ALPHA HUMAN ATRIAL NATRIURETIC PEPTIDE IN MITRAL VALVE DISEASES WITH AND WITHOUT ATRIAL FIBRILLATION

THESIS

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BY

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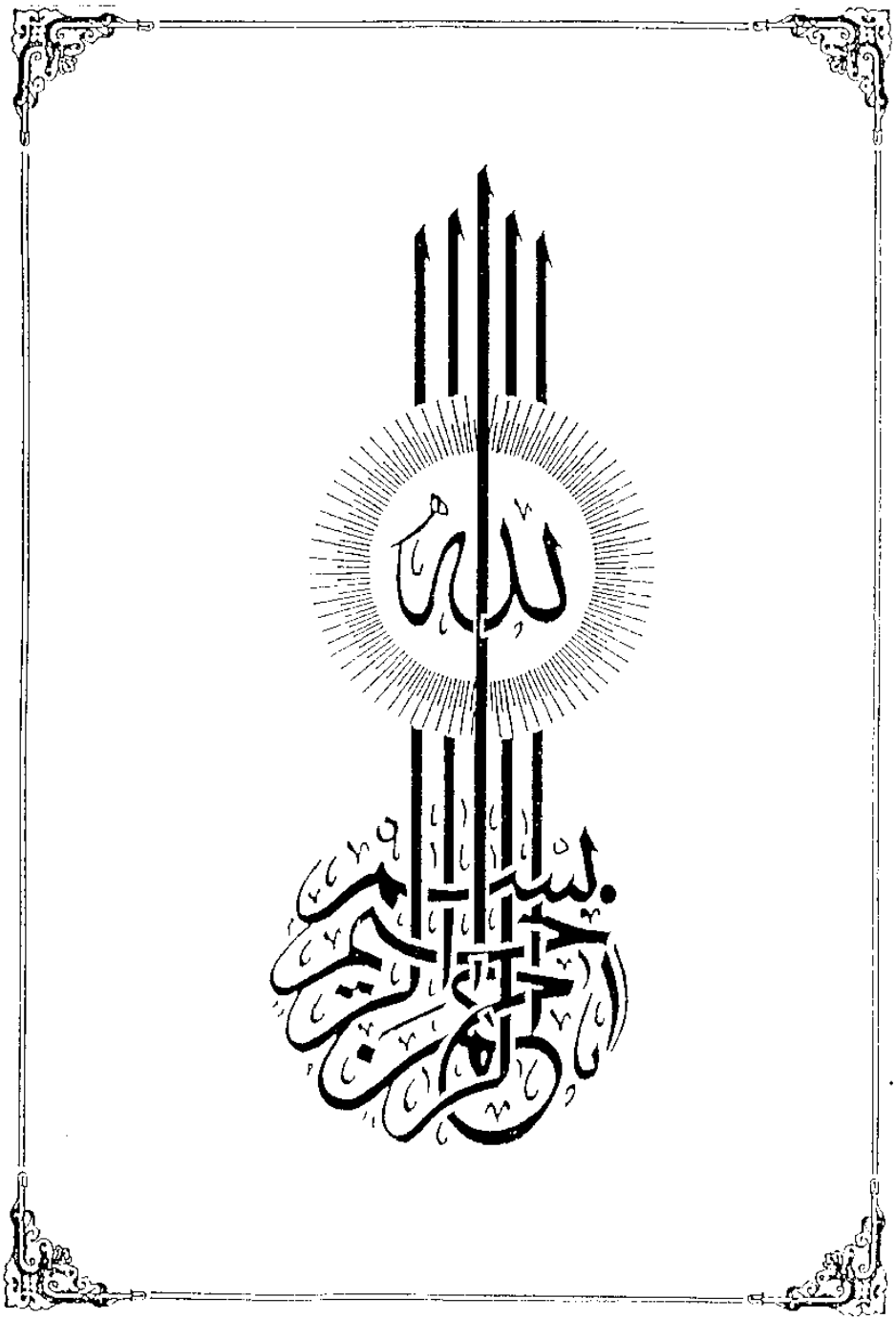

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CONTENTS

LIST OF ABBREVATION

(i)

