# Cardiac Resynchronisation Therapy and its effects on Systolic Heart Failure

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# ABSTRACT

Cardiac Resynchronisation Therapy (CRT) is now an established therapeutic option for patients with symptomatic left ventricular systolic dysfunction, broad QRS duration (>120 milliseconds on surface electrocardiogram) and on optimal tolerated medical therapy. The numbers of implants are rising throughout the Westernised world. The United Kingdom has also had a rapid increase in the rate of CRT implantation.

Despite the large randomised trials which prove clinical effectiveness, there is a realisation that a significant minority of patients who undergo CRT implantation do not derive the anticipated clinical benefit. This has been labelled as non-response with up to 40 percent of patients being affected depending on diagnostic criteria.

However potential solutions to a lack of clinical benefit do exist. These include medical optimisation of the patient's heart failure pharmacotherapy following CRT implantation, and device based optimisation adjusting atrioventricular and ventriculo-ventricular (AV and VV) intervals. Other reasons for a lack of clinical improvement may be explained by pathophysiology which is currently not accounted for in the guidelines and selection criteria.

The thesis is therefore dedicated to the exploration of these issues using the dataset from the specialist heart failure pacing clinic at the Royal Brompton Hospital.

The study of medical optimisation following CRT implantation observed increased rates of neurohormonal antagonists and anticoagulants when a systematic structured clinical approach was adopted.

One potential method of evaluating device based optimisation is impedance cardiography and within chapter V, a cohort of 44 patients underwent device based optimisation with either conventional echocardiographic techniques or impedance cardiography. Though underpowered and a pilot study, the impedance cardiographic method within this cohort performed adequately.

Heart failure remains a complex syndrome with complex pathophysiology. One of the potential reasons for non-response is the lack of acknowledgement of other physiological criteria in the selection criteria. The study performed using cardiac magnetic resonance (CMR) imaging to evaluate right ventricular function on cardiovascular outcomes in patients following CRT implantation. Here it was demonstrated that right ventricular dysfunction as assessed by CMR is a powerful predictor of adverse outcomes and of a failure to undergo left ventricular remodelling.

The last study chapter was a small pilot study which compared impedance cardiographic performance to echocardiography within an intensive care setting. Whilst the numbers of patients recruited were small (n=6), the adjustment of atrioventricular and ventriculo-ventricular delays did induce a change in haemodynamics.

In conclusion the thesis represents studies and work focussed on the problem of lack of clinical benefit experienced by patients following CRT implantation. It has covered a prognosticator and two potential methods for improving the rate of clinical response following CRT implantation.

# STATEMENT OF INVOLVEMENT

I hereby certify that I was the primary investigator for all the studies described within this thesis. I designed, collected clinical data and other relevant data, performed statistical analysis and wrote up the thesis with support from my supervisors (Professor Martin Cowie, Dr Rakesh Sharma and Professor Theresa M$^{c}$Donagh) and Winston Banya (Statistician)

The collection of all clinical data from the heart failure pacing clinic at the Royal Brompton Hospital, was performed by myself. Echocardiography was performed by the Derek Gibson echocardiography department, Royal Brompton Hospital. All biochemical results quoted within the studies were analysed by the biochemistry department at the Royal Brompton Hospital. All cardiac magnetic resonance studies were performed at the cardiac magnetic resonance unit, Royal Brompton Hospital.

## COPYRIGHT DECLARATION



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# PUBLICATIONS ARISING FROM THIS WORK

## PUBLISHED PAPERS

1. F Alpendurada[*], **K Guha**[*], R Sharma, TF Ismail, A Clifford, W Banya, RH Mohiaddin, MR Cowie, TA M[c]Donagh and SK Prasad. Right ventricular dysfunction is a predictor of non-response and clinical outcome following cardiac resynchronization therapy. J Cardiovasc Magn Reson. 2011 Oct 31;13(1):68. (* = Joint First Authors)

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1. F Alpendurada, **K Guha**, R Sharma and S Prasad. Right ventricular dysfunction predicts clinical outcomes following cardiac resynchronisation. J Cardiovasc Magn Reson;2011; 13 (Suppl 1): O104

2. **K Guha**, F Alpendurada, S Prasad, T M[c]Donagh, MR Cowie, R Sharma. Right ventricular dysfunction identifies clinical outcomes following cardiac resynchronisation therapy. Heart; 2011; A53.

3. **K Guha,** Z Khalique, N Pareek, B Chandrasekaran, TA M[c]Donagh, MR Cowie and R Sharma. The use of cardiac resynchronisation therapy may allow the optimisation of beta blocker therapy. Eur J Heart Fail Suppl; 2011;10;(S1),S20.

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# List of Abbreviations

123MIBG = Metaiodobenzylguanidine 123 Iodine

6MWT = 6 Minute Walk Test

AAI = Atrial Inhibited Pacing

ACEI = Angiotensin Converting Enzyme Inhibitors

AF = Atrial Fibrillation

ARB = Angiotensin II Receptor Antagonists

ATP = Adenosine Tri-phosphate

AV = Atrio-ventricular

AV = Atrio-ventricular

BB = Beta Blockers

BNP = B Type Natriuretic Peptide

BPM = Beats per Minute

cAMP = Cyclic Adenlyl Cyclase

cICU = Cardiac Intensive Care Unit

CMR = Cardiac Magnetic Resonance

CO = Cardiac Output

CO = Cardiac Output

CRT = Cardiac Resynchronisation Therapy

CRT-D = Cardiac Resynchronisation Therapy + Defibrillator

DCM = Dilated Cardiomyopathy

DDD = Dual Chamber Mode of Pacing

dP/DT Max = Change in pressure over time

ECG = Electrocardiogram

EDV = End Diastolic Volumes

EHRA = European Heart Rhythm Association

EROA = Effective Regurgitant Orifice Area

ESC = European Society of Cardiology

ESV = End Systolic Volumes

HDU = High Dependency Unit

HF = Heart Failure

HFpEF = Heart Failure with Preserved Ejection Fraction

HFSA= Heart Failure Society of America

HFSN = Heart Failure Specialist Nurse

HRS = Heart Rhythm Society

ICD = Implantable Cardioverting Defibrillator

ICG = Impedance Cardiography

ISDN = Isosorbide Dinitrate

ITU = Intensive Care Unit

LBBB = Left Bundle Branch Block

LGE = Late Gadolinium Enhancement

LV = Left Ventricular

LVEF = Left Ventricular Ejection Fraction

LVOT = Left Ventricular Outflow Tract

LVSD = Left Ventricular Systolic Dysfunction

MLHFQ = Minnesota Living with Heart Failure Questionnaire

MMP = Matrix Metalloproteinases

MPI = Myocardial Performance Index

MR = Mitral Regurgitation

MRA = Mineralocorticoid Receptor Antagonists

$MVO_2$ = Maximal Oxygen Demand

NHS = National Health Service

NICCOMO = Non Invasive Cardiac Output Monitoring

NICE = National Institute for Health & Clinical Excellence

NYHA = New York Heart Association

PAP = Pulmonary Artery Systolic Pressure

PATH-CHF = Pacing Therapies in Congestive Heart Failure

PISA = Proximal Isovolumic Velocity Area

QRSd = QRS duration

RA = Right atrium

RAAS = Renin-Angiotensin-Aldosterone- System

RBBB = Right Bundle Branch Block

REC = Research Ethics Committee

RV = Right Ventricle

RVEF = Right Ventricular Ejection Fraction

RVM = Right Ventricular Mass

RyR = Ryanodine Receptor

SCD = Sudden Cardiac Death

SD = Standard Deviation

SERCA = Sarcoplasmic Reticulum Calcium Exchanger

SR = Sarcoplasmic Reticulum

SV = Stroke Volumes

TAPSE = Tricuspid Annular Plane Systolic Excursion

TAVI = Transcutaneous Aortic Valve Implant

TD = Target Dose

TiMPs = Tissue Inhibitors of Matrix Metalloproteinases

TTE = Transthoracic Echocardiography

UK = United Kingdom

VTI = Velocity Time Integral

VV = Ventriculo-ventricular

VVI = Ventricular Inhibited Pacing

# Chapter I: Introduction

# Introduction

Heart Failure (HF) is a widely prevalent, costly and lethal condition. It is responsible for approximately 1-2% of healthcare expenditure in developed countries. (1) Heart failure is a chronic condition where the metabolic demands of the body are not adequately met due to impairment of cardiac function. The most common causes are ischaemic heart disease, inherited cardiomyopathies including hypertrophic cardiomyopathies, dilated cardiomyopathy, hypertension, toxins including alcohol and prescribed drugs e.g. chemotherapy. However, any disease process which affects the heart can, in its advanced stages, lead to the heart failure phenotype. This can be subdivided into systolic impairment of the left ventricular function- left ventricular systolic dysfunction (LVSD) and those with preserved systolic function- heart failure with preserved ejection fraction. (HFpEF)

Heart failure is predominately a disease which affects the elderly, with the median age at presentation in the United Kingdom being 78 years.(2) The past three decades have witnessed the development of neurohormonal antagonists such as angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor antagonists (ARBs), beta adrenoceptor antagonists 'Beta blockers' (BB) and mineralocorticoid receptor antagonists (MRA). Cardiac resynchronisation therapy (CRT) and implantable cardiac defibrillators (ICDs) have also become established as treatment options for selected patients with heart failure. Despite the technological and pharmacological advances, heart failure remains a condition with a poor prognosis. Recent data from England and Wales demonstrates that inpatient mortality amongst patients with heart failure is 12 percent.(2) This is in comparison to data from the EuroHeart HF II Study, which represents 24 European countries, which shows an in hospital mortality rate of 6.6 percent and US data from the OPTIMISE HF registry which demonstrates a mortality rate of 4 percent of in-patients.(3, 4) CRT has been proven, through randomised controlled clinical trials to be efficacious in the improvement of symptoms and mortality in selected populations with advanced heart failure.(5-7) Since the initial publications of large randomised controlled trials, the emphasis has shifted to investigating the role of CRT in less symptomatic disease.(8, 9) In certain individuals it may be beneficial, with some patients showing a marked improvement in symptoms allied with features of advantageous structural change e.g. left ventricular remodelling.

The effect of CRT however in other patients may be unpredictable with some failing to experience the anticipated clinical benefit. A better understanding of the post implantation period would yield the possibility of ensuring optimal device based care for patients with heart failure, which should translate into improved clinical outcomes, better quality of life and a reduction in costly hospitalisations. Healthcare professionals may be able to exploit the beneficial effects following CRT implantation by careful surveillance with renewed focus on electrical optimisation of the timing cycles within the device and review of the concurrent medication. These concepts will be discussed in more detail later in the introduction. For the purpose of this thesis 'device therapy' refers to both cardiac resynchronisation therapy and/or implantable cardioverting defibrillators.

## 1.1 Definition of Heart Failure

The current European Society of Cardiology guidelines define heart failure as 'a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles and displaced apex beat) resulting from an abnormality of cardiac structure or function.(10) The definition places emphasis on the collection of symptoms in association with disorder of cardiac structure. Hence both national and international guidance stress the need for echocardiography in suspected cases of HF as the more readily available method for confirming and assessing the underlying cardiac disorder.(10, 11)

## 1.2 Epidemiology

The original prospective cohort studies from Framingham, Massachusetts, US and the "Men born in 1913", Gothenburg, Sweden demonstrated an increased incidence of HF with age.(12, 13) More recently within the Hillingdon Heart Failure Study, in West London, using a rigorous definition of heart failure, the incidence was documented to rise significantly with age.(14) The incidence rose from 0.02 cases per 1000 in the age group 25-34 years of age to 11.6 cases per 1000 in the >85 years category. The median age at presentation within this study was 76 years of age. (See Figure 1)

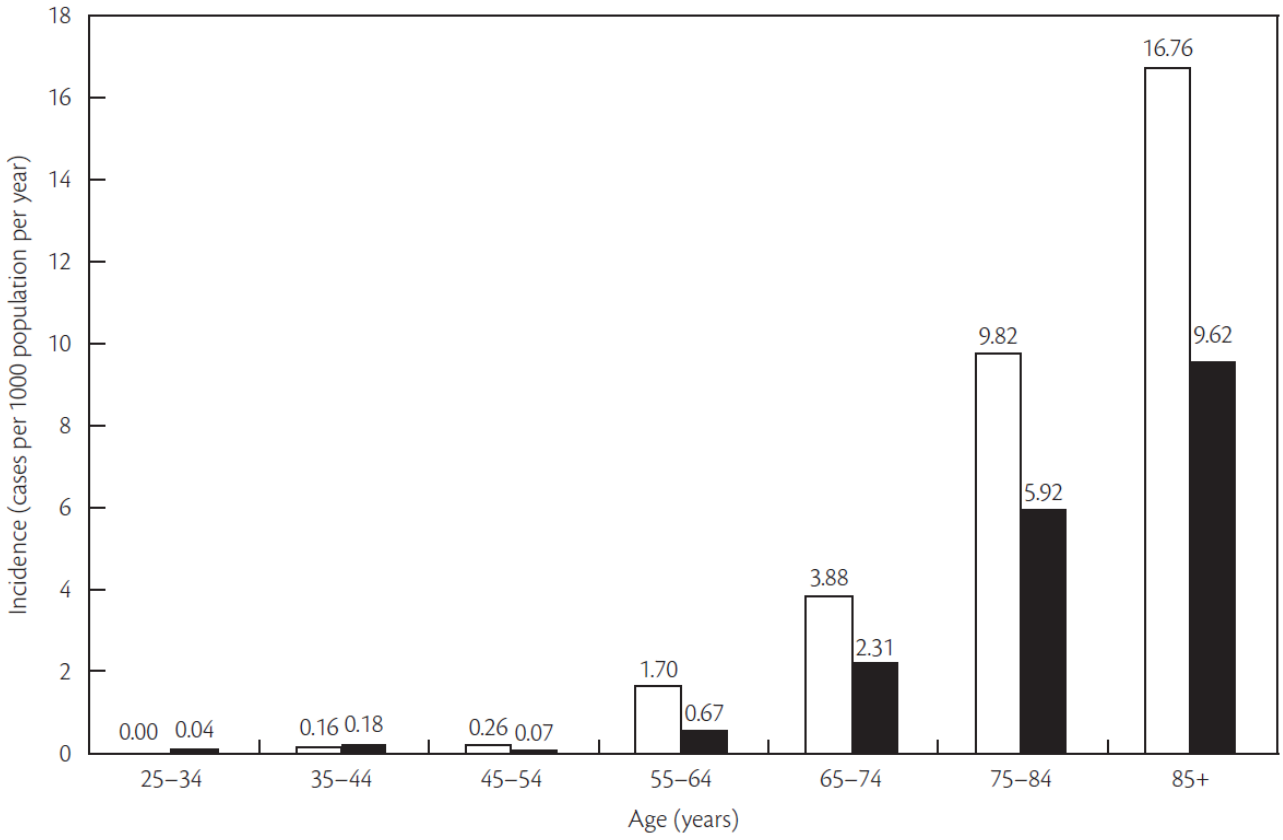


**Figure 1: Incidence of Heart Failure categorised by age groups: Data and Figure from Hillingdon Heart Failure Study**(14)

Several further studies have documented that heart failure remains a condition which primarily affects the elderly. Contemporary national audit data of hospitalised patients reveals a current median age of presentation of 78 years of age within England and Wales.(2) It is estimated that in European healthcare economies HF management is responsible for up to 2% of all direct healthcare expenditure.(15) Within the United Kingdom this would currently be approximately £2 billion. A large proportion of this cost is due to expensive prolonged and repeated hospitalisation. Within the UK HF is responsible for a million in-patient bed days and accounts for 5% of all emergency admissions within the National Health Service (NHS).

American data are suggestive of an increasing trend towards hospitalisation with HF hospitalisations trebling between 1979 and 2004.(16) The configuration of European health services is different with significant variance between primary and secondary care. Recent Scottish and Dutch data suggests that the trend towards heart failure hospitalisation has reduced.(17, 18) The Scottish data are the most recent and indicates that HF hospitalisations reached a peak in the mid 1990s and have subsequently declined. (See Figure 2)

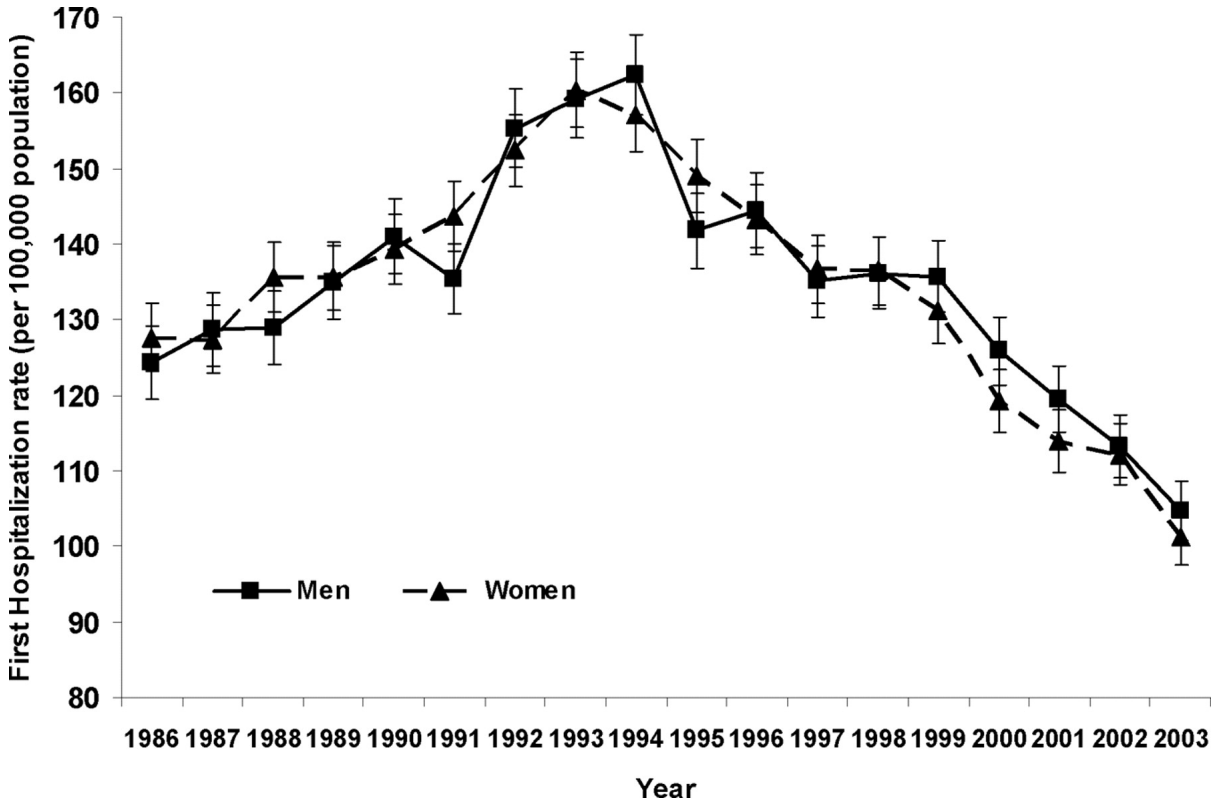


**Figure 2: Age-adjusted trends in discharges for a first hospitalization for HF according to sex(17)**

Despite the national and international guidance, many patients remain sub optimally treated.(19) Hospital admission carries an increased risk of mortality, with the recent national data indicating a projected one year mortality of 26% for patients below the age of 75 and 56% for those above the age of 75.(2)

## 1.3 Diagnosis

Heart failure is a syndrome characterised by a collection of symptoms which may include fatigue, breathlessness, reduction in exertional capability, decreased appetite and fluid retention. In certain patients, particularly the elderly, it may present more insidiously with cognitive decline, delirium, anorexia, cachexia, insomnia or malaise. Due to the variation in symptoms, the clinician needs to have a degree of suspicion to activate further appropriate investigations.

Guidelines from NICE and the ESC suggest that patients with suspected heart failure should be evaluated by a physician with specialist expertise within the field.(10, 11) Initially the patient should have a full history, physical examination, electrocardiogram, chest radiograph and natriuretic peptide measurements. (See Figure 3) Though this process may reveal

characteristics consistent with a possible diagnosis of heart failure, ultimately the patient should have cardiac imaging to produce detailed information on cardiac structure and function. The most commonly used imaging modality is transthoracic echocardiography. A clinical response to therapy is no longer part of the definition of heart failure; though a degree of improvement may help corroborate the diagnosis.

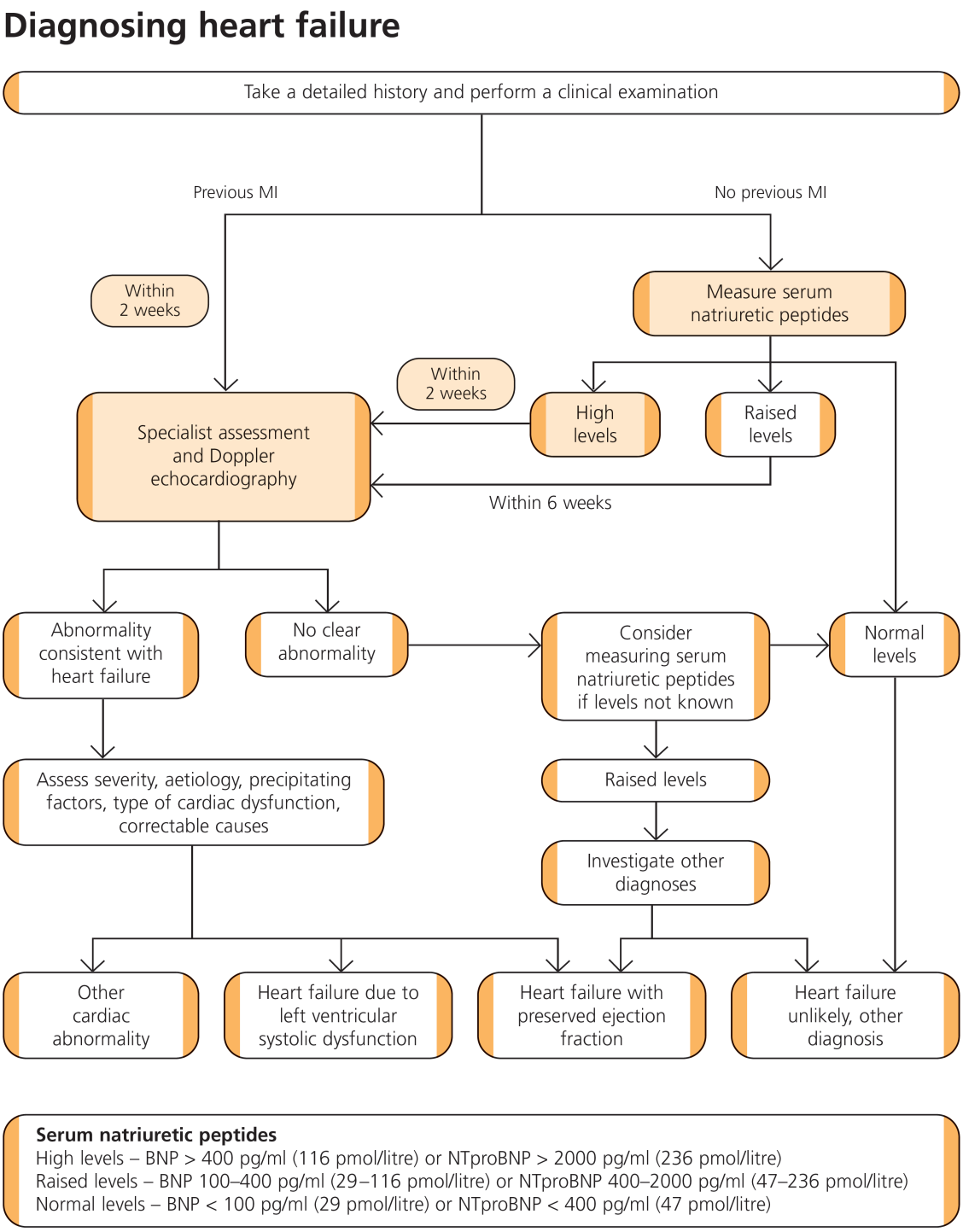


**Figure 3: Diagnostic Algorithm from National Health and Clinical Excellence Guidelines for suspected heart failure (2010)(11)**

## 1.4 Aetiology

The most common causes for heart failure in the Western world remain ischaemic heart disease and hypertension. However there are numerous other conditions which may result in left ventricular systolic dysfunction, which are listed in table 1.1.

