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Review article

REVIEW ARTICLE

Perioperative management of rare coagulation factor deficiency states in cardiac surgery

E. R. Strauss[1], M. A. Mazzeffi[1], B. Williams[1], N. S. Key[2] and K. A. Tanaka[1,*]

[1]Department of Anesthesiology, University of Maryland School of Medicine, 22 South Greene Street, Suite S8D12, Baltimore, MD 21201, USA and [2]Department of Medicine, University of North Carolina, Chapel Hill, NC, USA

*Corresponding author. E-mail: ktanaka@som.umaryland.edu

Abstract

Rare bleeding disorders (RBDs) include the hereditary deficiency of fibrinogen, factor (F)II, FV, FV + FVIII, FVII, FX, FXI or FXIII. RBDs do not confer a protective effect against atheromatous plaque formation, and thus the need for cardiovascular (CV) surgery in RBD patients is expected to increase with improved healthcare access (diagnosis and management) and longevity of the population. Clinical data regarding the management of RBDs in this setting are sparse, but the perioperative care team is obliged to gain a better understanding on available biological and pharmacological hemostatic agents. Perioperative management of RBDs in CV surgery is further complicated by heparin anticoagulation, haemodilution, and consumption of procoagulant and anticoagulant proteins associated with cardiopulmonary bypass (CPB). The aims of this review are to summarize pathophysiology of RBDs and laboratory monitoring pertinent to CV surgery, available factor replacement agents, and to provide the framework for perioperative coagulation management of RBD patients.

Key words: blood coagulation factors; blood transfusion; coagulants; thoracic surgery

Major bleeding requiring re-exploration occurs in about 3–14% patients undergoing various types of cardiovascular (CV) surgery.[1–3] Coexisting bleeding disorders can further complicate perioperative coagulation management. Multi-disciplinary approaches and careful surgical planning are thus crucial to prevent major bleeding, massive transfusion, and associated complications after CV surgery.[4] There have been numerous reports on the perioperative management of haemophilia, and von Willebrand disease (VWD).[5] The hereditary deficiency of fibrinogen, factor (F)II, FV, FV + FVIII, FVII, FX, FXI or FXIII is considered a rare bleeding disorder (RBD) (Table 1).[6–8] Diagnostic criteria, replacement therapy, and perioperative management of RBDs are not as standardized as haemophilia and VWD.[7–9] In recent years, our knowledge base and clinical management of RBDs have been significantly improved by early screening,[10] and shared medical information among the RBD networks.[6 7] Although RBDs are presumed to reduce the risk of thrombotic vascular occlusion, coronary atherosclerosis and plaque rupture seem to develop similarly between haemophilia and non-haemophilia subjects.[11–14] With the increasing globalization and longevity of the population, the need for CV surgery in patients with RBDs is expected to increase. CV procedures are often associated with major blood loss and haemodilution with the use of cardiopulmonary bypass (CPB). Multifactorial coagulopathy can develop, and thus it is important to better understand the bleeding risk and replacement strategies for RBDs in this setting.

The aims of this review are: i) to discuss the pathophysiology and laboratory monitoring of RBDs, ii) to review the published RBD cases pertinent to CV surgery, and iii) to summarize currently available replacement therapies, and perioperative coagulation management strategies.

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Table 1 Bleeding symptoms of rare bleeding disorders. *Treatment effect could not be ruled out; †Percenages were calculated on the basis of the numbers of procedures; ‡Percentage was calculated based on one patient. Abbreviations: GI, gastrointestinal; CNS, central nervous system. Reprinted with a permission from: What are Rare Clotting Factor Deficiencies? 2009, World Federation of Hemophilia. http://www1.wfh.org/publications/files/pdf-1337.pdf (accessed August 3, 2017)

