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Title

Coexisting Cardiac and Hematologic Disorders

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Manuscript Body

Introduction

Patients with concomitant cardiac and hematologic disorders presenting for non-cardiac surgery are challenging to even the most experienced anesthesiologists. Understanding the rationale of a patient's therapy and calculating the risk of changing this regimen in the perioperative period is essential. This chapter will focus on several of the more common disorders and will discuss strategies to optimize care in patients with coexisting cardiac and hematologic disease.

Sickle Cell Anemia

Sickle cell disease results from a variety of inherited genetic mutations in the hemoglobin beta (HBB) gene resulting in defective beta-globin synthesis and culminating in attenuated oxygen transport. One particular HBB gene mutation produces an altered beta-globin molecule known as hemoglobin S (Hb S). Two genotypes are expressed: 1) heterozygous (sickle cell trait) or 2) homozygous (sickle cell disease).

Sickle Cell Disease

The clinical characteristics of sickle cell disease (SCD) include anemia and recurrent vaso-occlusive crisis that commonly affect the cardiac, pulmonary, renal, neurologic, and musculoskeletal systems. A growing body of literature suggests, within the natural history of SCD, cardiovascular disease may play a role in disease progression and early mortality [1]. In a cohort study of 240 patients with SCD,

cardiopulmonary compromise resulted in 39.5% of the recorded mortalities [1]. Causes of cardiovascular mortality include myocardial ischemia, malignant arrhythmia, heart failure, and pulmonary hypertension.

Chronic anemia of SCD results in an increased cardiac output and intravascular volume retention to maintain oxygen delivery. Increased intravascular volume results in left ventricular dilation and eccentric hypertrophy. Arrhythmias, including atrial fibrillation, supraventricular tachycardia, and ventricular fibrillation frequently arise secondary to chronic volume overload and have been linked to cardiovascular mortality. Baseline QT prolongation has been reported in 38% of pediatric and young adult patients with SCD [2]. Left ventricular systolic function is typically preserved; however, myocardial hypertrophy and increased LV mass lead to diastolic dysfunction and increased LV filling pressure. Diastolic dysfunction has been associated with increased age, hypertension, and renal failure and has been identified as an independent risk factors for mortality in patients with SCD [3,4].

Chronic hemolytic anemia results in release of free hemoglobin and other red blood cell intracellular enzymes that inhibit nitric oxide signaling pathways causing vasoconstriction [3]. Within the pulmonary vasculature, this mechanism is responsible for the development of primary pulmonary hypertension. Pulmonary hypertension, either secondary to volume overload and underlying diastolic heart failure, or as a primary pathology, is encountered in up to 60% of adult patients with SCD and contributes to early cardiovascular mortality [5,6]. Increased pulmonary

pressures should be treated aggressively in order to reduce right ventricular afterload and mitigate right ventricular failure.

Myocardial infarction in the SCD population results from microvascular vessel occlusion and thus coronary angiography is typically normal [7]. Supportive care including hydration, supplemental oxygen therapy, and blood transfusion may be initiated; however, exchange transfusion appears to be the definitive therapy during severe coronary ischemia. Exchange transfusion to replace Hb S with normal adult hemoglobin (Hb A) results in reduced microvascular viscosity, inhibition of the inflammatory cascade, and restoration of the intrinsic nitric oxide pathway [8].

Patients with SCD frequently present for anesthesia and surgery. An understanding of the pathophysiology of this disease is critical to provide optimal care. Perioperative transfusion has been shown to decrease both vaso-occlusive and cardiac complications in patients undergoing low and medium risk surgery [9]. A transfusion threshold of 10 g/dl is generally recommended; however, the need for exchange transfusion and reduced Hb S level is less clear. Conservative transfusion (maintain Hgb of 10 g/dl), compared to aggressive transfusion (maintain Hgb ≥10 g/dl *and* exchange transfusion to decrease Hb S <30%), results in 50% less blood administration and similar complication rates in low to moderate risk surgery [10]. Major cardiac surgery has been undertaken utilizing both aggressive exchange transfusion and conservative transfusion protocols with similar complication rates [11,12].

In patients with SCD and co-existing cardiac disease, a conservative transfusion strategy to a target Hgb of 10 g/dl should be undertaken. Although

aggressive exchange transfusion may significantly reduce Hb S content, the risk of blood product administration and volume overload must be reconciled in this population. Those with underlying pulmonary hypertension, diastolic dysfunction, or cardiomyopathy, require titrated transfusion and volume administration to avoid exacerbation of right heart failure or malignant arrhythmias.

