EFFECT OF SHORT TERM DOBUTAMINE THERAPY ON VENTRICULAR ARRHYTHMIA AND SERUM POTASSIUM LEVELS IN PATIENTS WITH REFRACTORY HEART FAILURE

THESIS

Submitted for Partial Fulfilment

of

The M.SC. Degree in Cardiology

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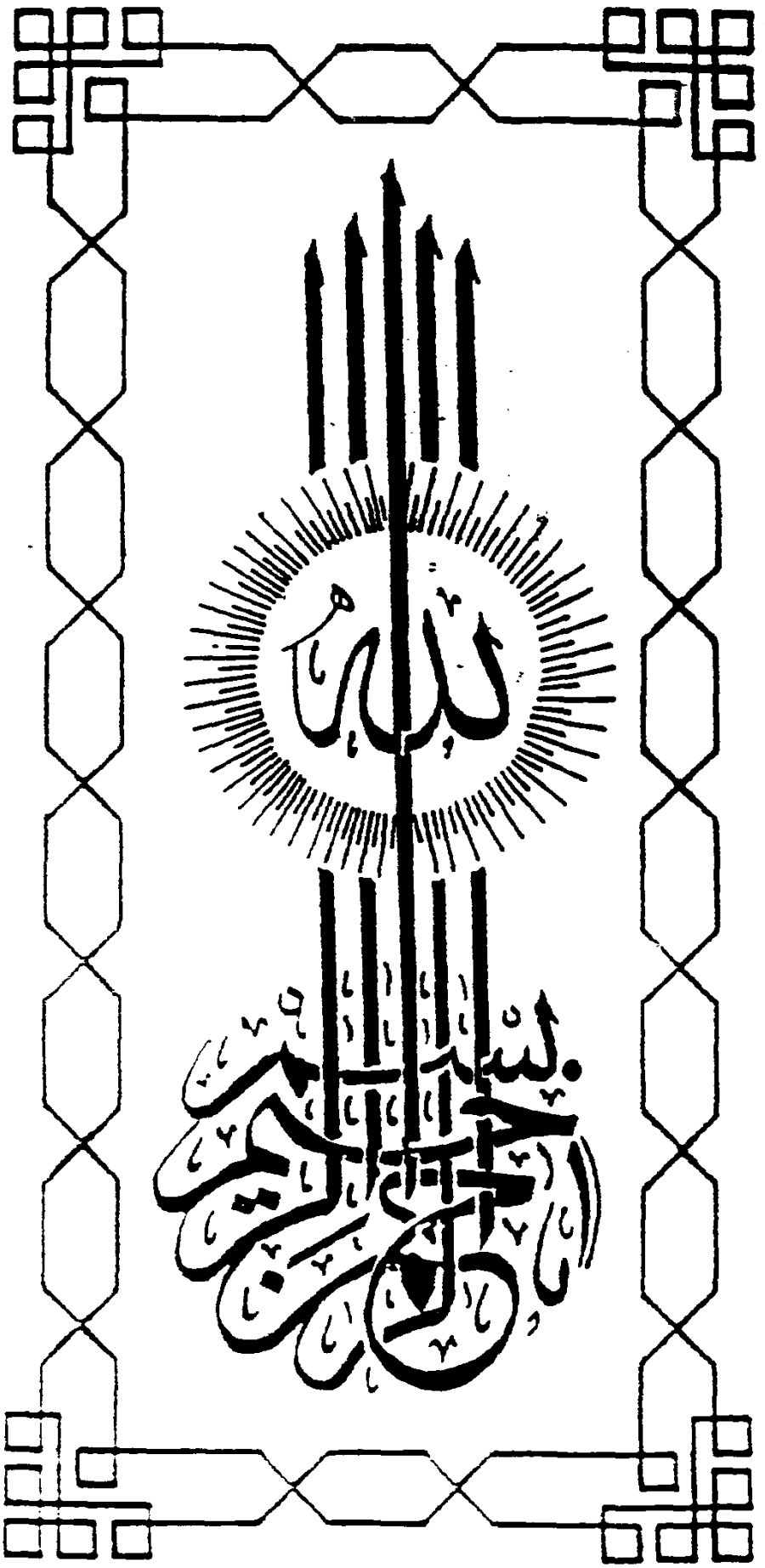