Using cardiac imaging, patients may be divided into groups with LVSD (Left Ventricular Ejection Fraction (LVEF) <45%) and preserved left ventricular systolic function. Having confirmed the diagnosis of heart failure, the aetiology needs to be identified. Once this has been identified appropriate treatment needs to be focussed on the underlying cause and the concomitant ventricular impairment. Additionally the severity of heart failure should be assessed, the prognosis should be defined and relevant concomitant disease such as anaemia, diabetes mellitus and hypertension should be identified and managed.

| **Causes of Left Ventricular Systolic Dysfunction** |
|---|
| Ischaemic Heart Disease |
| Hypertension |
| Cardiomyopathy (Inherited/Acquired): Hypertrophic, Dilated, Arrythmogenic |
| Peri-partum cardiomyopathy; Tako-Tsubo Cardiomyopathy |
| Right Ventricular; Restrictive |
| Drugs: Chemotherapy; Alcohol |
| Others: |
| Endocrine; Diabetes Mellitus; Hyper/Hypothyroidism; Adrenal Insufficiency |
| Phaeochromocytoma |
| Nutritional: Selenine, Thiamine, Carnitine Deficiency |
| Infiltrative: Sarcoidosis, Amyloidosis, Haematochromatosis |
| Infective: Chagas Disease, Human Immunodeficiency Virus |

Table 1: Causes of Left Ventricular Systolic Dysfunction quoted from ESC Guidelines for Acute and Chronic Heart Failure (2012)(10)

## 1.5 Bedside & Laboratory Investigations

Patients with suspected heart failure should have urinalysis performed. This is to detect proteinuria and glycosuria. The suggested laboratory investigations should include a full blood count, urea and electrolytes, thyroid function, liver function and lipid profile. If the patient is anaemic then full haematinics should be performed including complete iron studies, serum $B_{12}$ and folate.

### 1.5.1 Natriuretic Peptides

The family of natriuretic peptides are important biomarkers of heart failure. The most widely investigated and evaluated is B type natriuretic peptide (BNP). Previous work has demonstrated that higher concentrations of circulating BNP are to be found in individuals with HF. Currently they are advocated within the national and international guidelines to be used as a diagnostic tool to aid the diagnosis of incident cases of heart failure.(10, 11)

Natriuretic peptides are released in response to myocardial stress and raised levels underline the need for clinical assessment and cardiac imaging to identify the underlying cardiac dysfunction. Due to its release in response to myocyte stretch and volume overload, BNP has also been shown to have prognostic value. Others have investigated whether it should dictate levels of HF pharmacotherapy and be used to monitor the control of the HF syndrome, but thus far there is no consistent evidence within this area.(20, 21)

### 1.5.2 Electrocardiogram

This should be performed for every patient with suspected heart failure. A normal electrocardiogram (ECG) makes HF with LVSD unlikely. An abnormal ECG has relatively poor predictive value in heart failure, but suggests the need for further investigation. Many potential ECG abnormalities exist within patients with heart failure. Some, such as QRS duration carry prognostic value and also may identify potential candidates for device based therapy.(22)

The current National Institute for Health and Clinical Excellence (NICE) guidelines state that, in a patient with a prior history of ischaemic heart disease, symptoms and abnormal ECG,

there is sufficient justification for further specialist assessment and that in such patients a measurement of plasma natriuretic peptides is not necessary as this will not change the pre-test probability of disease.(11)

### 1.5.3 Echocardiography

Transthoracic echocardiography is the most widely available cardiac imaging modality. This is due to its portability, ease of access and safety in that it does not involve ionising radiation. It should be performed in those patients with suspected heart failure to delineate biventricular function and status of the valves and pericardium. Echocardiography may be used to determine whether the phenotype is one consistent with LVSD, or HF with preserved systolic function. (HFpEF)

### 1.5.4 Further Imaging

Further, more advanced cardiac imaging, may be necessary in patients with heart failure to accurately define and ascertain the underlying aetiology. An example is that coronary artery disease may mandate further investigation with radionuclide studies, cardiac magnetic resonance imaging and coronary angiography. Other supplemental investigations may be deemed necessary. These include pulmonary function tests, cardiopulmonary exercise testing and Holter monitoring. Other investigations may aid in formulating a diagnosis and/or help with risk stratification and prognostication.

Cardiac magnetic resonance imaging (CMR) when available has become an important imaging modality to consider within patients with heart failure. It offers a technique which is highly reproducible in terms of bi ventricular volumes, function, myocardial mass, intra-cardiac pathology and pericardial disease.(23, 24) Further information may also be added by a CMR study with the concurrent administration of a gadolinium based contrast. Patterns of gadolinium enhancement and distribution may signify areas of infarction, infiltration or myocardial fibrosis. Current experience with gadolinium enhancement suggests that it is of clinical importance amongst the cardiomyopathy population and also patients with prior ischaemic heart disease.(25-27)

### 1.5.5 Heart failure with Preserved Ejection Fraction (HFpEF)

The increasing use of echocardiography and CMR has demonstrated that a cohort of patients exist who possess signs and symptoms consistent with heart failure but who have normal or near normal left ventricular systolic function.

Demographical data indicates a prevalence of 30-50% of this group of patients among populations with heart failure. The pathophysiology of heart failure in such patients is less understood, but higher rates of hypertension, atrial fibrillation and diabetes have been observed within the group.(28)

The absolute mortality rate remains high in this group of patients with an observed mortality rate at five years of 68%.(29) A recent meta-analysis, which covered 41,972 patients demonstrates however that when such populations are compared to patients with LVSD, the mortality rate within the HFpEF population is lower.(30) The meta-analysis included 10,347 patients with HFpEF versus 31,625 with LVSD. Those with preserved ejection fraction were more likely to be older, female and have a history of hypertension. There were 121 [95% confidence interval (CI): 117, 126] deaths per 1000 patient-years in those with HF-PEF and 141 (95 percent CI: 138, 144) deaths per 1000 patient-years in those with HF-REF. HF-PEF had lower mortality than those with HF-REF (adjusted for age, gender, aetiology, and history of hypertension, diabetes, and atrial fibrillation); hazard ratio 0.68 (95 percent CI: 0.64, 0.71). Unfortunately the success of neurohormonal antagonists for patients with reduced ejection fraction has not been replicated for this group.(31-33) Further studies exploring therapeutic options are ongoing in this field.(10)

The literature has included only patients with LVSD within studies of device therapy. Hence there are no recommendations for device therapy within such populations, though studies are ongoing within this subgroup. Within this thesis no patient with HFpEF was studied.

## 1.6 Pathophysiology of Heart failure

The cardiovascular system is responsible for supplying oxygen via the circulation at both rest and exercise. It therefore has to be physiologically adaptive and this response may become blunted in most types of cardiovascular disease.

Heart failure is a complex clinical and pathophysiological syndrome characterised by cardiac dysfunction with subsequent systemic disruption.(34) The pathophysiology may be considered on a macroscopic, cellular and sub cellular level, including the effect on signalling pathways and protein expression.

Though clinically recognised for a number of years much is still unknown at cellular and subcellular levels in terms of mechanisms of dysfunction. Macroscopically, the clinical signs and symptoms of heart failure have long been associated with clear overt changes demonstrated with modern cardiac imaging techniques. The field is under intensive investigation, with the knowledge that once mechanisms have been reliably documented, they become a target for the design of future therapies.

### 1.6.1 Macroscopic changes in heart failure

The hallmark of late stage heart failure is a marked dilatation of the atria and ventricles. (See Figure 4: Demonstrates the diagramatic progression of macroscopic left ventricular dysfunction(34)) This phenomenon has been observed previously, with it being the end stage of multiple aetiologies. The atria and ventricles may alter dimensions and shape in response to acute insults e.g. myocardial infarction and chronic conditions e.g. valvular heart disease.

The changes may be induced by changes in haemodynamic load and increased wall stress.(35) The end stage of this process macroscopically is a dilated spherical shape with enlarged cardiac dimensions. The dilated globular left ventricle is associated with severely impaired systolic and diastolic function, a reduced cardiac output at both rest and on exercise and progressive annular dilatation resulting in marked atrioventricular valve regurgitation. It may co-exist with activation disturbance such as left bundle branch block. Acute myocardial insults may result in localised disruption which leads to regional territories of macroscopic

dysfunction, which in the longer term may become permanent due to myocardial scar or fibrosis.

Modern cardiac imaging techniques include echocardiography, cardiac magnetic resonance imaging, computed tomography and radionuclide imaging. With these methods, it is possible to record such changes in patients with heart failure and the progression of such change. The response to treatment can also be easily followed up with such imaging techniques. Regional macroscopic myocardial dysfunction can be easily demonstrated acutely with such techniques.

An alternative phenomenon is the myocardial response to increased intra-cardiac pressure. Pressure overload chronically will induce concentric left ventricular hypertrophy. Initially systolic function will be preserved, with visible abnormalities of relaxation and diastole. As the myopathic disease progresses, systolic function may become impaired with progressive dilatation and thinning of the ventricular walls. The ultimate phenomenon is similar to that described above with the ‘dilated cardiomyopathy’ phenotype.

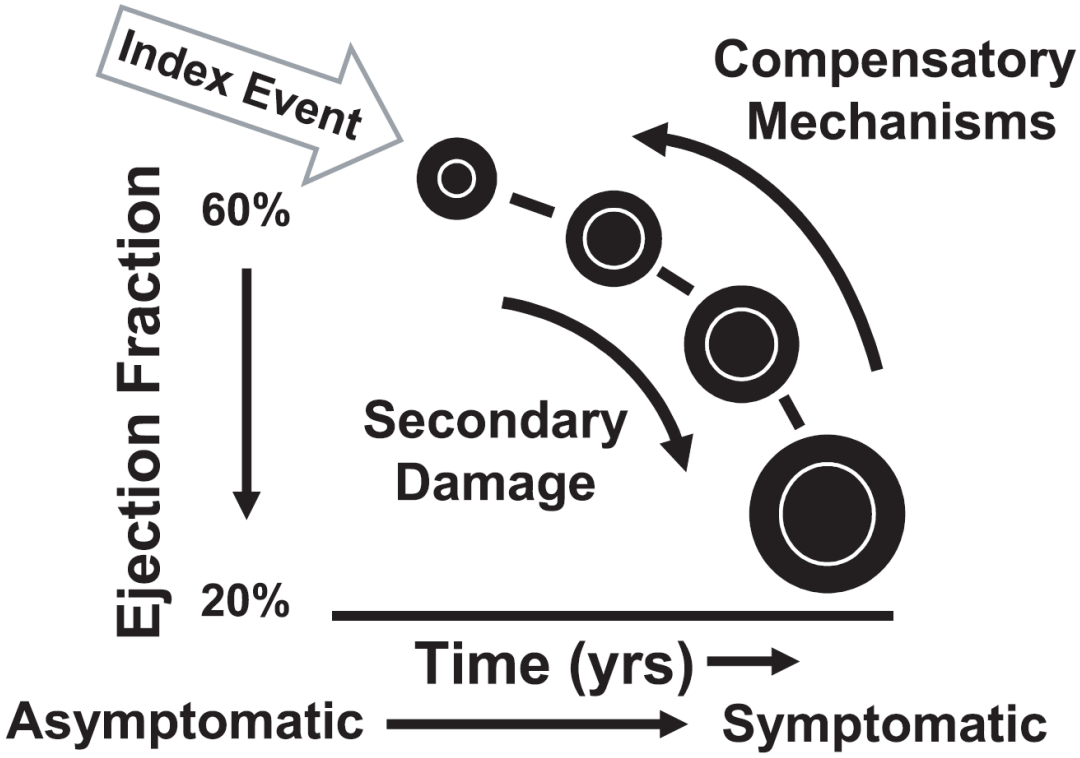


**Figure 4: Demonstrates the diagramatic progression of macroscopic left ventricular dysfunction**(34)

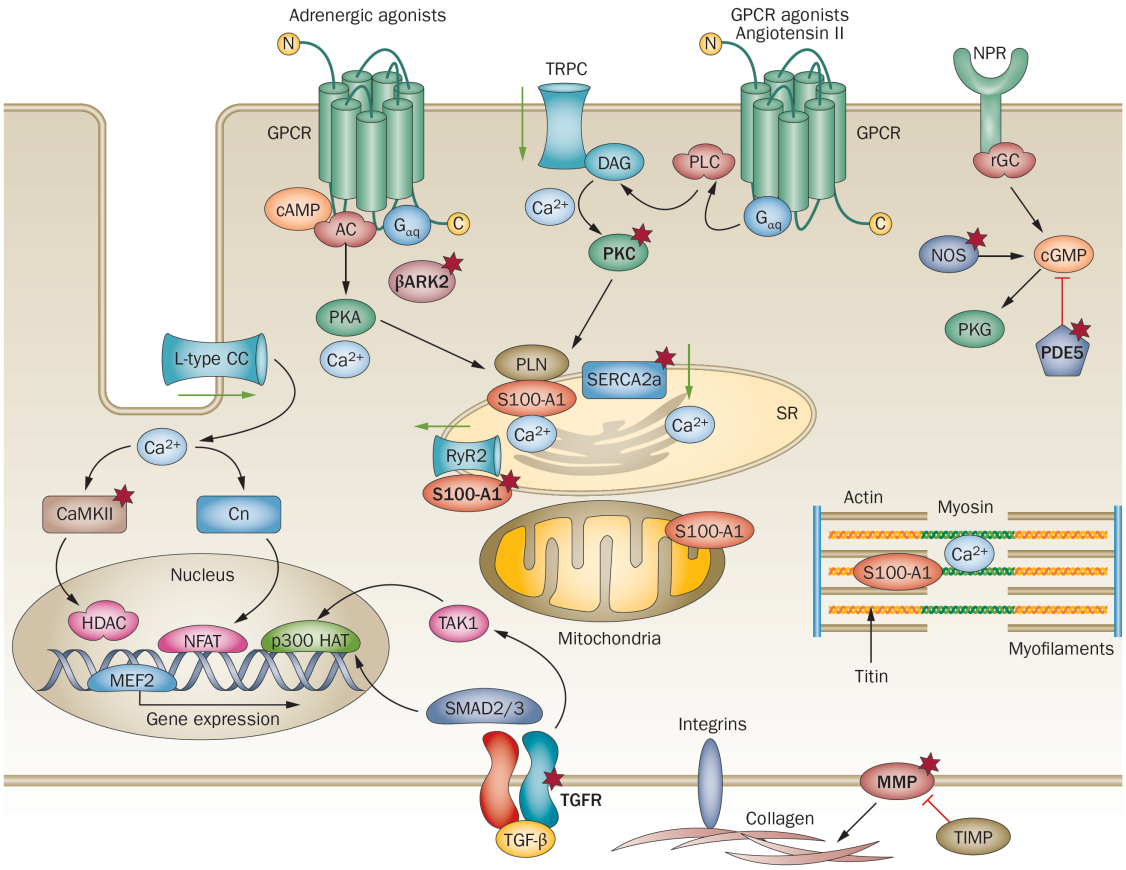


**Figure 5: Molecular signalling pathways targeted by novel approaches to reverse remodel the heart. Abbreviations:AC adenylate cyclase;βARK2,β-adrenergic receptor kinase;CaM, Calmodulin;CaMKII, calcium/Calmodulin-dependent protein kinase II;CC, calcium channel; CN, calcineurin; DAG, diacyl glycerol;GPCR, G protein coupled receptor; HDAC, histone deacteylase;MMP, matrix metalloproteinase;NFAT, nuclear factor of activated T cells; NOS, phosphodiesterase-5; PKA, protein kinase A; PKC, Protein Kinase C; PLN, phospholamban;rGc, receptor guanlyate cyclase;RyR2, ryanodine receptor 2;SERCA2a, sarcoplasmic/endoplasmic reticulum calciumATPase 2 isofrom2;SR, sarcoplasmic reticulum(35)**

### 1.6.2 Cardiomyocyte

Initially cardiomyocytes were thought to be terminally differentiated cell lines which were unable to undergo further cellular division. There is now increasing evidence that this may not be correct and some myocytes do undergo cell division but it is uncommon.(36) Published data corroborates this statement, with the observation that some precursor cells do occur in the myocardium. It remains unknown whether this represents a population of cells which are present from birth onwards or are derived from a circulating pool of stem cells which become myocytes following appropriate stimulation.

The potential therapeutic option of stem cells and cellular regeneration has been investigated previously. A recent meta-analysis, published in 2012 has reviewed the literature with regards to stem cells and their role in myocardial regeneration following myocardial infarction.(36) Having reviewed thirty-three randomised controlled trials and analysed data from 1765 patients, stem cells seemed to have some effect on left ventricular reverse remodelling, which was sustained into the longer term. However the authors noted a high degree of heterogeneity among the included studies which made direct comparison of the data difficult.

Cardiomyocytes may undergo structural change in either their longitudinal or transverse diameters. The change in appearance is related to the exposure of the myocyte to stimuli. Longitudinal change is more often observed in dilated cardiomyopathy. Altered gene expression affects both the cellular cytoskeleton and the contractile proteins. However the lengthening of the myocyte alone cannot explain the macroscopic change in ventricular dimensions and cavity size. There may be insertion of the myocytes between muscle fibres which are normally tightly apposed.

Cardiomyocyte hypertrophy is observed in conditions with chronic pressure overload such as hypertension or aortic stenosis. There is minimal longitudinal change in the myocyte with compensatory cellular hypertrophy observed. Sub nuclear changes may be observed, with alterations in the intracellular signalling pathways and transcription factors.
Gap junctions are the link between the individual myocytes and represent a series of transmembrane channels which permit electrical communication and cross talk. The constituent proteins of a gap junction are connexins. Anomalies of connexins have been observed in patients with heart failure.(37) Connexin-43 is the principal connexin in healthy human hearts, but its expression in patients with heart failure has been found to be down regulated. This may then underpin the electrical disarray with potential tendencies to generate arrhythmias.

Apoptosis is the process of programmed cellular death. This is part of normal physiology and is reliant on intracellular signalling pathways. The main signalling pathway for apoptosis is

the caspase pathway.(38) This leads to the eventual fragmentation of nuclear and cytoplasmic contents. Cardiac necrosis however is normally induced by a severe insult e.g. acute myocardial infarction in which there is no time for compensatory hypertrophy to take place. Chronically cells may undergo necrosis from an ongoing process of increased oxidative stress, the rupture of such myocytes leads to a spontaneous release of intracellular contents which induces a pro-inflammatory reaction which eventually leads to myocardial fibrosis.

### 1.6.3 Myocardial Fibrosis

The use of modern cardiac imaging techniques has led to the in vivo demonstration of myocardial scar/fibrosis in situ in living patients. This is especially true for cardiac magnetic resonance imaging with concurrent gadolinium contrast. The delayed enhancement of segments of myocardium leads to 'late gadolinium enhancement (LGE)' which is a macroscopically visible marker of cardiac fibrosis or scar. Certain pathological patterns of LGE have been associated with different aetiologies of heart failure. The LGE represents a reduction in washout of the gadolinium contrast from within the extracellular matrix.

The presence of myocardial fibrosis requires increased numbers of fibroblasts which undergo transformation to myofibroblasts with release of signaling molecules, cytokines and enzymes. Excessive collagen deposition eventually leads to diastolic interference with eventual impact on cardiac systole.

The extracellular matrix is regulated by a constant balance between matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases. (TIMPs) MMPs represent a family of proteolytic enzymes which degrade extracellular matrix proteins. There is normally a balance between different isoforms of MMPs, with a major MMP being MMP-13. Within healthy hearts, there is limited expression of such isoforms, however in diseased hearts; levels have been noted to be unregulated. Conversely MMPs found in the normal heart are downregulated. The imbalance in MMP expression leads to extracellular matrix degradation which in turn leads to increased rates of myocardial fibrosis. Some potential stimulants of collagen synthesis and turnover are cytokines, oxidative stress, angiotensin II and aldosterone.

### 1.6.4 Depolarisation of the myocytes and electro-mechanical coupling

The coupling process of electromechanics in relation to the myocytes is dependent on the movement of intracellular calcium. It is recognised that action potentials are prolonged in heart failure.(39)

The depolarisation of a myocyte may be viewed in several stages. Initial depolarisation leads to the entry of extracellular calcium through the L type voltage dependent channels (See Figure 5). Further calcium is then released from intracellular stores, predominately from the sarcoplasmic reticulum (SR). The initial influx of calcium acts as a signal on the surface of the SR via the cardiac ryanodine receptor (RyR-isoform 2). These receptors are adjacent to DHPR channels in the sarcolemma membrane. The influx of calcium ultimately causes a synchronised release of calcium - a calcium 'spark'. The wave of calcium release induces depolarisation and contraction. Diastole represents the reverse of this process with a rapid uptake of the intracellular calcium into the SR via the Ca2+/ATPase (SERCA) or by its removal from the cell via the surface membrane Na+/Ca2+ exchanger.

Beta adrenoceptors mediate intracellular signalling pathways which govern parts of the process described above via phosphorylation. Specific steps of the pathway may become hyperphosphorylated e.g. RyR2(40) The overall effect is a reduction in intracellular calcium stores particularly from the SR. SERCA has also been observed to be downregulated with a lack of removal of calcium and hence a prolonged diastolic component of the cardiac cycle.

There may also be structural change in the t-tubule, ryanodine receptor and DHPR channels. The t tubular system runs from deep within the cell and brings the SR membrane into close contact with the other components of intracellular coupling. Hence a loss of the t tubule network in heart failure may impair efficient electromechanical coupling.

### 1.6.5 Myocardial Energy Metabolism

Normal physiology relies on the delivery of oxygen and energy substrate to the cell for the production of adenosine-triphosphate (ATP) via aerobic respiration. The majority of normal energy metabolism is derived from β phosphorylation of fatty acids, with a significant

minority being derived from the glycolysis pathway. An alternative pathway is the phosphocreatine/creatine pathway which supplies a high energy phosphate energy store from the mitochondria to the myofibril myosin ATPase.

Under abnormal conditions including ischaemia, metabolism switches to the glycolysis pathway with the change in energy substrate leading to the production of lactic acidosis. Within models of heart failure, abnormalities of myocardial metabolism have been noted. Left bundle branch block itself is associated with an imbalance in myocardial metabolism which may be corrected by the implantation of CRT.(41) This offers one potential mechanism for the beneficial effects of CRT.

Free radicals, including the superoxide anion and hydroxyl radical, are transiently generated during normal myocardial metabolism. In health, free-radical scavengers (super-oxide dismutase and catalase) remove these molecules prior to any damage occurring. Within heart failure, there is both an increase in free radical generation and also a down regulation of the scavenger system, the overall impact is an increase in oxidative stress.(42) The term defines the damage to intra-cardiac structure mediated by the free radicals.

### 1.6.6 Contractile Protein Dysfunction

Abnormalities of sarcomeric protein expression have been found in patients with heart failure. Hereditary cardiomyopathies such as hypertrophic cardiomyopathy have been linked with anomalies of the beta-myosin heavy chain.

