THE EFFECTS OF CALCIUM CHANNELS BLOCKERS ON THE DIASTOLIC FUNCTIONS OF THE LEFT VENTRICLE IN PATIENTS WITH ISCHEMIC HEART DISEASE: AN ECHOCARDIOGRAPHIC STUDY

THESIS

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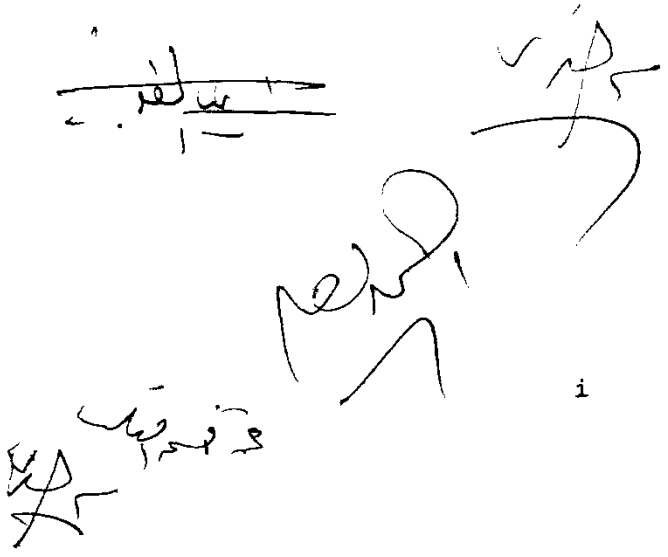

