioperative bleeding after cardiac surgery – it is reasonable to combine hemostatic therapy consisting of fresh frozen plasma, platelet concentrates, factor concentrates and antifibrinolytics in a rational sequence, at least initially while the etiology is sought. Subsequently, goal-directed therapy can proceed in a fashion that is tailored to clinical findings, laboratory results and institutional protocol.[22] It remains important to titrate therapy in a multimodal fashion, keeping in mind test results and the prothrombotic dangers of targeted therapy.[31-34]

Anesthesiologists should keep hemophilia in mind as a differential diagnosis in the face of severe perioperative bleeding, even if this disease is very rare in both clinical routine and the respective literature. Surgery of patients with known hemophilia B is already demanding in the elective setting. The emergency setting, as outlined in this case presentation, provides even more challenges, since the preparation and planning that was possible in the elective setting is not possible. In terms of this case, we will never know whether the diagnosis of hemophilia B would have been possible earlier, but a lesson from this challenging case is that investigating the history is key to the successful diagnosis and therapy of a bleeding disorder, especially when unexpected.

Second Expert Commentary - The Hematology Perspective

(Dr Miller)

A review of the current literature reveals that routine preoperative laboratory assessment for hemostasis remains controversial.[35] A thorough history including known hemostatic disorders, prior-bleeding events, family bleeding history, and /or relevant medications does, however, remain recommended and not controversial.[35] In our experience, it is common for routine laboratory assessment to remain part of the initial work-up for

cardiovascular surgery. The presence of an important subclinical bleeding disorder may still defy detection despite these measures, as illustrated in this case conference.

The most common types of hemophilia (hemophilia A and hemophilia B) are result from X-linked genetic mutations, typically affecting males through maternal heritage, resulting in insufficient levels of coagulation factor(s) and thus a inclination for bleeding.[5-6] The risk of major bleeding events is correlated with the percentage of deficiency. Hemophilias are classically categorized based on factor levels as follows: mild (5% – 40% of normal); moderate (1% - 5% of normal); and, severe (< 1% of normal).[5-6] While bleeding manifestations typically occur early in life, patients with mild forms of hemophilia may not have a notable bleeding event until later in life. Typically, a significant stress on coagulation, such as trauma or surgery, results in otherwise unexplained bleeding or lack of normal thrombosis.[5]

It has been estimated that currently there are approximately 400,000 people living with hemophilia in the world, although there is concern that many undiagnosed hemophiliacs are living in countries with underdeveloped medical care.[5; 36] Hemophilia A (factor VIII deficiency) is the most common, accounting for (80-85)% of all hemophilias and occurs in approximately 1:5000 live male births.[6;37] Hemophilia B (factor IX deficiency) occurs in approximately 1:30,000 live male births.[6;37] Severe disease has been estimated in about 65% of Hemophilia A patients and 50% of Hemophilia B patients.[37] Hemophilia can also rarely manifest in live female births, most commonly as a mild form in female heterozygotes, however, due to compound heterozygosity and complex X chromosome genetics, severe forms can very rarely occur.[37]

Coagulation studies, such as a prothrombin time and partial thromboplastin time are commonly evaluated to determine the functional activity of factors.[35; 38-39] Although these tests assess extrinsic and intrinsic coagulation pathways respectively, they are not totally representative of *in vivo* coagulation.[38-39] These coagulation tests are both time-based utilizing the patient's platelet poor plasma and respective activators to assess the time required for a clot to develop.[38] Prolongations in this setting can indicate either a factor deficiency or an inhibitor which can be further distinguished with a mixing study and specific factor levels.[38] In principle, mixing studies that correct with the addition of pooled normal plasma to the sample tends to indicate a factor deficiency, whereas lack of correction or re-prolonging tends to indicate a factor-specific inhibitor.[38]

Relatively recent studies indicate that life expectancy for people with hemophilia has increased. [40-41] A study performed by the Centers for Disease Control and Prevention in the United States reported a life expectancy of at least 64 years, especially since the risks of blood-borne infections such as human immunodeficiency virus has significantly decreased in the contemporary era.[40] A 2007 study from the United Kingdom reported a median life expectancy of 75 years for people with mild to moderate disease and 63 years for those with severe disease when blood-borne infection was excluded.[41] This improved life expectancy for hemophiliacs means that they increasingly will be at risk for age-related complications such as cardiovascular disease that may require surgical intervention.