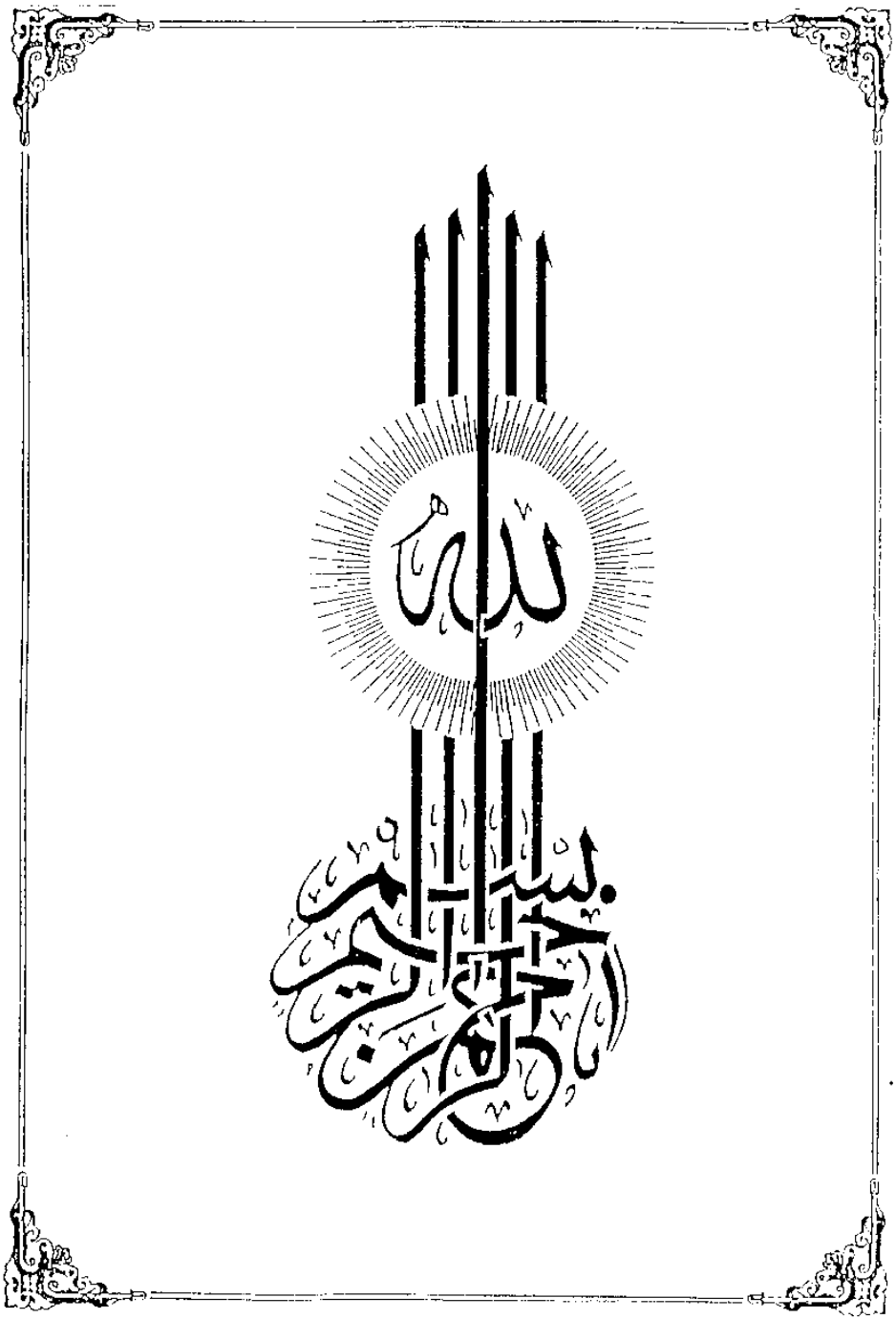

TO

My Parents

My Wife

and

My Daughter

CONTENTS

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Page

ACKNOWLEDGEMENT

I would like to express my deep gratitude to prof. **Dr. Adel El-Etriby,** Assistant prof. of cardiology, Ain Shams University, under whose supervision I had the honour to proceed with this work, for his continuous encouragement in initiating and completing this work.

I do feel greatly indebted to **Dr. Maiy Hamdy El-Sayed,** Lecturer of cardiology, Ain Shams University for her constant support and valuable remarks that have been of utmost help in performing this work.

I would also like to thank **Dr. Nevine Nabil Kassem,** Lecturer of clinical pathology, Ain Shams University, who was of great help to me in this work and to whom I will always be indebted.

INTRODUCTION

Dobutamine is known to be a potent, intravenously administered inotropic agent used for temporary circulatory support in patients with severe pump failure (Leier and Unverferth, 1983).

Recent reports also have advocated its intermittent use on a long term basis for treatment of refractory congestive heart failure (Berger and McSherry 1985).

Dobutamine exerts significant beta 1 stimulatory effect. with only modest stimulation of beta 2 receptors (William and Bishop, 1981).

