ROLE OF CARDIAC RESYNCHRONIZATION THERAPY IN CHRONIC HEART FAILURE

Essay

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List of Contents

List of Abbreviations

ACC	American college of cardiology.
ACE	Angiotensin converting enzyme.
AF	Atrial fibrillation.
ARB	Angiotensin-receptor blocker.
AV	Atrio-ventricular.
BNP	Brain natriuretic peptide.
BiV	Biventricular.
CARE-HF	Cardiac resynchronization therapy in heart failure.
CCTA	Cardiac computed tomography angiography.
CHADS II	A clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF).
CMR	Cardiac magnetic resonance.
COMPANION	Comparison of medical therapy , pacing and defibrillation
CRT	Cardiac resynchronization therapy.
CRT-D	Cardiac resynchronization therapy with biventricular defibrillator.
CRT-P	Cardiac resynchronization therapy with biventricular pacing.
CS	Coronary sinus.
DFT	Diastolic filling time.
dP/dtmax	Maximum rate of pressure change in the ventricle.
DGK	German society of cardiology.
EF	Ejection fraction.
ESD	End systolic diameter.
HF	Heart failure.
HR	Heart rate.
HRS	Heart rhythm society.

ICT	Isovolumetric contraction time.
INR	International normalization ratio.
IVCD	Intraventricular conduction delay.
IVMD	Interventricular mechanical delay.
LBBB	Left bundle branch block.
LOA	Left anterior oblique.
LLWC	Left lateral wall contraction.
LPEI	LV pre-ejection interval.
LV	Left ventricle.
LVEDV	Left ventricle end diastolic volume.
LVEF	Left ventricular ejection fraction.
LVESV	Left ventricle end systolic volume.
MADIT-CRT	Multicenter automatic defibrillator implantation trial - Cardiac resynchronization therapy.
MIRACLE	Multicenter in sync randomized clinical evaluation.
MUSTIC	Multisite stimulation in cardiomyopathy.
NPV	Negative predictive value.
NYHA	New York heart association.
NT-proBNP	N-terminal inactive protein that is cleaved from proBNP to release brain natriuretic peptide.
PNS	Phrenic nerve stimulation.
PPV	Positive predictive value.
PROSPECT	Predictors of response to CRT.
PVC	Premature ventricular contraction.
QOL	Quality of life.
REVERSE	Resynchronization reverse remodeling in systolic left ventricular dysfunction.
RV	Right ventricle.
SD	Standard deviation.
SHFM	Seattle heart failure model.
SPWMD	Septal to posterior wall motion delay.

SR	Sinus rhythm.
SRI	Strain rate imaging.
TDI	Tissue Doppler imaging.
TSI	Tissue synchronization imaging.
Ts-SD-12	Dyssynchrony index.
VTI	Velocity time integral.
VVI	V – Ventricle paced V – Ventricle sensed I – Pacing is inhibited if beat is sensed
VVIR	Rate adapted ventricular inhibited pacing.
Peak VO_2	Maximum volume of oxygen uptake.

List of Figures

List of Tables

Introduction

Heart failure is a common clinical syndrome which represents the end-stage of a number of several cardiac diseases. Which can result from many structural or functional cardiac disorders that impair the ability of the ventricle to fill with or eject blood. Heart failure is one of the fastest growing cardiovascular diseases which carries a poor prognosis, even with optimized pharmacotherapy **(Hunt et al., 2009).**

The mortality in patients with heart failure is mostly due to progression in heart failure process or sudden death related to arrhythmias even though medications such as beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been shown to decrease morbidity and mortality**.** A significant number of heart failure patients have electromechanical dyssynchrony which increases their mortality rates **(Chen et al., 2011).**

The known types of electromechanical dyssynchrony in a sequential manner are the atrioventricular delay, intraventricular delay, interventricular delay and intramural delay **(Mann, 2012)**.

Cardiac resynchronization therapy (CRT) is a highly effective treatment for some patients with heart failure. Current guidelines recommend the implantation of CRT devices in patients with left ventricular (LV) dysfunction and electrical dyssynchrony, evidenced by a left bundle branch block **(Holzmeister et al., 2011).**

The exact mechanisms by which cardiac resynchronization therapy improves mechanical LV function in patients with heart failure and ventricular dyssynchrony are not fully understood. A number of randomized controlled trials have shown improved

outcomes with cardiac resynchronization therapy (CRT) in appropriately selected patients with systolic heart failure (HF) who have an intraventricular conduction delay (IVCD) or left bundle branch block (LBBB). Potential mechanisms of benefit include improved contractile function and reverse ventricular remodeling. The molecular basis for these mechanical changes has not been established. Preliminary data from an experimental model suggest that CRT reduces regional and global molecular remodeling, generating more homogeneous activation of stress kinases and reducing apoptosis **(Holzmeister et al., 2011)**.

Aim of the work

The aim of this work is to demonstrate the importance of Cardiac resynchronization therapy (CRT) in restoring the appropriate timing of the cardiac contraction pattern and thereby not only reduces cellular, hemodynamic and structural maladaptation to dyssynchrony but also ultimately improves functional status, decreases the risk of hospitalization and increases survival.