Sickle Cell Trait

Sickle cell trait (SCT) is a carrier state of the Hb S mutation occurring in 1.6% of the US population [13] . Patients with SCT have a higher incidence of urologic disease including: hematuria, chronic kidney disease, and renal medullary carcinoma. A small percentage of these patients may display some vaso-occlusive phenomenon; however, cardiovascular manifestations of SCD are absent and life expectancy is typically normal. Patients with SCT presenting for surgery and anesthesia should be managed according to their underlying co-morbidities; no discrete management due to their status as a SCT carrier is indicated.

Anemia of Chronic Disease

Anemia of chronic disease (ACD) is typically a mild anemia with a normocytic, normochromic profile primarily due to reduced red blood cell production. ACD (Hgb <12 g/dl for female, Hgb < 13 g/dl for male) is associated with increased age, diabetes, renal insufficiency, chronic immune activation, and cardiac disease; present in 10% of those with coronary disease and as high as 79% of patients with advanced heart failure [14-16] . In the general population,

observational studies have shown the non-inferiority of restrictive transfusion protocols (compared with more liberal targets) in the perioperative period; however, less robust clinical data exists for patients with perioperative anemia and advanced cardiac disease. One study evaluated the natural history of anemia, following a subset of anemic patients who refused blood transfusion in the perioperative period. In those patients with co-existing cardiac disease, the refusal of blood products was associated with an increased risk of death.[17] A randomized pilot trial of 110 anemic patients with acute coronary syndrome or stable angina undergoing cardiac catheterization revealed greater than twice the risk of myocardial infarction, unscheduled revascularization, or death within 30 days when treated with a restrictive (transfusion for symptomatic anemia or Hbg <8 g/dl) transfusion protocol[18]. However, recent registry data further obfuscates the decision whether or not to transfuse these patients; data have shown an increased risk of cardiovascular morbidity with as little as one unit of red blood cell transfusion during the perioperative period[19]. In support of restrictive transfusion practices, a post-hoc analysis of a subset of 796 patients with known coronary disease from a large, randomized, controlled trial of hip fracture patients randomized to restrictive (Hbg <8 mg/dl or symptomatic anemia) or liberal (Hbg < 10 mg/dl) transfusion found similar 30-day mortality rates between the two groups[20,21]. In addition, subgroup analysis of patients with cardiovascular disease from the Transfusion Requirement in Critical Care (TRICC) trial found no difference in 30 day, 60 day, ICU, or in-hospital mortality when randomized to restrictive (Hbg 7.0-9.0 g/dl) or liberal transfusion (Hbg 10.0-12.0 g/dl)[22,23]. Even in the setting of

acute coronary syndrome liberal transfusion is not without risk, as a greater degree of complications related to heart failure has been observed in anemic patients [24] .

While patients with ongoing ischemia may benefit from transfusion to restore myocardial oxygen delivery, the treatment of anemia in those patients with CAD or severe heart failure should be approached in a methodical fashion based upon underlying symptomatology, with a focus on end-organ perfusion and oxygenation. Physical exam (mental status, urine output), lab monitoring (arterial lactate, acid/base status), and physiologic monitoring (heart rate, blood pressure, cardiac index) should all be used to optimize goal directed transfusion therapy in this complex patient population.

Platelet Abnormalities

Thrombocytosis

Essential thrombocytosis (ET) is a rare disorder affecting approximately 3/ 1,000,000 patients and is associated with both thrombosis and hemorrhage. Acute coronary thrombosis may occur in up to 9.4% of patients with ET [25] . Age, smoking, hypertension, hyperlipidemia, history of thrombotic events, duration of thrombocytosis, and platelet count >1,500,000 /μL are associated with increased thrombotic risk [26,27] . Patients with existing risk factors and a history of occlusive CAD requiring stents or open revascularization should be treated aggressively with a platelet lowering regimen to decrease the likelihood of stent thrombosis or

recurrent thrombotic occlusion. Hydroxyurea has been utilized in both ET and polycythemia vera; and, when compared to control, decreases both platelet count and thrombotic events in those patients at high risk for thrombotic complications from thrombocytosis [28]. Strategies to decrease platelet count, generally below 600,000/μL, have been proven to reduce thrombosis [27,28]. Aspirin and hydroxyurea should be continued throughout the perioperative period in patients with ET. High-risk patients, especially those with a history of CAD, should be aggressively managed with hydroxyurea to a target platelet count <600,000/μL in order to decrease the incidence of thrombotic complications. If signs of acute coronary syndrome develop, emergent cardiac catheterization is indicated, as the inciting lesion should be assumed to be occlusive coronary thrombosis until proven otherwise.

