The Role of ventricular Dysrhythmias and their management in the Prognosis of Patients with Congestive Heart Failure Due to Rheumatic valvular Heart Disease

Thesis

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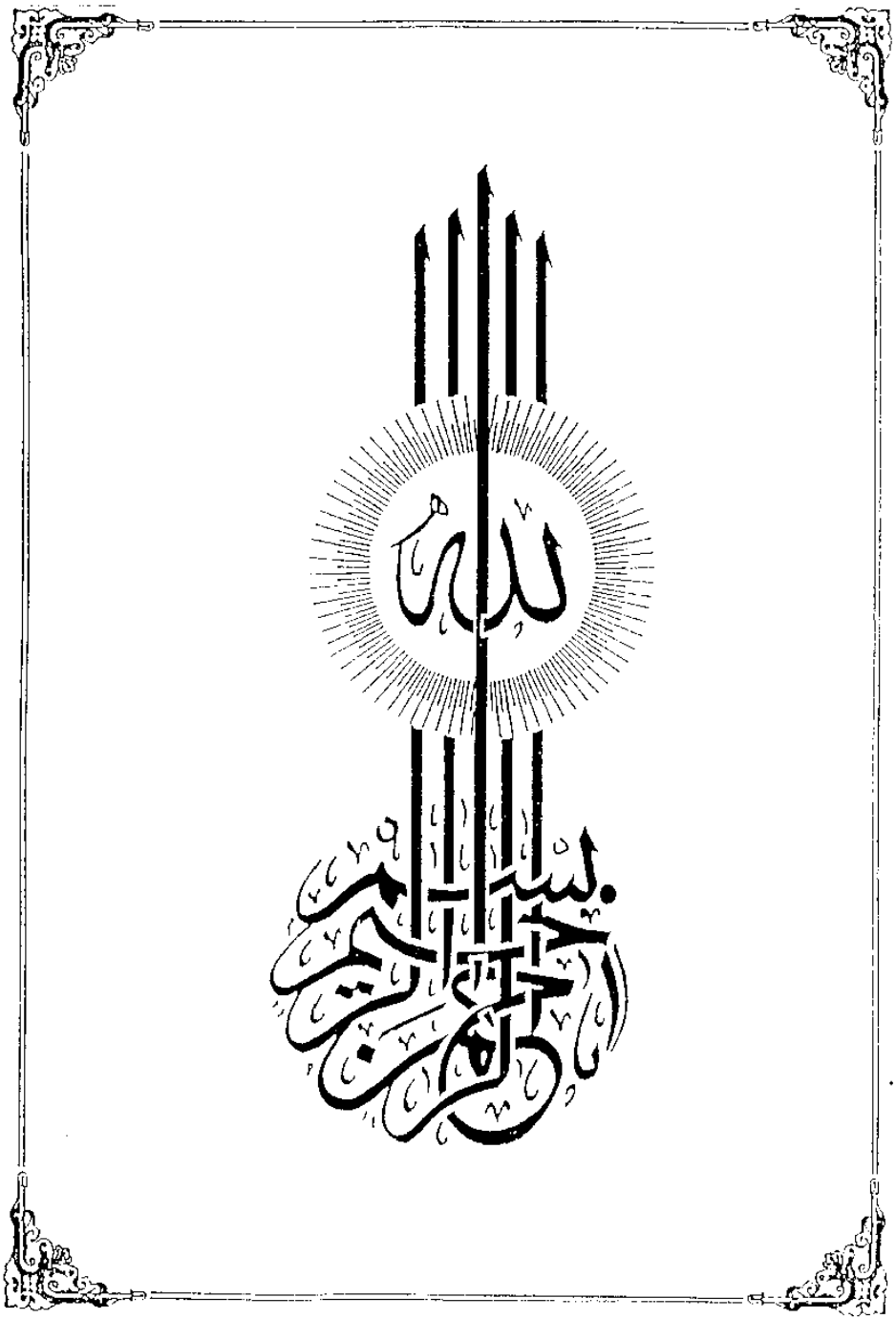

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Introduction and Aim of the Work

INTRODUCTION AND AIM OF THE WORK

Congestive heart failure is a highly fatal disorder with a 5 year survival rate less than 50%.