Other beta agonists (such as epinephrine and salbutamol) by a postulated beta 2- receptor mechanism have been shown to cause a significant decrease in plasma potassium in normal subjects (Brown, 1985).

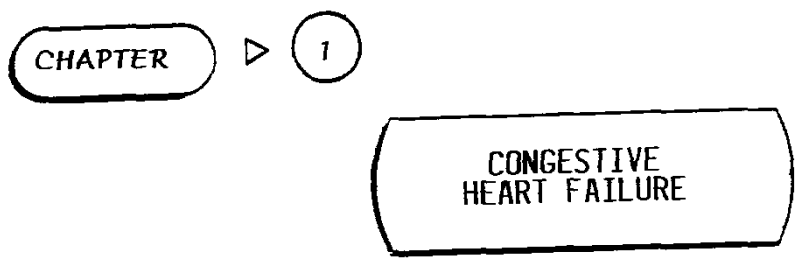
Ventricular arrhythmias are often present in patients with congestive heart failure and probably contribute to the high incidence of sudden death in this syndrome (Cohn, 1988).

Whereas beta agonists like dobutamine have been reported to worsen or precipitate these ventricular arrhythmias by multiple mechanisms including increased automaticity and decreased ventricular fibrillation threshold, their effect on altering potassium fluxes has only recently been stressed (Goldenberg et al, 1989).

Because potassium shifts could potentially contribute to arrhythmia production, the present study was designed to determine whether dobutamine, a predominant beta 1 agonist, could produce significant serum potassium changes in patients with congestive heart failure that may lead to or exacerbate ventricular arrhythmias in those critically ill patients.

PART I

REVIEW OF LITERATURE



CONGESTIVE HEART FAILURE

A. DEFINITION :

A traditional physiological definition of heart failure is that it represents a syndrome in which cardiac output doesn't keep pace with the peripheral demands for blood flow (Cohn, 1988).
This definition, however, does not fully describe the syndrome of congestive heart failure as seen in clinical practice. Thus, from a functional view point, it is clear that congestive heart failure also includes the symptoms of dyspnea and fatigue and a decrease in exercise tolerance.

Therefore, there is not only a decrease in peripheral blood flow to meet metabolic demands but also an increase in atrial pressures leading to the signs and symptoms of either right or left heart failure or. both (Parmley 1989).

Regardless of specific definition used, heart failure is a syndrome with multiple aetiologies in which low output and congestive symptoms are prominant, exercise capacity is generally decrease and life expectancy may be significantly reduced (Schlant and Hurst, 1990).

B. AETIOLOGY :

Myocardial dysfunction eventuating in systolic and diastolic pump function abnormalities is a consequence of a wide variety of cardiac diseases (Cohn. 1988).

The major pathophysiologic processes that contribute to the development of congestive heart failure incluce pressure overload. volume overload, loss of muscle, decreased contractility and restricted filling.

- **Pressure overload** is commonly caused by systemic hypertension or by outflow tract obstruction such as valvular aortic stenosis (Parmley, 1985). Over the past 2 decades. however. better recognition and treatment of high blood pressure have reduced the relative importance of hypertension as a cause of heart failure (Parmley 1989).

- **Volume overload** can be caused by several different conditions, such as aortic or mitral regurgitation. High output states can also contribute to volume overload of the left ventricle (Parmley, 1985).

Prolonged pressure or volume overload leads to intrinsic changes in myocardial contractility which appear to be mostly irreversible (Braunwald 1992 A).

- **Loss of muscle** as a cause of CHF is best exemplified by the patient with coronary artery disease who has one or more myocardial infarctions. This loss of muscle decreases the pumping capabilities of the heart and can lead to the same irreversible changes in the remaining normal myocardium (Parmley 1985).

Coronary artery disease is the underlying cause in about 50 to 75% of patient with heart failure (Franciosa et al., 1983). When 40% or more of the myocardium is lost in acute myocardial infarction, this results in cardiogenic shock (Page et al. 1971).

- **A decrease in the intrinsic contractility** of heart muscle is exemplified by conditions such as volume and pressure overload and cardiomyopathy (Parmley, 1985).

The prolonged volume or pressure overload causes the myocardium to undergo a sequence of structural and biochemical changes that lead to fibrosis and cell death due to chronic increase in energy expenditure that make the cardiac muscle in an energy starved state (Katz, 1989A).

- **Restricted filling** of the heart includes hypertrophic cardiomyopathy, hypertrophy from any cause, restrictive cardiomyopathy, pericardial disease, certain infiltrative diseases such as amyloid or any process that impedes filling of the ventricle and thus leads to an increase in atrial pressures when cardiac output is increased (Parmley, 1989).

