HORMONAL CHANGES AND COAGULATION FACTORS DISTURBANCES AFTER OPEN HEART SURGERY

THESIS

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BY

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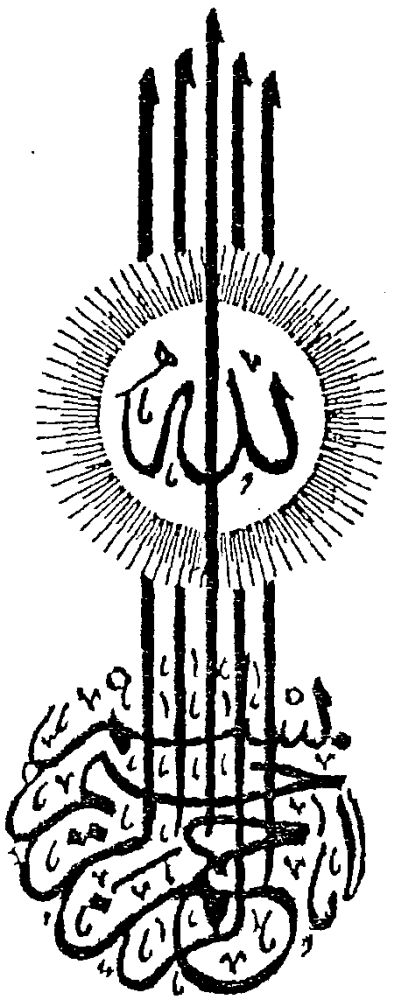

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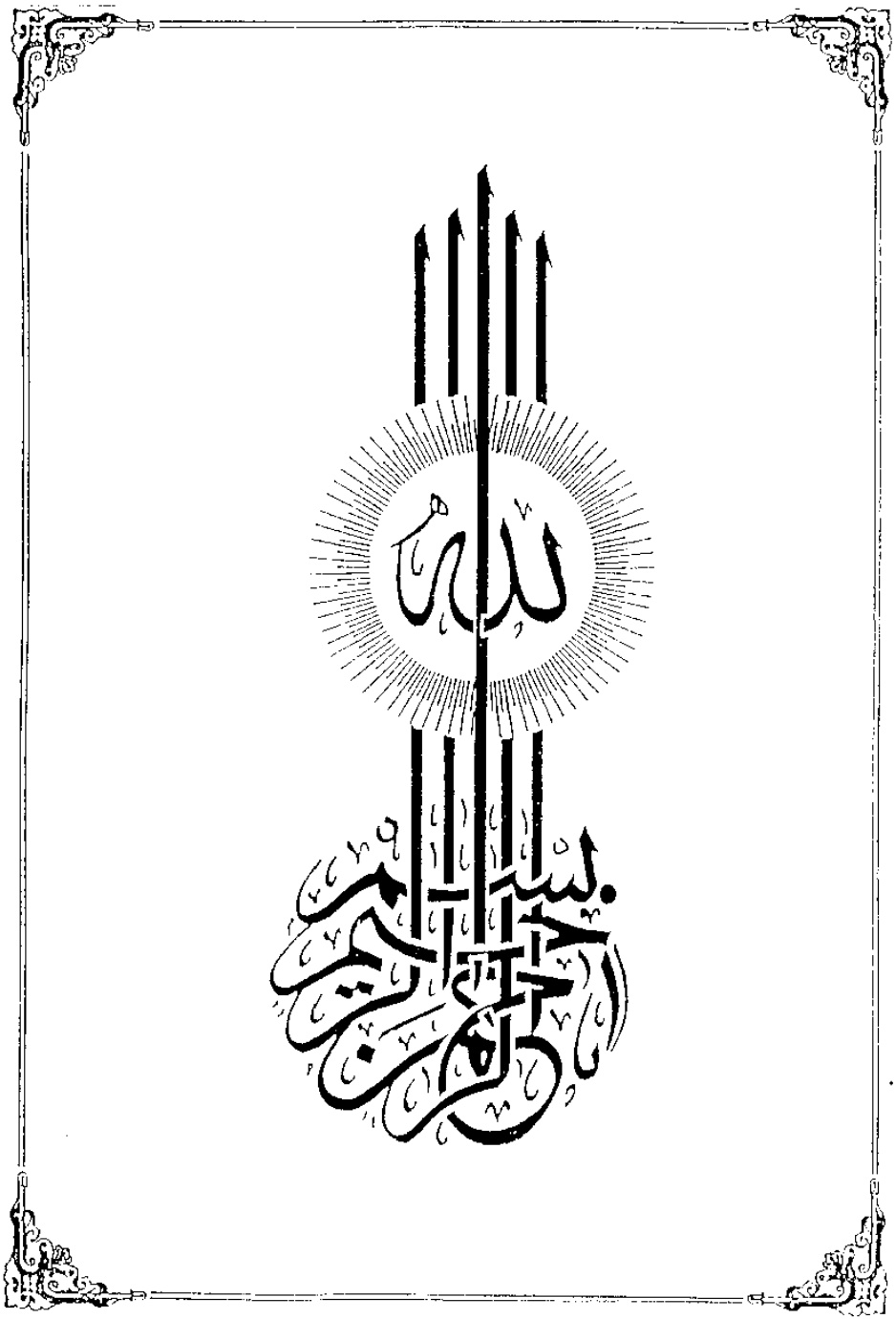

