

Tissue Doppler Echocardiographic
Evidence of Reverse Remodeling and
Improved Synchronicity After Biventricular
Pacing Therapy in Heart Failure

Thesis

*Submitted for Partial Fulfillment of M.D. Degree
In Cardiology*

By

Hesham Abd El-Wahab Hafez

M.B.B.Ch., M.Sc. (cardiology) - Ain Shams University

Under Supervision of

Prof. Dr. Saied A.Hafeez Khalid

Professor of Cardiology

Faculty of Medicine – Ain Shams University

Prof. Dr. Mohsen Mahmoud Mahdy

Professor of Cardiology

Faculty of Medicine – Ain Shams University

Prof. Dr. Mohsen Fahmy Aly

Prof. of Cardiology

Faculty of Medicine – Ain Shams University

**Faculty of Medicine
Ain Shams University**

٢٠٠٩

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



(صدق الله العظيم)

(سورة الأنعام. جزء من الآية ٩١)

Acknowledgment

The few words written here can never express the feeling of gratitude and kind regards that I have for my supervisors.

*I would like to express my deepest gratitude and appreciation to **Prof. Dr. Saied Abd El-Hafeez Khalid**, Prof. of Cardiology, Faculty of Medicine, Ain Shams University, for his kind support, advices and great help. I really feel great pleasure for working under his kind supervision.*

*I am greatly indebted to **Prof. Dr. Mohsen Mahmoud Mahdy**, Prof. of Cardiology, Faculty of Medicine, Ain Shams University, for his valuable help and support.*

*I will remain grateful to **Prof. Dr. Mohsen Fahmy Aly**, Prof. of Cardiology, Faculty of Medicine , Ain Shams University, for his kind support, help and encouragement during the progress and finalizing this work. I would like to thank him for spending much of his precious time in fulfillment of this work. I will always be grateful for his assistance. I enjoyed the most marvelous of the human relations with him, the pleasure of sharing views and ideas on our work.*

I would like also to thank all my professors, senior staff and my colleagues for their help and cooperation throughout the conduction of this work.

Finally, my best wishes go to my patients who were the corner stone in this study.

LIST OF CONTENTS

Title	Page No.
Introduction.....	١
Aim of the work.....	٤
Review of literature	
○ Heart failure.....	٥
○ Cardiac dyssynchrony	٩
○ Assessment of cardiac dyssynchrony.....	١٨
I. Conventional echocardiography.....	١٩
II. Newer echocardiographic techniques.	٣٤
○ Assessment Cardiac dyssnchrony by tissue Doppler imaging	٣٩
○ Left ventricular remodeling	٤٥
○ Left ventricular reverse remodeling by cardiac resynchronization therapy	٥١
○ Responders and non responders to cardiac resynchronization therapy	٥٦
○ Benefits of cardiac resynchronization therapy.....	٧٦
○ Risk of cardiac resynchronization therapy.....	٨٧
Patients and methods.....	٨٨
Results.....	٩٤
Discussion.....	١٢٥
Summary.....	١٤١
Conclusion and recommedation	١٤٥
References.....	١٤٧
Arabic summary	---

LIST OF TABLES

Tab. No.	Title	Page No.
Table ١:	New York Heart Association (NYHA) classification of Heart failure.....	٦
Table ٢:	Inclusion criteria in the cardiac resynchronization Therapy (CRT) randomized studies.....	٨
Table ٣:	Studies defining changes in QRS following CRT.....	١٥
Table ٤:	Prevalence of intraventricular dyssynchrony in patients with wide QRS complex	١٦
Table ٥:	Prevalence of interventricular dyssynchrony in patients with wide QRS complex	١٧
Table ٦:	Early and late effect after CRT	٤٤
Table ٧:	Markers of chronic response to CRT	٥٧
Table ٨:	Summery of echocardiographic predictors of response to CRT	٧٢
Table ٩:	Measurements of the mean LV end systolic and diastolic volumes before and after pacing therapy	٩٥
Table ١٠:	Measurements of the mean and average LV end systolic diameter before and after pacing therapy	٩٧
Table ١١:	Measurements of the mean and average LV end diastolic diameter before and after pacing therapy	٩٨
Table ١٢:	Measurements of the mean and average LV ejection fraction (EF) before and after pacing therapy	٩٩
Table ١٣:	Measurements of the mean and average LV Fractional shortening (FS) before and after pacing therapy	١٠٠