An imbalance between alpha and beta myosin chains has been noted with an upregulation of beta myosin proteins with an accompanying downregulation in alpha proteins. The imbalance in levels of expression results in dysfunctional myosin expression which ultimately reduces myosin-ATPase activity and leads to systolic impairment.(43) A precursor phase of myosin abnormal expression exists prior to the overt manifestation of systolic impairment.

### 1.6.7 Systemic Manifestations of Heart Failure

Though molecular and cellular pathways are now being intensively researched and targetted for potential therapies, it has long been recognised that heart failure represents a complex syndrome of cardiac and systemic dysfunction. The pathways of systemic dysfunction have been better characterised, and the selective inhibition of such pathways now forms the cornerstone of current heart failure pharmacological management.

### 1.6.8 Sympathetic Nervous System

The sympathetic nervous system forms half of the autonomic system and hence plays critical roles in the maintenance of homeostasis. Hence an acute deterioration or insult to the cardiovascular system results in increased sympathetic tone mediated by an increased release in adrenaline and noradrenaline. These hormones then, via direct and indirect effects, mediate an increase in cardiac output. The effect on the myocardium is mediated by catecholamine responsive intracellular signalling pathways that promote increased myocardial excitation coupling and an increased contractile response. The release of such hormones is governed by central and peripheral baroceptors which regulate blood volume, pressure and cardiac output.

Initially this response promotes a beneficial effect on the myocardium, vasculature and renal system. However, continual stimulation leads to a maximal effect on the signalling pathways and a down regulation of the adrenoceptors. The continuous release of catecholamines leads to a tachyphylaxis like phenomenon.

The effects on intracellular signalling pathways are an upregulation of the beta-adrenergic receptor kinase-1 (β-ARK-1), upregulatory expression of inhibitory G proteins and increased turnover of cyclic AMP. All of which result in interrupted intracellular signalling and a decreased efficacy of β receptors.

### 1.6.9 Renin-Angiotensin-Aldosterone-System

Activation of the renin-angiotensin-aldosterone system is mediated by catecholamine release and subsequent effects on the juxtaglomerular apparatus. The release is stimulated by reduced circulatory volume and is an intrinsic response to hypovolaemia. The physiological effect of

stimulation of the RAAS pathway is sodium and water retention and maintenance of ventricular filling pressures. In health a negative feedback cycle exists which permits the termination of such hormone production.

Within heart failure, the regulatory cycles become disturbed and lead to a continual expression of renin. Ultimately the pro-hormone is cleaved to form angiotensin II and aldosterone. These potent steroid based hormones have deleterious effects on vasculature, renal tract and myocardium. The expression of aldosterone promotes abnormalities of collagen synthesis and turnover which ultimately leads to myocardial fibrosis. Angiotensin II is a potent vasoconstrictor and hence potentiates an already abnormal cardiovascular disease state.

Aldosterone also leads to the recruitment of pro-inflammatory mediators and increased levels of NADPH oxidase which leads to increased oxidative stress. The overall environment created by the release of angiotensin II and aldosterone is pro fibrotic.(44) Clinical trials using aldosterone antagonists in patients with LVSD have demonstrated significant effects upon cardiovascular mortality and morbidity. The randomised trials will be discussed in more detail in section 1.7.5. A potential mechanism which may explain the beneficial effects of aldosterone antagonists are their effects on myocardial and systemic fibrosis.

### 1.6.10 Endothelium in Heart Failure

The endothelium in arteries and larger arterioles is a constant local source of regulation of peripheral vascular resistance. The release of endothelium derived nitric oxide promotes vasodilatation via smooth muscle relaxation and the peptide, endothelin counter balances this with effects of vasoconstriction.

Hence in health there is a continual balance between the two. However, in heart failure there is down regulation of nitric oxide expression with a corresponding increase in endothelin release. This has been demonstrated to induce myocardial fibrosis. The available amount of nitric oxide is further diminished by the scavenged reactive oxygen species.

### 1.6.11 Overview

The clinical syndrome of heart failure comprises a collection of cellular, molecular and macroscopic dysfunction. Macroscopic changes are easily charted with current imaging techniques and progression of such changes can be tracked. The molecular side of the field is less well characterised. It represents a complex network of pathways, protein expression and receptors which, though they have been investigated, have yielded little in terms of therapeutics. It remains to be seen whether selective targeting of such cellular and sub cellular pathological dysfunction results in meaningful clinically relevant treatments for patients with heart failure.

## 1.7 Management of Heart Failure

Contemporary management of heart failure is based on a cohesive multi-disciplinary approach to patient centred care utilising amendments in lifestyle factors, pharmacological evidence based therapies, appropriate device based therapies, cardiac and surgical intervention where appropriate, cardiac transplantation and mechanical assist devices and palliative care. NICE has produced guidance within the area since 2003, with an updated set of guidelines issued in 2010.(11, 45)

These are similar to the ESC guidelines which were most recently revised and published in 2012 (See Figure 6), having been previously issued in 2005.(10, 46, 47) American guidelines were most recently released in 2010 by the Heart Failure Society of America (HFSA).(48)

### 1.7.1 Lifestyle Management

Patients with heart failure should be educated in terms of their disease and its practical daily management. This includes attention to fluid and salt consumption, daily and weekly alcohol intake, smoking status and participation in aerobic exercise. Alcohol excess may also promote fluid retention; in cases where it is deemed to be the cause of ventricular dysfunction complete abstinence is the recommendation. For patients, particularly those with ischaemic heart disease, smoking status should be reviewed and patients offered assistance for smoking cessation.

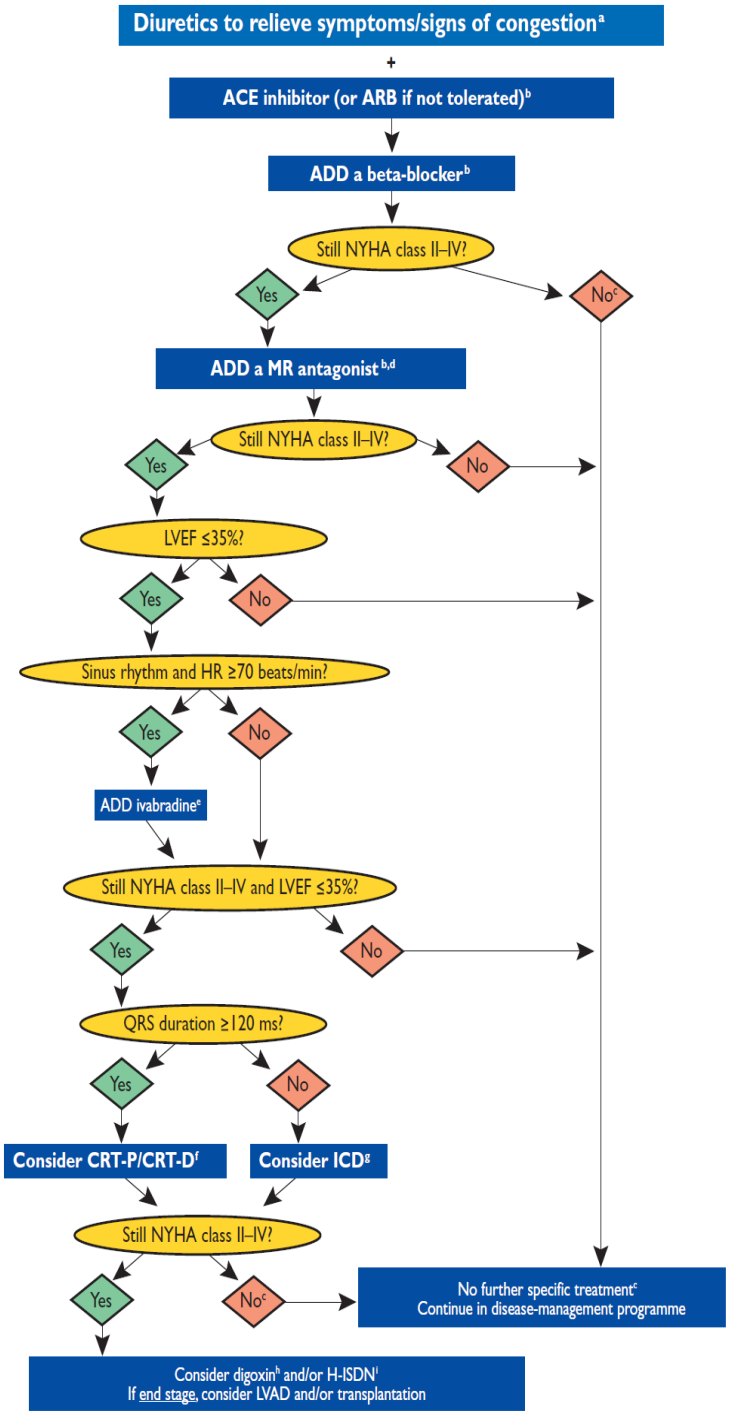


**Figure 6: Figure demonstrating the treatment algorithm as per ESC guidelines-2012.(10) Angiotensin Converting Enzyme; ARB = Angiotensin Receptor Blocker; CRT-D = Cardiac Resynchronisation Therapy Defibrillator; CRT = Cardiac Resynchronisation Therapy; H-ISDN = Hydralazine and Isosorbide dinitrate; HR = Heart rate; ICD= Implantable Cardioverter Defibrillator; LBBB = Left Bundle Branch Block; LVAD = Left Ventricular Assist Device; LVEF = Left Ventricular Ejection fraction; MRA = Mineralocorticoid Receptor Antagonist; NYHA = New York Heart Association**

### 1.7.2 ACEI

The initial neurohormonal antagonists which were used in LVSD were ACEI.(49, 50) They are effective at improving heart failure morbidity and mortality. They should be started at low doses and cautiously uptitrated to the recommended target dose as used in the randomised controlled trials. During the adjustment period, one should monitor patient's symptoms (including cough), blood pressure and renal function. Though the recommendation is for patients to achieve target dose, a lower dose of ACE inhibitor is still effective and some patients may not reach target dose. The maximal tolerated dose is described as the 'optimal' dose providing uptitration has been trialled.

### 1.7.3 ARB

Angiotensin II receptor blockers are now used as an alternative therapy for patients intolerant of ACEI. The largest trial to date which demonstrates efficacy of such agents was the CHARM- Alternate study, which demonstrated that candesartan in this patient population improved morbidity and mortality compared to placebo (and for patients intolerant of ACEI)(51) Similar caveats exist with regards to uptitration of dosage. The side effect profile of ARBs is similar to ACEI except for the occurrence of cough which is rare in patients on ARBs.

### 1.7.4 ß- Adrenoceptor Antagonists 'Beta Blockers'

Originally reservations existed regarding the use of BB for patients with heart failure due to the short term negative inotropic effects of BB. However, several large randomised controlled trials have shown an improvement in both morbidity and mortality with such agents.(52-54) However it should be noted that this effect is not a class wide effect and hence the recommendations are only to utilise beta adrenoceptor antagonists which are proven for heart failure.(10) Within the UK this includes carvedilol, bisoprolol and nebivolol. They should be initiated at a low dose when the patient is in a clinically euvolaemic state and should be carefully uptitrated with a view to achieving target dose.(11)

### 1.7.5 Mineralocorticoid Antagonists

In current UK practice, this class of drug includes spironolactone and eplerenone. The landmark trial in the area was RALES published in 1999, which demonstrated efficacy of spironolactone in patients with severe symptomatic heart failure due to LVSD.(55) This provoked an initial over prescription of spironolactone with resultant increased rates of hyperkalaemia and acute kidney injury.(56) This is due to the direct effects on the androgenic receptor and other remote actions which lead it to have some pro-oestrogenic properties.

Eplerenone is a more refined molecule which was initially trialled in the EPHESUS study.(57) This was a population with post myocardial infarct heart failure. Having demonstrated efficacy at reducing mortality and morbidity, EMPHASIS-HF then investigated the use of eplerenone in patients with less symptomatic disease.(58) This reported a reduction in cardiovascular hospitalisation and mortality with eplerenone in patients with much milder symptoms (NYHA II) and who were already on optimal ACEI and BB therapy.

Ultimately a patient should be considered for aldosterone antagonism after having been established on other neuro-hormonal antagonists detailed above firstly. Caution should be exercised with regards to initiation of such drugs in patients with poor renal function. Careful monitoring is necessary to ensure hyperkalaemia is detected and managed appropriately.

### 1.7.6 Ivabradine

With the increasing uptake of beta blocker therapy, there were certain patients with left ventricular systolic dysfunction who could not tolerate such agents. Ivabradine is a novel I*f* channel inhibitor. I*f* channels being predominately located within the sino-atrial node. After experimental studies confirmed that ivabradine mediated a heart rate reduction, it was studied in two large in vivo studies. BEAUTIFUL was designed to assess its capabilities within patients with ischaemic heart disease.(59) Its effect was most marked in patients with heart rates >70 beats per minute (bpm). To evaluate this relationship further it was investigated in SHIFT.(60) Using 6,505 participants, ivabradine significantly reduced the composite endpoint of HF hospitalisation and cardiovascular death. The findings were strongest in those patients with a heart rate which was higher at rest. These findings have been incorporated into the latest guidance issued by NICE and the ESC.(10, 11) The recommendation is that ivabradine

should be considered as an agent for those patients with heart failure due to LVSD who remain symptomatic despite ACEI, BB and MRA, with a heart rate >70 bpm in sinus rhythm and on maximally tolerated BB.

### 1.7.7 Digoxin

Digoxin has been widely used for more than two hundred years as a treatment for 'dropsy' - heart failure. The only major randomised controlled trial to date suggests that it did not reduce overall mortality but did improve rates of cardiovascular hospitalisation (in patient with sinus rhythm). Currently it is recommended as adjunctive therapy beyond the standard neurohormonal pathway.(10) It is also indicated in patients with concomitant atrial fibrillation and systolic dysfunction due to its potential control of the ventricular response to atrial fibrillation.

### 1.7.8 Diuretics

Currently two classes of diuretics are used in the modern treatment of heart failure. Loop and thiazide diuretics exert their effects on different parts of the nephron. They promote excretion of sodium and water and relieve fluid retention and hence consequently may reduce ventricular filling pressures. However, they may also induce neurohormonal activation. There is no evidence with regards to either group of medication on mortality benefit within patients with heart failure.(61)

### 1.7.9 Hydralazine and Isosorbide Dinitrate

The awareness that differences existed in RAAS pharmacokinetics and pathophysiology within African –Americans led to the consideration of alternative therapies. Another mechanism of inducing systemic vasodilatation was to use therapies which exploited the endothelial nitric oxide pathway. The combination of hydralazine and Isosorbide Dinitrate (ISDN) were studied in A-HeFT and V-HeFT studies and were found to be efficacious at reducing mortality and morbidity particularly in those patients of African-American origin.(62, 63) The initial study which was performed was the Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure (V-HeFT) which evaluated the effects of the

combination of isosorbide dinitrate and hydralazine. Using a cohort of 642 patients, the group was randomised to either placebo, prazosin 20 mg once daily, or a combination of hydralazine (300mg once daily) and isosorbide dinitrate (160mg per day). The risk reduction in patients at two years was 34 percent for those randomised to the combination of vasodilators as compared to the other groups. ($P<0.028$) On non specified sub group analysis it was noted that the African American population within this study had an increased longevity. Hence a dedicated study was created. The A-HeFT (Combination of Isosorbide Dinitrate and Hydralazine in Blacks with Heart Failure) was tasked to investigate the effect of the combination therapy in an African American population. Using a group of 1050 patients, who were randomised to either the combination or placebo in addition to conventional medical therapy, it was noted that there was a significant mortality benefit between the two arms. ($P=0.02$) (62)

### 1.7.10 Cardiac Surgery and Percutaneous Valve Techniques

Cardiac transplantation is a therapeutic option for patients with advanced symptomatic disease who fulfil prespecified criteria. The rate of cardiac transplantation is diminishing, due to poor organ availability.(64) Mechanical assist devices have gradually improved in technological capability and reliability and are increasingly being implanted worldwide. Within the UK, currently such devices can only be considered for patients who ultimately have potential to enter the active cardiac transplantation list i.e. ‘bridge to transplant’

Valvular disease is an aetiology of HF which is increasingly common amongst elderly patients. Traditional surgery remains a viable option for certain patients, but more novel approaches now exist. For aortic valvular disease, there is now the option of transcutaneous aortic implants (TAVI) and for functional mitral regurgitation, a percutaneous clip device may be considered.(65, 66)

The indications for revascularisation and HF remain controversial. The fundamental principle is that revascularisation may aid the recovery of ‘hibernating’ myocardium. Hibernation is where the myocardium is alive but not contracting. It may be demonstrated by a variety of cardiac imaging modalities including radionuclide imaging, cardiac magnetic resonance imaging and stress echocardiography. The recent STICH randomised controlled trial did not demonstrate a clear improvement in patients with ischaemic heart disease and reduced left

ventricular systolic function who were randomised to bypass grafting versus medical therapy.(67)

### 1.7.11 Disease Monitoring

The traditional hospital based model of heart failure care is gradually changing. Due to increasing prevalence and the high rates of co- morbidities amongst elderly patients- it is recognised that there is a need to amend current care pathways.

Due to the complexity of patients with heart failure, multidisciplinary care is essential. A dedicated specialised nurse service has been shown to reduce hospitalisation and mortality.(68, 69) A suggested model of multidisciplinary care should include specialist physicians, general practitioners, nurses, palliative care input and other relevant members e.g. geriatricians or social workers.

Careful dedicated follow up should detect adverse symptoms e.g. a reduction in exercise tolerance or signs e.g. increasing peripheral oedema. Natriuretic peptides may also be used to monitor progress.

Remote telemonitoring has also been shown to have a role in the care of these patients. Several challenges exist to optimal care including, frail elderly patients with physical limitations, geographical distance from the secondary care institution and brittle unstable disease. Telemonitoring may aid in their care, by the transmission of physiological variables including weight, blood pressure and heart rate to a monitoring centre. This may reduce the need for physical consultations. A number of systems are commercially available and the initial work within the area is promising.(70, 71) Further studies are ongoing as to how best to deploy the current technology, the optimal method of harnessing transmitted information and to characterise which variables should be collected and transmitted. Nevertheless remote monitoring offers a sophisticated method of patient follow up.

## 1.8 Device Based Therapies

For the purpose of this thesis 'device based therapies' refers to CRT and/or ICD therapy. Patients with heart failure are at increased risk of sudden cardiac death as compared to the general population. A proportion of these deaths are attributable to arrhythmia.

The rates of sudden cardiac death (SCD) have been reduced by pharmacotherapy yet many patients still suffer this as a mode of death. Hence device therapy has become an important part of HF management in addition to the optimal tolerated evidence based medical therapy.

### 1.8.1 Implantable Cardioverting Defibrillators

Implantable cardioverting defibrillators (ICD) are implanted to counteract life threatening ventricular arrhythmias by a combination of internal DC cardioversion or anti-tachycardia pacing. Dual chamber ICDs may also provide univentricular back up pacing. A potential ICD implant may be a dual chamber system with right atrial and right ventricular leads or a biventricular with an additional left ventricular lead system. Randomised studies have demonstrated the efficacy of ICDs in a range of populations and they are now an established therapy for patients with HF. (72-74)

The concept of an implantable cardioverting defibrillator was first reported in the late 1960's and pioneering work by a group in Sinai Hospital, Baltimore translated the concept into clinical technology with the first case report occurring in 1980, the successful implantation of a functioning ICD at John Hopkins Hospital, Baltimore.(75) During this period of time a rival group from the University of Missouri was also working on such technology(76) The realisation that ventricular arrhythmias could be successfully cardioverted with external defibrillators and pads had led the drive towards the development of ICDs.

Throughout the 1980s and 1990s ICD technology was continuously refined so that battery life became more prolonged, leads became robust and less prone to displacement or fracture and size of generator box was reduced, and by the 1990s there was a sufficiently technologically competent device to permit phase III randomised clinical trials to take place.

In terms of ICD therapy, the scientific community was interested in primary prevention (i.e. those with history of non-sustained ventricular arrhythmias with other risk factors for sudden cardiac death) and secondary prevention (i.e. prior history of ventricular arrhythmia mediated cardiac arrest or significant ventricular arrhythmias inducing haemodynamic compromise.)

Hence initial studies focused on either of these two aspects with numerous studies being published in the late 1990s. For secondary prevention the cumulative evidence from the studies performed in the late 1990s was strongly suggestive that ICD therapy should be considered in such survivors.(77, 78) However the different inclusion criteria amongst the individuals recruited to the primary prevention trials meant this aspect of ICD therapy was less clear.

The landmark study in the area for those patients with left ventricular systolic dysfunction and prior history of ischaemic disease (myocardial infarction) was MADIT II (Multicentre Automatic Defibrillator Implantation Trial II) published in 2002.(74)

This North American trial randomised patients who had suffered myocardial infarction with sustained areas of myocardial scar and a residual LVEF of <30 percent. Crucially whereas previous primary prevention trials had included cumbersome, expensive and potentially dangerous electrophysiology studies, MADIT II did not require such information as part of its inclusion criteria.

1232 patients were recruited and randomised in a 3:2 manner to either ICD therapy or conventional medical therapy. The primary endpoint was all cause mortality. Following a mean period of 20 months (range 6 days to 53 months) ICD therapy significantly reduced deaths HR= 0.69 (95 percent confidence interval, 0.51 to 0.93; P=0.016). The findings from this study were unquestionably significant but alarmed health economists as the inclusion criteria primarily hinged on prior history of myocardial infarction and reduced left ventricular ejection fraction. This meant large numbers of patients on this basis could be considered for ICD therapy which even by the turn of the century remained relatively expensive. However nonetheless the trial had demonstrated ICD therapy was potentially a therapeutic option in such individuals.

The studies performed in patients with non ischaemic dilated cardiomyopathy were less uniform in their findings. The CAT (The Cardiomyopathy Trial) was one of the first within the area and focused on patients with dilated cardiomyopathy and reduced LVEF <30

percent.(79) The CAT study was also published in 2002 and took a cohort with recent onset dilated cardiomyopathy (<9 months) and unobstructed coronary artery disease (deemed by coronary angiogram) and in NYHA II/III heart failure. The trial recruited solely in Germany and the recruitment period ran from May 1991 until November 1997. The primary end point was all cause mortality at one year. Considering the recruitment period only a 104 patients were enrolled into the study and were randomised in a 1:1 manner to ICD therapy or conventional medical therapy. The effect of ICD therapy on all-cause mortality was non-significant both at one year and in longer term follow up. The overall survival of the cohort was much greater than that originally predicted and hence the trial was clearly underpowered to detect differences. The findings hinted that ICD therapy may not be appropriate for patients with dilated cardiomyopathy but further larger studies were needed.

The study which resolved the debate was the SCD-HeFT study published in 2005.(73) The SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) was deliberately conceived to answer the role of ICD therapy in all groups with symptomatic heart failure as compared to amiodarone and conventional medical therapy. From September 1997 until July 2001, a total of 2521 patients were randomised to medical therapy + placebo, medical therapy + amiodarone or medical therapy + single lead ICD. Inclusion criteria were a LVEF <35 percent and NYHA class II/III heart failure. ICD therapy was deliberately chosen to be single lead shock only with no dual or biventricular devices allowed to be implanted. The primary endpoint was all cause mortality. A total of 666 patients died: 244 (29 percent) in the placebo group, 240 (28 percent) in the amiodarone group and 182 (22 percent) in the ICD group. As compared with placebo, amiodarone therapy was associated with a similar risk of death (hazard ratio, 1.06; 97.5 percent confidence interval, 0.86 to 1.30; P = 0.53) and ICD therapy was associated with a decreased risk of death (hazard ratio, 0.77; 97.5 per- cent confidence interval, 0.62 to 0.96; P = 0.007). Hence a conservatively programmed ICD with shock only capacity had been shown to improve outcomes in heart failure populations. The authors stressed that these results should not be extrapolated to dual chamber or biventricular ICDs.

