IDENTIFICATION OF VIABLE MYOCARDIUM IN PATIENTS WITH TRANSMURAL MYOCARDIAL INFARCTION BY LOW-DOSE DOBUTAMINE ECHOCARDIOGRAPHY

THESIS

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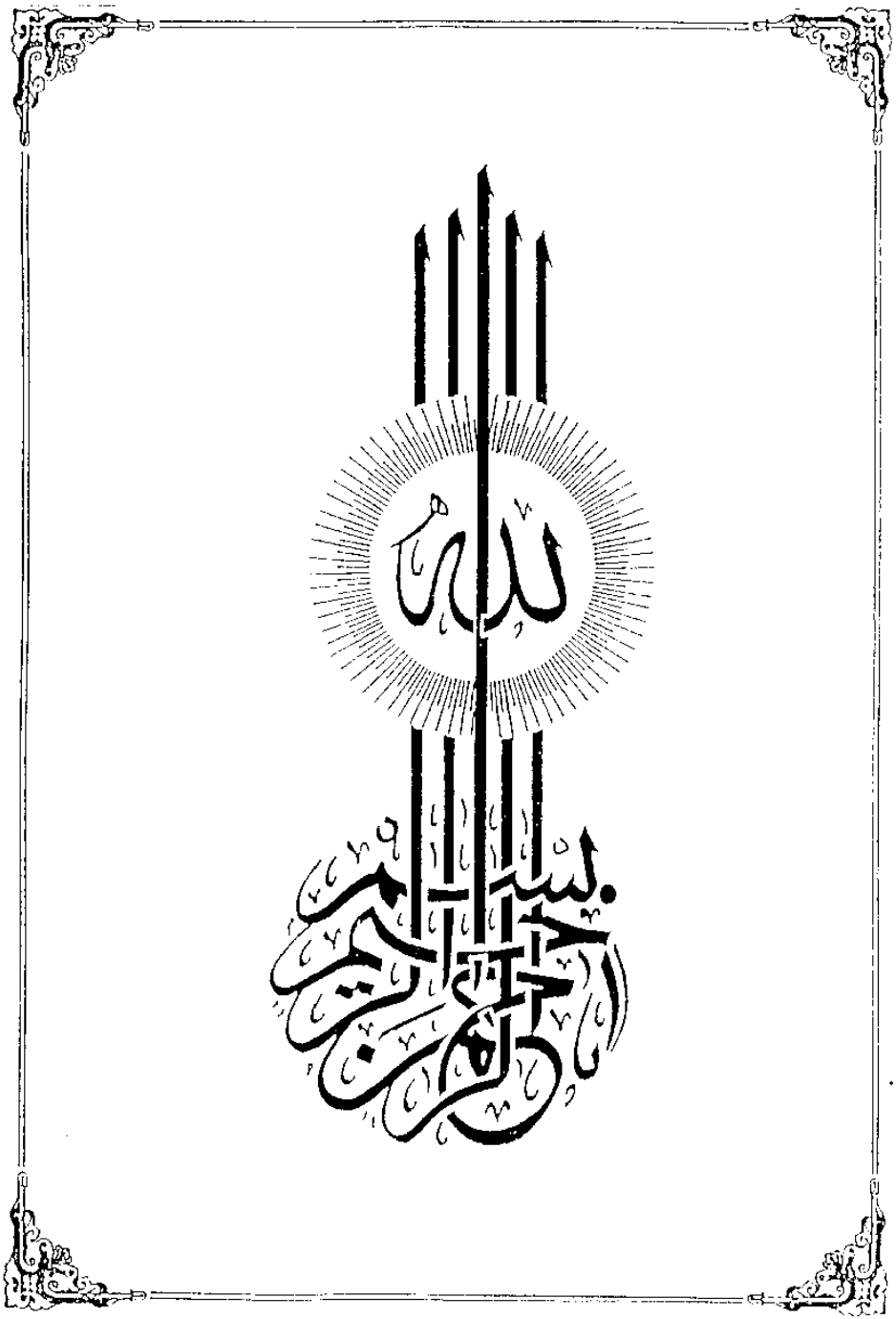
To My Family