Idiopathic Thrombotic Purpura

Immune thrombocytopenic purpura (ITP) is an acquired deficiency of both platelet count and function. ITP may be classified as either primary (idiopathic) or secondary (typically due to infection such as hepatitis C, human immunodeficiency virus, or other autoimmune syndromes such as systemic lupus erythematosus). Thrombocytopenia in ITP is caused by antibodies to platelet antigens resulting in decreased platelet lifespan and impaired platelet production. Circulating platelets are often large and immature, increasing the risk of thrombotic events [30]. Although rare, coexisting ITP and CAD has been managed by either traditional coronary artery bypass or percutaneous intervention; however, both pose significant management dilemmas. Open revascularization is associated with increased bleeding risk due to thrombocytopenia, whereas stent implantation is complicated

by the need for post-intervention antiplatelet therapy. IVIG and steroid therapy, coupled with perioperative platelet transfusion, has been used with acceptable results; however, in those with ITP both open revascularization and percutaneous intervention are associated with a moderate increase in bleeding [31]. The preponderance of percutaneous interventions in these patients have utilized bare metal stents in an effort to limit the duration of post-intervention antiplatelet therapy [31,32]. A critical assessment of the balance of thrombosis prevention and bleeding risk must be achieved. Aspirin and clopidogrel have been used successfully; however, GP IIb/IIIa inhibitors are associated with uncontrolled bleeding and should be avoided [33,34]. Post intervention antiplatelet agents can be used until the platelet count falls below 20,000/μL or clinical bleeding occurs.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purura (TTP) is a rare and often fatal disorder characterized by thrombocytopenia, hemolytic anemia, renal failure, and mental status changes. The incidence of TTP in the general population is approximately 3.7/1,000,000 however, following percutaneous coronary intervention the incidence is much higher due to antiplatelet induced TTP [35]. TTP has been reported in be 1/4,814 patients treated with ticlopidine [36]. Clopidogrel has a safer side effect profile, however reports of TTP following administration exist [37]. Early diagnosis and treatment of antiplatelet induced TTP is essential as mortality approaches 67% without prompt plasmapharesis [36].

Anticoagulation for Cardiac Devices

Artificial Valves

Artificial heart valves may be implanted for acute or chronic valvular dysfunction, resulting in stenotic or regurgitant heart disease. Two main classes of devices are mechanical valves and bioprosthetic valves. Bioprosthetic valves may be either a cadaveric homograft or a xenograft composed of porcine or bovine pericardium mounted on a stent. Although the lifespan of bioprosthetic valves is generally reduced compared with mechanical valves, use of the tissue material precludes the need for anticoagulation unless special circumstances arise. In contrast, mechanical valves are composed of pyrolytic carbon and last an indefinite period of time. However, due to the high rate of thrombosis, mechanical valves require aggressive long-term anticoagulation. According to the AHA/ACC guidelines, patients with a mechanical valve in the mitral position should be anticoagulated to a target median INR of 3.0 [38]. Due to an accelerated transvalvular flow pattern, the target median INR of a valve in the aortic position in those without thrombotic risk factors (atrial fibrillation, left ventricular dysfunction, hypercoagulable state, previous thrombotic event) is 2.5 [38]. Although major guidelines differ in their specific recommendation, aspirin, in addition to warfarin, is generally recommended in those without increased bleeding risk [38-40].

Anticoagulation therapy in preparation for non-cardiac surgery must take into account both the bleeding risk of surgery and the thrombotic risk of abruptly discontinuing anticoagulation. In general, minor dental or cutaneous procedures may be accomplished without interruption of anticoagulation; however, if the surgical site is not amenable to local hemostasis or major surgery is planned, a

preoperative INR <1.5 is desirable. Warfarin should be discontinued 5-6 days prior to surgical intervention and anticoagulant bridging with a heparin analogue is indicated.

On rare occasions, patients on chronic anticoagulation for mechanical heart valves may suffer from warfarin overdose. This is typically manifest by an elevated INR and frequently results from medication mismanagement or a change in absorption pharmacokinetics. If no significant bleeding occurs, warfarin can be held and oral vitamin K administered until target INR is reached. In those with severe bleeding, prothrombin complex concentrates or fresh frozen plasma may be used to expeditiously normalize the INR. Complications from severe bleeding generally outweigh the risk of valve thrombosis. Anticoagulation can be safely interrupted for 7-14 days even in those at high risk for thromboembolic events [41].