The question then arose whether CRT-D would be superior to conventional ICD therapy in heart failure populations with the CRT component being helpful against left ventricular disease progression and the ICD being protective from ventricular arrhythmias. Two large trials have reported on this question.

The first was MADIT-CRT, published in 2009, from the MADIT group and the same steering committee from the earlier MADIT studies.(80) A total of 1820 patients was recruited into the study providing they had NYHA I/II (underlying ischaemic aetiology) or NYHA II (dilated cardiomyopathy), sinus rhythm, LVEF <30 percent and prolonged QRS duration >130ms. Participants were then randomised to ICD implantation (mixture of single and dual chamber) or CRT-D (biventricular ICD). The primary endpoint was a composite of all-cause mortality and a heart failure event. The primary end point occurred in 372 patients: 187 of 1089 patients in the CRT–ICD group (17.2 percent) and 185 of 731 patients in the ICD-only group (25.3 percent). These end-point events included 36 deaths (3.3 percent) and 151 heart-failure events (13.9 percent) in the CRT–ICD group and 18 deaths (2.5 percent) and 167 heart-failure events (22.8 percent) in the ICD-only group. (P=0.001) Hence the effect of CRT-D was superior to ICD but the effect was predominately driven by a 41 per cent reduction in heart failure events. The effect was most marked in a prespecified sub group analysis of those patients with a QRS duration >150ms.

The RAFT study was the last study to report in the area and reported in 2010.(9) RAFT (Resynchronisation-Defibrillation for Ambulatory Heart Failure Trial) was an alternative study. It recruited from predominately Canadian centres but also included centres in Australia and Turkey. Patients were randomised to CRT-D or ICD in addition to conventional medical therapy. The inclusion criteria were NYHA class II/III, A LVEF <30 percent, intrinsic QRS duration >120ms and a paced QRS duration >200ms. The primary endpoint was all cause mortality and hospitalisation for heart failure.

A total of 1798 patients were recruited and followed up for a mean of 40 months +/- 20 months. The primary outcome occurred in 297 of 894 patients (33.2 percent) in the ICD–CRT group and 364 of 904 patients (40.3 percent) in the ICD group (hazard ratio in the ICD–CRT group, 0.75; 95 percent confidence interval [CI], 0.64 to 0.87; P<0.001). In the ICD–CRT group, 186 patients died, as compared with 236 in the ICD group (hazard ratio, 0.75; 95 percent CI, 0.62 to 0.91; P=0.003), and 174 patients were hospitalized for heart failure, as compared with 236 in the ICD group (hazard ratio, 0.68; 95 percent CI, 0.56 to 0.83; P<0.001).

Hence the most recent European guidelines published this year suggest that patients being considered for ICD should be strongly considered for CRT-D providing they have met the other selection criteria.(22) (LVEF <35 percent and complete left bundle branch block) However what is less clear is whether a patient who is being considered for CRT-P should be considered for CRT-D. There has not been a published trial which has published on head to head basis - COMPANION did contain three arms with two of them containing CRT-P and CRT-D.(5) However the trial design meant that the study was not powered to allow a direct comparison. The sector needs further investigation and potentially even a trial which contains a direct comparison between CRT-P and CRT-D.

### 1.8.2 Historical perspective

Cardiac Pacing in humans was originally described in the 1950's.(81, 82) Modern percutaneous transvenous techniques have been developed and refined over the past thirty years. The concept of pacing in patients with heart failure has steadily evolved over this time period.

One of the initial pilot studies was performed by Derek Gibson in 1971. It demonstrated the acute effects of biventricular pacing.(83) Using six patients with Starr-Edwards aortic valve prostheses in the acute post-operative period, biventricular pacing using the surgical epicardial leads was shown to reduce the surface QRS duration on the electrocardiogram (ECG). Using the stroke distance as calculated by the movement of the ball in the prosthesis itself, the authors also demonstrated that biventricular pacing resulted in improved ventricular work.

Other groups performed small limited pilot studies around this time period.(84, 85) but no further investigational work was performed in this area for the following thirty years. Though the large randomised controlled trials of heart failure pharmacotherapy started to report in the late 1980s and early 1990s, there was a large number of patients with symptomatic advanced disease. Hence a renewed focus was placed on pacing as a potential treatment for this cohort.

Hochleitner, in 1990, demonstrated, using conventional dual chamber pacing set in dual chamber pacing mode (DDD), a marked clinical and haemodynamic improvement in sixteen

patients with dilated cardiomyopathy (DCM).(86) All patients had advanced symptomatic disease and had proven dilated cardiomyopathy with normal coronary angiography and myocardial biopsies. The severity of their disease meant that all 16 patients have been initially referred for cardiac transplantation with seven on the current transplant list. All patients were on the optimal tolerated medical therapy of the time (vasodilators, diuretics and digitalis). A total of seven patients had left bundle branch block (LBBB) on the surface electrocardiogram. (ECG) All patients underwent standardised implantation of a transvenous dual chamber system (right atrial and ventricular leads). Following the implantation of dual chamber pacemakers which were set at DDD mode with a ventricular rate of 50 beats per minute (BPM) with an atrioventricular (AV) delay of 100 milliseconds. The results demonstrated an improvement in clinical symptoms such as breathlessness, NYHA class improved from 3.6 ± 0.4 to 2.1 ± 0.5 ($P<0.001$), left ventricular dimensions improved, left ventricular end diastolic diameter improved from 74 ± 11 mm to 72 ±10 mm ($P<0.05$). All patients were discharged from hospital three weeks following their pacemaker implantation and after one year of clinical follow up, 4 patients had died, 12 individuals had persistent clinical improvement and subsequently a third of these patients received cardiac transplants. In three patients the impact of pacing was so marked that they were removed from the transplant list all together. This cohort was then subsequently followed up for an extended period of time. The effects of pacing seemed to persist after the acute period and the median survival for the cohort was 22 months. Three patients survived beyond the extended five year period of follow up.(87)

Following this initial work others evaluated the role of dual chamber pacing in patients with heart failure, particularly due to dilated cardiomyopathy. Brecker and colleagues, in 1992, investigated the effect of atrioventricular delay in patients with dual chamber pacing and dilated cardiomyopathy.(88) A cohort of twelve patients was identified with dilated cardiomyopathy and concomitant mitral and tricuspid regurgitation. As a consequence of the regurgitation, all patients possessed shortened ventricular filling times. A shorter atrioventricular delay resulted in improved biventricular filling times (65 (35-95) ms and 90 (60-120)ms, $P<0.001$). A shortened AV delay also resulted in an increased cardiac output (by 1.1 [0.8-1.4] l/min, $p < 0.01$) and rises in exercise capacity (104 [45-165] s, $P < 0.05$) and maximal oxygen demand (2.1 [1.5-2.7] ml kg-1 min-1, $P< 0.05$). Linde and colleagues replicated the experiment in a smaller cohort of similar patients in 1995.(89) A day after successful DDD permanent pacemaker implantation, AV delay was optimised using Doppler flows across the aortic valve. The cohort was then re-evaluated at one, three, and six month

intervals following pacemaker implantation. Clinical data was collected at these time points including NYHA class, stroke volume, left ventricular ejection fraction and cardiac output. The initial optimisation did induce a short term improvement in haemodynamics (Baseline stroke volume = 22 ± 7 ml, day 1 = 28 ± 12 ml; p = 0.03: Baseline cardiac output = 1.9 ± 0.6 L/min, day 1 = 2.2 ± 1.1 L/min; p = 0.10) however the authors found no longer term effect on any of the documented variables.

Whilst some work, as described previously, had evaluated the role of predominately right atrial and ventricular pacing in patients with dilated cardiomyopathy, other groups decided to revisit the potential of biventricular pacing. Initial reports of multisite pacing started to emerge around this time. Cazeau and colleagues issued one of the first case series in 1996.(90) This involved eight patients who had advanced symptomatic heart failure, a broadened QRS duration on the surface ECG and who had either been refused or had turned down a cardiac transplant. Using temporary pacing leads and a series of connectors and pacing boxes, multisite pacing (including biventricular pacing) was tested. Biventricular pacing increased the mean cardiac index (CI) by 25 percent (from a baseline of 1.83 +/- 0.30 L/min per $m^2$, $P < 0.006$) and decreased pulmonary capillary wedge pressure by 17% (from a baseline of 31 +/- 10 mmHg, $P < 0.01$). Notably half (50 percent) of the patients suffered either intra-procedure or peri-procedural death but for the four survivors there was an improvement in NYHA class. The remaining question about biventricular pacing was whether the effect on short term haemodynamics would translate into longer term clinical benefit and outcomes.

Bakker and her colleagues were the first to release data in this area in 2000.(91) A series of twelve patients with end stage heart failure and aetiologies comprising both ischaemic (33 percent) and non-ischaemic (67 percent) aetiologies with prolonged PR interval and QRS duration on their surface ECGs (PR interval 217 ± 20ms and QRS duration 194±21 ms). All patients had left bundle branch block (LBBB) on their surface ECG. They all had successful biventricular pacing systems implanted under general anaesthesia with a surgical epicardial left ventricular lead being implanted using a small left mini-thoracotomy. Clinical follow up was then performed at set intervals. The cumulative survival at one, two and three years was 66.7 percent [40.0,93.4] at 1 year and 50 percent [21.8, 78.2] respectively. The median NYHA class improved from IV to II at 1 year. (P=0.008). There were improvements in LVEF and end diastolic diameter at one year, though these were non-significant (P=0.10 and P=0.20

respectively). There were significant changes observed in dP/dt and stroke volume at one year (466±130 to 243 ± 113 (p=0.03)) and 37±9 to 42± 10 (P=0.05))).

The beneficial effects in these reports, led to further clinical trials, including randomised controlled trials. For the purpose of the rest of the thesis, atrio-biventricular pacing will be considered to be synonymous with cardiac resynchronisation therapy. (CRT)

### 1.8.3 Randomised Controlled Trials of CRT

The major randomised controlled trials investigating the effects of CRT have been summarised in Table 2.

| Study | Year of Publication | Design | N | Inclusion Criteria | Exclusion Criteria | Primary/ Secondary Endpoints | Results |
|---|---|---|---|---|---|---|---|
| PATH-CHF | 2002 | Single Blind Randomised Crossover | 41 Patients | NYHA III-IV Symptoms;Optimal tolerated medical therapy; PR interval >150ms;QRS duration>120ms;SR >55bpm; dilated cardiomyopathy | Severe Valvular disease;indications for an ICD implant; shortened life expectancy due to non-cardiac disease | Primary: Peak oxygen uptake at exercise, 6MWT test distance and anaerobic threshold at peak exercise. Secondary: Changes in NYHA class and QOL | Primary: P<0.001, P<0.001, P=0.037 Secondary: P<0.001 |
| MUSTIC | 2001 | Randomised Crossover | 47 Patients - Sinus Rhythm, 41 patients in AF substudy | Dilated or underlying ischaemia; LVEF <35%;LVEDD <60mm; NYHA III, QRS duration>150ms | Severe Valvular disease;indications for an ICD implant; shortened life expectancy due to non-cardiac disease; Coronary intervention within the last three months or acute coronary syndrome within the last three months | Primary Endpoint : 6MWT distance<br><br>Secondary Endpoint: Peak Oxygen uptake; HF hospitalisations; death | Primary: P<0.001<br><br>Secondary: P<0.004 and P<0.05 |
| MIRACLE | 2002 | Prospective, Randomised,Controlled Trial | 453 Patients | Dilated or underlying ischaemia; LVEF <35%;LVEDD <55mm; NYHA III, QRS duration>130ms; 6MWT <450 m | Indication for ICD implant, cardiac pacing; cardiac or cerebral event in last 3/12; atrial arrhythmia in last 3/12; hypertension; Creatinine >265mmol/L;AST > *3 ULN | Primary:NYHA; 6 MWT; QOL<br><br>Secondary:peak oxygen con-sumption, time on a treadmill, left ventricular ejection fraction and end-diastolic dimension, severity of mitral regurgitation, duration of QRS interval, and a clinical composite response, | P=0.005, P=0.001, P=<0.001<br><br>P=0.009, P=0.001, P=0.001 |
| CONTAK-CD | 2003 | Prospective, Randomised, Double- Blind, Controlled Trial | 490 Patients | Dilated or underlying ischaemia; LVEF <35%;NYHA III; QRS duration>120ms; Indication for ICD | Atrial tachyarrhythmias; Indication for cardiac pacing; Recent cardiac and cerebral event in lst 3/12; Coronary revascularisation in last 3/12 | Primary:All-cause mortality; Hospitalisation for HF; Ventricular tachyarrhythmias requiring device therapy Secondary: NYHA, QOL, peak VO2, 6MWT | Primary: Non-Significant Secondary: P=0.003, P=0.029, P=0.006, P=0.017 |
| COMPANION | 2004 | Prospective, Randomised, Controlled Trial - randomised in 1:2:2 manner randomised to optimal medical therapy, CRT-P, CRT-D | 1520 Patients | Dilated or underlying ischaemia; LVEF <35%; NYHA III-IV;QRS duration 120ms;PR interval >150 ms, Sinus Rhythm | Atrial tachyarrhythmias; Indication for cardiac pacing; Recent cardiac and cerebral event in lst 3/12; Coronary revascularisation in last 3/12 | Primary: All-cause mortality and all cause hospitalisation | P=0.014 (HR =0.81)- CRT-P P=0.01 (HR=0.8) |
| CARE-HF | 2005 | Prospective, Randomised,Controlled Trial | 813 Patients | NYHA III-IV Symptoms;Optimal tolerated medical therapy;QRS duration>120ms (120-149 ms needed evidence of mechanical dyssynchrony) | Atrial Arrhythmias; Major cardiovascular event in last 6/52; Indications for pacemaker and defibrillator; Heart Failure requiring continuous intravenous therapy | Primary: All-cause mortality and cardiovascular hospitalisation Secondary: All-cause mortality, Unplanned hospitalisation with heart failure, NYHA class and quality of life measured by Minnesota and EuroQol 5D | Primary: Hazard ratio, 0.63; 0.51 to 0.77; P<0.001 Secondary: P<0.001 |
| MADIT-CRT | 2009 | Prospective, Randomised,Controlled Trial - randomised in 3:2 manner to ICD or CRT-D | 1820 Patients | NYHA I-II;dilated and underlying ischaemia;LVEF <30%; QRS duration>130 ms | Existing indication for CRT; pre-existent ICD or Pacemaker; NYHA III-IV, prev CABG, MI or PCI within the last 3/12, AF within last 1/12 | Primary: All-cause mortality or non-fatal heart failure event. | Hazard ratio in the CRT–ICD group, 0.66; [CI], 0.52 to 0.84; P=0.001 |
| REVERSE | 2008 | Prospective, Randomised, Crossover, Double Blind, Controlled | 610 Patients | NYHA I-II;QRS >120ms;LVEF <40% | Pacemaker dependence; Pre-existing Pacemaker in situ; NYHA III-IV; HF hospitalisation in last 3/12 | Primary: Worsening in clinical composite score (HF hospitalisation, worsening NYHA class or mortality) Secondary: Change in LVESVi | Primary: P=0.10<br><br>Secondary: P=0.0001 |
| RethinQ | 2007 | Prospective, Randomised, Controlled, Double Blind | 172 Patients | NYHA III;LVEF <35%; QRS <130 ms; stable HF medical therapy;fulfil indication for ICD | AF; unable to perform 6MWT; standard pacing indication; Recent CVA or TIA within 3/12; CABG, MI or PCI within last 40 days | Primary: Peak VO2 Secondary: NYHA class; QOL | Primary: P=NS Secondary: P=NS |
| RAFT | 2010 | Prospective, Randomised, Controlled; Double Blind; Randomised to 1:1 between ICD and CRT-D | 1798 Patients | NYHA II-III; LVEF <30%, QRS>120 ms or paced QRS >200ms; AF or A. Flutter;SR | Recent cardiovascular event in last 3/12; Major life threatening non cardiac disease | Primary: All-cause mortality and HF hospitalisation Secondary: All-cause mortality; HF hospitalisation; All cause cardiovascular mortality | Primary: HR=0.75 (CI = 0.64 -0.87 P=<0.001) Secondary: HR=0.75 (CI=0.62-0.91 P=0.003) |

**Table 2: List of all major trials to date performed evaluating cardiac resynchronisation therapy**

The large randomised trials evaluating CRT can be viewed in three phases. The earliest trials focused on clinical effectiveness as measured using markers of quality of life, exertional capacity and exercise tolerance. Once CRT had been demonstrated to have a beneficial effect on such endpoints, the emphasis then moved to proving a more prolonged effect on 'harder' clinical endpoints such as heart failure hospitalisation, cardiovascular hospitalisation, all cause mortality and cardiovascular mortality. The results of these trials published in the mid 2000s, really established CRT as an effective clinical treatment for selected patients with symptomatic left ventricular systolic dysfunction and broadened QRS duration on the surface electrocardiograms. Since that time point, the question was whether CRT would prove as effective for HF populations outside of the established criteria including those with milder forms of disease, whether CRT should be combined with a defibrillator, and those with mild or moderate LVSD or narrower QRS durations than the guidelines recommendation of 120 ms.

The earliest randomised trials were the MUSTIC (Multisite Stimulation in Cardiomyopathies) study published in 2001 and the PATH-CHF (Pacing Therapies in Congestive Heart Failure) Study published in 2002. The two studies do possess similarities but were performed either in continental Europe (MUSTIC) or North America (PATH-CHF).(92, 93)

The MUSTIC study had a crossover trial design.(93) Using 67 patients, with NYHA class III, LVEF <35 percent, LVEDD =60mm, QRS duration >150 milliseconds, optimal tolerated medical therapy and sinus rhythm, CRT was implanted and then investigated with a randomised protocol which had a period of 12 weeks during which the patients had their left ventricular lead turned off and mode of pacing changed to univentricular with minimal right ventricular pacing. The primary endpoint was six minute walk test distance. The results demonstrated that CRT within this population increased the 6 MWT distance by 23 percent (375 +/- 83 m in the inactive period to 424+/-83m in the active period $P<0.004$). There were also significant improvements in quality of life score, which improved by 32 percent ($P<0.001$) and peak oxygen uptake which increased by 8 percent ($P<0.03$).

PATH-CHF (Pacing Therapies in Congestive Heart Failure), was published in 2002.(92) The study used a crossover randomised study to investigate whether biventricular pacing was superior in comparison to univentricular pacing (right or left ventricular). A series of 41 patients were recruited who had dilated and severely impaired left ventricular function with

underlying aetiologies of either dilated cardiomyopathy or ischaemic heart disease. All were in sinus rhythm and had a surface ECG QRS duration of >120 milliseconds. The primary endpoints in the study were oxygen uptake at peak exercise and 6MWT distance. Secondary endpoints within the study were quality of life assessment using the Minnesota Quality of Life for Heart failure Questionnaire and NYHA classification. Cardiac resynchronisation therapy improved exertional capacity and peak oxygen uptake and there was also significantly improved NYHA functional class and quality of life score. (From 12.57 +/-0.63 at baseline to 15.63 +/- 0.86 at one year - peak oxygen uptake - P<0.001). Due to the trial structure there was one crossover period after 4 weeks followed by an open label phase. Due to this structure some patients received univentricular pacing twice and were noted to have decreased exertional ability as measured by the parameters above.

The next three studies, which were published, were the MIRACLE study in 2002, CONTAK-CD study published in 2003 and the MIRACLE-ICD study in 2004. These studies collectively investigated the same endpoints as before on a much larger scale but also collected data on clinical endpoints.

The MIRACLE (Multicentre In Sync Randomised Clinical Evaluation) recruited 571 patients predominately from American centres over a time period between November 1998 and December 2000.(7) Several patients had to be withdrawn with 47 patients unable to have a CRT device implanted, two patients becoming clinically unstable and two patients requiring emergency cardiac pacing. A pilot study was also performed which recruited the initial 71 patients and therefore the study cohort described in the manuscript is actually 453 patients. The cohort was randomised to CRT (228 patients) and a control group (225 patients). The trial inclusion criteria were NYHA class III or ambulatory IV heart failure, LVEF below 35 percent with an LVEDD of greater than 55mm, a QRS duration of >130 milliseconds and a 6 MWT distance of less than 450m. All patients were on optimal tolerated HF medication including diuretics, ACEI, beta blockers and digoxin. The primary endpoints of the study were NYHA class, quality of life score assessed by Minnesota Quality of Life Score and 6 MWT distance. Secondary endpoints were a clinical composite score, severity of mitral regurgitation, duration of QRS and end diastolic dimension. Clinical data was also collected on all-cause mortality, heart failure progression and hospitalisation. CRT was effective at improving all primary endpoints, with an improvement in 6MWT (P=0.005), QOL (P=0.001) and NYHA class (P<0.001). The effect was also replicated on secondary endpoints with

improvements in left ventricular ejection fraction, end diastolic dimensions, area of mitral regurgitant jet and duration of QRS interval (P<0.001). It also improved markers of exercise performance (total exercise time P=0.001) and peak oxygen consumption (P=0.009). During the six months of follow up there was also a reduction in heart failure hospitalisations (P=0.02). The effectiveness of CRT had been evaluated within a randomised format for the first time and demonstrated to have effectiveness over a six month follow up period on symptomatic, mechanical and also clinical endpoints.

As technology advanced it became possible to combine cardiac resynchronisation therapy with a implantable cardioverting defibrillator (CRT-D). The next two summarised trials were specifically conceived to evaluate the effects of CRT-D within patients who fulfilled other criteria for CRT.

CONTAK-CD was published in 2003.(94) It recruited 490 patients from North American centres and randomised the group to CRT-D and conventional medical therapy and ICD only on a 1:1 basis. All patients had to be in NYHA II-IV heart failure, with LVEF <35 percent, QRS duration >120 milliseconds and had conventional indications for implantation of an ICD. Due to the necessity of implanting an ICD, the steering committee proposed a period of 30 days after device implantation where no device therapy was active. This allowed pharmacotherapy optimisation following device implantation. The study design was initially a randomised crossover design with three month observational periods however following concerns about morbidity and mortality associated with CRT and with sponsor interference (Boston Scientific) the study was amended into a parallel randomised CRT-D vs medical therapy and ICD only. The initial endpoints selected by the steering committee were similar to those of previous studies (peak VO2 max, quality of life as assessed by Minnesota Quality of Life Questionnaire and 6MWT distance) however following sponsor intervention this was changed to a composite endpoint predominately powered by HF progression. The composite endpoint was made up of all-cause mortality, heart failure hospitalisation and ventricular tachyarrhythmias requiring device therapy.

In the 245 patients randomised to CRT there was a lower event rate with a total event rate of 79 events (comprised of 11 deaths, 32 patients with HF hospitalisation and 36 patients with a ventricular tachycardia/fibrillation episode). This is compared to the non CRT group with a total event rate of 94 events (16 deaths, 39 patients with at least one HF hospitalization, and

39 patients with at least one VT/VF event). Therefore there was a fifteen percent reduction in the composite endpoint, which was not statistically significant (P=0.35). In terms of the other endpoints, CRT-D did improve peak VO2 (0.8 ml/kg/min vs. 0.0 ml/kg/min, P = 0.030) and 6MWT distance (35m vs 15 m P=0.043), but had a statistically non-significant effect on NYHA class (P=0.10) and quality of life as assessed by the Minnesota questionnaire (P=0.40). CRT did have a significant effect on markers of left ventricular remodelling with improvements documented in both left internal diameters at end systole and diastole. (left ventricular internal diameter in diastole = −3.4 mm vs. −0.3 mm, P< 0.001 and left ventricular internal diameter in systole = −4.0 mm vs. −0.7 mm, P< 0.001) and improvement in left ventricular ejection fraction (5.1 percent vs. 2.8 percent, P = 0.02). The steering group reflect in their conclusions that CONTAK-CD was underpowered to detect changes on clinical endpoints and hence the result of CRT-D on clinical endpoints was non-significant. They also note for those with advanced heart failure (NYHA III-IV), CRT seemed to be effective at all of the original primary endpoints, i.e. exertional capacity, NYHA grade and quality of life.