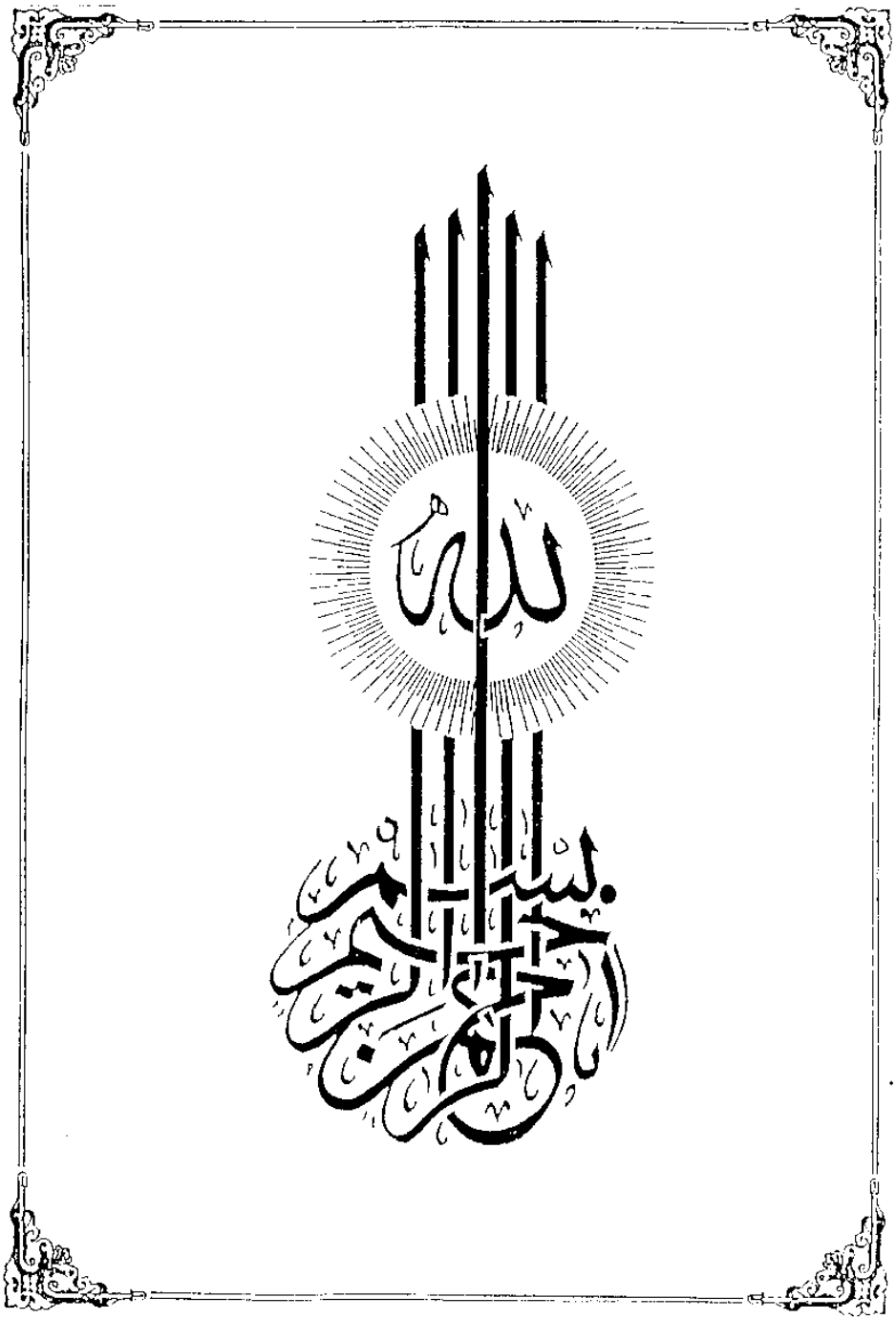

CONTENTS

Abbreviations

A:	peak velocity of late filling wave
A_i:	time-velocity integral of late filling wave
APC(s):	atrial premature contraction(s)
CAD:	coronary artery disease
CCBs:	calcium channel blockers
COP:	cardiac output
DBP:	diastolic blood pressure
dD/dT:	rate of change of ventricular diameter
DHP(s):	dihydropyridine(s)
dH/dT:	rate of change of ventricular thickness
E:	peak velocity of early filling wave
E_i:	time-velocity integral of early filling wave
ECHO:	echocardiography
EDD:	end-diastolic diameter
EDV	end-diastolic volume
EF:	ejection fraction
ET:	ejection time
ESD:	end-systolic diameter
ESV:	end-systolic volume
FS:	percentage fractional shortening
HCM:	hypertrophic cardiomyopathy
HR:	heart rate
IHD:	ischemic heart disease
IRP:	isovolumic relaxation period
IV(I):	intravenous (injection)
JPC(s):	junctional premature contraction(s)
LAD:	left atrial diameter
LV:	left ventricle
LVF:	left ventricular failure
MI:	myocardial infarction
MNSER:	mean normalized systolic ejection rate
PWT:	left ventricular posterior wall thickening
QRS-Ao:	QRS-aortic valve closure interval
QRS-M:	QRS-mitral valve opening interval
RtBBB:	right bundle branch block
SBP:	systolic blood pressure
SL:	sublingual
ST:	interventricular septal thickening
TC:	time constant of relaxation
VCF:	velocity of circumferential fibre shortening
VPC(s):	ventricular premature contraction(s)
VR:	venous return

Errata

Page no.	Para-graph no.	Line no.	Error	Correction
1	1	8	missed line	DCM: dilated cardiomyo-pathy (after DBP...)
5	2	3	missed word	to (before reduce)
7	1	3	missed word	of (before ischemic)
11	2	2	missed word	during (before balloon)
12	2	4	translate	translates
19	1	6	decreases	decrease
23	3	8	lower	Lower
24	2	4	missed bracket	) (after slope)
28	1	1	T (in the mathematical	t
	3	1	expressions)	
	4	1,2, 3		
	last	8	benzothia-zepines	benzothiazepines
31	1	2	of	in
32	3	5	,	and
36	2	6	increase .. improve	increased .. improved
37	3	8	6	5
38	3	last	missed lines	** (end of paragraph)
42	3	1	following	followings
	3	10	FC, EDV, ESV	FS, EDD, ESD
44	1	1	First sentence (The results ....)	The results are expressed in tables as mean value together with SD & SEM.
45	2	6	DBP	SBP
		7	SBP	DBP
50	1	5	CITE	ST
73	1	8	table (19)	table (20)
	2	12	table (20)	table (19)
76	1	10	table (21)	table (22)
	2	9	table (22)	table (21)
96	1	5	missed word	effect (before of)
98	1	1	make	makes
99	1	1	2-21/2	12-21/2
101	1	2	hurries	to hurry
104	1	4	a	at
105	2	4	missed word	with (before heart)
106	2	14	missed word	IV (after mg/kg)
109	1	2	10	20
arab sum	1	1	10	20

