AUTOLOGOUS BLOOD TRANSFUSION IN CARDIAC SURGERY

Thesis Submitted for Partial Fulfillment of the M.D. Degree in Anesthesia

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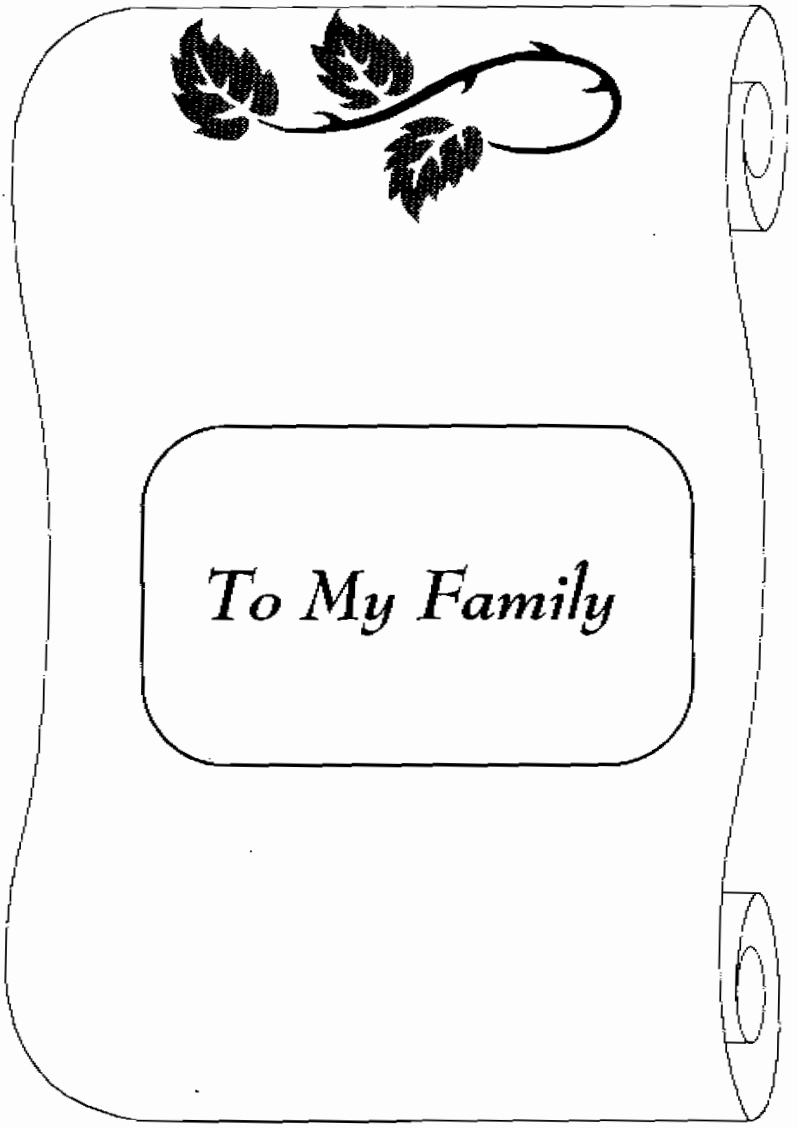
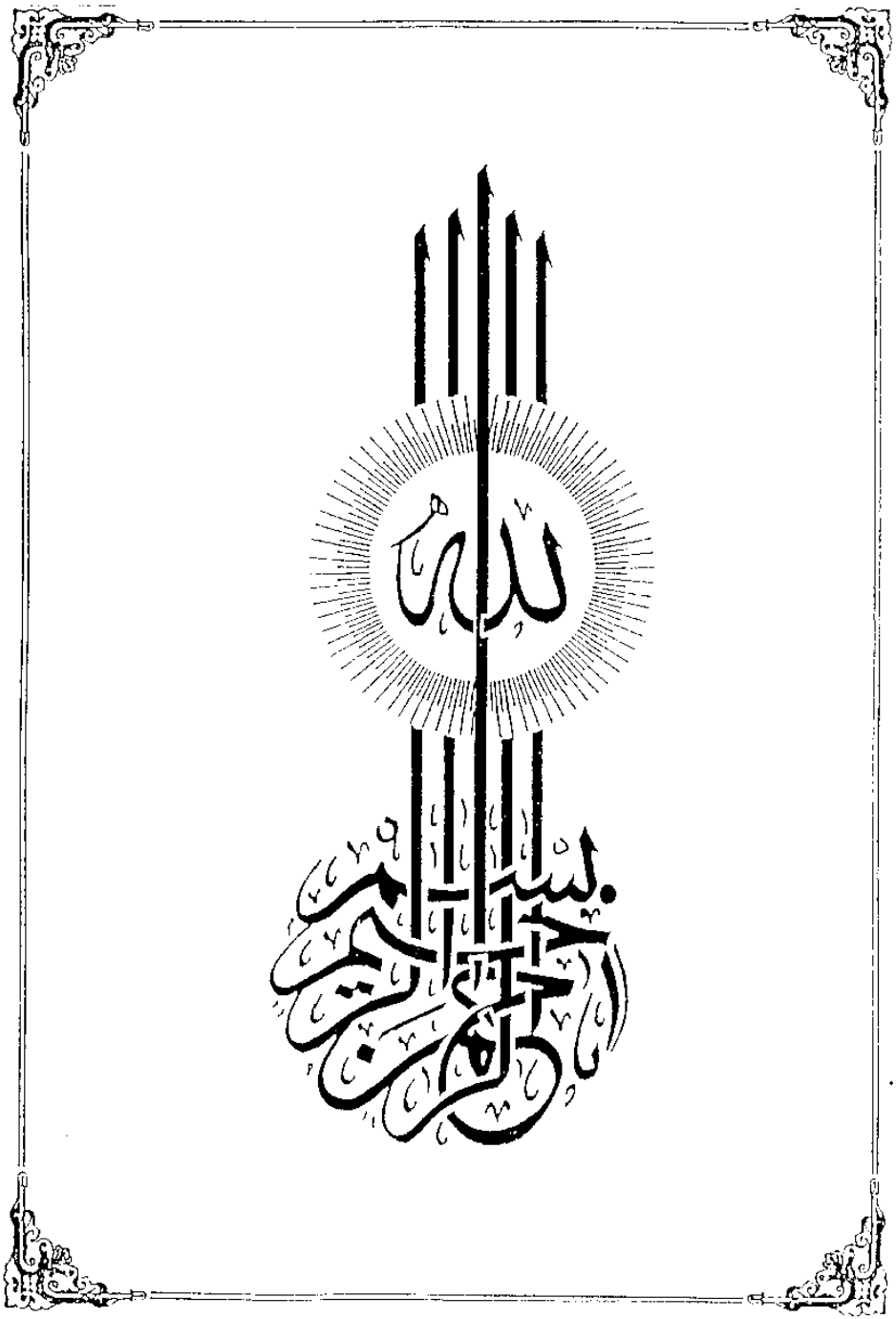