MIRACLE-ICD II (Multicentre InSync ICD Randomized Clinical Evaluation II) was the next large randomized trial which published in 2004.(95) Using a smaller cohort patients were randomized to conventional medical therapy and an ICD versus CRT-D and medical therapy. The investigators deliberately sought to evaluate the effects of CRT –D in a less symptomatic population. The inclusion criteria for participation were NYHA class II, a LVEF <35 percent, LVEDD>5.5cm and a QRS duration >130 ms and conventional indications for ICD. The trial design was a double blinded randomized controlled trial. The primary endpoint was a change in $VO_2$ Max over the six month follow up period. The secondary endpoints were similar to those of previous studies and included echocardiographic (LVEF, LVEDD), functional (6MWT, NYHA class) and quality of life. A total of 186 patients were recruited and randomized with 85 patients being randomized to the active arm. Notably, CRT within this population had an effect on ventricular volumes, left ventricular ejection fraction and ventilatory response (P=0.04, P=0.02 and P=0.01 respectively) but not on the other endpoints. This was potentially explained by the study having investigated less symptomatic patients who had preserved exercise tolerance. Hence the effect of CRT-D within this population was to induce reverse LV remodelling independent of markers of functional status.

The results of the MIRACLE studies and CONTAK-CD hinted at the longer term effect of CRT and particularly on HF hospitalization, morbidity and mortality. However despite having

larger numbers of patients within their trial cohorts they were underpowered to evaluate the effects of CRT on clinical endpoints. Hence the last two major trials to report around this era were the COMPANION trial published in 2004 and CARE-HF in 2005. The two studies are viewed as landmark studies within the area due to their evaluation of the effects of CRT on clinical endpoints including hospitalisations and mortality.

COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) study was published in 2004.(5) A total of 1520 patients were recruited from American centres and were randomised in a 1:2:2 manner to conventional medical therapy only, medical therapy and CRT-P and medical therapy and CRT-D. The inclusion criteria were NYHA class III-IV heart failure, either ischaemic or non-ischaemic aetiology, a LVEF <35 percent, a QRS duration >120ms, a PR interval >150 ms, sinus rhythm and a preceding hospitalisation for heart failure in the twelve months preceding enrolment. Patients randomised to CRT implantation had commercially available systems implanted and were optimised with a device based algorithm which concentrated on atrioventricular delay. The primary endpoint was a composite of all-cause mortality and all cause hospitalisation. The secondary endpoint was all cause mortality. The study recruitment period ran between January 2000 and November 2002. Notably 26 per cent of the medical therapy group withdrew from the original protocol due to heart failure events and the need for cardiac devices.
The rates of the primary end point differed between the medical therapy group and CRT-P group (68 per cent in the pharmacological group as compared to 56 per cent in the CRT-P group) and 56 per cent in the CRT-D group). The hazard ratios were respectively hazard ratio for the primary end point, 0.81; 95 percent confidence interval, 0.69 to 0.96; P = 0.014; adjusted P = 0.015 by the log-rank test (medical therapy vs CRT-P) and hazard ratio, 0.80; 95 percent confidence interval, 0.68 to 0.95; P = 0.010; adjusted P=0.011 (medical therapy vs CRT-D). Thus irrespective of defibrillator capacity - CRT reduced the incidence of the primary endpoint by approximately twenty percent. There were also a significant reduction in the secondary endpoint (all-cause mortality) with the hazard ratios for medical therapy versus CRT-P being (hazard ratio, 0.76; 95 percent confidence interval, 0.58 to 1.01; P = 0.059; adjusted P = 0.06) i.e. a trend towards improvement but not statistically significant. This compared to CRT-D versus medical therapy (hazard ratio, 0.64; 95 percent confidence interval, 0.48 to 0.86; P = 0.003; adjusted P = 0.004) i.e. with the additional defibrillator capacity there was a marked reduction in all-cause mortality. The study also had embedded prespecified sub group analysis. One of the substudy groups were patients with dilated

cardiomyopathy, there was a fifty per cent reduction in all-cause mortality within this subgroup hazard ratio(0.50; 95 percent confidence interval, 0.29 to 0.88). This finding is noteworthy because prior literature had concentrated on the relationship of ICDs to clinical outcomes in patients with prior ischaemic heart disease.

The trial which was last to report from this era is often viewed as the landmark trial - this is due to its simplistic design, lack of complexity in terms of intervention and the fact that it has periodically released data from its extended follow up period.

CARE-HF (Cardiac Resynchronisation Therapy - Heart Failure), published in 2005, was the last study to report and was focused on the clinical effects of CRT without the added issue of defibrillators.(6) A series of 813 patients was enrolled from 82 European centres with recruitment running from January 2001 and ended in March 2003. The study was not blinded - it was run independent of the sponsor. All decisions with regards to trial design, conduct and statistical analysis were executed by the steering committee.

Inclusion criteria included a diagnosis of heart failure for at least six weeks preceding enrolment, NYHA III-IV heart failure, on optimal tolerated evidence based pharmacotherapy, a LVEF <35 percent, a QRS duration of >120 ms and an indexed EDD to height of at least 30 mm and sinus rhythm. Patients who had a QRS duration between 120 and 149 milliseconds had to fulfil two out of three following markers of dyssynchrony (aortic pre-ejection delay >140ms, an interventricular delay >40 ms or delayed activation of the posterolateral left ventricular wall).

Patients randomised to CRT implantation had a standardised commercially available system transvenously implanted. Following successful implantation all devices had echocardiographically optimised AV delays. The primary endpoint for the study was a composite of all-cause mortality and hospitalisation for a cardiovascular event. The secondary endpoints were all-cause mortality, composite of death and unplanned HF hospitalisation, NYHA and quality of life scores at 90 days as measured by Minnesota Living with Heart Failure Questionnaire and European Quality of Life-5 Dimensions (EuroQOL EQ-5D).

Patients were randomised on a 1:1 basis to medical therapy or CRT-P and medical therapy. The median duration of follow up was 29.4 months (range 18 -45 months). By the end of the

study the primary end point had been achieved in 224 patients in the medical therapy arm versus 159 patients in the CRT-P group. (39 percent vs. 55 percent; hazard ratio, 0.63; 95 percent confidence interval, 0.51 to 0.77; P<0.001) CRT also reduced the risk of composite end point of death and HF hospitalisation (hazard ratio, 0.54; 95 percent confidence interval, 0.43 to 0.68; P<0.001). (See Figure 7).There was also a universal improvement in patients with CRT implants versus medical therapy in LVEF, quality of life scores and NYHA class. Hence for the first time CRT-P had been shown to improve functional and symptomatic endpoints but also improve morbidity and mortality.

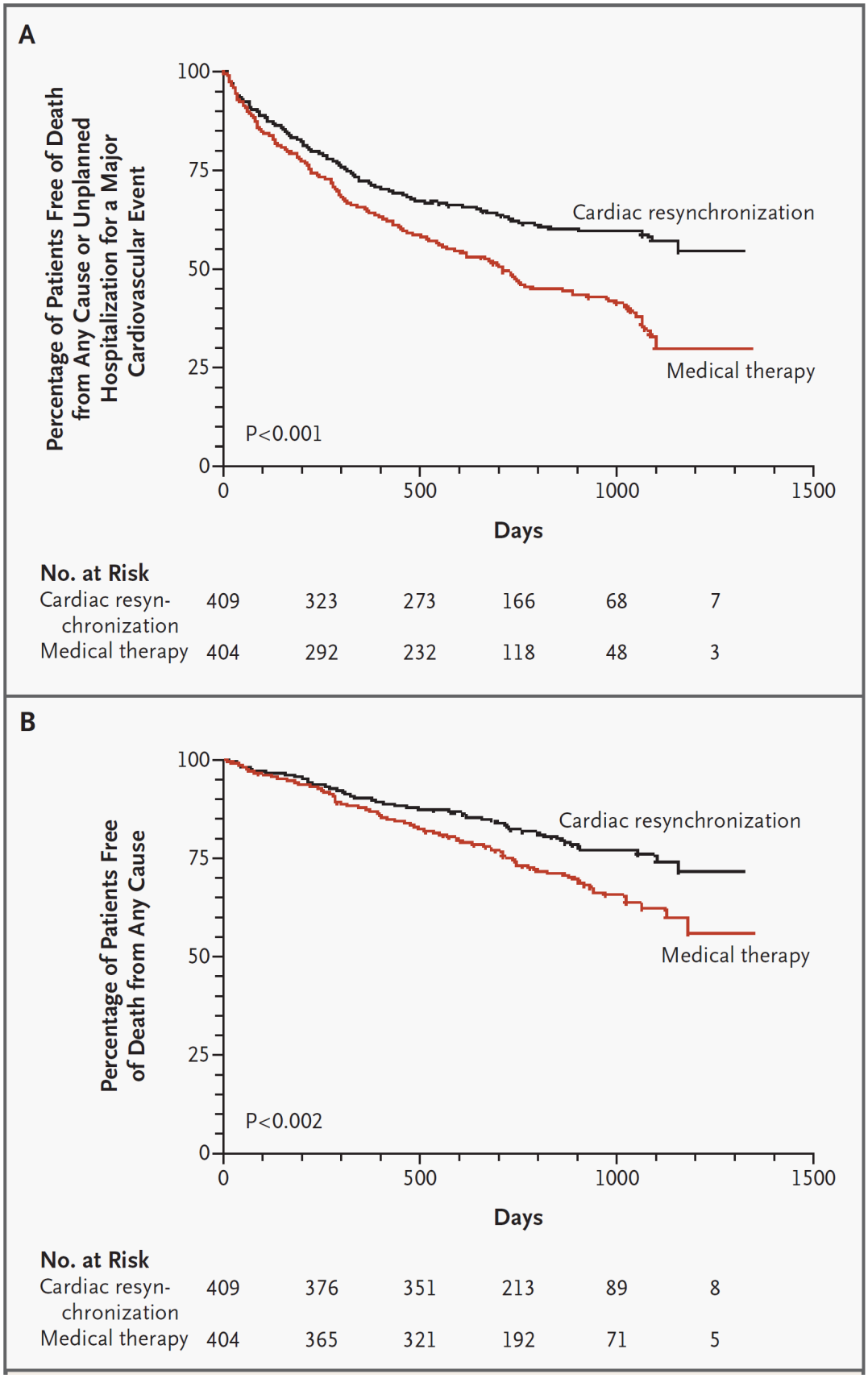


**Figure 7: Kaplan- Meier Plots for Time to primary outcome and principal secondary outcome -CARE-HF(6)**

Following the initial publications of the above trials, CRT became an established clinical therapeutic option for patients with symptomatic left ventricular dysfunction and a broad QRS duration on optimal tolerated medical therapy and sinus rhythm. However logically the scientific community questioned whether CRT would be effective in groups which fell outside of the evidence base; this included those with milder forms of heart failure in terms of symptoms, those with narrower QRS durations on the surface ECG and those who meet current criteria for an ICD and whether this group should receive the additional benefit of a left ventricular lead. The most recently published trials evaluating CRT have investigated some of these questions.

REVERSE (Resynchronisation reverses remodelling in symptomatic left ventricular dysfunction), published in 2008, and evaluated the role of CRT in patients who were either asymptomatic or mildly symptomatic (NYHA I-II) heart failure.(96) Potential participants had to have a LVEF<40 percent, QRS duration >120 ms and LVEDD >55 mm and in sinus rhythm. All patients underwent CRT implantation (some with ICD capacity and some without) and were randomised in 2:1 fashion to CRT - ON or CRT-OFF. The European sub cohort stayed within their randomised arms for 24 months to evaluate the effect of early CRT intervention on heart failure hospitalisations. A total of 601 patients were recruited into the study and underwent randomisation. There was no statistically significant effect on the primary endpoint between the two groups. (P=0.10) The LVESVI improved (18.4 +/-29.5 $ml/m^2$) in the CRT-ON group (n = 324) compared with the CRT-OFF group (1.3+/-23.4 $ml/m^2$; n= 163; P =0.0001). There was no effect from CRT on functional and quality of life scores in the study. The authors felt the beneficial effects of CRT on left ventricular remodelling were a success and justified the risk of exposing patients to a CRT implant when they had no or little symptoms. (16 percent of patients experienced device based complications during the study including lead revisions and displacements, atrial arrhythmias, cardiac tamponade and diaphragmatic capture). The trial had limited scheduled follow up. Hence in terms of data it was the first to contribute to this area of potential expansion of indications for CRT but further data are needed to clarify the relationships in this area.

In terms of a narrow QRS duration, there has been a small randomised trial which has investigated the area. RethinQ (Cardiac Resynchronisation Therapy in patients with heart failure and narrow QRS) published first in 2007.(97) Using a series of patients with either ischaemic or a non-ischaemic aetiology and a LVEF <35 percent and a QRS duration

<130ms. All patients underwent CRT implantation and were randomised to ICD only or CRT-D in a 1:1 manner. The primary endpoint was peak oxygen uptake during cardiopulmonary testing at 6 months post baseline. A total of 172 patients were recruited and comprised the group on whom statistical analysis was performed. The group receiving CRT had a biventricular pacing rate during the study of greater than >85 percent. There was no difference between the groups in neither primary endpoint nor echocardiographic or functional testing. All results were non-significant. On prespecified sub group analysis in patients with a QRS duration <120 milliseconds there was improvement on peak VO2 (p=0.02) and NYHA class (p=0.01) with CRT but not in 6 MWT test distance or quality of life scores. (p=0.63 and p=0.31 respectively). Hence the trial though not conclusive due to the low numbers enrolled into the study is suggestive that CRT is not efficacious in individuals without a QRS duration >120 ms.

### 1.8.4 Patient Selection

Cardiac Resynchronisation Therapy has now become a clinically established therapeutic option for patients with symptomatic left ventricular dysfunction. Guidance has been regularly issued in the area by the European and American bodies.(22, 98)

The current guidelines for CRT in England & Wales are being revised and are due for publication. The previous guidance issued by NICE was published in 2007 and hence are now outdated, due to the publication of new trial evidence as described above. The current guidance was issued by the European Society of Cardiology, with new guidelines released this year and a consensus document issued in 2012 as a joint venture between European Heart Rhythm Association and Heart Rhythm Society.(99)

Irrespective of which guidelines are consulted, certain criteria are now viewed as fundamental for patient selection. The patient should have severe left ventricular dysfunction with a LVEF <35 percent, a broad QRS duration >120 ms (preferably in LBBB morphology) and on optimal tolerated heart failure medical therapy and in symptomatic NYHA II-IV heart failure.

However, despite the guidelines, the proposition of a patient as a candidate for CRT and the implant process of CRT have both been studied in detail. Each step of the process has been

analysed to improve ‘response’ rates and the rest of this section is devoted to the discussion of these issues.

### 1.8.5 Dyssynchrony

Despite the current selection criteria as recommended by the contemporary guidance, there has been much focus on dyssynchrony. This is the quantification into a continuous variable, of the degree of in-coordination between septal and posterolateral walls. The purpose of quantifying incoordination is to then use the information to predict post CRT implantation improvement or even rationalise the use of CRT.

The pre implant measurement of dyssynchrony may be performed with a variety of imaging modalities but conventionally has been performed using echocardiography. Initial work performed in non-randomised cohorts, with small numbers of patients in single centre studies, was able to demonstrate the predictive capacity of such measurements.(100-102) The published reproducibility and repeatability coefficients are high and initially indicated that these may be able to inform the CRT selection process.

However there have now been three large trials using echocardiographic markers of dyssynchrony with no positive findings and the concept of prospective dyssynchrony imaging has been challenged by the findings of these studies.

The most famous of the three is the PROSPECT study (Predictors of Response to CRT Study). Published by Chung and colleagues in 2008, they evaluated the role of dyssynchrony measurement in a prospective cohort.(103) The trial enrolled 498 patients across 53 worldwide centres and was designed to investigate the sensitivity and specificity of echocardiographic markers of dyssynchrony in a multicentre prospective study. The endpoint for the study was an improvement in a clinical composite score (based on NYHA class, HF hospitalisation and all-cause mortality) and a LV remodelling endpoint of reduction of <15 percent in LVESV. The techniques used within the study for identifying dyssynchrony were a mixture of conventional echo (M Mode and Pulsed Wave Doppler) and Tissue Doppler derived techniques. There were three core echo laboratories which read all echoes for all patients, the USA and Hong Kong used the core laboratory based at Emory University,

Atlanta, USA. Europe used a core laboratory based in Pavia, Italy and the Hammersmith Hospital, London performed Tissue Doppler derived measurement for Europe.

The cohort was followed up for six months and the endpoints recorded. The overall rates of clinical improvement (69 percent) and rates of left ventricular remodelling (56 percent) are consistent with other published data in the area. However the various echocardiographic markers ranged widely for sensitivity and specificity for clinical composite response (6 percent to 74 percent and specificity ranging from 35 percent to 91 percent) and LV remodelling (sensitivity ranged from 9 percent to 77 percent and specificity from 31 percent to 93 percent). Notably the reproducibility of the techniques was also variable with volume assessments having low variability (CV, 3.8 percent) and Tissue Doppler derived indices had both poor intra-observer (CV 15.8 percent) and inter-observer variability (CV 33.7 percent). The findings of the study were widely debated due to the surprising result as compared to the single centre smaller studies. Potential explanations for these findings offered by the authors included heterogeneous CRT implantation criteria (a difference in practice between USA and Europe), the poor reproducibility of Tissue Doppler techniques, the use of different echo equipment at different core laboratories and whether the LV leads had been implanted to reach the actual area of dyssynchrony. The findings of this study however were interpreted by those outside of the specialised field of complex echocardiography as removing the need for such measurements prior to CRT implantation.

The Mayo Clinic, Rochester, Minnesota US also investigated this issue and published their data in 2010.(104) The study was a prospective study analysing echocardiographic markers in 131 patients undergoing CRT implantation at the Mayo Clinic from 2005 until 2007. The study used fourteen measures including some which had been analysed in PROSPECT but had to been found to have poor reproducibility. The measures involved M Mode, tissue velocity imaging, tissue Doppler strain, 2D speckle strain, 3D echocardiography and total isovolumic time. The study period ran for six months following CRT implantation and used the conventional endpoints of clinical response and QOL, 6MWT distance and $MVO_2$ . None of the echo measures had strong predictive value only M-mode, tissue Doppler strain, and total isovolumic time had a receiver operating characteristic area better than chance but none of these were strongly predictive of LV reverse remodelling. (AUC, 0.63 to 0.71). None of the indices measured predicted clinical response, 6MWT, improvement in QOL or $MVO_2$.

The most recent trial involving dyssynchrony markers was that published in 2013. Echo CRT (Cardiac Resynchronisation Therapy in Heart Failure with a Narrow QRS Complex) examined the previously documented findings of dyssynchrony in patients with QRS durations below 120 milliseconds.(105) This represented an area devoid of previous trial evidence and hence outside of the guidelines. The investigators recruited 809 patients on the basis of symptomatic LVSD (LVEF <35 percent) and narrow QRS durations (<130 milliseconds). All patients had to satisfy a dyssynchrony assessment comprised of Tissue Doppler imaging and/or radial strain rate imaging. All patients underwent CRT-D implantation. Patients were then randomised in a 1:1 fashion to CRT-D or ICD only therapy. The primary endpoint was a composite of all-cause mortality and HF hospitalisation. The trial was stopped prematurely by the data and monitoring safety committee. This was due to the number of deaths in the CRT group. There had been 45 deaths in the CRT group and 26 in the control group (11.1 percent vs. 6.4 percent; hazard ratio, 1.81; 95 percent CI, 1.11 to 2.93; P=0.02). Hence the authors conclude that CRT within this population does not improve clinical endpoints and may even cause an increased rate of mortality.

### 1.8.6 Electrocardiogram

Due to the results of the previously discussed randomised trials of dyssynchrony - the 12 lead electrocardiogram remains the tool by which candidates for CRT are identified.(22) The duration of QRS complex and the cut point of 120 milliseconds arise from the previously accrued data. However both the QRS duration and the morphology of the bundle branch block have been debated in the literature.

The trials covering CRT implantation in narrow QRS durations (Echo-CRT and RethinQ) have been discussed in detail elsewhere in this introductory chapter.(97, 105) Both represent large randomised controlled trials with negative outcomes and hence the data currently supports the guidelines' position of CRT should only be considered for those patients where QRS duration is >120 ms.

It has been documented from substudy analysis of the randomised controlled trial cohorts, that the QRS duration on the pre-implantation ECG correlates with improved clinical response and outcomes following CRT implantation.(106-108) However outside of a trial environment the effect of more prolonged QRS durations in relation to clinical outcomes following CRT

implantation was unknown. There have been recent large datasets released by North American groups which indicate that a prolonged QRS duration on the ECG prior to implantation is an important predictor of clinical outcomes.

The largest and most recent dataset comes from the Medicare ICD registry with data from 2006-2009.(109) In total 24,169 patients were surveyed and followed up until December 2011. All patients received CRT-D implants. The cohort was divided on the basis of QRS duration and ECG morphology into three groups; LBBB and QRS >150 ms, LBBB and QRS<150 ms and non LBBB (Right Bundle Branch Block (RBBB) and non specific intraventricular conduction delay (IVCD)). The endpoint was all cause mortality, cardiovascular and heart failure related hospitalisation. The lowest rates of death and hospitalisation were for those patients with LBBB and broad QRS duration>150ms as compared to the other groups (20.9 percent), compared with LBBB and QRS duration of 120 to 149 ms (26.5 percent; adjusted hazard ratio [HR], 1.30 [99 percent CI, 1.18-1.42]), no LBBB and QRS duration of 150 ms or greater (30.7 percent; HR, 1.34 [99 percent CI, 1.20-1.49]), and no LBBB and QRS duration of 120 to 149 ms (32.3 percent; HR, 1.52 [99 percent CI, 1.38-1.67]). Hence a prolonged QRS duration (>150ms) and LBBB are considered to be prognosticators. This position has been quoted within the most recent ESC guidance in the area.(22)

Left Bundle Branch Block on a surface electrocardiogram may represent heterogeneous electrical activity at a myocardial level. From the original experiments by Sir Thomas Lewis in the early 1900s, a recognition of the characteristic pattern emerged and the conventional diagnostic criteria were agreed on by an expert panel originally convened in the 1940s.(110, 111) The advent of CRT has led to further investigational work in the area, due to the presence of LBBB being a core part of the selection criteria.

LBBB on a surface electrocardiogram has a distinct phenotypic appearance but comprises heterogeneous electrical activation of the right and left ventricles. When mapped using invasive electrophysiology, a surface LBBB pattern may conceal complex patterns of myocardial activation.(112) Due to the patterns of activation, the scientific community questioned whether CRT would have an effect in patients with right bundle branch block. However this has now been discredited with recent publications, from substudy analysis of the randomised trials, meta analyses and recent registry data.

Zareba and colleagues released prespecified substudy data from the MADIT-CRT cohort in 2011.(108) Using surface morphology as part of clinical response score, the authors demonstrated that QRS morphology was one of several factors when combined into a clinical score predicted the degree of left ventricular remodelling at one year.