The World Federation of Hemophilia has published recommendations for the perioperative management of hemophiliacs.[5] The notable recommendations include management in a comprehensive hemophilia treatment center, adequate laboratory

support for monitoring of clotting factor and inhibitor levels, preoperative assessment with inhibitor screening, and adequate supplies of patient specific factor replacement products.[5] The International Society on Thrombosis and Haemostasis has published criteria for effective hemostasis for surgical procedures.[42] In this definition, excellent adequacy of hemostasis in hemophiliacs is classified as perioperative blood loss similar (within 10%) to non-hemophiliac patients, without unplanned doses of factor or bypassing agents needed and with transfusion of blood products similar to non-hemophiliac patients.[42] These guidelines progress from excellent through the grades of good and fair to poor adequacy of hemostasis, defined as significant perioperative blood loos greater than 50% of expected for non-hemophiliac patients and not explained by another medical or surgical complication.[42] This set of definitions is different to the universal definition of perioperative bleeding in adult cardiac surgery that has selected clinical end-points such as chest tube output at 12 hours, allogeneic blood products transfused, surgical re-exploration, delayed sternal closure and the need for salvage treatment.[43]

The World Federation of Hemophilia has published recommendations for dosing and duration of factor replacement during surgery.[5] Expert multidisciplinary care with experienced subspecialty consultants has been recommended in this setting, as illustrated in this case conference. Overall, the patient in this clinical case scenario had a favorable outcome with an undiagnosed bleeding disorder. This case exemplifies the importance of detailed past medical and family history to identifying possible unknown bleeding disorders in the setting of unexpected major bleeding.

Third Expert Commentary - The Concluding Perspective

(Drs Ripat and Fabbro)

The authors present a challenging case of hemophilia B diagnosed in real time during cardiac surgery. The case highlights the importance of having a broad differential when bleeding is out of proportion to the clinical context. Appropriate diagnosis in patients with congenital or acquired bleeding diatheses can facilitate early management changes and improve outcomes. This is particularly important given the well-documented association between mortality and transfusion in cardiac surgery.[43-45] Several small series of cardiac surgery cases in hemophilia have shown similar transfusion rates to the general population.[1-3] These cases all had pre-established diagnoses and prophylactic factor replacement, again emphasizing the importance of early diagnosis in cases similar to the one presented in this case conference.

With a broad spectrum of factor activity and disease severity, hemophilia patients unsurprisingly present with a broad spectrum of clinical manifestations. Diagnosis is established readily in children of known carriers or patients who undergo testing following a major bleeding event.[45] When patients with mild factor deficiencies have only slight elevations in the partial thromboplastin time, the diagnosis may not be made for much of the patient's life.[45] Some reports of hemophilia patients with normal PTT values have also been published, further complicating the identification of these patients.[23] Establishing a hemophilia diagnosis in unexpected cases the diagnosis usually begins with the workup for an elevated partial thrombolplastin time.[45] The mainstay of this work up is mixing studies and factor assays.[45-46] The partial thromboplastin time is the only routine coagulation test that is typically abnormal in hemophilia.[5-6] The high

normal preoperative partial thromboplastin time in this presented case was an important finding in retrospect. Patients, however, may have an elevated PTT for numerous other reasons, including lupus anticoagulant.[46-47] Consensus algorithms support further work up of isolated PTT elevations using mixing tests, as outlined earlier.[37-38] With over fifteen recognized causes of an isolated elevation in the partial thromboplastin time and frequent perioperative coagulation testing, detailed investigation in all these settings may be impractical.[48] A more practical approach may be to limit more intensive work ups to patients with higher elevations in PTT, patients undergoing major surgery or patients undergoing neuraxial or other critical site instrumentation.[46-48] Emergent surgical procedures may provide further barriers to completing the work up. Perhaps more importantly, professional society guidelines do not support the use of routine coagulation testing, and favor a more selective approach.[5] The usefulness of routine coagulation testing in cardiac surgery is undetermined. Viscoelastography, although incorporated more and more into the management of cardiac surgery patients, does not add any specific benefit in this patient population.[5; 49]

Hemophilia management guidelines from the World Federation of Hemophilia are widely available for reference.[5-8] Factor concentrates are administered perioperatively, factor VIII or IX for hemophilia A and B respectively, to achieve recommended factor levels.[5] The duration of therapy, dosing and goal levels for factor replacement are based on surgery type.[5-8] The consensus document does not address patients with a suspicious clinical presentation and no definitive diagnosis.[5] Perioperative blood management guidelines also fail to address this patient group.[49] Fresh frozen plasma remains a mainstay of bleeding management and is also an alternative therapy for hemophilia

patients in limited resource scenarios.[5-8] Although not used in the United States for hemophilia since the 1970's, fresh frozen plasma has been shown to produce modest increases in Factor VIII and IX activity.[5-8] Factor VIII is the least stable factor once thawed, with some estimates of about 67% normal activity after 24 hours.[50] Cryoprecipitate, also a mainstay of surgical bleeding management, may be more effective than fresh frozen plasma for hemophilia A patients given its factor VIII levels.[5-8] Guidelines are also increasingly providing support for the use of prothrombin complex concentrates in major bleeding events outside of anticoagulant use.[51] Prothrombin complex concentrate predated high purity factor IX and was the initial factor concentrate used in hemophilia patients.[52] Recombinant activated Factor VII has is also used in bleeding cases.[53] As one of the preferred treatment regimens for hemophilia patients with factor inhibitors, factor VII therapy may also help in patients with an unconfirmed diagnoses.[53] Factor inhibitors are a major concern in hemophilia patients, however, less likely in a case like the one presented where no long standing history of treatment exists.[5-8]