Pregnant patients with mechanical heart valves pose multiple challenges. Parturients are hypercoagulable due to changes in blood viscosity, decreased fibrinolysis, and upregulation of clotting factors. All pregnant patients with artificial heart valves should be deemed "high risk" as the percentage of pregnancies ending with both a live mother and child is approximately 81% [42]. Adequate anticoagulation to prevent mechanical valve thrombosis must be balanced against the risks of bleeding and teratogenicity of the anticoagulant. In a large registry series 4.5% of such patients experienced mechanical valve thrombosis with half of the events occurring in the first trimester [42]. Anticoagulation regimens in the first trimester remain a matter of debate, as warfarin has been proven to be superior to heparin analogues for thrombosis prophylaxis; however concerns for teratogenicity,

miscarriage (<24 weeks), and late fetal death (>24 weeks) exist [42]. Multiple medication regimens have been studied including warfarin, unfractionated heparin, and low molecular weight heparin. Current guidelines suggest either administration of low dose (<5mg/day) warfarin or discontinuation of warfarin in the first trimester [38]. If resumed, complete discontinuation of warfarin is indicated after 36 weeks in preparation for delivery. Anticoagulant coverage can be provided during warfarin-free periods; or, alternatively maintained for the duration of pregnancy with unfractionated or low molecular weight heparin. Regardless of the medication choice; pregnancy in this patient population is best managed by a multi-disciplinary team and the risk/benefit of anticoagulant medications must be discussed with the patient.

Ventricular Assist Device

A left ventricular assist device (LVAD) can be utilized in three clinical scenarios: 1) acute ventricular failure as a bridge to recovery; 2) chronic ventricular failure as a bridge to heart transplantation; or 3) for permanent implantation in those not suitable for heart transplantation. All LVADs fall into one of two physiologic categories based on how blood is circulated through the device: pulsatile or non-pulsatile. Non-pulsatile, or continuous flow, LVADs are smaller in size, operate silently, and have greater durability when compared to pulsatile flow LVADs [43].

Careful consideration of the anticoagulation status in patients with an LVAD is important for optimal management. Thrombus formation within the device, reported to occur between 2-12% at 24 months, can lead to embolic events or LVAD

failure [44]. LVAD patients are anticoagulated with a regimen consisting of anti-platelet agents and warfarin. Target median INR varies between centers from 2.0-2.5 [43].

Major bleeding may occur in patients with an LVAD secondary to aggressive anticoagulation, hemolysis, and down regulation of clotting factors. Although the etiology is not yet completely understood, many continuous-flow LVADs cause reduced levels of von Willebrand factor, which may further increase the risk of bleeding. The need to reverse or withhold anticoagulation depends on the severity and location of hemorrhage. Prothrombin complex concentrates or fresh frozen plasma can be administered to reverse warfarin. Anticoagulation therapy should immediately resume when the risk of thrombosis outweighs the risk of further bleeding.

The extended lifespan of new generation LVADs, coupled with their use for destination therapy, has resulted in a large proportion of these patients presenting for elective, non-cardiac surgery. In patients without additional indication for anticoagulation (atrial fibrillation, left ventricular thrombus) cessation of warfarin 5-6 days before surgery and continuation of aspirin has reduced the need for perioperative blood transfusion without an increase in thrombosis [45]. In patients at high risk for thrombosis, anticoagulation bridging with a heparin analogue is indicated. Warfarin anticoagulation can be safely resumed in the postoperative period when bleeding risk has subsided.

Heart Failure with Reduced Ejection Fraction

Heart failure is associated with significant morbidity and mortality from thromboembolic events leading to stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolus. The pathophysiology of thromboembolism in heart failure is primarily related to blood stasis within the left ventricle, endothelial dysfunction, and increased platelet activation. The addition of anticoagulant and/or antithrombotic therapy in those with coexisting atrial fibrillation or previous thromboembolic event is recommended; however, anticoagulant therapy for patients in sinus rhythm with reduced ejection fraction is less clear. Multiple randomized controlled trials have compared the use of warfarin, aspirin, and clopidigrel in this patient population with conflicting results [46-48]. Aspirin has been associated with increased risk for hospitalization and gastrointestinal bleeding; however, this may be due to an as yet undefined interaction with ACE inhibitors [49]. Baseline warfarin use has been associated with a reduction in all-cause mortality and acute coronary syndrome; however, the rate of major bleeding is increased when compared with aspirin or clopidogrel [49]. Antiplatelet and antithrombotic use in patients with normal sinus rhythm and reduced ejection fraction should be dictated based upon underlying co-morbidities and heart failure pathology. Although controversial, aspirin may be of benefit in patients with underlying coronary disease and heart failure secondary to ischemic cardiomyopathy. Alternatively, warfarin can be used to decrease thrombosis risk and improve intermediate morbidity and mortality in those with reduced ejection fraction and

normal cardiac rhythm.; however, therapy should be reserved for only patients at low risk for bleeding complications.

Conclusion

Patients with concomitant hematologic and cardiac issues represent challenges to everyone involved in their perioperative care. An understanding of the pertinent pathophysiology, the appropriate therapy and the risks are essential. In the end, management decisions should be based on a thoughtful discussion with other involved providers and a balanced approach that explicitly addresses the risk and benefit of each intervention.

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