To My Family



List of Abbreviations

2,3-DPG	2,3-diphosphoglycerate.
ABT	Autologous blood transfusion.
ACT	Activated coagulation time.
ADP	Adenosine diphosphate.
ANH	Acute normovolemic hemodilution.
ATP	Adenosine triphosphate.
BS	Blood salvage.
cAMP	Cyclic adenosine monophosphate.
CaO_2	Arterial O_2 content.
cGMP	Cyclic guanosine monophosphate.
CMV	Cytomegalovirus.
CO	Cardiac output.
COP	Colloidal osmotic pressure.
CPB	Cardiopulmonary bypass.
DHTR	Delayed hemolytic transfusion reaction.
DIC	Disseminated intravascular coagulation.
DO_2	Oxygen delivery.
EACA	Epsilon aminocaproic acid.
EDRF	Endothelium derived relaxing factor.
EPO	Erythropoietin.
ER	Extraction ratio.
FDPs	Fibrin degradation products.
FSPs	Fibrin split products.
HBT	Homologous blood transfusion.

Hct	Hematocrit.
HGB	Hemoglobin.
HIV-1	Human immunodeficiency virus 1.
HIV-2	Human immunodeficiency virus 2.
HMWK	High molecular weight kininogen.
HTLV-I/II	Human T-cell lymphotrophic virus - I/II.
KIU	Kallikrein inhibitor units.
NHFTR	Non-hemolytic febrile transfusion reactions.
NO	Nitric oxide.
PABD	Preoperative autologous blood donation.
PAF	Platelet activating factor.
PAI	Plasminogen activator inhibitor.
PaO_2	Arterial oxygen tension.
PK	Prekallikrein.
PtO_2	Tissue oxygen tension.
PTP	Post-transfusion purpura.
PvO_2	Mixed venous oxygen tension.
rpm	Round per minute.
SaO_2	Oxygen saturation.
TA	Tranexamic acid.
TA-GVHD	Transfusion associated-graft versus host disease.
tPA	tissue-type plasminogen activator.
TRALI	Transfusion-related acute lung injury.
TxA_2	Thromboxane A_2.
USFDA	United States Food and Drug Administration.
VO_2	Oxygen consumption.
vWF	von Willebrand factor.