Tab. No.	Title	Page No.
Table١٤:	Measurements of the echocardiographic parameters of left ventricular systolic function	١٠٢
Table١٥:	Measurements of the echocardiographic parameters of LV diastolic function	١٠٥
Table١٦:	Measurements of the mean time to peak systolic velocity in different ventricular segments before and after pacing therapy.....	١٠٧
Table١٧:	Measurements of the mean peak systolic velocity in different ventricular segments, before and after pacing therapy	١٠٨
Table١٨:	Compassion of electrocardiographic, clinical and echocardiographic parameters between responders and non responders to LV reverse remodeling	١١٣
Table١٩:	Master table I: Echocardiographic parameters	١٢٣
	II: Tissue Doppler parameters	١٢٤

LIST OF FIGURES

Fig. No.	Title	Page No.
Figure ١:	Relation between the QRS duration and left ventricular dyssynchrony	١٦
Figure ٢:	Schematic drawing illustrating the negative impact of delayed electrical activation on aortic and mitral flow	٢٠
Figure ٣:	Effect of CRT on transmitral regurgitation profile.....	٢٢
Figure ٤:	Effect of electerical activation changes on transmital Inflow	٢٣
Figure ٥:	Simultaneous representation of ECG and Doppler LV filling flow	٢٤
Figure ٦:	Measurement of aortic and pulmonary pre-ejection Intervals	٢٥
Figure ٧:	Determination of LV pre-ejection period	٢٧
Figure ٨:	Schema for measurements of Doppler time intervals.....	٣٢
Figure ٩:	Color ٢-D tissue Doppler imaging in apical four chamber view	٣٨
Figure ١٠:	Proposed mechanisms of benefit of biventricular pacing.....	٨٦
Figure ١١:	Changes in the mean LV end systolic volume before after pacing therapy	٩٦
Figure ١٢:	Changes in the mean LV end diastolic volume before and after pacing therapy	٩٦
Figure ١٣:	Changes in the mean LV end systolic diameter before and after pacing therapy.....	٩٧
Figure ١٤:	Changes in the mean LV end diastolic diameter before and after pacing therapy	٩٨

Fig. No.	Title	Page No.
Figure ١٥:	Changes in the mean LVEF before and after pacing therapy.....	١٠٠
Figure ١٦:	Changes in the mean LV fractional shortening before and after pacing therapy	١٠١
Figure ١٧:	Changes in the mean dp/dt before and after pacing therapy.....	١٠٣
Figure ١٨:	Changes in the mean myocardial performance index before and after pacing therapy	١٠٣
Figure ١٩:	Changes in the mean mitral regurgitation jet area before and after pacing therapy.....	١٠٤
Figure ٢٠:	Changes in the mean LV filling time before and after pacing therapy	١٠٥
Figure ٢١:	Changes in the mean time to peak systolic velocity in Different ventricular segments	١٠٨
Figure ٢٢:	Changes in mean time to peak regional systolic velocity before and after pacing therapy	١١٢
Figure ٢٣:	TDI recordings of responder.....	١١٧
Figure ٢٤:	TDI recordings of non-responder	١٢٠