**: Each patient received 20 mg nifedipine SL and 0.15 mg verapamil IV in a cross over design. The interval between the 2 doses was not < 24 hours.

INTRODUCTION
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Introduction

Myocardial ischemia alters not only the systolic performance but also the diastolic characteristics of the left ventricle. The mechanism responsible for ischemic impairment of myocardial relaxation has not been fully elucidated but it has been proposed that calcium uptake from the vicinity of the myofibrils to the sarcoplasmic reticulum may be affected. This directed the attention to the role of calcium channel blockers in this respect.

The calcium channel blockers are a diverse group of compounds which differ in chemical structure, pharmacological profile, and clinical effects. They act on both the cardiac tissues as well as the wall of the blood vessels. Some of these calcium channel blockers are relatively cardioselective (i.e. direct myocardial effects are more prominent) while the others are relatively vasoselective (i.e. vasodilator effects are more prominent). This discrimination does not only depend on the chemical structure of the drug but is also affected by the route of administration as well as the myocardial state.

This study aims at holding a comparison between the effects of the 2 famous calcium channel blockers verapamil (as a prototype for the phenylalkylamine group) and nifedipine (as a prototype for dihydropyridine group) on left ventricular diastolic functions in patients with ischemic heart disease in whom the diastolic functions are already impaired. Besides, the effects on systolic functions and the haemodynamic alterations will be evaluated in an attempt to correlate these effects with the effects on the diastolic functions.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Physiology of myocardial relaxation and diastole of the heart:

Diastole of the cardiac muscle -from the physiological point of view- is the interval between 2 cardiac contraction-relaxation cycles. Diastole of the heart -from the clinical point of view- includes four phases: isovolumic relaxation phase, rapid filling phase, slow filling phase and atrial contraction phase (figure 1) **(Brutsaert and Sys, 1989)**.

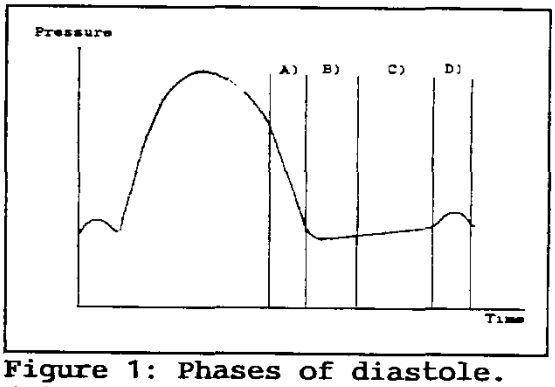

Figure 1: Phases of diastole. (A): isovolumic relaxation phase, B): rapid filling phase, C): slow filling phase, D): atrial contraction phase.)

The cardiac muscle properties in diastole is determined by its passive characteristics as well as its active behaviour. The passive characteristics of the cardiac muscle originates from its viscoelastic nature. The *viscous component* is ascribed to the extracellular collagen matrix as well as the contribution of many structures inside the cardiac muscle cell. This viscous component accounts for phenomena such as stiffness, creep (continuous increase in strain under fixed stress) and stress relaxation (continuous decrease in stress under fixed strain) [1] **(Winegrad, 1974, Borg et al., 1981, and Brady and Farnsworth, 1986)**. It is mainly restricted to longer sarcomere lengths and become apparent only at higher velocities of shortening **(Little and Wead, 1971, and Noble, 1977)**.