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CONTENTS

ABBREVIATIONS

Ab coated	Antibody coated.
ACT	Activated clotting time
ATP	Adinosine triphosphate
C_5	Complement - 5.
Ca++	Calcium ions
c. AMP	Cyclic adinosine monophosphate
C1-inhibitors	Complement -1- inhibitor.
CK	Creatine kinase
CK-MB	Creatine kinase-MB
CPB	Cardiopulmonary bypass
HDL-cholesterol	High density lipoprotein cholesterol
HFf.	Hageman factor fragment
HMW-kininogen	High molecular weight-kininogen
^{125}I	Radioactive iodine 125.
INR	International normalized ratio
LDH	lactate dehydrogenase
LDL-cholesterol	Low density lipoprotein cholesterol
LH	Lutinizing hormone
LMW-kininogen	Low molecular weight kininogen
MW	Molecular weight
PCV	Packed cell volume
PF_3	Platelet factor -3

PT	Protrombin time
RIA	Radioimmunoassay
SGOT	Serum glutamic oxaloacetic transaminase.
TF5	Thymosin fraction 5.
TRH	Thyrotropin releasing hormone
Va	Factor V active
VIIa	Factor VII active
VIII Ag	Factor VIII antigen
VIIIc	Fctor VIII coagulant
vWF	Von Willebrand factor
vWFAg	Von Willebrand factor antigen
vWfc	Von Willebrand factor coagulant
Xa	Factor X active
XIa	FactorXI active
XIIa	Factor XII active
XIIf	Factor XII fragment

INTRODUCTION
&
AIM OF THE WORK

INTRODUCTION

The modern cardiac surgery becomes possible with development of cardiopulmonary bypass (CPB). CPB is a technique in which blood is diverted away from the heart and lungs into a machine that substitutes for pumping and ventilatory functions of these organs. The major component of CPB system are venous catheters, blood reservoir, pump, oxygenator, heat exchanger, filter and arterial catheter. This system also involves two cardiotomy sucker systems and a venting system for the left ventricle *(Edmunds et al., 1978).*

Appropriate anticoagultion, induced by heparin is a fundamental requisite for heart surgery with CPB. Variation above or below an optimal range of anticoagulation may cause severe complications, as intraoperative thrombosis or excessive bleeding, which occur occasionally using these operations *(Ponari et al.,1979).*

The anti-coagulant effect is measured by the activated clotting time (ACT) of whole blood *(Hattersley, 1966).* In 1975, *Bull et al.* recommended a therapeutic range for ACT of 400 to 600 seconds during CPB.

At the end of bypass, the residual heparin must be neutralized by protamine to achieve effective haemostasis. The heparin-protamine complex remains stable only in the presence of an excess of protamine *(Bachmann et al., 1975).*

Open heart surgery may be followed by hypo or hypercoagulability state. In 1976, Gollub reported that the hypocoagulability state may be due to appearance of heparin in the circulation. This phenomenon was known as heparin rebound. *Shanberg et al. (1987)* explained heparin rebound by the loss of the free heparin from intravascular sources, the excess release of antithrombin III from the liver and the transfusion of fresh blood as source of antithrombin III to the patient.