In summary, a broad differential for unexpected bleeding rates after cardiac surgery is an imperative to achieve a diagnosis and administer effective therapy. In situations where patients have mild undiagnosed hemophilia, guideline-directed therapy will often manage these patients effectively. This is especially true in cardiac surgery patients where multimodal coagulopathy contributes significantly to the clinical picture. As seen however, these patients will need continued management following surgery stressing the importance of multidisciplinary diagnosis and management.

Figure Legends

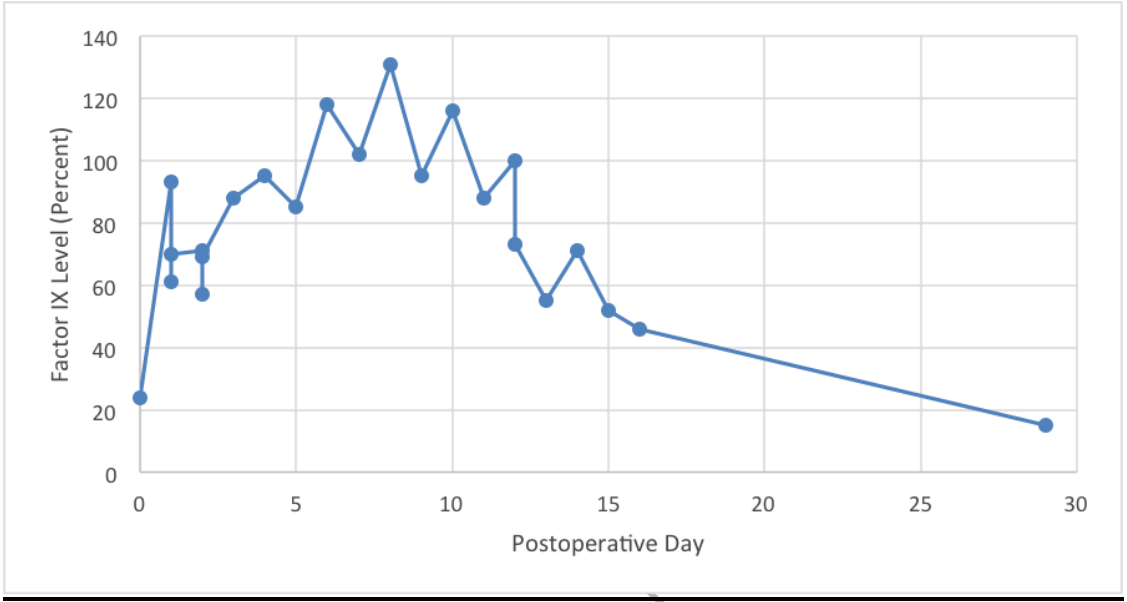

Figure 1: Postoperative Factor IX Levels as Percentage of Normal

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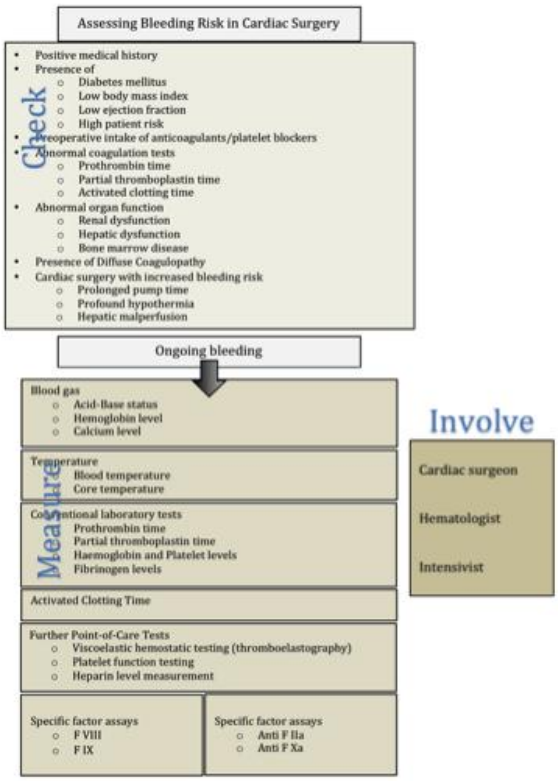

Figure 2: A Diagnostic Approach to Bleeding in Cardiac Surgery

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