CORRELATION BETWEEN QRS DURATION AND CARDIAC OUTPUT MEASURED BY LEFT VENTRICULAR OUTFLOW TRACT VELOCITY IN PATIENTS WITH CARDIAC RESYNCHRONIZATION THERAPY

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INTRODUCTION

Cardiac resynchronization therapy (CRT) has made a dramatic impact on the treatment of most patients with heart failure and an abnormal QRS duration. It was introduced in the 1990s and revolutionized therapy for many patients with persistent symptoms of systolic HF ***(Owen et al. 2009)***. There is strong evidence that CRT reduces mortality and hospitalization, improves cardiac function and structure in symptomatic chronic heart failure patients with optimal medical treatment, severely depressed LVEF (i.e. ≤35%) and complete LBBB (***Brignole et al. 2013)***.

However, 30% of system recipients do not benefit from CRT, though the proportions of non-responders vary depending on the definition and criteria applied ***(Prinzen et al. 2013)***. Non-response to therapy has remained a great limitation to the application of CRT in heart failure treatment over the years, offering considerable medical and financial challenges, such that efforts must be pursued to clarify and resolve its determinants***(Mullens et al. 2009).***

The QRS complex on a surface 12-lead electrocardiogram (ECG) which represents ventricular depolarization is a simple and strong predictor of response to CRT (***Ponikowski et al. 2016***). A prolonged QRS has been shown to be a marker for atrioventricular, interventricular, and intraventricular dyssynchronies (***Freemantle et al. 2006***). The net result of these disturbances in timing of cardiac contraction is a reduced ventricular systolic function and cardiac output (***Tracy et al. 2012***).

Left ventricular outflow tract velocity time integral (LVOT VTI) is a measure of cardiac systolic function and cardiac output (***Tan et al. 2017***). It is a Doppler-derived measure of the distance traveled by midstream blood through the left ventricular outflow tract in a single cardiac cycle (i.e., stroke distance). Studies have validated the correlation between cardiac output measured by stroke distance and cardiac catheterization in adults. Data in adult

subjects have also shown that LVOT-VTI is an independent predictor of heart failure (***Navaratnam et al. 2017***).

As mentioned before, both QRS duration and LVOT VTI are recognized as a significant predictors of response and long term prognosis in CRT implanted patients (***Bonakdar et al. 2009***). The electrocardiogram is less sensitive than echocardiography in detecting lesser degrees of mechanical dyssynchrony, although it provided strong predictors of CRT response like QRS width and left bundle branch block (***Spartalis et al. 2017***).

Although echocardiography is a widely used technique to optimize CRT, the process is time-consuming and, as yet, not well standardized. It was conceivable that an alternative method could be sought, which proved reliable, non-operator dependent, inexpensive, and suitable to become a built-in feature of a CRT device (***Nawar et al. 2011***). ECG- guided CRT optimization is a simple method and a trial of it is strongly recommended to ensure an early and sustained response to CRT, and should be performed for non-responders to ensure the paced QRS morphology predicts a positive response while waiting for evidence of benefit (***Kneller et al. 2016***).

In our research we are studying the correlation between QRS duration and echocardiographic measurement of cardiac output (through LVOT VTI) in CRT implanted patients, so that we can use the QRS duration as a simple guiding method for CRT optimization.

Chapter I

Heart failure

Heart failure (HF) remains one of the most prevalent and costly cardiovascular disease to treat in the health care system ***(Benjamin et al. 2017)***. Data from the hospitalized heart failure registries in 2014 showed that 26 million subjects had heart failure in 2014 ***(Ambrosy PA et al. 2014)***. Another registeries projected that the prevalence of heart failure among the US population would increase from 2.4% in 2012 to 3.0% in 2030***(Heidenreich et al. 2013)***. This obvious increase would also come with a corresponding increase in medical costs associated with treating and managing the disease, about 1-2% of health care expenditure is attributed to heart failure in Europe and North America ***(Cowie MR et al. 2014)***.

