Study ofthe effect of percutaneous balloon mitral valvoplasty on the levelof inflammatory mediators (high sensitive CRP, IL6) and their impact on the outcome ofBMV in patients with mitral stenosis

Thesis

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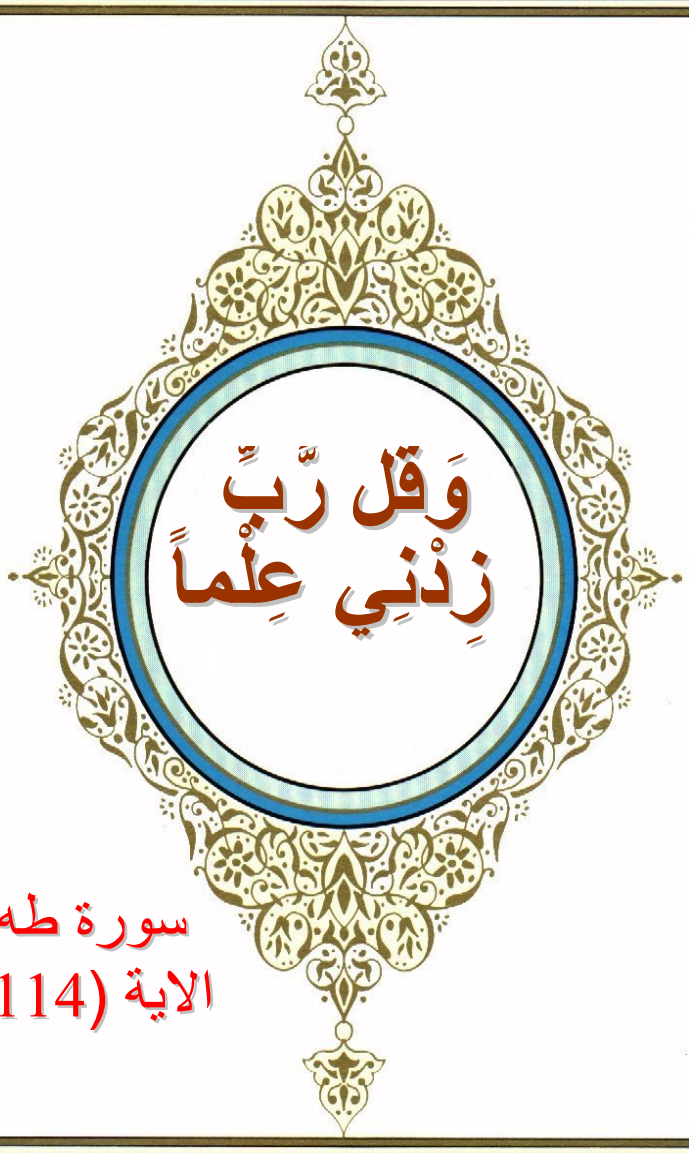

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List of Abbreviations

AF	Atrial fibrillation
AOPP	Advanced Oxidation Protein Products
ARF	Acute Rheumatic Fever
BMV	Balloon mitral valvuloplasty
CRHD	Chronic rheumatic heart disease
CRP	C-reactive protein
d-MVA$_{BMV}$	Change in MVA before and after BMV
d- MVA$_{followup}$	Change in MVA after 1 month
ECM	Extracellular matrix
ESR	Erythrocyte sedimentation rate
FN	Fibronectin
GM-CSF	Granulocyte-monocyte colony stimulating factor
HLA	Human Leucocytic Antigen
Hs-CRP	High sensitivity C-reactive protein
IFN	Interferon
IL	Interleukinn
ICAM-1	Intacellualr adhesion molecule -1
LAD	Left atrial diameter
LAP	Long acting penicillin
MR	Mitral regurgitation
MS	Mitral stenosis
MV	Mitral valve
MVA	Mitral valve area
MVA$_{BMV}$	Mitral valve area immediately after

List of Abbreviations

(Cont.)

MVA$_{followup}$	Mitral valve area at 1 month follow up
MVR	Mitral valve replacement
RHD	Rheumatic heart disease
RVSP	Right ventricular systolic pressure
RF	Rheumatic fever
TGF	Tumor growth factor
TH cell	T helper cell
VCAM	Vascular cell adhesion molecule -1

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INTRODUCTION

Almost all cases of mitral stenosis (MS) are secondary to rheumatic fever and the consequent rheumatic heart disease**(10)**. Rheumatic fever is an inflammatorydisease that occurs following a Streptococcus pyogenes infection, believed to be caused by antibodycross-reactivity. Once infection has occurred, innate and adaptive immune responses unfold several intertwining mechanisms in both the acute and chronic phases of rheumatic heart disease**(3)**. CRP and IL6 are two of the most important mediators of the inflammatory response. Acting as both pro-inflammatory and anti-inflammatory cytokines to stimulate the immune response during infection or other forms of tissue damage**(122)**.

Balloon mitral valvuloplasty (BMV) was introduced in 1984 by Inoue who developed the procedure as a logical extension of surgical closed commissurotomy. Since then, BMV has emerged as the treatment of choice for severe pliable rheumatic mitral stenosis**(97)** .There are many factors which may affect the result of valvuloplasty procedure such as extrinsic factors related to the technique of BMV or intrinsic factors related to patient age ,sex ,rhythm , pathological affection of the mitral valve,initial valve area ,presence of mitral incompetence**(102)**.

AIM OF THE STUDY

Tostudy the correlation between inflammatory mediators (Interleukin 6 and high sensitive CRP) and Balloon Mitral Valvuloplasty in patients with mitral stenosis as regard the effect of BMV on the levels of Interleukin 6 and high sensitive CRP before and immediately after 24 hour from the procedure and follow up after one month,also we study the impact of this inflammatory mediators on the outcome of BMV.