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Contents

List of Abbreviattions

AMI	Acute myocardial infarction
ANT	Anterior
ATP	Adenosine triphosphate
BL	Baseline
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
DE	Dobutamine echocardiography
2-D	Two dimensional
ECG	Electrocardiogram
GL	Global
IHD	Ischemic heart disease
IPL	Inferior, Posterior or Lateral
IVS	Interventricular septum
IZ	Infarct zone
LAD	Left anterior descending coronary artery
LCx	Left circumflex coronary artery
LV	Left ventricle
MI	Myocardial infarction
Mvo_2	Myocardial oxygen consumption
PDA	Posterior descending coronary artery
PET	Positron emission tomography
PTCA	Percutaneous transluminal coronary angioplasty
RCA	Right coronary artery
SPECT	Single-photon emission computed tomography
WMA	Wall motion abnormality
WMAs	Wall motion abnormalities
WMSI	Wall motion score index

INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

The identification of viable myocardium has important therapeutic and prognostic implications in the patients with coronary artery disease (CAD) **(La Canna et al., 1992)**.

A number of tests are used for the non invasive detection of CAD, which results from the combination of different stimuli (exercise, pacing, pharmacological agents, e.g., dobutamine, dipyridamole etc.) and different signals and methodologies (EGG, echocardiography and scintigraphy) **(L'Abbate, 1991)**.

Echocardiography can be used in conjunction with a protocol for either exercise or pharmacological cardiovascular stress in order to identify the distribution and severity of CAD, with the induction of regional wall motion abnormality (WMA) being a sign of myocardial ischemia.

In addition to the evaluation of inducible ischemia, preliminary work is being performed with dobutamine stress echocardiography for the assessment of risk and patient's prognosis following myocardial infarction and as an indication of tissue viability for myocardium that remains dysfunctional at rest following thrombolytic therapy and hence usefulness to assess the effects of coronary revascularization on viable but non contractile myocardium **(Barilla et al., 1991)**.

AIM OF THE WORK

The aim of the study is to evaluate myocardial viability and function in patients with acute transmural myocardial infarction who received thrombolytic therapy and those who did not receive it by low-dose dobutamine echocardiography.

REVIEW OF LITERATURE

Dobutamine

Dobutamine is a synthetic cardioactive sympathomimetic amine that stimulates $ß_1$-, $ß_2$-and α-adrenoreceptors (**Majeurus. et al., 1989**). It resulted from systematic modification to the chemical structure of isoproterenol (**Tutlle and Mills, 1975**). **Williams and Bishop, (1981)**, suggested that $ß_1$ activity predominates over $ß_2$, and that α_1 predominates over α_2 agonist activity.

Basic Pharmacology

Dobutamine is a racemic mixture; the (-) enantiomer is a potent α_1- agonist, while the (+) enantiomer is a potent stimulant of both $ß_1$- and $ß_2$-receptors (**Majeurus et al., 1989**). Myocardial contractility is augmented by the stimulation of ß and α_1-receptors, while stimulation of each of these receptors in the systemic vascular bed counteracts the other. So that there is little net effect (**Leier et al., 1983**).

Dobutamine does not activate dopaminergic receptors and does not release norepinephrine from adrenergic nerve endings (**Robie and Goldberg, 1975**). At equivalent inotropic responses, dobutamine exerts a much weaker $ß_2$-adrenergic action than does isoproterenol and a much weaker α_1-adrenergic action than do either norepinephrine or dopamine. When given to patients with heart failure, dobutamine results in a reduction in systemic vascular resistance as cardiac output rises, and arterial pressure remains relatively constant (**Ruffolo et al., 1981**).

It is generally accepted that the positive inotropic action of dobutamine is mediated through direct stimulation of $ß_1$ adrenergic receptors in the myocardium, which in turn increases cyclic AMP **(Sonnenblick et al., 1979)**.

Dobutamine is presently the cardiotonic agent, which exerts the most potent inotropic action while producing limited and undesirable effects on the heart rate and blood pressure **(Sonnenblick et al., 1979)**.

Clinical Pharmacology

*Pharmacokinetics

Plasma dobutamine concentration correlates well with infusion rates. Cardiac output and stroke volume increased linearly, whereas pulmonary capillary wedge pressure, and total pulmonary and systemic resistances decreased linearly with increasing dobutamine concentrations **(Leier et. al., 1979)**.

The onset of action of a continuous infusion is within two minutes with maximal effect occurring at 10 min. or more **(Leier and Unverferth 1983)**.

Kates and Leier, (1978), administered dobutamine by a constant intravenous infusion at rates of 2.5, 5.0, 7.5 and 10.0 μg/kg/min. Steady state plasma levels increased in proportion to the infusion rate. The average total body clearance was found to be 2.35 $\pm$ 1.01 L/min./m^2, the elimination half-life was 2.37 $\pm$ 0.7 min and the distribution volume was 0.202 $\pm$ 0.084 L/kg **(Kates and Leier, 1978)**.