Currently known risk factors for the development of heart failure include coronary heart disease (CHD), hypertension, increasing age, male sex, diabetes, valvular disease, and obesity ***(Mann, 2011)***. However, the two factors of CHD and hypertension alone are believed to account for fully three-fourths of all heart failure cases, although interaction with other factors such as race, sex, and age may exacerbate or ameliorate the effects of CHD or hypertension, or both ***(Berliner et al. 2017)***. With respect to CHD, it has been proposed that increased survival from myocardial infarction in recent decades have led to a corresponding increase in HF prevalence ***(Dégano et al. 2015)***.

Pathophysiology of Heart Failure itself is a complex, multifaceted disease, and has been broadly defined as a condition where the heart is rendered incapable of ejecting blood supplied to it by the venous system ***(Johnson 2014).*** An important concept to understand in heart failure is that of cardiac output, which is a combination of both stroke volume as well as heart rate. Therefore, heart failure does not include diseases where insufficient blood is supplied to the heart due to blood loss or other impairment of blood return ***(Vincent 2008)***.

Classification of Heart Failure

Heart failure can be categorized into two main types: heart failure with reduced ejection fraction (HFrEF) formerly known as systolic heart failure, and heart failure with preserved ejection fraction (HFpEF) formerly known as diastolic heart failure, both of which affect the left ventricle(***Nadar 2017***). HFrEF and HFpEF are both estimated to be equally prevalent at around 50% of heart failure cases, but the dividing line between both of them are debatable(***Oktay et al. 2014***). In general, HFrEF is defined by the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines as a clinical diagnosis of heart failure with a reduced ejection fraction (***Yancy et al. 2017***).

NYHA classification refers primarily to the day-to-day functional capacity of the patient, and its classification is shown in Table 1.

Table 1. NYHA classification of Heart Failure ***(Raphael et al. 2007)***

NYHA Class	Patient Symptoms
class I	no limitation of physical activity; (includes asymptomatic left ventricular dysfunction)
class II	slight limitation of physical (symptomatically 'mild' heart failure)
class III	a marked limitation of physical activity; (symptomatically 'moderate' heart failure)
class IV	inability to carry out any physical activity without discomfort; (symptomatically 'severe' heart failure)

NYHA classes are subjective, but are often used as predictors in some studies, and as outcomes in others (***Russell et al. 2009***). It is interesting to note that the ACC/AHA classified patients who are not actually diagnosed with heart failure, but are merely at risk of developing heart failure as Stage A heart failure. Further, it could be considered that after a myocardial infarction of any type or severity, that a patient would be in Stage B heart failure,

even though there may be no actual functional physiological impairment (table 2) (***Yancy et al 2013***).

Table 2. ACC/AHA Classification Guidelines (*Athilingam et al. 2013*).

HF Stage A	Patients at high risk for developing HF in the future but no functional or structural heart disorder
HF Stage B	A structural heart disorder but no symptoms at this stage
HF Stage C	Previous or current symptoms of heart failure in the context of an underlying structural heart problem, but managed with medical treatment
HF Stage D	Advanced disease requiring hospital-based support, a heart transplant or palliative care

By etiology, there are many specific types of heart failure including ischemic, dilated, valvular, hypertrophic, infiltrative, toxic and inflammatory (***Johnson 2014***).

Ischemic cardiomyopathy is characterized by regional hypokinesis and thinning of the ventricles in areas of full-thickness injury. The final common pathway is LV remodelling, which can occur at different stages in this spectrum. Early remodelling results in wall thinning and dilatation, with irreversible late remodelling resulting from myocardial fibrosis and scar ***(Briceno et al. 2016)***.

Dilated cardiomyopathy is characterized by ventricular enlargement and global hypokinesis . It can be attributed to genetic and non genetic causes including hypertension ,direct toxicity (eg, alcohol) or mechanical insults (eg, chronic volume overload in mitral valvular regurgitation). With myocyte failure, the chambers become dilated. The degree of LV systolic dysfunction is variable, and LV systolic dysfunction is often progressive.(***Johnson 2014***)***(McNally et al. 2017).***

Hypertrophic cardiomyopathy (HCM) is defined by the presence of increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions, the disease is an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes. Five to ten percent of adult cases are caused by other genetic disorders including inherited metabolic and neuromuscular diseases, chromosome abnormalities and genetic syndromes (***Elliot et al. 2014***).