Sipahi and colleagues released a recent meta-analysis covering all trial participants from the CARE-HF, COMPANION, RAFT and MADIT CRT trials.(113) This totalled 5, 356 patients and again the cohort was analysed on the basis of QRS duration and morphology. Patients with LBBB at baseline, had a highly significant reduction in composite adverse clinical events with CRT (RR = 0.64 [95 percent CI (0.52-0.77)], P = .00001). However no such benefit was observed for patients with non-LBBB conduction abnormalities (RR = 0.97 [95 percent CI (0.82-1.15)], P = 0.75). When examined separately, there was no benefit in patients with right bundle branch block (RR = 0.91 [95 percent CI (0.69-1.20)], P = 0.49) or non-specific intraventricular conduction delay (RR = 1.19 [95 percent CI (0.87-1.63)], P =0.28). When directly compared, the difference in effect of CRT between LBBB versus non-LBBB patients was highly statistically significant (P = .0001 by heterogeneity analysis).

Bilchick and colleagues analysed data from the Medicare ICD registry for the period 2005-2006 and published in 2010.(114) Using the original data and merging with clinical outcomes, the authors were able to identify, using Cox regressional analysis techniques, significant predictors of mortality within the cohort. The cohort totalled 14,946 patients and all patients underwent CRT-D implantation. RBBB was a significant predictor of mortality at both 1 year and 3 years. (1-year HR, 1.44; 3-year HR, 1.37; P<0.001). The QRS duration in the context of RBBB had no effect on the statistical relationship.

### 1.8.7 Implantation of CRT devices

The implantation process of CRT has now become standardised with simplified transvenous techniques. The principles of aseptic technique, incision location and peripheral venous access are derived from basic pacing. Once the chosen mode of access has been cannulated (normally cephalic vein or axillary vein) a right atrial lead (if patient is in sinus rhythm, or

likely to return to sinus rhythm), right ventricular lead and left ventricular lead are implanted under fluoroscopic guidance.

The implantation of the left ventricular lead is not only a crucial part of the process but is also under investigation. Currently a coronary sinus (CS) venogram is obtained with hand injections of iodinated contrast (5-10mls) at a time and a delayed acquisition obtained to identify the main CS body and all tributaries. A left ventricular lead is then advanced into a tributary using 'lead over wire' technique and implanted and tested for electrical thresholds, capture and stability. The positioning of the left ventricular lead is a vitally important part of the process as if it is implanted incorrectly there is risk of LV lead displacement, loss of capture and diaphragmatic pacing.

Due to the necessity of functioning LV and RV leads, much attention has been paid to LV lead design, position and implantation over the last decade. The challenge for an operator using conventional CRT systems is to find a satisfactory stable electromechanical position for the LV lead. This is dependent on many factors: the operator's experience level, the CS venous anatomy and the lead design itself. Thus currently LV leads are placed anatomically with traditional fluoroscopy rather than targeted LV lead placement.

An early trial published by Aurrichio and colleagues in 2001, demonstrated an adverse haemodynamic profile for LV pacing when an anterior position was selected.(115) The best haemodynamic profile was induced by positioning the LV lead in the postero-lateral area with the postulated benefit being the targeting the area of delayed activation. The discussion has been whether the LV lead should attempt to target the area of greatest delayed activation or target the segment with the greatest amount of dyssynchrony.

A recent substudy from MADIT-CRT, published in 2011 demonstrated in 799 of the trial cohort, that an apical LV lead position was associated with an increased risk of HF hospitalisation (hazard ratio=1.72; 95 percent confidence interval, 1.09 to 2.71; P=0.019) and death.(116) (Hazard ratio=2.91; 95 percent confidence interval, 1.42 to 5.97; P=0.004) An alternative substudy from the REVERSE randomised trial documented similar findings with LV leads in the apical versus non apical position.(117) The time taken to achieve death or HF hospitalisation was quicker in the LV lead apically paced population.(HR 0.27; 95 percent CI 0.11-0.63; P= 0.001)

The explanation for these findings from both groups is that a LV lead positioned at the apex may be in close proximity to RV depolarisation from the RV lead and therefore there is not much separation between the two areas of depolarisation. Secondly LBBB is associated with delayed activation of the lateral and postero-lateral LV wall. Thus by pacing from an apical segment, there is the possibility that the area of interest is not being reached by the depolarisation of the LV lead and also that it may also be inducing further dyssynchrony.

A further consideration which relates to LV lead position is the positioning in relation to the area of latest activation. A tailored approach is dependent on both the operator being able to reach such an area of delayed activation and also suitable venous anatomy. Apart from selective targeting of the area of maximal dyssynchrony, the other factor which is postulated to govern delivery of LV pacing is the avoidance of myocardial scar or fibrosis.

Khan and colleagues published a randomised controlled trial in 2012, looking at selective LV lead placement.(118) The TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy) study randomised patients to a conventional CRT implant or a speckle tracking two dimensional radial strain guided approach to avoid myocardial scar. The LV lead in the active arm was implanted at the latest site of peak contraction with an amplitude of >10 percent which indicated absence of scar. The primary endpoint was a reduction in LVESV >15 percent with secondary endpoints being clinical response, all-cause mortality and combined all-cause mortality and heart failure hospitalisation. The targeted CRT implant group had higher rates of LV remodelling at 6 months (P=0.031) and improved clinical response. (P=0.003)

Another potential imaging technique to visualise macroscopic myocardial scar is a cardiac magnetic resonance study with gadolinium contrast. The delayed phase of such a study would represent late gadolinium enhancement (LGE) which represents defects in the myocardial extracellular matrix and therefore depending on clinical context may represent myocardial scar or fibrosis. These patterns of LGE carry an adverse prognosis in a variety of cardiovascular disease states. Little is known about the distribution of myocardial scar and application of CRT and particularly LV pacing. Though there is a lack of data within this area, intuitively pacing regions of myocardial scar and fibrosis may prevent the delivery of

successful pacing, may lead to localised exit block and may even be pro-arrhythmic.(119, 120)

The data in the area is limited and should be viewed as hypothesis generating. Ypenburg and colleagues in 2007 demonstrated in 34 patients with severe LVSD with prior ischaemic heart disease, that large amounts of late gadolinium enhancement, when treated as a dichotomous variable, was associated with a failure to undergo LV remodelling. ($P<0.05$)(121)

The data acquisition from a CMR study is currently done 'offline' i.e. separate to the catheter laboratory, and the data therefore is not accessible to the current methods of fluoroscopic guided CRT implantation. Duckett and colleagues published a pilot study in 20 patients undergoing CRT implantation with CMR enhanced fluoroscopy in 2011. (122) Using a conventional fluoroscopy image in the catheter laboratory, regions of CMR measured dyssynchrony were overlaid with different colour schemes to indicate areas of maximal dyssynchrony. At six months 92 percent of the cohort paced with a CMR assisted protocol had developed significant reduction in LV volumes as compared to the control group. ($P=0.04$)

The principle issue which underpins all further attempts at LV lead position is coronary venous anatomy. Despite the possibility of tailoring the LV lead position to target areas of dysynchrony, the operator is limited by the anatomy. A couple of methods have been suggested: firstly multisite pacing has been investigated in small numbers. It has been demonstrated to be successful in pilot studies on acute haemodynamics but needs larger amounts of data before proceeding to a randomised controlled trial. The alternative, which started off as a research prospect but is now clinically established, is a multi-polar LV lead. St Jude Corporation (St. Paul, Minnesota, US) and Medtronic Inc (Minneapolis, Minnesota, US) have released quadripolar leads onto the market and these can permit a much larger number of configurations via vectors than normal unipolar or bipolar LV leads.

### 1.8.8 Optimisation

Following successful CRT implantation there has been much focus on the process of 'optimisation' or more specifically device based optimisation. This is the adjustment of atrioventricular and ventriculo-ventricular delay under some method of assessing

haemodynamics which results in the optimal AV and VV delay to ensure optimal left ventricular filling. Though the process of device based optimisation has had numerous studies published within the area it remains an area of contention and hence in the most recent ESC guidance it is now reserved for those patients who fail to respond following CRT implantation.(22) One other area of 'optimisation' which is lacking in terms of data and evidence is the medical optimisation of such patients - this is the process of uptitrating and initiating evidence based pharmacotherapies. The two facets of optimisation are not mutually exclusive and the recent consensus document issued by the European Heart Rhythm Association and the Heart Rhythm Society US suggests that both should be taking place simultaneously.(99)

### 1.8.9 Device Based Optimisation

Device based optimisation should be considered as a separate entity to medical optimisation and is the adjustment of the AV and VV intervals for maximal haemodynamic benefit, improvement in cardiac output, reduction in pre-systolic mitral regurgitation and optimal left ventricular filling.(22) The process of device optimisation may of course indirectly influence and aid the uptitration of medical therapies by improving cardiac performance, work and indirectly systolic blood pressure. The field of device optimisation is associated with a high level of debate due to the fact that prior literature is inconsistent and that no definitive longer term association has been proved for clinical outcomes. Several potential techniques and methods have been investigated but the lack of consistent findings means the current position in the recent joint Consensus statement released from a panel of US and European experts states that it should be reserved for patients not experiencing the desired clinical benefit following CRT implantation.(99) This viewpoint is further supported by the recent ESC guidelines in the area, published this year which state a similar role for device based optimisation.(22)

The historical basis for optimisation of intervals within CRT devices comes from experience within dual chamber pacing systems and the large randomised clinical trials of CRT which have been previously described.

The original studies using dual chamber pacemakers in heart failure published in the 1990s have been summarised and discussed above. Though performed with earlier generations of

pacing systems, they did possess the ability to have an adjusted AV delay via programming. Brecker and colleagues investigated this in 1992, and found that in a population of patients with dilated cardiomyopathy, the best haemodynamic profile was induced by a much shortened AV delay as compared to manufacturer settings.(88) There were significant reductions in pre systolic mitral and tricuspid regurgitation.

Other groups investigated this relationship around this timepoint. Hayes and colleagues analysed these findings using invasive catheters which generated pressure volume loops.(123) Taking two groups of patients with severe LVSD but differing degrees of conduction delay the authors were able to demonstrate in those who had conduction abnormalities (PR interval >200ms on surface electrocardiogram) that cardiac output was increased with adjustment of the AV delay. However in the seven individuals with normal surface electrocardiograms, variation in AV delay resulted in a deterioration in cardiac output.

The non-uniform findings behind AV delay optimisation in basic pacing was further complicated by work by Mehta and colleagues, published in 1989 who demonstrated in a pacing dependent population (n=9) with preserved LV systolic function that the optimal AV delay at rest of 140 to 150 milliseconds was reduced on exercise with an optimal AV delay of 75-80ms.(124) The field was divided as to whether device based optimisation would be something beyond a research interest.

The first generations of CRT devices had fixed AV delays which were preset by the manufacturer with no option of varying the AV delay via programming. As time progressed, further generations of CRT devices began to have the ability of variable AV delays and eventually VV delays. These second generation CRT devices were the ones tested within the large randomised controlled trials. The most recent studies from the era 2000 to 2005 incorporated device based optimisation within them and it is this start point which led to their inclusion within guidelines on CRT. The two studies focused on mortality and clinical endpoints, (CARE-HF published in 2005)(6) and COMPANION in 2004(5)) both had device optimisation protocols embedded within the trial structure. CARE-HF had echocardiographic optimisation of the AV delay using Doppler traces of the transmitral flow with the optimal AV delay in the study being the one with greatest E and A wave separation. COMPANION contained different methodology using a device based algorithm which automatically

calculated optimal AV delay from intrinsic PR interval, intrinsic QRS duration and the intra-cardiac AV interval at time of implantation.

These methods and the positive results of the trials led to the inclusion of device based optimisation within the contemporary ESC guidelines of the time.(125) However as the field has expanded, and with more publications and data, the viewpoint on device based optimisation has become divided. Some groups view it as an essential part of the overall CRT care process whereas others view it as an inappropriate technique with misallocation of healthcare resources. The consensus document issued jointly by an intercontinental panel of experts in 2012, suggests that AV and VV optimisation may be considered and certainly should be offered to patients who fail to respond following CRT implantation.(99) The major difficulties in offering clear guidelines in the area is the differences in available techniques, the publication of small datasets predominately from centres with non-randomised studies and the lack of longer term clinical data on patients who have undergone device based optimisation.

The rest of this section will discuss each potential methodology of performing device based optimisation.

### 1.8.10 Algorithms for CRT device AV and VV delay optimisation

As technology has progressed, CRT leads and generators have become more sophisticated with potential ability to offer remote monitoring, intra-thoracic impedance measurement and measures of volume status. In conjunction with these, all major manufacturers have considered whether a dedicated device incorporated algorithm would improve the process of optimisation. The rationale being that due to constant beat to beat monitoring via atrial and ventricular leads, the CRT device would be able to use intrinsic and paced delays to self-adjust AV and VV delays to improve a preset cardiac haemodynamic variable.

These algorithms have been tested in large randomised studies which thus far have not shown any significant superiority over other methods of optimisation.

The SMART-AV (The SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy) Study was the first algorithmic based clinical trial to publish in 2010.(126) The study recruited a cohort of 1014 patients and randomised them to one of three arms following implantation with a CRT-D device. The population fulfilled modern criteria for CRT implantation and were randomised to either a fixed AV delay of 120 ms, SMART-AV™ delay optimisation or an echocardiographic guided optimisation using the iterative technique and transmitral Doppler flows. The SMART AV delay was a programme based on detection of paced and intrinsic AV delays and resulting self-adjustment. The primary end point was a change in left ventricular end systolic volume. The usual collection of secondary endpoints comprising NYHA class, quality of life scores and 6MWT test distance were used within the study. The findings demonstrated no statistical significance between any of the three arms (SMART AV delay as compared to echocardiography P=0.52 and fixed delay P=0.66) in terms of left ventricular volume changes. The follow up period ran for six months following enrolment into the study. There was also no positive effect on any of the secondary endpoints.

Alternative studies have been performed or are underway from rival manufacturers and different algorithms to investigate the area, further. The FREEDOM (Frequent Optimization Study Using the QuickOpt Method) study was performed using the Quick Opt algorithm from St Jude.(127) Again a large number of patients (n=1580 patients) were recruited into the study and randomised either to a one off echocardiographic optimisation following CRT implantation or algorithmic optimisation 'QuickOpt™'. Further attempts at echocardiography guided optimisation could be considered but were completely up to the investigator on site. If the patient whilst in this arm had symptomatic deterioration the trial structure encouraged a review and further attempt at optimisation of the AV and VV intervals. The other group were subjected to algorithm guided frequent optimisation of AV and VV intervals. The primary and secondary endpoints were clinical and focussed on clinical response, all-cause mortality and hospitalisation with heart failure. The trial completed recruitment in 2010 but thus far there has been no publication of data. Both Quick Opt and Smart AV relied on intra-cardiac electrocardiograms to calculate the optimal AV and VV delays.

Sorin had a different algorithm, the SonR™ algorithm which works by calculating myocardial contractility from VV delay and then finding the ideal AV delay from the figures derived from the above, the process being termed peak endocardial acceleration. SonR was then tested

in the pilot randomised trial, the CLEAR (Clinical evaluation on advanced resynchronisation) study which evaluated its performance as compared to traditional echocardiographic guided optimisation.(128) Slightly differently as compared to other modern CRT trials, the steering group decided on inclusion criteria which replicated those of CARE-HF.(6) This was a more severe group of patients with NYHA III/IV heart failure with QRS durations above 120 ms (and evidence of mechanical dyssynchrony if in the 120-149 ms bracket - using echo measures as per CARE-HF protocol). The primary endpoint was a clinical composite made up of improvement in NYHA class, quality of life, HF hospitalisations and all-cause mortality. A total of 238 patients were recruited and randomised to frequent device based optimisation or conventional echocardiographic measurement on a 1:1 basis. Each patient was followed up for one year and the SonR optimised group had significant improvement in functional class (P=0.002) and which drove a significant improvement in the primary endpoint as compared to those with conventional optimisation. (P=0.03)

The most recent data was published from the Adaptive-CRT study in 2012.(129) This was a study designed to evaluate the Medtronic Adaptive™ algorithm which offered dynamic ambulatory optimisation of AV and VV intervals. The trial was designed as a non-inferiority trial. A total of 522 patients were randomised in a 2:1 fashion to the Adaptive optimisation versus conventional echocardiographic optimisation. Patients were reviewed at one, three and six months following enrolment. The study successfully proved on the non-inferiority basis that the proportion of clinical improvement between the two arms was the same. (73.6 per cent vs 72.5 percent, with a non-inferiority margin of 12 percent; P = .0007). Evaluating the haemodynamic profiles using measured aortic velocity time integral between the two groups demonstrated high rates of correlation. (Concordance correlation coefficient = 0.93; 95 percent confidence interval 0.91-0.94) and at 6-month post randomisation (Concordance correlation coefficient = 0.90; 95 percent confidence interval 0.87-0.92). There were no significant differences between the arms with respect to heart failure events or ventricular arrhythmia episodes.

The DECREASE-HF (The Device Evaluation of CONTAK RENEWAL 2 and EASYTRAK 2: Assessment of Safety and Effectiveness in Heart Failure) study was a study focused on VV optimisation via a device based algorithm.(130) The Expert-Ease™ algorithm was based on the measurement of intrinsic VV interval with data derived from the PATH-CHF studies.(92) The trial randomised 306 patients in a 1:1:1 fashion to sequential and simultaneous

biventricular pacing and left ventricular pacing only. Echocardiography was performed at baseline, 3 and 6 months. There were uniform reductions in LV end systolic and diastolic dimensions. (P<0.001). The simultaneous VV pacing group had the greatest reduction in LV end systolic dimensions (P<0.007). Stroke volume and ejection fraction improved in all three groups. (P<0.001).

### 1.8.11 Echocardiography Guided Optimisation

The most widespread and established technique of device based optimisation are those derived from transthoracic echocardiography. The ease of access to transthoracic echocardiography and its portability and ability to measure haemodynamics quickly have all meant that the first optimisation studies were based on this methodology. Amongst the echocardiographic literature there is data which supports AV and VV optimisation, with the majority of the data being devoted to AV delay adjustment. As previously discussed the subject of AV delay was first investigated using dual chamber pacing in heart failure populations and once CRT was clinically established, further studies were performed within this area.

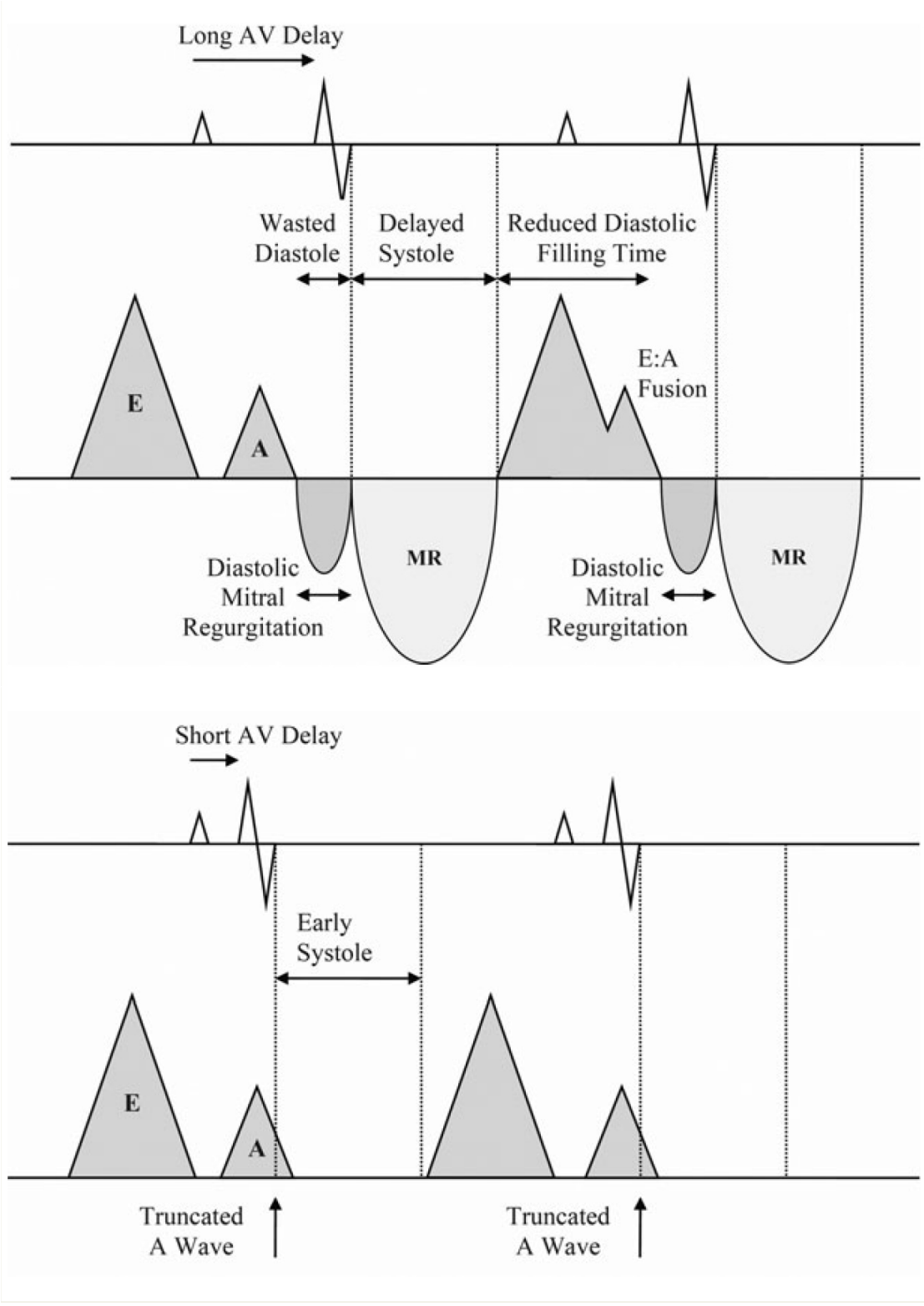


**Figure 8: Demonstrate the effect of shortened and prolonged atrioventricular delay on ventricular filling.**

It is reported that atrial contraction contributes 20-30% of stroke volume at rest, which may increase on exercise.(131) A prolonged AV delay would result in late ventricular contraction and interrupted diastole with impaired ventricular filling. (See Figure 8) This is further compounded by the presence of pre-systolic mitral regurgitation. Correct AV programming

can abolish diastolic MR and improve the timing of the cardiac cycle to further enhance left ventricular filling.

A shortened AV delay causes early ventricular contraction and premature onset of ventricular contraction and early mitral valve closure. This also may have negative effects in ventricular filling times. Therefore the role of optimisation is to ensure maximal E and A wave separation and to complete diastolic filling prior to the onset of ventricular contraction.

The criticisms of echocardiographic optimisation are several. Firstly the historical basis on which optimisation was founded was based on small single centre studies, which were often not randomised and had limited follow up periods.(131-133) The range of echocardiographic techniques means that direct comparison of different studies and data are difficult. The other area of difficulty is that the majority of studies did not contain a control group in whom a fixed AV interval was delivered. Without such control groups it is hard to characterise the effect of AV and VV delay adjustment on endpoints. Another major limitation of optimisation is that most previous studies have optimised a patient whilst lying on the couch at rest. This may not be ideal for younger, fitter patients and does not necessarily replicate the findings re AV delay on exercise. Due to these limitations, the field is still widely debated and further work is ongoing in the area.

A number of transthoracic echo techniques exist, the major ones will be discussed below but others do exist albeit in smaller studies with limited data.