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Introduction and Aim of the Work

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Autologous blood transfusion (ABT) is not a new concept. Reinfusion of shed blood was employed as early as 1818 *(Blundell, 1819)*, and preoperative donation of autologous blood was advocated in the 1930s when the first blood banks were established *(Fantus, 1937)*. However, the last 20 years have brought a marked increase in the use of autologous transfusion. Complex operative procedures such as open heart surgery have prompted the search for alternatives to homologous blood transfusion (HBT) and technologic advances have made possible the development of safe, easy-to-use devices for blood salvage *(Stehling, 1994)*.

There has been much concern regarding HBT as it carries the risk of transmitting diseases particularly viral hepatitis and AIDS, the risk of alloimmunization to red blood cells, platelets and leukocytes antigens, and the risk of hemolytic, febrile and allergic reactions *(De Christopher, 1990)*.

Patients undergoing open heart surgery are among the top users of HBT *(Spence et al., 1992)*.

The two major reasons for employing ABT are avoidance of complications associated with HBT and conservation of blood resources. Furthermore, it can provide a source of blood for persons who have rare blood types or antibodies that make it difficult to find compatible blood *(Eckstein, 1989)*, and also for Jehovah's Witnesses

who refuse to accept transfusions of blood and blood products under any circumstance, even in view of the lethal risk of major hemorrhage *(Gombotz et al., 1989)*.

These are three types of ABT: preoperative blood donation, acute normovolemic hemodilution, and intraoperative and postoperative blood salvage. Appropriate use of ABT is one aspect of an integrated blood conservation program. Other measures include meticulous surgical hemostasis, and employment of pharmacologic agents to decrease blood loss *(Stehling, 1994)*.

This study is designed to evaluate the efficacy of ABT as a safe mean to reduce the need for HBT during open heart surgery and to compare the different methods of blood conservation.

Review of Literature

Coagulation and Hemostasis

There is a unique and complex hemostatic system that normally limits the amount of hemorrhage and blood loss associated with damage to blood vessels. However, excessive hemorrhage may occur when the hemostatic system is overwhelmed by wounds to major blood vessels or when hemostatic mechanisms are impaired by congenital and acquired disorders. Dilution and/or consumption of coagulation factors may also be associated with secondary bleeding and excessive hemorrhage ***(Edward and Juan, 1996)***.

Normal hemostasis is dependent on precisely regulated interactions between endothelial cells of the blood vessels wall, subendothelium, platelets, and plasma coagulation factors ***(Edward and Juan, 1996)***.

Components of the Coagulation System :

[A] Endothelium and Subendothelium :

In addition to its thromboresistant surface, endothelial cells of vessels possess both antithrombotic and prothrombotic factors (**table 1**). Normally, these opposing factors are in balance, maintaining the thromboresistant environment; however, even minor disturbances in the vasculature can activate either one of these factors ***(Gimbrone, 1986)***.

Endothelial cells have several antithrombotic mechanisms that protect against the unchecked action of thrombin, the terminal enzyme of the plasma coagulation system. Thrombomodulin is a surface protein that downregulates the coagulation system by binding thrombin and activating the natural anticoagulant protein C. The endothelium also has heparin-like molecules on its surface that potentiate the effects of antithrombin III, a plasma protein that inactivates thrombin. Thrombin itself induces endothelial cells to synthesize and release prostacyclin (PGI_2), a prostaglandin derivative that is potent inhibitor of platelet aggregation. In addition to these mechanisms, endothelial cells are capable of producing tissue-type plasminogen activator (tPA) which stimulates the fibrinolytic system to dissolve blood clots ***(Dittman and Majerus, 1990)***.

Table (1) : Endothelial Antithrombotic and Prothrombotic Factors

Antithrombotic Factors	**Prothrombotic Factors**
- Thrombin inhibition :	- Coagulation factors :
* Thrombomodulin conversion of protein C to activated protein C.	* Tissue factor / thromboplastin
* Antithrombin III acceleration of surface heparin-like molecules.	
- Platelet inhibition :	- Platelet aggregation
* Prostacyclin (PGI_2)	* von Willebrand factor (vWF)
	* Platelet activating factor (PAF)
- Fibrinolysis enhancement :	- Inhibition of fibrinolysis
* Tissue plasminogen activator (tPA)	* Tissue plasminogen activator inhibitor (PAI)

(Gimbrone, 1986)

Endothelial cells are able to counterbalance these antithrombotic activities by secreting platelet-activating factor, a substance that induces platelet aggregation, and synthesizing von Willebrand factor, a cofactor necessary for platelet adherence to the subendothelium. In addition, the endothelium is able to secrete plasminogen-activator inhibitor which inhibits the fibrinolytic system from dissolving clots ***(Prescott et al., 1990)***.