Symptom	Factor I	Factor II	Factor V	Factors V+VIII	Factor VII	Factor X	Factor XI	Factor XIII
Nosebleed	common	common	common	occasional	common	common	common	common
Easy bruising	common		common	common	common	common	common	common
Heave or prolonged menstrual bleeding	common	common	common	common	common	occasional	common	occasional
Blood in urine	Absent	rare	Absent	Absent	rare	occasional	Absent	occasional
GI bleeding	occasional	occasional	occasional	Absent	occasional	common	occasional	occasional
Joint bleeding	common	common	rare	rare	occasional	common	common	common
Muscle bleeds	common	common	occasional	occasional	occasional	common	Rare	occasional
Umbilical cord bleeding	common	occasional	Absent	Absent	rare	common	Absent	common
CNS bleeding	occasional	rare	rare	Absent	occasional	occasional	Absent	common
Bleeding from mouth/gums	common	common	common	common	common	common	occasional	common
Bleeding during pregnancy or childbirth*	Absent		Absent	Absent	occasional	Absent‡	Absent	Absent‡
Major surgery†	occasional	occasional	occasional	common	occasional	common	common	Absent
Minor surgery†	common	occasional	occasional	common	common	common	common	common
Other	rare		Rare	occasional	Absent	occasional	Rare	Absent

rare	0–10% of patients
occasional	10–30% of patients
common	>30% of patients
Absent	No bleeding symptom
	Insufficient data

General considerations for RBDs

RBDs are generally inherited in an autosomal recessive fashion. The majority of RBDs is reported as a homozygous or double heterozygous mutation with estimated prevalence from 1:500,000 to 1:2 million. This is in contrast to symptomatic autosomal dominant VWD with a prevalence of 1:10,000 to 1:50,000.[15] FVII and FXI deficiencies are the most prevalent RBDs (37.5% and 26.5%, respectively), followed by deficiencies of fibrinogen, FV, and FX (8 to 9%) and FXIII (6%).[9]

It is common to make an assumption that residual coagulant factor activity inversely correlates with bleeding risk, but significant variability in symptoms exists among different RBDs (Table 2).[6 8] It is thus important to assess each patient with a RBD individually by comprehensive history taking, physical examination, and laboratory testing.

Cardiovascular disease and antithrombotic therapy in RBDs

Ischaemic heart disease (IHD) has been reported as an important cause of morbidity and mortality in the ageing haemophilia population.[11–14]

Early stages of atherosclerotic plaque formation may be delayed by coagulation factor deficiency,[16 17] but it generally does not prevent CV disease. The presence of typical risk factors, such as hypertension and diabetes, strongly influences the incidence of CV disease and subsequent mortality.[18]

Treatment algorithms for IHD in patients with RBDs should follow evidence-based guidelines for the general population, and for haemophilia patients.[5 19] In haemophilia patients undergoing percutaneous coronary interventions (PCI), a factor replacement target greater than 80% is used for 48 h to reduce bleeding risks associated with heparin and dual antiplatelet therapy.[20] Use of bare metal stents is preferred over drug-eluting stents for a shorter duration of dual antiplatelet therapy in high bleeding risk patients.[5] However, drug-eluting stents with enhanced endothelialisation are currently in development, and may prove to be safe in RBD patients with IHD.[21]

Maintenance of trough factor activity greater than 30% for the duration of dual antiplatelet therapy, and 5–10% thereafter are recommended for haemophilia patients.[5 19 22] Target factor activity in RBD should be individualized per case basis because significant variability in severity and symptoms exists among different RBDs (Tables 1 and 2).

Laboratory testing for RBDs

Standard diagnostic tests

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are the most common screening tests for RBDs (Table 2). PT and aPTT are also the basis of 1-stage clotting assays to quantify residual factor activity (PT-based for FII, FV, FVII, FX, and aPTT-based for FVIII, FIX, FXI).[23] The results of 1-stage clotting assay is expressed as clotting activity (e.g. FVII:C) in %, or international units per dL (IU/dL). Plasma mixing test is useful when acquired factor inhibitors or non-specific antibodies (lupus anticoagulant) are suspected. In the case of an isolated factor deficiency, 1:1 mixing of the patient's and normal plasma corrects PT or aPTT, and non-correction calls for further testing for factor inhibitors or lupus anticoagulant.[24] Chromogenic and fluorogenic assays are also available for some factors (e.g. FII, FVIII).[25] The distinction of quantitative (type I) *vs*