IMMUNOLOGICAL BACKGROUND

Introduction:

In developing countries, Rheumatic fever (RF) remains an endemic disease with annual incidence ranging from 100 to 200 per 100.000 school-aged children and is a major cause of cardiovascular mortality[1].

According to ***Abdel-Moula et al.***[2] study in 1998, the prevalence of rheumatic fever in Egypt is about 6.2/1000 students, Which is very high to alert all health care providers to set guidelines in order to prevent rheumatic fever with all its cardiac complications.

Rheumatic fever is an inflammatory disease that occurs following a Streptococcus pyogenes infection, such as streptococcal pharyngitis or scarlet fever. It is believed to be caused by antibody cross-reactivity that can involve the heart, joints, skin, and brain, the illness typically develops two to three weeks after a streptococcal infection. Acute rheumatic fever commonly appears in children between the ages of 6 and 15, with only 20% of first-time attacks occurring in adults[3].

Modified Jones criteria were first published in (1944) by T. Duckett.According to revised Jones criteria, the diagnosis of rheumatic fever can be made when two of the major criteria or one major criterion plus two minor criteria, are present along

with evidence of streptococcal infection: elevated or rising antistreptolysin O titre or DNAase, or positive throat culture. Exceptions are chorea and indolent carditis, each of which by itself can indicate rheumatic fever**.** [(4)]

Major Criteria:

- ***Polyarthritis:*** A temporary migrating inflammation of the large joints, usually starting in the legs and migrating upwards.
- ***Carditis:*** Inflammation of the heart muscle which can manifest as congestive heart failure with shortness of breath, pericarditis with a rub, or a new heart murmur.
- ***Subcutaneous nodules:*** Painless, firm collections of collagen fibers over bones or tendons. They commonly appear on the back of the wrist, the outside elbow, and the front of the knees.
- ***Erythema marginatum:*** A long lasting rash that begins on the trunk or arms as macules and spreads outward to form a snake like ring while clearing in the middle. This rash never starts on the face and it become worse with heat.
- ***Sydenham's chorea (St. Vitus' dance):*** A characteristic series of rapid movements without purpose of the face and arms. This can occur very late in the disease for at least three months from onset of infection.

Minor Criteria:

- Fever of 38.2–38.9°C.

- Arthralgia*:* Joint pain without swelling (Cannot be included if polyarthritis is present as a major symptom).
- Raised erythrocyte sedimentation rate (ESR) or C reactive protein.
- Leukocytosis.
- ECG showing features of heart block, such as a prolonged PR interval (Cannot be included if carditis is present as a major symptom).
- Previous episode of rheumatic fever or inactive heart disease.[4]

Genetic susceptibility in rheumatic fever/rheumatic heart disease

The search for genetic markers revealed that human leukocyte associated antigen (HLA) class II genes were potentially involved with the development of RF and rheumatic heart disease (RHD). HLA class II genes arelocated in human chromosome 6 and are responsible for the control of immune responses. HLA class IImolecules play an important role in antigen presentationto the T-cell receptor (TCR) and consequentlyin the triggering of cellular and humoral immuneresponses. Association with different HLA class IIantigens has been found in several populations. Among the HLA class II alleles described, the association of DR7 with different DQ-B or DQ-A alleles seems to be associated with the development of multiple valvularlesionsor mitral valve regurgitation in RHD patients. HLA-DR53,another HLA class

II molecule, was found to be in strong association with RF/RHD in two studieswith mulatto Brazilian patients. HLA-DR4 and DR9 were found to be associated with RF in American Caucasian and Arabian patients, whereas in Egyptian and Latvian patients, HLA-DR7 was associated with the disease [5].

Pathophisiology

- RF is a systemic disease affecting the peri-arteriolar connective tissue and can occur after an untreated Group A Beta hemolytic streptococcal infection. It is believed to be caused by antibody cross-reactivity named as type II hypersensitivity reaction. During a Streptococcus infection, mature antigen presenting cells such as B cells present the bacterial antigen to CD4-T cells which differentiate into helper T2 cells. Helper T2cells subsequently activate the B cells to become plasma cells and induce the production of antibodies against the cell wall of Streptococcus mainly M protein. ***Goldstein***[6]and colleaguesshowed that antibodies to the *N*-acetylglucosamine carbohydrate cross-reacted with glycoproteins present in the heart valves that contain *N*-acetylglucosamine . ***Cunningham's***group[7] has shown that human monoclonal antibodies also react with *N*-acetylglucosamine, cardiac myosin and laminin. They have also demonstrated the *in vitro* cytotoxic activity of human

and murine monoclonal antibodies. Using anti-myosin antibodies purified by affinity from acute RF patient sera, they identified cross-reactive epitopes on myosin and the M5/M6 proteins. In addition, they demonstrated the potential role of these cross-reactive antibodies in the development of RHD by showing that they are able to bind to the endothelial surface, which may lead to inflammation, cellular infiltration and valve scarring [(7)].

- The first evidence of CD4 helper T-cell involvement in rheumatic heart disease lesions was described by ***Raizada et al***. [(8)] also to investigate their role in the development of heart-tissue lesions. Molecular mimicry between streptococci and hearttissue proteins was demonstrated through an analysis of the heart-tissue infiltrating T-cells leadingto local tissue damage in RHD. By generating T-cell clones from heart lesions of RHD patients, it was demonstrated that 7.5% of these cells recognize M protein peptides and heart tissue-derived proteins. An extension of this work defined the M5 as an immunodominant region recognized by both peripheral blood mononuclear cells (PBMC) and intralesional T-cell clones .In murine models, in which mice were immunized with intact cardiac myosin, lymph-node T-cells cross reacted with overlapping M5 peptides reinforcing the dominance of this region. [(8)]