Many patients with congestive heart failure die suddenly and unexpectedly and most of these sudden deaths are probably arrhythmic in origin. However, several studies confirm that short term survival in severe congestive heart failure is related to both functional status and the presence of high grade ventricular arrhythmias. Those patients with markedly impaired left ventricular function in whom complex ventricular arrhythmias detected by 24 hours ambulatory Holter monitoring are at the highest risk of sudden death. Thus it can be argued that antiarrhythmic therapy is indicated in those patients although there is no evidence that antiarrhythmic therapy prevents sudden death.

AIM OF THE WORK

1. To evaluate the prevalence of ventricular arrhythmias in cases of congestive heart failure due to rheumatic valvular lesions.
2. To investigate the correlation between the frequency and severity of ventricular arrhythmias and the various variables in heart failure, e.g., age, sex, functional status and left ventricular function.
3. To find out whether complex ventricular arrhythmias represent an independent mortality risk factor in patients with heart failure.
4. To evaluate the effectiveness of amiodarone in abolishing significant ventricular arrhythmias in the setting of congestive heart failure and the effect of such treatment on the short term prognosis.

Review of Literature

PATHOPHYSIOLOGY OF HEART FAILURE

DEFINITIONS AND CONCEPTS

In physiologic terms: heart failure may be defined as that circumstance in which the heart does not deliver oxygen to the tissues at a rate in keeping with their oxygen requirements *(Weber et al., 1987).*

This definition, however, does not fully describe the syndrome of congestive heart failure as we see it in clinical practice. *Wilson et al. (1988)* choose to define heart failure as "A clinical syndrome caused by an abnormality of the heart, which is recognized by characteristic patterns of hemodynamic, renal, neural and hormonal responses".

Thus, heart failure is present when ventricular dysfunction is accompanied by certain body responses to the primary abnormality of the heart. Such a definition distinguishes between ventricular dysfunction and heart failure; ventricular dysfunction could be, and often is, present in the absence of heart failure. This definition has the advantages of:

1) Making no-statement about particular physiologic or biochemical features of heart failure, and
2) Conforming with the common usage of the term in medical practice.

The syndrome of heart failure may present as different clinical entities, e.g, acute pulmonary oedema, circulatory collapse or chronic heart failure.

Additional adjectives, such as forward and backward, right and left, congestive, and high and low output are useful clinical abbreviations but have no other virtue.

In 1989, Parmley concluded that, the two major symptoms of heart failure are dyspnea (particularly dyspnea on exertion) and fatigue. These two major symptoms relate to the two major hemodynamic abnormalities of congestive heart failure namely, an increase in left atrial pressure and a decrease in cardiac output.

It is also important to determine whether the signs and symptoms are primarily due to ventricular systolic dysfunction, diastolic dysfunction or a combination of the two. In most cases, systolic dysfunction,as manifested by a decreased ejection fraction, will be the most common cause of congestive heart failure. In a minority of cases, diastolic dysfunction will be the predominant cause.

Compensatory Mechanisms

A number of cardiac and circulatory compensation serve to restore an adequate output whenever it is threatened by disease. When these adjustments succeed in maintaining an adequate blood flow without distressing symptoms. the heart and circulation are said to be in a state of compensation. In mild heart failure, these compensatory mechanisms are able to restore to normal or near normal, the arterial blood pressure, organ perfusion, and cardiac output at rest and perhaps during moderate exercise. But it should be remembered that many of the symptoms and organ dysfunctions that occur in patients with heart failure are the result of overcompensation by the same mechanism *(Schlant et al., 1982).*

Neurohormonal Influences in the Pathogenesis of Congestive Heart Failure (CHF)

A number of neurotransmitters and hormonal substances constitute the "neurohormonal influence" in the clinical syndrome of CHF. However, the terminology itself, "neurohormones," "neurohumors" and their associated adjectives and descriptors, conjure up an image of medieval alchemy. More important this terminology gives the impression that these substances are equal in their impact on vascular tone and sodium balance, that they respond to the same stimuli, and that the extent of abnormality of each component is of similar magnitude *(Cody, 1989).*

A complex series of neurohormonal changes takes place consequent to the principal hemodynamic alterations in heart failure, i.e., reduction of cardiac output and atrial hypertension. Many of these neurohormonal changes occur in response to the inadequate arterial volume characteristic of systolic heart failure. These changes - heightened adrenergic drive, activation of the renin - angiotensin - aldosterone axis, and the augmented release of vasopressin - are truly compensatory and act to maintain perfusion to vital organs and to expand the inadequate arterial blood volume. However, each of these mechanisms may be thought of as a "double-edged sword" *(Braunwald, 1992).*

The Adrenergic Nervous System

In view of the importance of the adrenergic nervous system in normal regulation of the circulation, considerable attention has been directed to the activity of this system in heart failure. A crude index of the activity of this system, at rest and during exercise is provided by the concentration of norepinephrine (NE) in arterial blood.