The active components of the cardiac diastolic properties is represented by the resting myocardial activity and myocardial

[1] : see appendix

relaxation. In resting or non-stimulated isolated cardiac muscle, a calcium-dependent *resting tone* has been observed (**Rumberger and Schwartz, 1969, Matsubara and Millman, 1974, and Moss et al., 1976**). This tone has been attributed in part to spontaneous Ca^{++} release with activation of at least a few cross-bridges (**Capogrossi et al., 1986 and Matsuda et al., 1982**). However, this may be considered "pathologic" or at least "unphysiologic" since it occurs only in non-stimulated muscle and in the interstimulus interval at low frequency stimulation (**Stern et al., 1983 and Capogrossi et al., 1986**). This is consistent with purely passive behaviour during diastole of a stimulated muscle and would exclude the effect of myocardial tone in physiologic conditions. In ischemic conditions, however, it is generally agreed that residual cross-bridges may persist during diastole and induce myocardial tone (**Pollack et al., 1972 and Loeffler and Sagawa, 1975**). Stiffness due to myocardial resting force -unlike that arising from the viscous properties- is relatively high at optimal muscle length (**Allen and Kentish, 1985**).

Concerning *myocardial relaxation*, **Brutsaert and Housmans, (1977)** reported that in mammalian ventricular cardiac muscle it is normally extremely sensitive to loading conditions. In the intact heart of highly developed animal species, the relaxation is load-dependent rather than activation-dependent. Load dependency of relaxation would mean that re-establishment of the optimum precontractile configuration is controlled mainly by the surrounding loading conditions and not by the decaying activation.

The load that controls relaxation is represented by internal and external restoring forces:

The internal restoring forces result from any attempt reduce the length of a resting muscle fibre. The resistance to shortening during systole will try to return the fibre to its original length during diastole (Parsons and Porter, 1966). Jewell (1977) has ascribed these intrinsic forces to: 1) the resistance to overlapping of the thin filaments in the middle of the sarcomere at lengths below 1.95 μm, 2) the longitudinal compression of thick filaments at sarcomere lengths less than 1.65 μm, and 3) the constraints imposed by the sarcomere and the surrounding connective tissue that will be stretched circumferentially at short lengths because of the constant volume behaviour of the cell (figure 2).

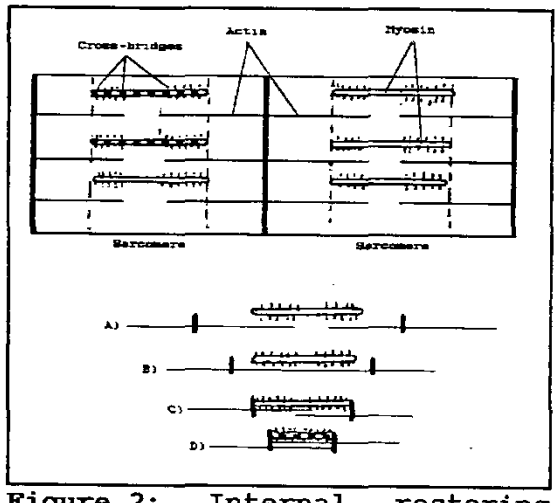

Figure 2: Internal restoring forces due to change in sarcomere length.(A): resting sarcomere, B): maximum contraction, C): overlap of actin filaments, D): compression of myosin filaments)

Variation in the mechanical uniformity of relaxation (*nonuniformity*), either on beat to beat basis or from one ventricular area to another, constitutes another possible intrinsic control mechanism of the return of the relaxing intact heart to its configuration. Non uniformity of relaxation of the ventricular wall may result from spatial inhomogenicity in the distribution of force along cardiac fibres, from temporal

inhomogenicity in the distribution of force along cardiac fibres (Cleworth and Edman, 1972, Edman and Flitney, 1977, and Krueger and Strobeck, 1978) or from other, still unknown factors that might be related to the specific kinetics of return of the heads of myosin molecules to the thick filaments after contraction (Yagi et al., 1977).