α h ANP	Alpha human atrial natriuretic peptide
ACTH	Adrenocorticotrophic hormone
AF	Atrial fibrillation
ANP	Atrial natriuretic peptide
AoP	Aortic pressure
AR	Aortic regurgitation
Arg	Argenine
AS	Aortic stenosis
Asp	Aspartic acid
ATP	Adenosine triphosphate
AV	Atrioventricular
AVD	Aortic valve disease
AVP	Arginine vasopressine
cGMP	Cyclic guanosinemonophosphate
CHF	Congestive heart failure
cpm	count per minute
CSF	Cerebrospinal fluid
Cys	Cysteine
D	Diastolic
dDAVP	deamino-D-argenine vasopressin
DHEA	Dehydro epiandrosterone acetate
DOCA	Deoxycorticosterone acetate
ECG	Electrocardiograph
ED	End-diastolic pressure
EDTA	Ehylene diamine tetraacetic acid
Gln	Glutamic acid
Gly	Glycine
HR	Heart rate
i.c.v	Intra-cerebro-ventricular
IDDM	Insulin dependent diabetes mellitus
I.H.	Idiopathic hypercalcuria
Ile	Isoleucine
IV	Intravenous

IVC	Inferior vena cava
KIU	Kallikrein inactivator units
LAD	Left atrial diameter
Leu	Leucine
LT_4	L thyroxine
LVP	Left ventricular pressure
m	mean
Meth	Methionine
MR	Mitral regurgitation
mRNA	messenger riboneucleic acid
MS	Mitral stenosis
MVD	Mirtal valve disease.
NSB	Non specific binding
PAP	Pulmonary artery pressure
PAT	Paroxysmal atrial tachycardia
PCWP	Pulmonary capillary wedge pressure
Phe	Phenylalanine
RAP	Right atrial pressure
RIA	Radioimmunoassay
RNA	Riboneucleic acid
rpm	round per minute
RVP	Right ventricular pressure
S	Systolic
SD	Standard deviation
Ser	Serine
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SVT	Supraventricular tachycardia
TB	Total binding
TR	Tricuspid regurgitation
TSH	Thyroid stimulating hormone
Tyr	Tyrosine

REVIEW OF LITERATURE

MITRAL VALVE DISEASE

Mitral Stenosis

Etiology and pathology :

The predominant cause of mitral stenosis (MS) is rheumatic fever (Roberts, 1983). For less frequently, it is congenital, and this form is observed almost exclusively in infants and young children. Rarely mitral stenosis is a complication of malignant carcinoid (Braunwald, 1988), systemic lupus erythematosus (Evans and Sloman, 1981), rheumatoid artheritis (Bortolotti et al., 1984) and the mucopolysaccharidoses of the Hunter-Hurley phenotype (Johnson et al., 1981). It has been suggested, although without proof, that a number of viruses, especially coxackie virus, may be responsible for chronic volvular heart disease, including MS (Chandy et al., 1980). Amyloid deposits may occur on rheumatic valves and contribute to the obstruction to left atrial emptying (Ladefoged and Rohr, 1984). Methysergide therapy is an unusual but documented cause of MS (Misch, 1974). Left atrial tumer, particularly myxoma, ball valve thrombus in the left atrium, and a congenital membrane in the left atrium may also obstruct left atrial outflow and therefore simulate MS (Braunwald, 1988).

Approximately 25 per cent of all patients with rheumatic heart disease have pure MS. and an additional 40 per cent have combined MS and MR (Kumar et al., 1982).

Rheumatic fever results in four forms of fusion of the mitral valve apparatus leading to stenosis: (1) commissural, (2) cuspal, (3) chordal, and (4) combined (Braunwald, 1988). Characteristically, mitral valve cusps fuse at their edges, and fusion of the chordae results in thickening and shortening of these structures. The stenotic mitral valve is typically funnel-shaped and the orifice is frequently shaped like a "fish mouth" or button-hole, with calcium deposits in the valve leaflets sometimes extending to involve the valve ring, which may become quite thick (Waller, 1986). Enlargement of the left atrium and resultant elevation of the left main stem bronchus, calcification of the left atrial wall, the development of mural thrombi and obliterative changes in the pulmonary vascular bed may all result from chronic MS (Braunwald, 1988).

Pathophysiology :

In normal adults the mitral valve orifice is 4 to 6 cm^2 . When the orifice is reduced to approximately 2 cm^2, which is considered mild MS, blood can flow from the left atrium to the left ventricle only if propelled by an abnormal pressure gradient.

When the mitral valve opening is reduced to 1 cm^2, which is considered critical MS, a left atrioventricular pressure gradient of approximately 20 mmHg is required to maintain normal cardiac output at rest. The elevated left atrial pressure in turn raises pulmonary venous and capillary pressures, resulting in exertional dyspnea (Braunwald, 1988).

In order to assess the severity of obstruction of the mitral valve, it is essential to measure both the transvalvular pressure gradient and the flow rate. The latter depends not only on cardiac output but on heart rate as well. An increase in heart rate shortens diastole proportionately more than systole and diminishes the time available for flow across the mitral valve. Therefore at any given level of cardiac output, tachycardia augments the trans-mitral valvular pressure gradient and elevates left atrial pressure further (Dalen, 1987). This explains the sudden development of dyspnea and pulmonary oedema in previously asymptomatic patients with MS who experience atrial fibrillation with a rapid ventricular rate (Selzer, 1960).