LIST OF ABBREVIATIONS

ACC	American collage of cardiology
ACE	Angiotensin Converting Enzyme
AHA	American Heart Association
ARB	Angiotensin Receptor Blockers
BVP	Biventricular pacing
CHF	Congestive heart failure
CRT	Cardiac resynchronization threapy
DT	Deceleration time
EF	Left ventricular ejection fraction
EMD	Electromechanical delay
ESC	European society of cardiology
ET	Ejection time
FS	Fractional shortening
ICD	Implantable cardioverter defibrillator
IVCT/ICT	Isovolumic contraction time
IVRT/IRT	Isovolumic relaxation time
IVCD	Interventricular conduction delay
IVMD	Interventricular mechanical delay
LV	Left ventricle
LVEDD	Left ventricular end diastolic diameter
LVEDV	Left ventricular end diastolic volume
LVESD	Left ventricular end systolic diameter
LVESV	Left ventricular end systolic volume
LV-PEI	Left ventricular pre-ejection interval
MPI	Myocadrial performance index
MR	Mitral regurgitation
ms	Milliseconds
NYHA	New York Heart Association
RV-PEI	Right ventricular pre-ejection interval
SPWMD	Septal to posterior wall motion delay
TDI	Tissue Doppler imaging

ABSTRACT

Background — Cardiac resynchronization therapy (CRT) is an effective therapy for patients with moderate to severe heart failure and prolonged QRS duration. The purpose of this study was to investigate the effect of biventricular pacing on left ventricular reverse remodeling and, cardiac function and cardiac synchronicity in patients with heart failure.

Methods and Results — Twenty patients with NYHA class III to IV heart failure and electrocardiographic wave complex duration ≥ 120 ms receiving biventricular pacing therapy were assessed serially up to 3 months after pacing. Conventional echocardiography was used to estimate the left ventricular dimensions, volumes and functions. Tissue Doppler echocardiography was performed using a 6-basal, 6-mid segmental model to assess the time to peak systolic contraction (Ts). The standard deviation of the Ts of the 12 LV (Ts-SD-12) segments in each patient was calculated as an index of systolic synchronicity.

There was significant improvement of ejection fraction, dp/dt, and myocardial performance index; decrease in mitral regurgitation, left ventricular (LV) end-diastolic (118 ± 36 versus 140 ± 34 mL, $P < .05$) and end-systolic volume (162 ± 24 versus 129 ± 24 mL, $P < .05$). There was a significant improvement in LV synchrony, as evident by homogeneous delay of Ts to a timing close to the latest (the lateral) segment abolishing the intersegmental difference in Ts and decreasing the standard deviation of Ts within the left ventricle (36.3 ± 10) at baseline versus 23.1 ± 0.8 ms after three months, $P < .05$). There was also improvement in interventricular synchrony. The dyssynchronous index (SD-Ts-12) failed to predict responders to cardiac resynchronization therapy.

Conclusions — Biventricular pacing reverses LV remodeling and improves cardiac function. Improvement of LV mechanical synchrony seems to be the predominant mechanism. The dyssynchronous index (SD-Ts-12) is not efficient predictor of cardiac resynchronization therapy response.

Key Words: heart failure– echocardiography – remodeling pacing.

INTRODUCTION

Heart failure is a progressive disease that is characterized by progressive left ventricular (LV) dilatation and loss of contractile function, a condition referred to as remodeling. The severity of LV remodeling has been shown to carry independent prognostic importance (Lee *et al.* 1993).

Therefore, treatments that are able to prevent or even regress LV remodeling are potentially beneficial. The use of angiotensin- converting enzyme inhibitor has been shown to prevent LV dilatation, conferring an associated survival benefit (Cleland *et al.* 1999).

Markers of reverse remodeling were reduction of left ventricular volumes, increase in LVEF without an increase in oxygen consumption, reduction of mitral regurgitation (Cazeau *et al.* 2001, Linde *et al.* 2002, Abraham *et al.* 2002, Saxon *et al.* 2002).

Synchronous biventricular pacing is a recent advance as an adjunctive non-pharmacological therapy for patients with chronic heart failure with electromechanical delay (Yu *et al.* 2002).

Resynchronization therapy is designed to help the right and left ventricles beat at the same time in a normal sequence treating ventricular dyssynchrony. It improves hemodynamic

Introduction

status acutely (Leclercq *et al.* 1998, Gras *et al.* 1998, Auricchio *et al.* 1999, Kass *et al.* 1999) and heart failure symptoms, exercise capacity, quality of life, and systolic function chronically (Cazeau *et al.* 2001, Linde *et al.* 2002).