Damage to the endothelial monolayer exposes blood to a highly thrombogenic subendothelial connective tissue which initiates clot formation. This connective tissue consists of various types of compounds including fibrillar collagen, which is a potent stimulus for platelet adhesion and activation. Simultaneously, subendothelial components convert inactive coagulation factors into powerful enzymes, initiating intrinsic stimulation of the plasma coagulation system ***(Edward and Juan, 1996)***.

[B] Platelets :

Platelets are produced by megakaryocytes in bone marrow and play a crucial role in hemostasis. Not only are platelets recruited when vascular integrity is disturbed, but they maintain the integrity of normal endothelium, as evidenced by the tendency of patients with platelet deficiencies to develop purpuric bleeding. With vascular and endothelial injury, the following sequence of platelet-mediated events occur ***(Edward and Juan, 1996)***.

(1) Adhesion :

Platelets recognize sites of endothelial injury and become activated, adhering to exposed subendothelial collagen. von Willebrand factor (vWF) is necessary for adhesion, serving as a molecular bridge between platelet and collagen. After being

stimulated, platelets change their shape, utilizing their internal actin and myosin microfilaments to spread broadly and become tightly adherent *(Kroll et al., 1991)*.

(2) Secretion :

With activation, platelets secrete granules, the two major types being -granules and dense bodies. -granules contain platelet specific proteins that include fibrinogen, fibronectin, vWF, factor V, platelet-derived growth factor, and an anti-heparin known as platelet factor 4. Dense bodies are rich in ionized calcium, adenosine diphosphate (ADP), histamine, epinephrine, and serotonin. Following platelet activation and granule secretion, a phospholipid complex known as platelet factor 3, becomes exposed on the platelet surface, this factor provides a site where several clotting factors (particularly factor X) are able to bind and ultimately form thrombin *(Shattil and Bennett, 1990)*.

3) Platelet Aggregation :

ADP is a potent stimulator of platelet aggregation. Activated platelets synthesize thromboxane A_2 (TxA_2), a prostaglandin that locally increases ADP release. The aggregation-associated ADP release results in an enlarging mass that serves as the primary hemostatic plug. Excessive platelet aggregation is inhibited by prostacyclin (PGI_2) via its ability to elevate cyclic adenosine monophosphate (cAMP) in the platelet cytoplasm. Recently, endothelium-derived relaxing factor (EDRF), one form of which is nitric oxide (NO), has similarly been shown to inhibit platelet aggregation by stimulating guanylate cyclase, increasing the level of cyclic guanosine monophosphate (cGMP) in the cytoplasm *(Ware and Heistad, 1993)*.

[C] Plasma Coagulation System :

The third component of the hemostatic process involves a series of plasma coagulation proteins which initiate the formation of a stronger hemostatic plug. This system consists of a series of reactions involving the conversion of inactive precursor enzymes (zymogens) to activated proteolytic enzymes (**figure 1 and table 2**). Traditionally, this system is divided into an extrinsic and intrinsic coagulation pathways, converging to a common pathway at the point where factor X is activated ***(Furie, 1988)***.

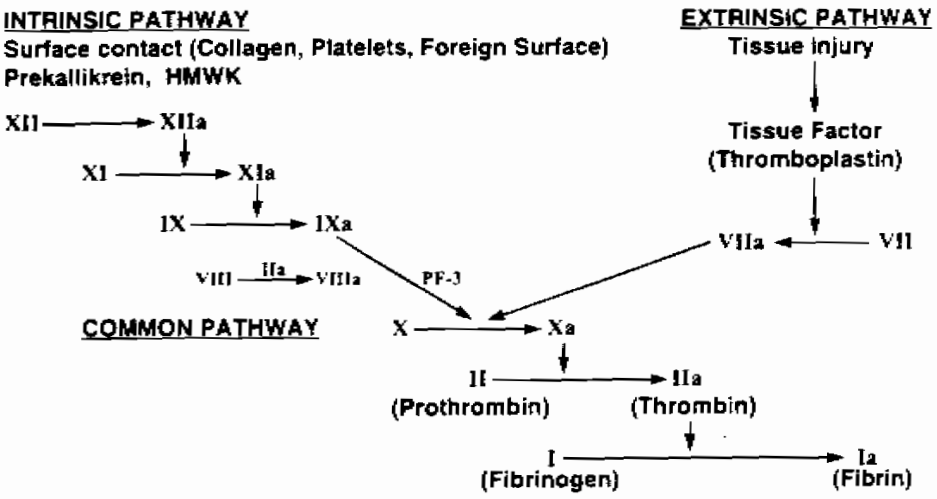

Figure (1) : Plasma Coagulation System *(Furie, 1988)*.

The extrinsic pathway of coagulation is activated by a tissue factor (a form of thromboplastin) which is released from injured cells. Tissue factor and factor VII form a complex which activates factor X to factor Xa, which itself is able to activate factor VII, which further