The Ritter method is based on methods derived from the early experience with regards to AV delay adjustment in dual chamber pacing in heart failure.(134) A long AV delay and very short AV delay are programmed and the optimal AV duration identified by the application of a complex equation. Due to the calculation of the optimal A wave without testing serial measurements it gives a result quicker than the iterative technique. The technique has not been tested in a large study and when compared to other techniques in a cohort of 28 patients was least likely to predict the optimal AV delay as compared to invasive haemodynamic monitoring.(135)

The mitral valve inflow velocity time integral equates to the left ventricular filling volume, providing the mitral valve has a constant area. The AV delay in this technique is tested at

multiple intervals to ascertain the delay which correlates with the maximal mitral valve inflow VTI. In a small prospective study of 40 patients undergoing CRT, aortic and transmitral VTI were increased by either method. There was no correlation between the two methods (r=0.03).(136)

The iterative method uses pulse wave Doppler through the mitral valve. The filling time is measured from the start of the E wave until the end of the A wave. A long AV delay is programmed and altered in 20 ms increments until the physician observes truncation of the A wave. Once this is observed the AV delay is increased in 10 ms intervals until no truncation of the A wave is observed.(131)

A recent study by Shanmugam and colleagues, published in 2013 investigated the effect of iterative optimisation on left ventricular end systolic volumes and also B type natriuretic peptide levels.(137) Using the Iterative method and a cohort of 72 patients, the authors demonstrated a marked improvement in NT-proBNP levels one week following optimisation. (P=0.00001). On further analysis of the cohort, which was divided into two groups - (Group I - no change in implant settings & Group II - A change in implant settings) it was found that the greatest reduction in circulating NT-proBNP levels was in the non-responder population (defined as those patients who demonstrated a <15 percent reduction in LV end systolic volumes). Seventy-three per cent of non-responders demonstrated a fall of 474 pg/mL in NT-proBNP post-AV optimisation. These results support a positive haemodynamic effect but the longer term clinical progress for such patients is unknown.

The longer term effects of echocardiography guided AV optimisation are mostly unknown. There is very limited data in this area. A retrospective observational study has previously been performed by a group from the Cleveland Clinic which published in 2006.(138) Using a series of patients who had undergone CRT implantation between 1999 and 2003, those who had received AV delay optimisation were compared to those who had not. AV delay optimisation was performed within thirty days of CRT implantation Though the optimal AV delay was different to the manufacturer preset interval (P=0.0001) there was a longer term effect over the mean follow up period of 23 months on NYHA class and LVEF. However what is unknown from the results of the study is what happened to the other 285 patients in whom CRT was implanted at the institution over the same time period. Therefore without the

results of a control group it is unknown as to whether the acute effects of the optimisation translated into longer term clinical benefit.

These three techniques are the major three techniques either incorporated into the randomised controlled trials or supported within the guidelines. Other echocardiographic techniques do exist for AV delay optimisation but with lesser degrees of data, and hence have not been discussed.

The predominant clinical and research focus in echocardiographic optimisation studies has been on atrioventricular delay - however there have been a few studies performed looking at ventriculo-ventricular delay. This period correlates with the delay in ventricular depolarisation and systole between right and left ventricles. CRT offers the possibility of restoring atrio-ventricular pacing but also synchronous biventricular pacing. However whereas the role of AV delay optimisation has been evaluated in historical cohorts with basic pacing and such methodology incorporated into clinical trials, VV delay adjustment has not been studied in either context.

Again the main methods which have been studied have been echocardiographic. Other potential methods do exist and are described elsewhere in this introductory chapter. By using Pulsed wave Doppler at the level below the aortic valve cusps gives the left ventricular outflow tract velocity time integral (LVOT VTI). By multiplying this number against the cross sectional surface area it is possible to calculate stroke volume. Some small pilot studies which were non randomised and contained small numbers of patients have been performed.(139-141)

The InSync III study investigated the role of VV optimisation in a larger trial format, and reported in 2005.(139) Using InSync III devices, it investigated whether VV optimisation resulted in improved functional and haemodynamic variables. A series of 422 patients was enrolled into a non-randomised prospective study with all participants followed up for six months. The results for this study were compared to the control group from the MIRACLE trial.

InSync III patients experienced greater improvement in 6MWT, NYHA functional class, and QoL at six months compared to control (all $P< 0.0001$). Optimization of the sequential pacing

increased (median 7.3 percent) stroke volume in 77 percent of patients. Though there was an improvement in stroke volume in the optimised cohort there were no changes in functional status or QOL.

Another clinical trial performed within the area has been the Rhythm ICD II trial (The Resynchronization for the HemodYnamic Treatment for Heart Failure Management II implantable cardioverter defibrillator study).(142) A total of 121 patients were recruited and randomised in a 1:3 ratio to simultaneous biventricular pacing or optimised biventricular pacing. All patients had CRT-D systems implanted and trial was performed as a prospective randomised study with the endpoints of NYHA class, 6 MWT distance and improvement in QOL. There was no difference between the two groups in any endpoint (p=non-significant for all endpoints).

### 1.8.12 Invasive Optimisation

Some of the initial CRT studies used invasive methods of CRT optimisation. By using on table catheters which could measure intra-cardiac pressures, the investigator is able to generate values for myocardial work. These can then be analysed to give the invasive dP/dt which reflects myocardial contractility but may be influenced by preload, afterload and heart rate. The PATH-CHF studies used this methodology to optimise CRT devices.(92) The benefits of this technique being a direct measure of intra-cardiac haemodynamics and can be performed as part of the implant procedure.

However the invasive nature means that the clinical use of such techniques is limited due to the added risk of performing measurements and also prolonging the implantation time. Since the publication of the initial studies as described above, there have been some small single centre studies with limited numbers of patients with no longer term outcome data.(143, 144) From a clinical perspective such techniques currently remain impractical and research orientated.

### 1.8.13 Impedance Cardiography

Impedance Cardiography is the non-invasive method of deriving cardiac haemodynamic measurement by the application of a small amount of pulsed alternating current through the surface electrodes (conventionally four electrodes). Electrical current seeks the path of least resistance and hence will travel through the blood filled aorta. Beat to beat variation exists and the technology measures a series of consecutive beats to give an averaged result.(132)

Early studies demonstrated some efficacy on early endpoints such as NYHA and LVEF.(145) Bioreactance measurement is a derivative of ICG. Bioreactance systems calculate CO by measuring real-time changes in the phase of the received voltage signal relative to the applied current signal. Thus rather than using the absolute values the technology relies on the phase shift i.e. the rate of change of electrical resistance and inductive properties.

There are several ICG and bioreactance systems available commercially but fundamentally all operate on the basis discussed above.

Khan and colleagues, in 2009, firstly documented the efficacy of the NICOM device (Bioreactance measurement) in the optimisation of CRT recipients.(145) Using a series of 47 patients and a primary endpoint of reduction in left ventricular end systolic volume (LVESV) by >15 percent, the group were able to establish the effectiveness of the equipment. In all patients, cardiac output (CO) increased significantly at optimized settings compared with baseline (5.66 ± 1.4 vs. 4.35 ± 1.1 L/min, $P < 0.001$). Importantly the reproducibility of measures derived from NICOM correlated well with transthoracic echocardiography for both AV and VV delays. 40 of 47 patients (85%, $r = 0.89$, $P < 0.01$) and for VV delay in 39 of 47 patients (83 percent, $r = 0.89$, $P < 0.01$).

Having established reproducibility and repeatability of the technique- the same group then investigated the effects of such NICOM based optimisation on AV and VV delays in a prospective study.(146) The results of this study were published in 2011. A total of 203 patients were randomised to fixed standard settings (n=54 (AV delay=120ms, VV delay =0 ms) or NICOM based optimisation. All were followed up for six months following enrolment and measured endpoints were LVEF, NYHA and 6 MWT. After six months the optimisation group had improved QOL (35 ± 18 vs 42 ± 20, $P = 0.045$) and NYHA class (2.1 ± 0.8 vs 2.4

± 0.8, P = 0.048) which correlated with improvements in left ventricular end systolic volumes and ejection fraction (108 ± 51 vs 126 ± 60 mL, P = 0.048) and (30 ± 7 vs 27 ± 8, P = 0.01) respectively. However there was no difference between the groups in 6MWT test distance. (P=0.81)

### 1.8.14 Finger Photoplethysmography

A conventional pulse oximeter uses a photo detector to detect arterial pulsation. From these recordings it is possible to deduce systolic blood pressure, pulse pressure and mean arterial pressure. The use of this technique is aided by its high degree of reproducibility and portability. However the waveforms are limited by peripheral arterial system and autonomic tone affecting the peripheral vascular resistance.

It has been shown to be highly reproducible with positive effects documented on acute haemodynamics.(147) Again longer term clinical data has not been published using this technique.

### 1.8.15 Overview

The varieties of techniques presented within this section suffer from similar limitations. Early work has documented acute effects on haemodynamics with positive effects on systolic blood pressure, stroke volume and cardiac output. However the longer term effects on the whole are unknown. One area of optimisation which has been explored in large numbers with randomised trials has been algorithmic based optimisation. The data that has been published from these trials to date has been disappointing with no longer term effects documented on clinical endpoints. However the field contains several smaller, single centre studies using variety of techniques and follow up periods. The heterogeneous literature makes direct comparison difficult and only allows limited conclusions to be made.

The limitations of the field have been heavily discussed in recent document issued by the ESC, EHRA and HRS.(99) The joint consensus document published in 2012 suggests a cautious approach to device optimisation with the process being reserved for those patients deemed non-responders. The ESC guidelines published this year, 2013, go further and suggest

routine device based optimisation should not be performed but due to the evidence accrued from the studies described above, device optimisation should be considered for those with pre-existent ischaemic heart disease, those patients who fail to derive clinical benefit following CRT implantation and those who receive inadequate degrees of atrio-biventricular pacing.(22)

### 1.8.16 Medical Optimisation

The process of uptitrating and initiating evidence based pharmacotherapies following CRT for the purposes of this thesis will be referred to as medical optimisation. There are two major issues which surround this option but both lack data. Firstly the question of what is the best model to facilitate medical optimisation is unanswered; there is limited American evidence for such specialised clinics but little from the European literature. Secondly the comment with regards to medical optimisation is whether it is feasible and more importantly translates into improved clinical outcomes and higher rates of symptomatic benefit for the patient.

### 1.8.17 Optimisation Clinics

The process of 'optimisation' may be carried out in dedicated heart failure pacing clinics. However the data available to support the creation and maintenance of such a service is limited. Generally throughout the western world there are multiple different models of healthcare for patients undergoing CRT implantation, partly this relies on financial reimbursement, structure of the overall health service and ownership of the patient between primary, secondary and possibly tertiary care. Hence it is not uncommon for an interventional electrophysiologist to implant CRT and to hand back the patient's ongoing care to a general physician, cardiologist or primary care practitioner. This model of healthcare is the status quo in many parts of the United Kingdom and Western Europe. What is currently unknown with this ad hoc pattern of service is what is happening to the patients following discharge and what is happening to their medical therapies. There is a real need for such data and the existing registry data from Britain, Europe and the US does not cover this period.

The only limited information that reflects on current healthcare models is the extended follow up data released from the European CRT Survey.(148) A total of 2111 patients were tracked

for one year (range of follow up 9 to 15 months) out of the original cohort of 2438 patients (87 percent). The data demonstrates significant rates of morbidity with 346 (16 percent) patients being hospitalised for HF over this time period and 207 (10 percent) patients dying. When looking at the characteristics of the patients who suffered clinical events (death or HF hospitalisation) there are significant differences in the levels of beta blocker use ($p<0.0001$) and a trend toward significance in angiotensin II receptor blockade ($p=0.08$). The data is not sufficiently detailed to investigate this relationship further. The patients who suffered clinical events may have had efforts to uptitrate or commence beta blockade but this information is lacking within the dataset. Nevertheless the difference between the two groups is striking and on absolute numbers, statistically significant.

Dedicated heart failure pacing clinics have been suggested more recently but the data which supports their existence has not been forthcoming. The necessary data is predominately American which reflects a different healthcare infrastructure and system. The first publication in the field was by Mullens and colleagues who described the initial experience of 75 patients following CRT implantation assessed in a structured clinical protocol format at the Cleveland Clinic, USA, published in 2009.(149) The protocol involved a heart failure physician, a heart failure specialist nurse, physiologist, echocardiographer and electrophysiologist (i.e. heart failure and device multidisciplinary team). In this group of patients who were not deriving the anticipated clinical benefit, a range of findings were documented: inadequate device settings (47 percent), suboptimal medical treatment (32 percent), arrhythmias (32 percent), and inappropriate lead position (21 percent). The majority of the patients were also uptitrated or initiated on evidence based pharmacotherapy (74 percent) and hence were on suboptimal medical therapy at the time of clinic attendance.

More recently there has been a publication from the group at Massachusetts General, Boston, USA published in 2012.(150) Here patients following CRT implantation were randomised to conventional care or a structured clinical protocol. The study consisted of 254 patients randomised to the clinical protocol arm and 173 patients in the conventional care arm. Patients were comparable in clinical characteristics and were reviewed by the multidisciplinary team at 1,3, and 6 months following CRT implantation. The patients' outcomes were then measured over the following two years with a primary endpoint of heart failure hospitalization, cardiac transplantation, or all-cause mortality. The event-free survival was significantly higher in the clinical protocol group versus the traditional care ($P = 0.0015$).

A significant reduction in clinical events was noted between those patients randomised to more intensive monitoring and intervention by the multidisciplinary team. (hazard ratio: 0.62, 95 percent CI: 0.46-0.83, P = 0.001).

### 1.8.18 Medical Therapy Following CRT Implantation

The period following CRT implantation may be characterised by an increased systolic blood pressure, the removal of bradycardia and, potentially, an improvement in the glomerular filtration rate.(22) All of these beneficial aspects mean that there is a window of opportunity to review HF medication. Hence the time period following CRT implantation may lead to increased doses of proven prognostically beneficial neurohormonal antagonists.

However, this period has not been adequately studied and there is limited data in this area. One group of drugs in particular that may be started following CRT implantation is beta adrenoceptor antagonists. This is due to the removal of the risk of bradycardia as a side effect and potential reason for the discontinuation for the drug. A study which focussed on beta blocker doses following CRT implantation was the CARIBE-HF trial (Beta blocker in advanced heart failure trial) published by Grosu and colleagues in 2011.(151) Using a prospective observational study design, 106 patients were identified and had their dose of carvedilol uptitrated towards target dose. This was Phase I of the study. Those then eligible for CRT based on standard selection criteria had CRT implanted. Following a second phase of the study the carvedilol dose was higher in the CRT group than the non CRT group.(+20.0 +/- 19.8 mg vs. -0.3 +/- 20.5 mg; P = 0.015). These changes were also associated with an improvement in NYHA class and LVEF. (P=0.011 and P=0.018 respectively).
However the actual numbers of patients in the CRT and non CRT groups were extremely small by the end of the seven year follow up period. This is a recurrent theme in the available data and needs to be investigated with a larger dataset.

Another group from Cardiff, Wales also documented significant improvements in 74 patients undergoing CRT implantation.(152) The group followed up such patients in a nurse led medical optimisation clinic and found that in the six months following CRT implantation there was a significant improvement in beta blocker dose and use. (P<0.01) and similar findings were demonstrated with ACE inhibitors. (P=0.02)

The scientific consensus is that uptitration and initiation of evidence based pharmacotherapies following CRT should translate into improved clinical outcomes. However again there is a lack of appropriate data to investigate this relationship. Adlbrecht and colleagues published on this subject in 2009.(153) Using a retrospective observational study design the authors described the progress of a cohort who had undergone CRT-P or CRT-D implantation. Following a mean duration of follow up of 16.8+/-12.4 months, there were 83 patients who suffered events (death or heart failure related hospitalisation). Sub optimal heart failure medical therapy following Cox regressional analysis was a significant predictor of adverse clinical outcomes (For CRT-P (HR = 2.080 (1.166-3.710), P = 0.013 and for CRT-D (HR = 2.504 (1.550-4.045), P < 0.001)).

Hence limited data exists within the area, but, when directly compared to other areas of clinical research allied to cardiac resynchronisation therapy, there is a significant lack of published data and investigation and further work is much needed in this area.

## 1.9 Response

The clinical effectiveness of cardiac resynchronisation therapy has been previously documented in the large randomised clinical trials.(5, 6) However, when CRT became established as a clinically available therapeutic option, it was soon recognised that some patients derived clinical benefit and some did not. This dichotomy has been labelled as response.

The origins of the term are unknown, it is unclear from the literature but as soon as the first randomised controlled trials were published, editorials from leading experts in the field included the term. A small clinical trial was published by Haissaguerre and colleagues in 2002 which specifically investigated the issue of response after CRT implantation.(154) A cohort of 102 patients receiving second generation CRT devices was followed up for a year. Response within the study was defined as improvement in NYHA class at one year. The non-responder rate within the cohort was 18 percent (n=18). According to the small dataset the predictors of the response endpoint were prior history of ischaemic heart disease, minimal mitral regurgitation and low cardiac output.

Following this initial work, the term has become widely accepted. The limitation of the term is that it is felt to represent the clinical improvement a patient may have following CRT implantation. Heart failure is a complex clinical syndrome with many potential methods of assessing endpoints within such patients. Previously used endpoints have included functional (NYHA classification, 6MWT distance, MVO2), symptomatic (QOL scores) and mechanical (LVEF, End diastolic and systolic diameters and end systolic volumes). The problem with response as a term is the lack of consensus either in the guidance or scientific literature. In the absence of an agreed definition, discussion and comparison of published literature is difficult.

The term 'response' also induces other problems. Firstly, by using a cut point, it can be viewed as a dichotomous variable and therefore patients fall into a response or non-response category. However when it comes to symptomatic improvement, the clinical effect may be subtle and hence incorrectly labeled as non-response. With certain heart failure characteristics, it may be that CRT induces a graded response and hence should not be viewed as a categorical variable.

Another issue is that the application of CRT to a patient in heart failure may modify the natural course of the disease but this is unknown in contemporary heart failure care. The large randomised controlled trials recruited patients from an era of evolving evidence for optimal heart failure pharmacological treatment. Hence the quantitative effect of CRT as compared to modern HF therapy is unknown. It is also now unethical to deny CRT to a population who qualify for it in order to carry out a longitudinal epidemiological study to document the natural history of a directly comparable population with and without CRT.

The implantation of a CRT device is also a minimally invasive procedure which takes between one and two hours. However, due to the emphasis of patient selection, patients may experience a placebo effect following CRT implantation similar to other medical procedures. To date there has been no data in this area which has analysed this.

The actions of CRT have been previously documented. However, little is known in terms of exact cellular and sub cellular mechanisms of action. This may differ according to different aetiologies of left ventricular systolic dysfunction. Though poorly characterised, sub study analysis from previous randomised controlled trials has demonstrated increased levels of

remodelling in non ischaemic dilated cardiomyopathy.(22) Again this raises the possibility that CRT is exerting a different effect in different populations.

Initially, CRT was implanted into patients with severe symptoms and marked limitation of functional capacity. However it is now advocated for patients with milder forms of disease, due to the publication of successful randomised trials in such cohorts.(96) The two groups of patients may view response differently, with patients with marked severe symptoms expecting a reduction in their symptoms; whereas patients with milder symptoms may expect a reduction in hospitalisation and mortality. Apart from patients, the attendant cardiologist or electrophysiologist may also share such viewpoints.

Lastly, response, though a heavily debated topic within the field, needs urgent clarification. It is only when a consensual definition has been agreed on and released that accurate scientific investigation may occur. Though now an established term, response as a concept is not used as a marker of clinical benefit in other treatments e.g. medical therapy. Therefore response has become a subject of great interest. By dividing populations who undergo CRT into a responder and non-responder group, the question arises as to what should be done for such non-responding individuals. Current ESC guidance suggests they should be carefully reevaluated with a process of device and medical optimisation, review of programming and the addressing of co-morbidities.(99) The suggested location for such care to occur is a dedicated specialised multidisciplinary clinic.

Limited data does exist for such clinical structure but comes from North America and has been presented and discussed elsewhere in the introduction. Hence the increasing numbers of patients who fail to derive the anticipated clinical benefit still need further investigation. The processes of device optimisation and medical optimisation have little published data and it is this subject which has formed the basis of this thesis. The recognition of this pool of patients means that appropriate healthcare infrastructure should be created to allow a systematic examination of any potential causes of ‘non-response’.

The endpoints most often used to adjudicate on response are those allied to reverse remodelling, e.g. LVEF or left ventricular end systolic volumes. Others endpoints have focussed on more functional assessments e.g. NYHA class improvement. Whichever is the chosen endpoint on which to base improvement leads to different quoted rates of response. A

non- response rate of 20-30 percent is often quoted but when using symptomatic endpoints may be more like 40-50 percent. Though a variety of endpoints exist, the most discussed are those relating to left ventricular volumes and NYHA improvement.

### 1.9.1 LV Remodelling - 'reverse' remodelling

The effect of CRT on reverse remodelling has been documented in several studies. The rate varies from study to study depending on endpoints. The major questions when using reverse remodelling as a marker of response are whether it correlates with clinical improvement, whether it is persistent and if observed then whether it is an indicator of longer term clinical course and prognosis.

An early study which demonstrated the potential for LV remodelling following the application of CRT was performed by Yu and colleagues and published in 2002.(101) Using a series of 25 patients, with LVEF <35 percent, QRS duration > 140 milliseconds, the authors demonstrated a significant reduction in end systolic and diastolic volumes at 3 months following CRT implantation. (205+/-68 versus 168+/-67 mL, P<0.01) and end-systolic volume (162+/-54 versus 122+/-42 mL, P<0.01) On withholding biventricular pacing, it was observed that there was a deterioration in left ventricular systolic function. Others subsequently replicated these findings in their own small, non-randomised cohorts with varying degrees of follow up.

However a natural question was whether reverse remodelling correlates with clinical improvement. Bleeker and colleagues investigated this issue and published results in 2006.(102) A cohort of 144 patients were analysed (all of whom fulfilled standard CRT selection criteria). Response was measured as a reduction in left ventricular end systolic volumes >15 percent at six months. A significant reduction in end systolic volumes was documented (P<0.0001). However the actual follow up period was heterogeneous and some patients were followed up for only three months. A clinical response rate (defined as improvement by NYHA grade of one or above) of 70 percent was observed at 3-6 months of follow up. There was an echocardiographic response rate of 56 percent. A total of 51 percent of patients had both a clinical and echocardiographic response (n=74). Clinical improvement without LV remodelling was observed in n=27 (19 percent) and n=7 (5 percent) demonstrated

LV remodelling without symptomatic improvement. When using a cut point of LV end diastolic volume reduction >15 percent, there was disagreement in n =47 (32 percent). The lack of correlation between the two measures was not explained by the authors but documented. One explanation is that there may be a placebo effect following CRT implantation which represents cardiac intervention. Another is that heterogeneous heart failure aetiologies and follow up periods with a limited number of study participants means that the actual effect beyond observation was not fully characterised. Hence the study should be viewed as observational.

However the longer term question was whether a patient who underwent reverse remodelling was more likely to have a better clinical outcome. Data has now been produced both from the randomised trial cohorts and original prospective studies

The CARE-HF study has been previously described, but the rates of remodelling were charted in 790 of its participants (90 percent of cohort).(155) All individuals whether randomised to CRT or not had repeat echocardiograms at 3, 9 and 18 months with a mean follow up period of 29 months. After 18 months of follow up there was a significant improvement in LV reverse remodelling in the CRT arm as compared to the medical therapy group. (49.2 percent versus 18.6 percent $P<0.001$) The substudy authors note that LV remodelling took time to occur, but when it did so after anything up to nine months, it persisted for up to three years. There were slight differences between the ischaemic and non-ischaemic cohort with CRT.