Valvular cardiomyopathy can be either inherited or acquired. The most common congenital valvular lesions are bicuspid aortic valve and myxomatous mitral valve. Acquired lesions are typically calcific degeneration or are caused by post inflammatory changes from infective endocarditis, rheumatic fever, rheumatologic disorders, carcinoid, fenfluramine/phentermine exposure. Among acquired lesions, calcific aortic stenosis is the most common, and primarily affects the elderly (***Johnson 2014***).

Restrictive cardiomyopathy is a rare disease of the myocardium and is the least common type of cardiomyopathy. (***Merio et al. 2014***) It is characterized by diastolic dysfunction with restrictive ventricular physiology, whereas systolic function often remains normal. Atrial enlargement occurs due to impaired ventricular filling during diastole, but the volume and wall thickness of the ventricles are usually normal. (***Huby et al. 2014***)

Investigations for Heart Failure

Clinical assessment is mandatory before detailed investigations in patients with suspected heart failure, although specific clinical features are often absent and the condition can be diagnosed accurately only in conjunction with more objective investigation, particularly echocardiography. Although open access echocardiography is now increasingly available, appropriate pre-referral investigations include chest radiography, 12 lead electrocardiography, and serum biochemistry (***Davies et al. 2000***).

The plasma concentration of natriuretic peptides (NPs) can be used as an initial diagnostic test, especially in the non-acute setting when echocardiography is not immediately available. Elevated NPs help establish an initial working diagnosis, identifying those who require further cardiac investigation; The upper limit of normal in the non-acute setting for B-type natriuretic peptide (BNP) is 35 pg/mL and for N-terminal pro-BNP (NT-proBNP) is 125 pg/mL (***Ponikowski et al 2016***)

ECG has high sensitivity for diagnosis of heart failure (sensitivity 89%).It is unlikely to present in patients with normal ECG. Therefore, it is important to be used routinely to exclude the diagnosis (***Mant et al. 2009***).

Moreover, prolongation of QRS (≥120 ms) is a significant predictor of LV systolic dysfunction in patients with HF. In patients with HF, an inverse correlation exists between QRS prolongation and LVEF. In a study of nearly 3,500 patients with HF, Shenkman et al. found a stepwise increase in the prevalence of systolic LV dysfunction as QRS complex duration increased progressively above 120 ms (***Kashani et al. 2005***). Thus, the association between QRS prolongation and worse outcomes mandate the use of life prolonging devices such as Cardiac Resynchronization Therapy (CRT) and this appear clearly in the latest ESC heart failure guidelines (***Ponikowski et al 2016***) .

Echocardiography is the most widely used test and the most versatile in providing relevant clinical information. In addition to providing information on EF, echocardiography provides information on LV volume, diastolic function, RV function, hemodynamics, and valvular regurgitation that has important prognostic and therapeutic implications (***Marwick 2015***)

Although LVEF does not correlate well with symptoms, exercise capacity, or myocardial oxygen consumption, it does convey important prognostic information . Indeed, current pharmacological and device therapies for HF are based on clinical trials using reduced LVEF as a major inclusion criterion, and LVEF still represents the ventricular phenotypic measurement recommended by the guidelines to categorize patients who are likely to respond

to drug or device therapy for HF (e.g., implanted defibrillator or cardiac resynchronization) (***Ambrosio et al. 2018***) .

The modified Simpson method is a 2D echocardiographic technique requiring area tracings of the LV cavity. This is the method recommended by the American Society of Echocardiography for measuring LVEF. It requires tracing the LV endocardial border in the apical 4- and 2-chamber views in both end-diastole and end-systole (***Folley et al. 2012***) .

LVEF is influenced by the degree of LV remodeling more than by any other factor. Thus the degree of LV remodeling is an important prognostic factor in patients with HF with reduced EF. The investigators have related its measurements more closely to prognosis and to the impact of therapy than does LVEF. (***Konstam et al. 2011***).