The short plasma half-life of dobutamine was found to be due to rapid redistribution of dobutamine from the plasma to the tissue and to the metabolism by catechol-o-methyl transferase (**Murphy et al., 1976**). This is favorable in the treatment of clinically unstable patients in whom the management of undesirable effects or inadvertent over administration of a drug is facilitated by rapid elimination (**Leier and Unverferth, 1983**). The major metabolites are glucuronide conjugates of dobutamine and 3-O-methyl derivative which are mainly exerted is urine (**Murphy et al., 1976**).

Theoretic plasma dobutamine levels (Cp) can be calculated from the equation

$$C_p = \frac{R_o}{V_d \times K}(1 - e^{-kt}) + C^1 p e^{-kt}$$

Where R_o is the infusion rate in μg/min/kg, V_d (volume of distribution) = 0.202 L/kg, t is the time (minutes) since the last change in the infusion rate, C^1p is the dobutamine plasma concentration at the end of the prior infusion rate interval, and k (elimination rate constant) = 0.3189 min^{-1}. (**Kates and Leier,1987**).

*Mechanism of Action :

Dobutamine acts through stimulation of ß-adrenergic receptors located on the cell surface. These receptors are coupled by a guanine-nucleotide-sensitive protein (G protein) to adenylate cyclase, an enzyme that causes increased generation of cyclic AMP (**Colucci, 1989**).

Cyclic adenosine monophosphate (cAMP) is the second messenger that mediates the cellular effects of sympathomimetic amines, to modify the Ca^{2+} fluxes responsible for cardiac excitation-contraction coupling (**Katz, 1989**), through voltage-dependent channels (**Colucci et al., 1988**), augmenting both contraction and relaxation of the myocardium (**Buser et al., 1989**).

Kass and Maugham, (1988), found that there was a marked shift of end systolic pressure-volume relation to the left and a steeping of the slope, consistent with substantial acute contractile reserve in response to intravenous infusion of dobutamine at 10 μg/kg/min. Dobutamine raises cardiac index while lowering left ventricular (LV) end diastolic pressure and leaving mean aortic pressure unchanged (**Smith, et al., 1992**).

Dobutamine has little effect on two other major determinants of myocardial oxygen consumption (MVo_2) i.e., heart rate and aortic pressure, and reduces a third, ventricular filling pressure, so it may be superior to dopamine in patient with low cardiac output states associated with ischemic heart disease (**Greene and Smith, 1976**). Dobutamine also affected a more favorable balance between myocardial oxygen supply and demand in patients with severee myocardial depression following cardiac surgery (**Fowler et al., 1984**).

In patients with severe heart failure, dobutamine in doses up to 10 μg/kg/min progressively increased cardiac output while decreasing systemic and pulmonary vascular resistance and filling pressure, without a significant effect on heart rate and ventricular irritability (**Leier, et al., 1978**).

Recent reports demonstrated that ß-adrenergic receptor stimulation with dobutamine causes significant acceleration of LV isovolumic relaxation. The positive inotropic response to dobutamine was significantly reduced in patients with congestive heart failure (CHF). Left ventricular isovolumic relaxation was significantly prolonged in CHF patients.

Intracoronary and intravenous dobutamine infusions caused significant acceleration of LV isovolumic relaxation in both normal subjects and patients with CHF (i.e. positive lusitropic response). This is mediated through the action of cAMP to :

1- Accelerate re-uptake of calcium by the sarcoplasmic reticulum

2- Reduce calcium sensitivity of the contractile apparatus.

3- Accelerate the rate of myofilament cross bridge detachment.

This lusitropic response to dobutamine is well preserved in patients with severe heart failure despite substantial attenuation of the ß-adrenergic positive inotropic response. Reduced cAMP generation in response to ß-adrenergic receptor stimulation might have little or no effect on LV relaxation (**Parker et al., 1991**).

*Dosage and Administration :

Reconstituted solution of dobutamine must be diluted to at least 50 ml prior to administration in 5% dextrose injection, 5% dextrose and 0.45% sodium chloride injection, 5% dextrose and 0.9 % sodium chloride injection, lactated Ringer's injection, 10 % dextrose injection 5% dextrose in lactated Ringer's injection, 0.9 % sodium chloride injection or sodium lactate injection. Dobutamine is incompatible with alkaline solutions such as 5 % sodium bicarbonate injection (**Olin et al., 1991**).