Hydraulic considerations dectate that at any given orifice size, the transvalvular gradient is a function of the square of the transvalvular flow rate (Gorlin and Gorlin, 1951). Thus a doubling of flow rate will quadruple the pressure gradient, so that a stress

such as exercise in patients with moderte or severe MS will cause marked elevation of left atrial pressure (Nakhjavan et al., 1969).

Hemodynamics :

Left ventricular diastolic pressure is normal in patients with pure MS (Braunwald, 1988). In approximately 85 per cent of patients with pure MS, the end-diastolic volume is within the normal range, whereas it is reduced in the remainder (Kennedy, 1984).

In approximately one-fourth of patients with pure MS the ejection fraction and other ejection indices of systolic performance are below normal, most likely resulting from chronic reduction in preload and elevated afterload caused by reduced left ventricular thickness (Gash et al., 1983).

Regional hypo-kinesis is common (Colle et al., 1984) perhaps caused by extension of the scarring process from the mitral valve into the adjacent posterior basal myocardium (Heller and Carleton, 1970). The left ventricular mass is normal or slightly reduced (Kennedy, 1984). the myocardial contractility is normal or only slightly impaired in the majority of patients (Bolen et al., 1975). Most patients with MS show a normal elevation of

ejection fraction and reduction of end-systolic volume during exercise (Johnston and Kostuk, 1986).

In MS and sinus rhythm, the left atrial pressure pulse generally exhibits a prominent atrial contraction (a wave) and a gradual pressure decline after mitral valve opening (y descent); the mean left atrial pressure is elevated (Braunwald, 1988).

In patients with mild to moderate MS without elevation of pulmonary vascular resistence, pulmonary arterial pressure may be normal or only slightly elevated at rest and rises only during exercise. However, in patients with severe MS and/or those in whom the pulmonary vascular resistence is slightly increased, pulmonary arterial pressure is elevated when the patient is at rest and in rare cases of extreme elevation of the pulmonary vascular resistence it may exceed the systemic atrerial pressure. Further elevations of left atrial and pulmonary vascular pressures occur during exercise or tachycardia or both (Braunwald, 1988).

With moderate elevation of pulmonary artery pressure, right ventricular performance is maintained (Wroblewski et al., 1981). An elevation of pulmonary arterial systolic pressure exceeding 70 mmHg represents a serious impedence to imptying of the right ventricle, and when this level is exceeded in patients with

rheumatic heart disease, right ventricular end-diastolic and right atrial pressures often rise (Braunwald, 1988). During exercise, patients with MS and pulmonary hypertension commonly fail to exhibit normal elevation of right ventricular ejection fraction (Johnston and Kostuk, 1986).

The clinical and hemodynamic features of MS of any given severity are dictated largely by the levels of cardiac output and pulmonary vascualr resistence. The response to a given degree of mitral obstruction may be characterized on one end of the hemodynamic spectrum by a normal cardiac output and a high left atrioventricular pressure gradient or, at the opposite end of the spectrum, by a markedly reduced cardiac output and low transvalvular pressure gradient (Braunwald, 1988).

The combination of mitral valve disease and atrial inflammation secondary to rheumatic carditis causes left atrial dilatation, fibrosis of the atrial wall, and disorganization of the atrial muscle bundles. The last leads to disparate conduction velocities. Premature atrial activation due either to automatic focus or to reentry may stimulate the left atrium during the vulnerable period and may thus precipitate bout of atrial fibrillation (Braunwald, 1988). Chronic atrial fibrillation results in turn in diffuse atrophy of the muscle, which causes further

inhomogenetty of refractoriness and conduction and leads to irreversible atrial fibrillation (Unverferth et al.. 1984).

Mitral Incompetence

Etiology and pathology :

The mitral valve apparatus involves the mitral annulus, the mitral leaflets per se, the chordae tendineae, and the papillary muscles. Abnormalities of any of these structures may cause mitral incompitence or regurgitation (MR) (Roberts, 1983).

Abnormalities of valve leaflets :

MR due to involvement of the valve leaflets occurs most commonly in chronic rheumatic heart disease and is more frequent in men than in women. It is a consequence of shortening, rigidity, deformity, and retraction of one or both cusps of the mitral valve as well as shortening and fusion of the chordae tendineae and papillary muscles (Davies, 1985). Distruction of the mitral valve leaflets can also be a consequence of systemic lupus erythematosus (Dajee et al.. 1983), penetrating and non penetrating trauma, and infective endocarditis. Retraction of the mitral valve cusps during the healing phase of endocarditis can also cause MR (Brounwald, 1988).