The elevation in plasma NE seen in CHF has been universally accepted as an indication that the sympathetic nervous system is activated excessively,

Thomas et al. (1978) have found that the elevation of plasma NE levels correlates with the degree of clinical decompensation. Moreover, they demonstrated that there is an inverse relation between plasma NE level and left ventricular ejection fraction.

Braunwald (1978) found that measurement of 24 hours urinary NE excretion revealed marked elevation in patients with heart failure, indicating that the activity of the adrenergic nervous system and, presumably secretion of catecholamines by the adrenal medulla are also augmented at rest in these patients.

These observations of increased sympathetic activity are in contrast to the finding that myocardial stores of NE are depleted both in the failing human myocardium and in experimentally induced cardiac failure *(Vogel et al., 1969).* They also found that depletion of myocardial stores as well as reduction of the terminal adrenergic nerves in close proximity to cardiac muscles are correlated with the degree of heart failure. Thus cardiac NE content is consistently lower in human and in animal models of CHF. This finding has been interpreted to mean that excessive neural firing causes depletion of neurotransmitter if synthesis cannot keep up with the release *(Zelis et al., 1988).*

However, it was found that cardiac stores of NE are not fundamental for maintaining the basic contractile state of the myocardium and that cardiac NE depletion that occurs in CHF is not responsible for the intrinsic depression of cardiac contractility in failing heart muscle and does not appear to be a major primary cause of myocardial failure although it is an important contributing

mechanism *(Spann et al., 1966).* However, it was found that NE depleted cardiac muscles from the failing heart is supersensitive to circulating catecholamines *(Karakoff et al., 1968).*

Since the circulating arterial NE concentration is increased in heart failure and the failing heart muscle is not only responsive to exogenous NE but even supersensitive to its positive inotropic effects, the circulating catecholamines may play an important role in supporting contractile function in the failing heart *(Thomas et al., 1978).*

Parmley (1989) concluded that an increase in contractility can be beneficial in maintaining cardiac function and the increase in catecholamines that is required to produce this increase in contractility may be too great and produce damage to heart muscle and result in arrhythmia and this is considered as overshoot of compensatory mechanisms.

Adrenergic Receptors

In the sympathetic nervous system the physiologic effects of the endogenous catecholamines NE and epinephrine (E) are mediated by α- and β-adrenoreceptors. Both adrenoreceptors can be subdivided into two major subtypes: α adrenoreceptors into α_1 (predominant effect: vasoconstriction) and α_2 (Presynaptic: inhibition of NE release; postsynaptic vasoconstriction). β-adrenoreceptors into β_1 (cardiac effect, renal renin release, and lipolysis) and β_2 (Presynaptic: facilitation of NE release; postsynaptic: vascular, bronchial and uterine smooth muscle effects) *(Brodde, 1990).*

Cardiac β-adrenergic pathways are among the most thoroughly investigated biologic mechanisms. β_1 and β_2 receptors are genetically and pharmacologically distinct, and both receptors mediate the contractile effects of

catecholamines in a similar manner. The biologic signal produced by the occupancy of β-adrenergic receptors by catecholamine agonists is transduced, amplified, and regulated by a family of guanine nucleotide - binding proteins (G proteins), which serve both stimulatory and inhibitory functions *(Bristow et al., 1990).*

The human myocardium (nonfailing) contains approximately 80% β_1 and 20% β_2 receptors. Moreover α_1 receptors in human myocardium also modulate positive inotropy, but the α-receptor is a low density, low affinity receptor *(Francis, 1989).*

In the last few years evidence has accumulated that in patients with chronic heart failure the density and functional responsiveness of cardiac β-adrenoreceptors are markedly reduced, and the amount of reduction is related to the degree of heart failure (as judged clinically by New York Heart Association Functional Class) *(Bristow et al., 1989).*

A recent study by *Fowler et al. (1986)* that used a right ventricular endomyocardial biopsy technique indicated that patients with mild heart failure have approximately 38% reduction in β-receptor density, consistent with the concept that β-receptor down regulation is an important feature of heart failure.