The external restoring forces arise from additional haemodynamic loading factors outside the heart. These forces are attributed to 1) Pressure waves transmitted to the ventricle; 2) Coronary perfusion; 3) Atrial contraction; and 4) Right ventricular effect.

Before aortic valve closure, arterial impedance will help to induce relaxation. Relaxation ensues as soon as the *aortic pressure* created for a given arterial impedance exceeds the load bearing capacity of the ventricular wall fibres. Variation in impedance, e.g., through neurohumoral adjustments or through reflected pressure waves, could result in a variable loading for the relaxing ventricle. A little later, after mitral valve opening early diastolic filling induced by the *atrial filling pressure* represents a dominant load during the final phase of relaxation. At this stage of relaxation, load sensitivity of the relaxing muscle fibres would be highly desirable in order to allow an instantaneous extension of the muscle fibres and hence rapid filling in early diastole. In addition, the transmission of the *pressure wave through the coronary system*, which results from abrupt aortoventricular pressure difference after closure of the aortic valve with the ensuing filling of these vessels, could also act as external restoring force on the relaxing

cardiac fibres in the ventricular wall.(Brutsaert and Paulus, 1979). This is particularly accused in the early relaxation abnormalities ischaemic heart disease (Serizawa et al., 1981).

Coronary perfusion pressure and *intramural vascular volume* were also postulated to affect left ventricular distensibility. A decrease in coronary perfusion pressure or flow would, by decreasing coronary vascular turgor, shift the diastolic pressure-volume relation to the right, thereby decreasing pressure and slope of pressure-volume relation at any volume (i.e., decreasing left ventricular stiffness or increasing left ventricular distensibility) (Salisbury et al., 1960).

In normal young subjects at rest, between 5 and 15% of filling is attributed to *atrial contraction*. An enhanced contribution of atrial contraction to ventricular filling, as in ischemic heart disease (IHD), is generally associated with a reduced early rapid filling and helps to maintain a normal cardiac output. An enhanced atrial contraction (or *atrial kick*) on 2-dimensional echocardiography, on transmitral Doppler velocimetry or on gated blood pool scintigraphy therefore constitutes an early and sensitive index of impaired early rapid filling (Sys and Brutsaert, 1989).

The mechanical interaction or *crosstalk* between the ventricles may affect rapid filling, but a major influence has been demonstrated on the end-diastolic pressure-volume relation of the left ventricle. Crosstalk has been explained by the fact that both ventricles share the interventricular septum as a common wall (direct interaction) and that they are connected in series through the pulmonary circulation (series interaction)

(Olsen et al., 1983, Visner et al., 1983 and Slinker and Glantz, 1986). Direct interaction between the ventricles is enhanced substantially in the presence of intact pericardium (Glantz et al., 1978, Ross, 1979 and Santamore et al., 1986).

From the aforementioned discussion, it appears that diastole at ventricular level is different from that of isolated cardiac muscle. The properties of isolated cardiac muscle during diastole are integrated with chamber geometry, coronary vascular and extraventricular components to determine diastolic behaviour of the intact ventricle (Mirsky and Rankin, 1979, Lewis and Gotsman, 1980 and Gaasch et al., 1985).

In diastole of the ventricle, significant deviations from the passive pressure-volume relation during ventricular filling particularly, although not only during rapid filling, have been documented. Myocardial relaxation during rapid filling and viscous effects during atrial contraction mask the elastic passive left ventricular pressure-volume relation. Passive viscous effects during rapid filling are less expected because they become apparent only at higher filling rates, at reportedly more than 1 diameter/s. They are, however, more pronounced during atrial contraction, i.e., the later phase of diastole when ventricular volume is largest since these effects appear to increase with longer sarcomere lengths. On the other hand, active muscle behaviour, in particular relaxation abnormalities, are much accused in the rapid filling phase (Pouleur et al., 1979). Diastasis, as the intermediate phase, appears the most appropriate phase for measuring, analyzing and evaluating passive pressure-volume relations; yet, even during diastasis, the left