Although heparin rebound is not usually seen when a significant excess of protamine is used in the neutralization of heparin, there has been a hesitancy on the part of surgeons to give too much protamine to a patient based on the idea that protamine itself can act as anticoagulant *(Anderson et al., 1979).* However, protamine is a very poor anticoagulant, and heparin would be taken in excess safely *(Ellison et al., 1981).*

On the other hand, *Kauffmann et al. (1978)* studied the

hypercoagulability state after open heart surgery. They reported that the deficiency in antithrombin III activity, the main inhibitor of thrombin, is the major factor of such complication.

During CPB, there is extensive contact between blood anticoagulated with heparin and synthetic surfaces of the extracorporeal circuit consequences of blood cell activation and plasma protein alteration which prolong the bleeding time and increase postoperative blood loss *(Harker et al., 1980)*.

Extracorporeal circulation has been associated with major qualitative and quantitative alteration of platelets including thrombocytopenia, reduced sensitivity to aggregating agent, depletion of α-granule contents *(Edmunds et al., 1982)*, decreased fibrinogen receptors *(Musial et al., 1985)*, decreased α_2-adrenergic receptors and secretion of thromboxane A_2 *(Wachtfogel et al., 1985)*. By scanning electron microscopy, the number of unactivated platelets significantly drop eight minutes after the onset of CPB.

Simultaneously, the percentage of "shape changed" platelets significantly increase. After the initial activation, platelets morphology begin to recover although the CPB continue. During

the late period of CPB, a highly significant correlation between increasing plasma levels of α-granule compounds (platelet factor 4 and ß-thromboglobulin) and lysis parameters (lactic dehydrogenase and free hemoglobin) is found *(Zilla et al., 1989)*.

Under CPB condition, neutrophils release lysosomal hydrolase *(Addonizio et al., 1982)*, the specific granule constituent, lactoferrin, the azurophilic granule enzyme and elastase *(Wachtfogel et al., 1987)*.

CPB activates both the contact and clinical complement pathways. Presumably both pathways are initiated by activation of Hageman factor (Factor XII) on the surface of the bypass circuit *(Wachtfogel et al., 1989)*.

Another risk in CPB is the ischemic cardiac damage during aortic clamping and avoidance of the damage is dependent upon sufficient myocardial energy being produced to meet energy demands *(Buckberg, 1981)*.

Ischemic cardiac arrest causes severe myocardial damage and all surgeons now use chemical cardioplegia which stops the heart more safely. Cardioplegia also creates an environment of continued energy production, and counteract the deleterious

effects of ischemia *(Buckberg, 1982)*.

There is much improvement in myocardial protection during cardiac surgery and much successful operations with a smooth postoperative period as regard to the use of high potassium cardioplegic technique in open heart surgery. The incidence of preoperative myocardial infarction and infarction within 24 hours of surgery is used widely as an index of intraoperative myocardial protection *(Follette et al., 1978)*.

Measurement of ATP and creatine phosphate contents of the myocardium has experimentally been used as an important determination of myocardial preservation *(Welt et al., 1988)*. Myocardial biopsies taken before and after cardiopulmonary bypass and examined by electron microscopy is now possible to identify those patients who have suffered ischemic damage *(Sawa et al., 1989)*.

Elevation of serum estradiol level has been reported in men who had recovered from myocardial infarction. This suggests that hyperestrogenemia may be risk factor for myocardial infarction *(Phillips, 1976)*. However, it is difficult to know whether the elevation of serum estradiol levels in survivors of

myocardial infarction are a cause or a result of the acute event. Whatever the explanation, there is a remarkable clear separation of estradiol levels between normal individuals and young men surviving of myocardial infarction *(Entrican et al., 1978)*.

In survivors of myocardial infarction, serum prolactin levels are also elevated and the prolactin level tends to be directly associated with elevated Hageman factor *(Gordon et al., 1987)*.

AIM OF THE WORK

This work is a trial to study the mechanism of hypo and hypercoagulability states following open heart surgery (valve replacement), which is accompanied by myocardial infarction, and its relationship to the hormonal changes that commonly occur with coronary heart disease.

The aims of this study are :

1) To detect changes of serum estradiol and prolactin following open heart surgery (valve replacement) with induced myocardial infarction.
2) To detect the relationship of these hormones and the perioperative myocardial infarction.
3) To detect the early working coagulation factor disturbances, using Hageman factor and prekallikrein as indicators, after open heart surgery.
4) To detect the relationship between hormonal changes (estradiol and prolactin) and early-working coagulation reactions using Hageman factor and Prekallikrein.