C. MYOCARDIAL CHANGES IN HEART FAILURE :

A fundamental problem for patients with systolic dysfunction is a decline in myocardial contractility. This can be the result of prolonged pressure or volume overload or an intrinsic decline associated with cardiomyopathy (Parmley, 1989).

The reduction in intrinsic contractility is associated with several myocardial changes (Parmley, 1985), These changes play an important role in the pathogenesis of the abnormal cardiac function seen in patients with congestive heart failure (Katz, 1989 A).

1- Mechanical Alterations :

Systolic Abnormalities :

A reduction in myocardial contractility is manifested by decreased force development, decreased rate of force development and decreased velocity of shortening at given loading conditions (Parmley, 1989).

Ejection phase indices including ejection fraction, fractional shortening and the mean velocity of internal diameter or circumferential fiber shortening are the most useful and practical means of detecting depressed myocardial function.

End systolic indices are new methods to evaluate left ventricular function that are independent on or account for, loading conditions. (Carabello and Spann, 1984).

In 1970, Bristow et al studied systolic and diastolic abnormalities in patients with coronary artery disease. Left ventricular volume and circumference were calculated from cineangiograms at 60 frams/sec. in 15 patients with coronary artery disease and five control subjects. They found that significant abnormalities of performance of the myocardium were often present in patients with coronary artery disease despite absence of significant left ventricular dilatation.

They demonstrated a depression of ejection fraction, and the extent and rate of circumferential fiber shortening, variables which are reasonable indicators of the competence of the contractile elements.

They also showed frequent abnormalities of left ventricular diastolic pressure volume relationships and often had raised end diastolic pressure (Bristow et al, 1970).

Three late systolic indices of ventricular contractility (end-systolic pressure-dimension relation, end-systolic pressure volume relation, and peak systolic pressure end-systolic dimension relation) were non invasively determined in subjects with chronic congestive heart failure (Binkley et al., 1988) to determine the feasibility of the method and to assess the linearity and slopes of the relationships in this population. They used M-mode echocardiogram, indirect carotid pulse tracing, phonocardiogram and electrocardiogram for recording these indices.

All slopes were markedly reduced compared to those reported in normal individuals, reflecting the left ventricular dysfunction clinically evident in this population with moderate to severe congestive heart failure.
These data indicate that measurments of late systolic indices of ventricular contractility by this non invasive technique is feasible in subjects with congestive heart failure and yields reduced slopes consistent with diminished contractile state of this population (Binkley et al., 1988).

Diastolic Abnormalities

Cardiac relaxation is a complex process influenced by anatomic and physiologic factors (Iskandrian et al., 1988).

- Basic components of diastolic function :-
  a. Active properties
     ventricular relaxation
  b. Passive properties
     1. Chamber stiffness
     2. Muscle stiffness

- Clinical phases of diastole :
  a. Isovolumic relaxation time.
  b. Rapid filling phase
  c. Slow filling phase
  d. Atrial contraction (Plotnick, 1989).

* Methods for assessing left ventricular diastolic function include:-

- **Rate of ventricular relaxation** : which can be estimated by using the equation :-

$$P(t) = (Po - P\infty)\, e^{-t/T} - P\infty$$

Where Po is pressure at time of dp/dt, t is time after dp/dt min, and T is time constant of isovolumic pressure fall, and $P\infty$ which is the pressure to which ventricle would relax if the ventricle was held at its end-systolic volume and allowed to relax completely (Gilbert and Glanz, 1989).

T shortens with beta adrenoceptor stimulation of the myocardium, and is prolonged with beta blockade during post ischemic reperfusion, and with advanced age (Braunwald, 1992 B).

- **Peak filling rate and time peak filling :-**

These variables have been found to be altered in a variety of disorders, including coronary artery disease, hypertension, heart failure and hypertrophic cardiomyopathy. (Zoghbi and Bolli. 1991).

Measures of abnormal filling by the radionuclide technique include reduced peak filling rate (P F R), prolonged time from end systole to peak filling rate (T P F R), and increase in the contribution of atrial systole to left ventricular filling (Iskandrian et al., 1988). P F R is reduced when left ventricular inflow is reduced: in hypovolemia, when relaxation is slowed, as occurs in myocardial ischemia, with concentric hypertropny secondary to hypertension or aortic stenosis, and especially in hypertrophic cardiomyopathy (Plotnick. 1989).

- **Left ventricular filling measured by doppler echocardiography :-**

with the advent of dopp.er echocardiography, intracardiac blood flow velocity can be easily determined with excelient time resolution depending on the changes in blood velocity during mitral inflow which reflect left ventricular filling dynamics and relate closely to the instantaneous pressure difference between the left atrium and left ventricle (Zoghbi and Bolli. 1991).