Pathophysiology of ventricular dyssynchrony

The syndrome of heart failure begins as an insult or injury to the heart and progresses with compensatory mechanisms that involve the neuro-hormonal system. Recently researchers were able to understand another aspect of heart failure, namely ventricular dyssynchrony. Not all heart failure patients have ventricular dyssynchrony and clinicians are still a long way from agreeing how to define and quantify grades of dyssynchrony. However, for many heart failure patients, a missing piece of the puzzle was found when electrophysiologists began to explore the term of out-of-sync activity **(Kenny, 2007)**.

In the healthy heart, timing is everything. the electrical impulse that originates in the sinoatrial node travel down over the atria to the atrioventricular node, experience a slight delay and then conduct downward and outward over the ventricles. If this occurs at the right conduction velocity, the result is a heartbeat that allows for proper atrial filling, the atrial contribution to ventricular filling, closure of the valves, ventricular depolarization and repolarization. The right and left ventricles contract at the same time and the left ventricle contracts coherently as one unit **(Kenny, 2007)**.

Thus there are two forms of dyssynchrony. Electrical dyssynchrony which involves conduction delays and disorders, while mechanical dyssynchrony which involves the heart's sequence of contraction and relaxation. Patients with heart failure frequently develop conduction abnormalities, which can alter the conduction sequence of the healthy heart **(Abraham et al., 2000)**.

The two main types of conduction abnormalities in HF patients are:

1. Delayed ventricular activation.
2. Prolonged atrioventricular conduction.

About half of patients with heart failure have some forms of conduction disorder. HF patients often develop delayed left ventricular activation due to the presence of left bundle branch block (LBBB). Left bundle branch block (LBBB) is a conduction disorder that may also occur independently of HF but is common in heart failure patients. In LBBB, the left-sided network of conduction fibers of the heart blocks or delays electrical signals. The result is that the left ventricle contracts after the right ventricle, instead of being contracted simultaneously **(Abraham et al., 2000)**.

Several patients without HF and without native LBBB experiences a bit of 'artificial LBBB' when they receive a pacemaker as the pacemaker paces the right side of the heart, which then conducts to the left side. When the right ventricle contracts prior to the left ventricle, the result is a condition known as interventricular dyssynchrony so that the right ventricle and left ventricles are out of sync. This type of dyssynchrony generally appears on a surface ECG as a prolonged or widened QRS complex. QRS durations generally > 120 ms have been identified as an independent risk factor for HF, although its value as a risk stratifier remains under debate. QRS duration is simple, inexpensive markers which correlate to some degree with electrical dyssynchrony **(Kenny, 2007)**.

Another conduction disorder that may have more clinical significance for HF patients is the intraventricular conduction delay. This occurs within the left ventricle. With intraventricular conduction delay, the left ventricle's lateral wall contracts before the inner wall. The result is that the

left ventricle contracts in segments or waves rather than as a single unit. Since the pumping chamber is contracting in sections, turbulent blood flow within the left ventricle will affect pumping of the blood outward. Intraventricular conduction disorders significantly reduce cardiac output. Both intraventricular and interventricular conduction delays have been associated with negative clinical consequences (**see Fig. 1**). Added to this there is a prolonged natural AV delay common in many HF patients. In this situation, there is a longer pause between atrial systole and ventricular systole. This AV conduction delay limits the atrial support to ventricular filling, encourages diastolic mitral regurgitation and shortens ventricular filling time **(Kenny, 2007)**.

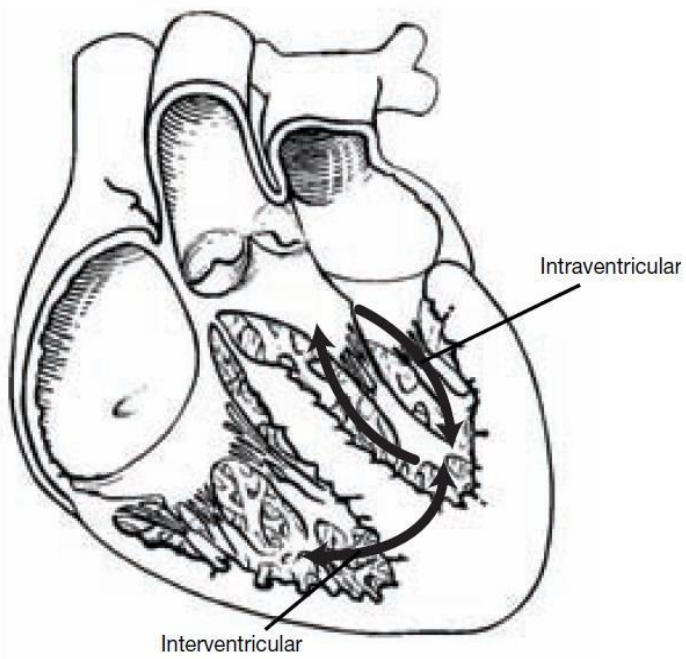

Fig. 1: Intraventricular versus interventricular conduction. Interventricular conduction refers to electrical conduction between right and left ventricles, while intraventricular conduction refers to conduction within a single ventricle as indicated here by two arrows forming a circle within the left ventricle **(Kenny, 2007)**.