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

Thesis

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بسم الله الرحمن الرحيم

وعلمتم ما لم تعلموا

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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 venticular 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 ≥١٢٠ ms receiving biventricular pacing therapy were assessed serially up to ٣ months after pacing. Conventional echocardiography was used to estimate the left ventricular dimensions, volumes and functions. Tissue Doppler echocardiography was performed using a ٦-basal, ٦-mid segmental model to assess the time to peak systolic contraction (Ts). The standard deviation of the Ts of the ١٢ LV (Ts-SD-١٢) 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 (٢١٨±٣٦ versus ١٨٥±٣٤ mL, *P*<٠.٠٥) and end-systolic volume (١٦٢±٢٤ versus ١٢٩±٢٤ mL, *P*<٠.٠٥). 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 (٣٦.٣±١٥) at baseline versus ٢٣.١±٥.٨ ms after three months, *P*<٠.٠٥). There was also improvement in interventricular synchrony. The dyssynchronous index (SD-Ts-١٢) 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 dyssynchrous index (SD-Ts-١٢) 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.* ١٩٩٣).

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.* ١٩٩٩).

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.*٢٠٠١, Linde *et al.* ٢٠٠٢, Abraham *et al.*٢٠٠٢, Saxon *et al.* ٢٠٠٢).

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.*٢٠٠٢).

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 status acutely (Leclercq *et al.* ١٩٩٨, Gras *et al.* ١٩٩٨, Auricchio *et al.*١٩٩٩, Kass *et al.* ١٩٩٩) and heart failure symptoms, exercise capacity, quality of life, and systolic function chronically (Cazeau *et al.*٢٠٠١, Linde *et al.*٢٠٠٢).

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.*٢٠٠٠).

In the current guidelines, patients with LVEF≤ ٣٥%, 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 > ١٢٠ ms, should receive cardiac resynchronization therapy (CRT) unless contraindicated *(Class: ١, Level of evidence: A)* (Swedberg *et al.* ٢٠٠٥).

However, about one third of patients in the large multicenter BVP studies did not improve (non responders) despite BVP (Anderson *et al.* ٢٠٠٨).

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.* ٢٠٠٢).

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.*٢٠٠٤).

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.*٢٠٠٠).

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.*٢٠٠٢*).

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.* ٢٠٠١).

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 ٤٠% accounts for two-thirds of the cases, and coronary artery disease is the cause of nearly ٧٠% of the cases (Bjorn *et al.*١٩٩٩).

Sixty percent of the HF populations have NYHA Class II and III symptoms (Table١). The annual mortality rate for this group of HF patients is ١٠%. Pharmacologic therapies have made a major impact in this group. However, despite the benefits of pharmacologic therapy, approximately ٢٠% of HF patients will have moderate to severe symptoms with an annual mortality rate as high as ٥٠%. The modes of death are progressive pump failure or sudden cardiac death (Cleland *et al.* ١٩٩٩).

In the Metoprolol Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF trial), which enrolled ٣٩٩١ heart failure patients with EF≤ ٤٠ %, NYHA class II, III, and IV, patients with NYHA Class II symptoms were more likely to die suddenly (٦٤%) rather than from progressive pump failure (٢٤%).Patients with advanced NYHA Class IV HF were