He also, reported that β-receptor down regulation is associated with a specific blunting of the contractile response to β-agonists.

Bristow et al. (1988) reported that the down regulation of the β_1 receptor serves an important purpose. Chronic exposure to high levels of cardiac derived NE might overload the cell with calcium, permanently injuring it. NE has an affinity for the β_1 receptor that is 10 times greater than the affinity for the β_2

receptor, and the level of myocardial adrenergic exposure correlates fairly well with the degree of β_1 down regulation.

Recently, *Bristow et al. (1990)* found that heart failure produces a loss in β_1 receptors, while β_2 receptors remains constant (Fig. 1).

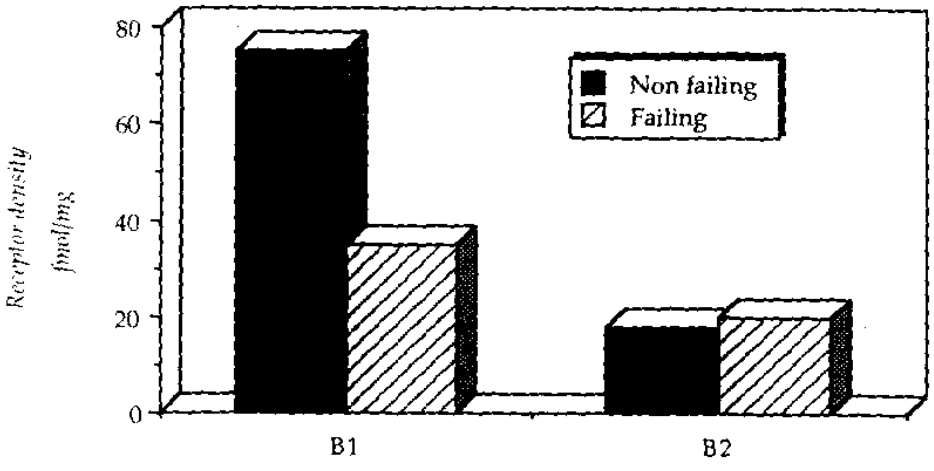

Fig. (1): **Bar graphs of β_1 and β_2 adrenergic receptor measurements in membranes extracted from failing and non-failing human left and right ventricular myocardium, with approximately equal numbers of left ventricle and right ventricle in each group.**

This selection subtype loss of β_1 receptors leads to a shift in the proportion of β_1 versus β_2 receptors from approximately 80 : 20 in non failing heart to 60 : 40 in failing ventricular myocardium *(Bristow et al., 1986)*. It therefore seems reasonable that β_1 down regulation serves an important biologic purpose in maintaining the viability of the myocardial cell in the face of severe adrenergic stress and the chronic β-blockade therapy in CHF may be acting to

prevent down regulation of β_1-receptors to be available for stimulation *(Francis, 1989)*.

Desensitization in the Failing Heart

The loss of the ability of the failing heart to respond to the sympathetic neurotransmitters arises from a mechanism referred to as desensitization. In this adaptive process, formerly called tachyphylaxis, tolerance to a neurotransmitter hormone, or drug develops after its repeated or prolonged administration. Although the sympathetic response to low cardiac output contributes to the circulatory adaptation to heart failure, a subsequent reduction in the ability of the failing heart to respond to β-adrenergic receptor agonists may contribute to the poor exercise tolerance in most patients with heart failure. It is by no means clear whether the desensitization of β-adrenergic receptors is beneficial or deleterious. For long term compensatory mechanism, it may be both beneficial, in reducing energy expenditure by the energy starved myocardium, and deleterious, in further depressing the output of the failing heart. This ambiguity underlies much of the current controversy over whether β-adrenergic-receptor agonists or antagonists should be used in treating CHF *(Katz, 1990)*.

Transmembrane Signal Transducers-G Proteins

When a β-adrenergic receptor in the myocardial membrane is stimulated by an agonist (e.g., NE), adenylate cyclase is stimulated, which catalyzes the conversion of intracellular adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Cyclic AMP activates cyclic AMP-dependent protein kinases, resulting in phosphorylation of various proteins, including voltage-dependent calcium channels and troponin I. The net result is the increased availability of calcium contractile proteins.