The hemodynamic assessment of patients presenting with HF is a fundamental strength of echocardiography. The assessment of cardiac output from volumetric approaches is based on tracing diastolic and systolic volumes or using Doppler to calculate stroke volume from blood flow, outflow tract diameter, and heart rate (***Marwick 2015***).

Using Doppler we can estimate Left ventricular outflow tract velocity time integral (LVOT VTI) which is a measure of the distance traveled by midstream blood through the left ventricular outflow tract in a single cardiac cycle (i.e., stroke distance). In ESC guidelines, LVOT VTI<15cm is defined as an abnormality suggesting reduced left ventricular stroke volume (***Chinen et al. 2013***). LVOT-VTI has been well described in the adult literature as a useful surrogate marker of cardiac output and global ventricular performance. Studies have validated the correlation between cardiac output measured by stroke distance and cardiac catheterization in adults . Data in adult subjects have also shown that LVOT-V TI is an independent predictor of heart failure (***Navaratnam et al. 2017).*** Moreover, extremely low LVOT VTI is associated with increased mortality and cardiac device implantation and is more predictive of adverse outcomes than EF or Doppler derived CO(***Tan et al. 2016***).

Cardiac Magnetic resonance (CMR) is acknowledged as the gold standard for the measurements of volumes, mass and EF of both the left and right ventricles. It is the best alternative cardiac imaging modality for patients with non-diagnostic echocardiographic studies and is the method of choice in patients with complex congenital heart diseases (***Mitchell et al. 2016***).

Other diagnostic tests should be performed in order to evaluate patient suitability for particular therapy, detect reversible causes of heart failure and co-morbidities interfering with heart failure include a complete blood cell (CBC) count, serum electrolyte levels, renal and liver function tests, glucose and HbA1c, lipid profile, TSH and iron studies (***Ponikowski et al 2016***).

Treatments for Heart Failure

Overall, there are three main strategies in treating heart failure. First, pharmacological and lifestyle-change strategies which are usually the initial approach taken in managing the disease. Lifestyle changes include dietary modifications, quitting smoking, and exercising. Often, though, if lifestyle adaptations have not been adopted at very early stages of the disease they are of very modest effectiveness in treating existing disease alone.(***Fleg 2016***)

Pharmacological options at this stage help manage risk factors, such as treating a patient's hypertension, diabetes, or dyslipidemia. In patients that remain or become refractory to medical treatment as the disease progresses, the second option is that of medical device implantation such as cardiac resynchronization therapy (CRT) or, in later stages of the disease, a ventricular assist device (VAD). The third and most drastic treatment for heart failure is that of heart transplantation ***(Inamdar et al. 2016)***.

I. Lifestyle changes

1. Patient Education.

Patient education included education about medications and strategies for treatment. This needs spending enough time with each patient to make a therapeutic relationship, identifying patient problems, putting the solution plan sharing the patient in decision making, involving multidisciplinary health care professionals, taking feedback from the patient and reinforcement (***Artinian et al. 2010).***

2.Physical activity.

It is a mainstay for health care and prevention of progression of the disease. Regular exercise is proven to improve functional capacity and symptoms and to reduce mortality and heart failure hospitalization. There is no universal agreement on the best training modality for heart failure patient, instead an individualized approach is recommended; based on clinical evaluation and patient preferences. It is recommended to start the training program in the hospital or health care system and to gradually transmitting the patient to a home based programmes aiming to keep the patient active for a longer time of period (***Craenenbroeck 2015).***

3.Nutrition.

A healthy diet is recommended as a cornerstone for prevention of cardiovascular disease progression. Healthy diet is low in saturated fat with focus on vegetable, fruits and fish. Restriction of salt to 2-3 gm/day is recommended, also 1-1.5 L/day fluid restriction is beneficial. Adherence to healthy dietary habits can influence cardiovascular disease progression through its effect on risk factors such as cholesterol level, BP, DM, body weight or through the effect on cardiovascular disease endpoints. Table 3 summarizes the characteristics of healthy diet (***Abshiri et al. 2015*****).**