The preliminary data have shown that biventricular pacing (BVP) is effective in regressing LV remodeling and is more powerful than medical therapy alone (Lau *et al.* 2000).

In the current guidelines, patients with LVEF $\leq 35\%$, sinus rhythm, and New York Heart Association functional class III or IV symptoms despite recommended optimal medical therapy and who have cardiac dyssynchrony, which is currently defined as a QRS duration > 120 ms, should receive cardiac resynchronization therapy (CRT) unless contraindicated (*Class: I, Level of evidence: A*) (Swedberg *et al.* 2000).

However, about one third of patients in the large multicenter BVP studies did not improve (non responders) despite BVP (Anderson *et al.* 2008).

There is increasing evidence, that there is only a weak correlation of electrical (QRS width) and mechanical dyssynchrony and the benefit of biventricular pacing. It seems that not all heart failure patients with LBBB have mechanical dyssynchrony (Ansalone *et al.* 2002).

These controversial data indicate the need for a more careful patient selection for biventricular pacing (BVP). Newer echocardiographic technique, such as Tissue Doppler Imaging, could potentially improve patient selection for BVP. The risks of pacemaker implantation and expenses in non-responders to BVP could be avoided. Furthermore, the cost-effectiveness of BVP would be augmented (Knebel *et al.* 2004).

Although the benefits of biventricular pacing have been long proposed to be related to resynchronizing LV contraction, especially pre-exciting the free wall region so that it will contract as early as the septal region, this has never been demonstrated objectively.

By using echocardiography with tissue Doppler imaging (TDI), it is possible to perform serial and quantitative assessment of regional cardiac synchronicity both before and after pacing therapy. These pre-implant parameters may help to select patients for biventricular pacing who will respond to therapy (Lau *et al.* 2000).

Many studies used TDI-based criteria to evaluate dyssynchrony and have generated a number of potential dyssynchrony indices. A few of these parameters have demonstrated the ability to distinguish CRT responders from nonresponders with a high degree of accuracy (Yu *et al.* 2002*).

AIM OF THE WORK

The aim of the present study is to assess:

The effect of biventricular pacing on left ventricular reverse remodeling, cardiac function and cardiac synchronicity in patients with heart failure by Echocardiography and Tissue Doppler Imaging.

HEART FAILURE

Heart failure (HF) is a clinical syndrome comprised of symptoms and signs associated with congestion and/or hypoperfusion. It can result from any structural or functional cardiac disorder that impairs the ability of the ventricles to eject blood (systolic dysfunction), to fill properly (diastolic dysfunction), or both (Hunt *et al.* 2001).

The implication of this system is that preventive strategies, including pharmacologic interventions, employed before the development of left ventricular (LV) dysfunction and before the development of HF symptoms may reduce HF progression, morbidity, and mortality in patients otherwise destined to develop HF symptoms. In those individuals with established HF, systolic dysfunction with cardiac dilation and an ejection fraction less than or equal to 40% accounts for two-thirds of the cases, and coronary artery disease is the cause of nearly 90% of the cases (Bjorn *et al.* 1999).

Sixty percent of the HF populations have NYHA Class II and III symptoms (Table 1). The annual mortality rate for this group of HF patients is 10%. Pharmacologic therapies have made a major impact in this group. However, despite the benefits of pharmacologic therapy, approximately 90% of HF patients will have moderate to severe symptoms with an annual mortality rate as high as 50%. The modes of death are progressive pump failure or sudden cardiac death (Cleland *et al.* 1999).

In the Metoprolol Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF trial), which enrolled 3991 heart failure patients with $EF \leq 40\%$, NYHA class II, III, and IV, patients with NYHA Class II symptoms were more likely to die suddenly (64%) rather than from progressive pump failure (94%). Patients with advanced NYHA Class IV HF were