Verhaert and colleagues also analysed this relationship in 2010, charting the effect of CRT on left ventricular end systolic volumes in a prospective study.(156) The effect of reverse remodelling was then correlated against a composite clinical endpoint of all-cause mortality, heart transplantation and implantation of a left ventricular assist device.

Patients with the highest rates of survival had lower baseline LVESVi (Change=8.6 $ml/m^2$, SE= 4.6 $ml/m^2$, $P < 0.0001$). These patients with higher LVESVi decreased LVESVi by -0.11 ml/m2/day during the first six months following CRT implantation, whereas the LVESVi remained unchanged in patients with adverse events ($P< 0.0001$). Within this study, six months represented a time point at which reverse remodelling becomes less prominent. Predictors of reverse remodelling were non-ischaemic aetiology, female sex, and a wider QRS duration ($P <0.0001$, $P =0.014$, and $P=0.001$, respectively). Hence the conclusions from the

data obtained from this study were that patients who experience clinical benefit had higher rates of reverse remodelling.

A more recent publication by Bertini and colleagues takes this analysis a step further.(157) The results were published in 2013. Using a cohort of patients undergoing CRT implantation (n=679) all with pre implantation echocardiograms and clinical assessments, the rates of response using the previously discussed definitions (<NYHA grade I improvement and LVESV reduction >15 percent) were measured at six months. At six months 77 percent (n=510) showed a clinical response and 62 percent (n=410) showed an echocardiographic response. After a mean follow up period of 37+/-22 months, 21 percent of the cohort had died. On multivariable Cox-regression analysis only echocardiographic response to CRT was independently associated with superior survival (hazard ratio: 0.38; 95 percent CI: 0.27-0.50; $P < 0.001$).

Hence the overall impression is that CRT in certain individuals may facilitate reverse remodelling, which may be long lasting. The exact mechanisms for this phenomenon are currently unknown. The rates of echocardiographic response lie between 50 and 60 percent. It still remains unknown as to predictors of reverse remodelling, and some patients experience this and others do not. Logically the application of CRT to an area of myocardial scar following prior ischaemic insult may not induce remodelling but other mechanisms which improve the overall survival of the patient.

### 1.9.2 Symptomatic Improvement following CRT

As already stated the most widespread measure of this in the literature is the improvement in NYHA grade by >1. However beyond such grading systems, other potential endpoints used to support a symptomatic improvement following CRT include 6MWT distance and maximal oxygen demand.

However little is known about the effect of CRT on these endpoints beyond the randomised controlled trials which have been presented above. Six minute walk test distance has been used as a prognosticator in CRT populations. However what is less characterised is the effect of CRT on such endpoints. A recent pilot study by Sherry and colleagues published this year demonstrates in 21 subjects an improvement in 6MWT at three months following CRT

(P<0.0001).(158) However such findings need to be fully investigated in much larger randomised cohorts.

The literature is similar for MVO2 with early randomised trials using it as a primary endpoint. Subsequently there has been little investigative work with a pilot study published this year (2013) by Larsen and colleagues who investigated with cardiopulmonary testing the effect of CRT within 21 patients at six months.(159) CRT induced a positive improvement in peak Vo2 (P=0.07). Again this was in a non-randomised pilot cohort. A much larger dedicated cohort would be needed to re-evaluate these findings.

### 1.9.3 Overview

Though response remains a debated element of post CRT implant care, there is now a wide body of literature which covers both functional and mechanical endpoints. Hence as a concept it has become established but, due to the lack of a consensual definition, still remains a difficult concept to analyse scientifically. Notably Fornwalt and colleagues in 2010, analysed the published response criteria up to that point in time in a landmark study.(160) Using the top fifty publications up until that point in time they extracted 17 different criteria which had been used as markers of response. See Table 3.

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**Response criteria Echocardiographic**

1. ↑LVEF ≥5% (absolute)

2. ↑LVEF ≥15%

3. ↓LVESV ≥10% and did not die of progressive HF within 6 months

4. ↓LVESV >15%

5. LVESV <115% of baseline

6. ↓LVESVI >15%

7. ↓LVEDV >15%

8. ↑Stroke volume ≥15%

**Clinical**

9. ↓NYHA ≥1

10. ↓NYHA ≥1 and did not die of progressive HF within 6 months

11. ↓NYHA ≥1 and ↑6MWD ≥25%

12. ↓NYHA ≥1 and ↑6MWD ≥25% and did not die of progressive HF within 6 months

13. ↓6MWD >10%, no heart transplant, did not die of progressive HF within 6 months

14. (↓NYHA ≥1 or ↑$\dot{V}O_2$max >10% or ↑6MWD >10%) and alive, no hospitalization for decompensated HF

15. Two of 3: ↓NYHA ≥1 ↑6MWD ≥50 m ↓QOL≥15

16. Clinical composite score improved

**Combined**

17. (↑LVEF ≥5% [absolute] or ↑6MWD ≥30 m) and (↓NYHA ≥1 or ↓QOL ≥10)

**Table 3: Lists seventeen different response criteria.↑indicates increase; LVEF, left ventricular ejection fraction; ↓, decrease; HF; heart failure; LVESV ; left ventricular end systolic volume; LVESVI, LVESV indexed by body surface area; LVEDV left ventricular end-diastolic volume; NYHA, New York Heart Association functional class; 6MWD, 6 minute walk distance; $VO_2$max oxygen consumption at peak exercise; QOL, quality of life score (160)**

The list comprised clinical and echocardiographic criteria. The Cohen correlation coefficient was used to statistically analyse the relationship between differing methodologies. The criteria showed poor correlation, with a mean kappa of 0.22+/- 0.24.

The authors then extrapolated their results to the PROSPECT study cohort.(103) When applied to the cohort, the response rate varied between 32 percent and 91 percent with 99 percent of the cohort being classified as responders when criteria were applied and 94 percent classified as non-responders when alternative criteria were applied. The group highlights the problems with response and the inconsistency of the data.

Further work is needed and, once a consensual definition has been agreed on, this would lead to more robust scientific discussion and investigation. For the purposes of this thesis where applicable, the studies have used both functional and mechanical endpoints similar to those in the published literature as described above.

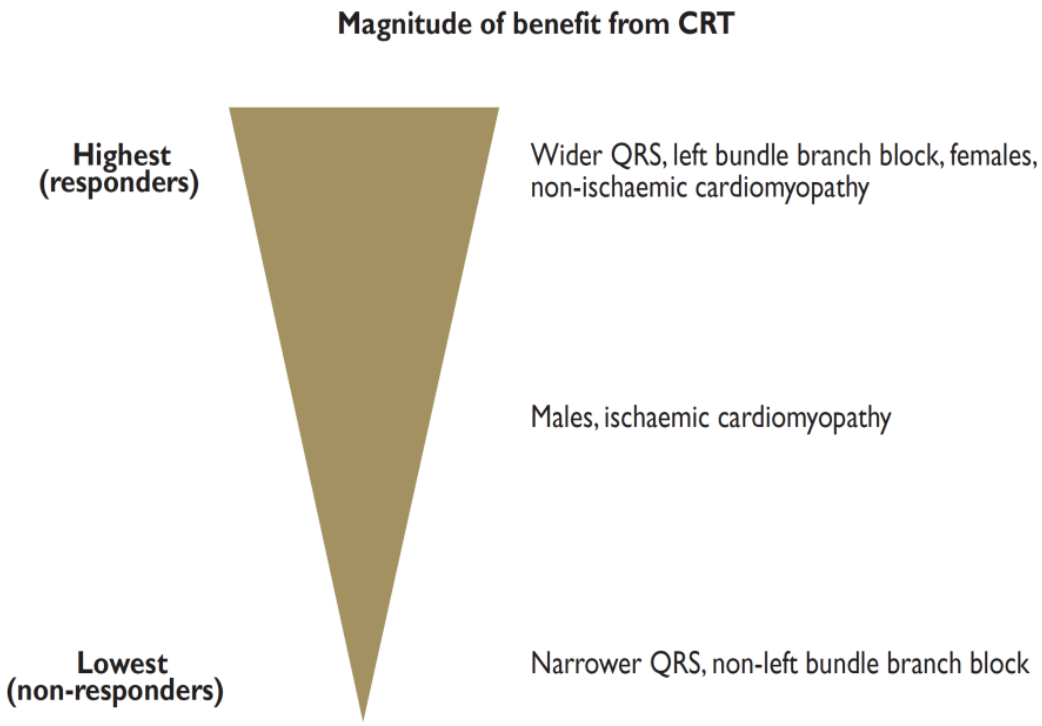



**Figure 9: Demonstrates the spectrum of response to the application of cardiac resynchronisation therapy, those with the highest degree of response at the top. From the European Society of Cardiology Guidelines for Cardiac Resynchronisation Therapy 2013(22)**

## 1.10 Mechanisms of CRT

Cardiac resynchronisation therapy is now an established treatment option for selected patients. However despite the clinical effectiveness in several large randomised controlled trials, its effects are not wholly understood.

The concept of response and non-response has been discussed elsewhere in this chapter but CRT probably exerts its effects on a multifactorial level. Currently with modern imaging techniques much is known and has been documented with macroscopic disease, what is less well characterised is the cellular, metabolic and effect on intracellular pathways that CRT may have. A non-responder is, according to the latest guidance, a patient who fails to develop symptomatic, mechanical, functional or neurohormonal benefit following CRT implantation.(22) The pathophysiology behind why some individuals experience this is unknown. Certain factors not currently included in selection criteria may have some impact on the overall effect and outcome of the patient, but their exact relationship with CRT is unknown. e.g. right ventricular dysfunction, renal impairment and anaemia.

### 1.10.1 Left Ventricular Remodelling and Functional Mitral Regurgitation

Macroscopically as previously stated, CRT may induce reverse remodelling. There may also be a reduction in functional mitral regurgitation (due to annular dilatation) and correction of dyssynchrony. With modern sophisticated cardiac imaging techniques, these positive effects of CRT have been previously documented. However CRT may also have effects at a sub cellular level, for which there is limited knowledge. The correction of electromechanical dyssynchrony is well understood, but what is less understood is the direct mechanism for the reduction in arrhythmias (independent of defibrillator capacity). Hence CRT may be viewed as having documented macroscopic effects, and poorly characterised and understood cellular, sub cellular and electrical effects.

LV remodelling following CRT has been investigated. One of the first investigative studies of CRT on mitral regurgitation (MR) intensity was performed by Breithardt and colleagues and published in 2003.(161) A series of 24 consecutive patients was studied after CRT implantation. The investigators then analysed the mitral regurgitation using the proximal isovelocity surface area (PISA) technique to calculate the effective regurgitant orifice area (EROA). The estimated maximal rate of left ventricular systolic pressure rise was also recorded. ($dP/DT_{max}$). Patients underwent CRT implants and then had them turned off and with CRT turned back on again. Effective regurgitant orifice area decreased from 25 +/- 19 $mm^2$ (OFF) to 13+/- 8 $mm^2$ (CRT). The change in EROA was directly related to the increase in LV $dP/DT_{max}$ ($r= -0.83$, $p <0.001$).

This was a short term haemodynamic assessment of mitral regurgitation; longer term evidence for the effect of CRT on functional MR comes from van Bommel and colleagues in 2010.(162) A total of 98 patients who had high operative risk and moderate to severe functional mitral regurgitation were studied. Two thirds of the cohort had an ischaemic aetiology and the mean QRS duration was 166 +/-29ms. After a follow up period of six months, 13 patients had died, but the ones who had survived had an improvement in NYHA class, 6 MWT distance and reductions in ventricular volumes and mitral regurgitation. ($P<0.0001$)
The cohort was then followed up for an extended period (median 32 months range 6-116 months) and death rates recorded. There was significant improvement in survival in the MR improvers as compared to the MR non-improvers ($P<0.001$).

### 1.10.2 Neuroendocrine effects and renal function

CRT may also exert its effects on other macroscopic systems which may be quantifiable. Neuroendocrine dysfunction is a characteristic of the heart failure syndrome and hence both renal function and B type natriuretic peptide may be easily measured using serum assays.

The relationship between CRT and renal function has been investigated but needs further data. The limitation is that renal impairment was a contraindication to participation in the some of the larger randomised controlled trials. Hence a lot of the work within the area comes from substudy analysis from the randomised studies. The substudy from the MIRACLE group was published in 2008. The cohort was divided into three groups on the basis of renal function at baseline (EGFR (estimated glomerular filtration rate)>90 mls/min – preserved renal function; eGFR 60-90mls/min- mildly impaired and eGFR 30-60mls/min - moderately impaired. CRT improved eGFR in the most impaired group but had no effect in the other groups on renal function. (-2.4 +/- 1.2 vs. +2.7 +/- 1.2 mL/min per 1.73 $m^2$; P = 0.003)(163)

Baseline renal function prior to CRT also seems to have some importance. The Mayo Clinic, published the results from their own registry data in 2011, with 482 patients stratified by renal function.(164) The rates of survival were higher in those patients with normal or mild renal dysfunction as compared to those with established chronic renal impairment. (72 vs. 57 percent at 3 years, $P < 0.01$). Chronic renal impairment remained a prognosticator in multivariable analysis.

A recent meta-analysis of 18 studies, published in 2012 demonstrated a modest improvement in eGFR following CRT implantation and also a slight improvement in left ventricular ejection fraction.(165) (Mean difference 6.24 percent; 95 percent confidence interval, 3.46 to 9.07). The authors reviewed a collection of studies dating back to the 1990s and suggest that more data within the area is needed.

The exact mechanism for an improvement in renal function following CRT implantation is unknown. Postulated theories are a reduction in central venous pressure and hence enhanced perfusion across the renal bed due to reduction in local renal venous pressure, an increase in systemic arterial blood pressure and increased renal arterial blood supply.(166) Further work

is needed to characterise the precise mechanism and interaction between renal function and CRT but it remains a potential prognosticator in populations undergoing CRT implants.

B type natriuretic peptide as discussed elsewhere in the introduction is a marker of neurohormonal activation. It has been previously been shown to be a prognostic marker in patients with systolic heart failure.(167) Hence logically, the levels of circulating BNP prior to or after CRT implantation may reflect a level of disease which is refractory to the effects of CRT.

There is a shortage of published data in this area, and the largest sets of data come from substudy analysis from the CARE-HF and MADIT-CRT studies. Brenyo and others released their data in 2013 and analysed BNP levels at baseline and one year after CRT implantation.(168) An elevated baseline BNP was a predictor of death in patients receiving either CRT-D (p=0.007 (68%)) or ICD (p-0.02 (58%)). At one year there was a greater reduction in BNP levels in the CRT-D recipients (26%) versus ICD recipients (8%) (p= 0.005). The one year BNP level was both a predictor of death and left ventricular reverse remodelling.

The CARE-HF substudy was published much earlier by Fruhwald and colleagues in 2007.(169) Embedded within the trial structure all participants had serum analysed at 3 and 18 months. NT pro-BNP was measured and the difference between the medians in the CRT group and medical group was highly significant at both 3 months (537pg/mL; P<0.0001) and 18 months (567 pg/mL; P<0.0001). The findings were independent of changes in pharmacotherapy and renal function, but were associated with improvement in ventricular volumes and renal function.

Hence BNP appears to be a prognostic marker in cohorts undergoing CRT implantation. However the relationship needs further characterisation and evaluation. Within this context it appears to be a surrogate for neurohormonal and sympathetic activation, which is readily available and quantifiable. However further work is needed to understand the relationships of circulating levels with clinical outcomes and important subgroups e.g. patients with prior ischaemic disease versus those with dilated cardiomyopathy.

### 1.10.3 Cardiac Haemodynamics

Prior work as summarised elsewhere in the introduction has illustrated the potential effect on acute haemodynamics of CRT. Initial enthusiasm for these observational studies was tempered by the need for pressure/volume conductance catheters, dedicated catheter laboratory time and the acknowledgement of an extension in procedural time and potential risk to the individual patient.

A recent example of such a study was that performed by Duckett and colleagues in 2011.(170) Using a consecutive series of 33 patients undergoing CRT implantation all had on table dP/dt generated by using a pressure wire and the data used to guide the LV lead position. There was a significant improvement in left ventricular $dP/dT_{max}$ (P=0.001) and left ventricular end systolic volume (P=0.001). There was an association between reverse remodelling and acute improvement in haemodynamics (P<0.001).

Hence CRT may induce a positive short term haemodynamic improvement which seems to be linked to longer term reverse remodelling. Whether this is reliably associated with clinical outcomes is unknown, longer term correlation of clinical endpoints with short term haemodynamic data is needed but this question should be analysed in a much larger format.

### 1.10.4 Systemic Blood Pressure

Cardiac resynchronisation therapy may exert some effect on systemic arterial blood pressure. However the evidence for such effects is limited and needs further investigative work.

Ather and colleagues performed a meta-analysis of observational study and randomised controlled study data, publishing in 2011.(171) The initial analysis of non randomised data demonstrated an increase (from baseline) in systolic blood pressure by 4.4 mm Hg (95% confidence interval [CI] 0.8 to 8.0, P = 0.02), no change in diastolic blood pressure (P = 0.21). Results from CARE-HF and COMPANION were concordant with an increase in systolic blood pressure by 3.9 mm Hg (95 percent CI 1.1 to 6.8, P = 0.007), no effect on diastolic blood pressure (P = 0.40), and an increase in pulse pressure by 4.3 mm Hg (95 percent CI 4.1 to 4.5, P <0.001) compared to medical therapy. (5,6) Hence CRT may have some limited effect on systemic blood pressure.

An alternative effect of CRT linked to optimisation has been documented by Whinnett and colleagues in 2006.(147) Using finger plethysmography and by adjusting AV delay in twelve patients, it was noted that AV delay adjustment also resulted in changes to systemic blood pressure. Altering the AV delay had a more pronounced effect on BP (average range of SBP=17.4 mmHg) compared with resting rates (average range of SBP=6.5 mmHg), P<0.0001.

### 1.10.5 Sympathetic activation and arrhythmias

One of the widely discussed potential benefits of CRT is its ability to prevent and treat ventricular tachyarrhythmias this is particularly of interest in the ischaemic population.

The previous randomised trials have been discussed and the clinical question of whether to implant an ICD or CRT-D has also been covered via presentation and discussion of the large randomised trials.

However beyond the trial format, some have advocated that CRT may by LV pacing mediate a reduction in arrhythmias. Others suggest that the application of an electrode contiguous to an area of myocardial scar or fibrosis may be pro-arrhythmic.(119) The exact cellular mechanism is unknown. Clinical observational studies performed in smaller cohorts generate different findings and hence the field is under active investigation.

Lin and colleagues analysed this issue from the Mayo Clinic dataset, in 2008.(172) Using 52 patients who underwent upgrade to CRT-D from dual chamber ICD, the frequency of ventricular arrhythmias was observed pre and post upgrade. There was no significant reduction in non-sustained ventricular tachycardia, sustained ventricular tachycardia and ventricular fibrillation with the upgrade to CRT. (P=non-significant for all measures) The authors found in this study this effect was unrelated to left ventricular remodelling.

However Thissjen and coworkers released a study in 2011, refuting the findings of the previous study(173) using a consecutive series of 115 patients, and documenting ventricular arrhythmia burden and left ventricular remodelling (<15 percent reduction in LVESV at 6

months). The group was able to demonstrate in those who remodelled (70 percent), there was a trend towards significant reduction in arrhythmic burden. (P=0.052) Those patients who failed to experience reverse remodelling had a higher rate of arrhythmias following CRT upgrade. (P=0.014)

Hence the data which reflects observational practice is conflicting and needs some clarification. Little is known about the anti-arrhythmic effect within ischaemic and non ischaemic populations following CRT implantation.

The actual mechanisms for such electrical effects are unknown. However apart from cellular level change and signalling pathway upregulation, an alternative explanation is offered by the use of radionuclide imaging.

Iodine-123 metaiodobenzylguanidine (123-MIBG) is a radioisotope of iodine which is taken up by adrenergic receptors. It therefore when used with scintigraphy can visually demonstrate the current sympathetic activity within an organ system. It has been validated in heart failure cohorts and has been shown to be a prognosticator.(174)

Marshall and colleagues in 2012, evaluated the role of 123-MIBG in a cohort undergoing ICD implantation at a tertiary centre in the United Kingdom.(175) A series of 27 patients was studied with a mixture of CRT-D (n=19) and ICD (n=7). By using 123-MIBG and single photon emission computed tomography (SPECT) the authors were able to correlate levels of sympathetic activity with the occurrence of ventricular arrhythmias. However in such a small cohort none of the cut points were robust enough to base clinical decisions upon.

Alternative data comes from Cha and colleagues, who published in 2008.(176) Using a series of 16 patients and documenting 123-MIBG washout rates, plasma noradrenaline levels and heart rate variability, the authors were able to show that in individuals who experienced reverse remodelling, CRT led to improved markers of sympathetic activity. The improvement in NYHA after CRT was significantly associated with baseline (123)I-MIBG washout rate ($r = 0.65$, $P = 0.03$). The improvement in LVESV index was associated with baseline (123)I-MIBG delayed ratio ($r = -0.67$, $P = 0.02$) and washout rate ($r = 0.65$, $P = 0.03$).

### 1.10.6 Metabolic Effects

Left Bundle Branch Block has been demonstrated to induce regional myocardial metabolic variation between septal and lateral walls. In the presence of LBBB, prior work has documented a low uptake of glucose within the septal wall with a compensatory response in the lateral wall of the left ventricle. (41)

The use of positron emission tomography (PET) scanning and radiolabelled glucose permits the analysis of metabolism. Ukkonen and colleagues released the first data in this area with an observational study performed in eight patients published in 2003.(41) Septal uptake of glucose was increased following CRT implantation (P=0.04) and the septal/lateral wall ratio also improved (P=0.01), hence this initial pilot study demonstrated that regional discrepancies of metabolism had been corrected by CRT.

Lindner and co-workers investigated this further in 2005, by analysing a myocardial oxygen demand and blood flow in a cohort undergoing CRT implantation.(177) A total of 42 patients (31 DCM and 11 dilated cardiomyopathy with prior history of ischaemic heart disease) undergoing CRT were studied using 11C-acetate-PET at baseline and four months following CRT implantation. Following CRT, the rate of blood flow and oxygen demand decreased in the lateral wall (P=0.045) and increased in the septum (P=0.045) in the non ischaemic DCM group. Similar observations were documented in the ischaemic group with no significance. Hence the authors suggest that on the basis of this study, CRT may have been more effective in patients with non ischaemic aetiologies.

More recent studies have investigated this and found similar findings, but once again with small numbers of patients.(178) Though of interest, the field needs a larger prospective study to correlate short term metabolic effects with longer term clinical outcomes. The apparent differences between ischaemic and non ischaemic aetiologies also requires further analysis as this may be a potential explanation of the mechanism of CRT in the two different groups and explain the increased rates of reverse remodelling observed in the non ischaemic aetiologies.

### 1.10.7 Cellular Effects and Signalling Pathways

With the application of CRT and the advent of sophisticated modern cardiac imaging, the effects described above may be directly observed with reproducible and established techniques. e.g. echocardiography.

However beyond the macroscopic level, what remains unknown is the effect of CRT at a cellular level both directly on individual myocytes and intracellular signalling pathways. The field of basic science allied to CRT is small and has followed the large clinical publications. However the desire to understand some of the observed phenomenon following CRT implantation has led to increased interest in this field. Particularly the phenomenon of reverse remodelling following the application of a depolarising electrode is not understood. The longer term aim of such investigation would be to guide patient selection, refine CRT itself and potentially even extrapolate such proteins and intracellular signals to the pharmacological arena to permit the development of future agents.

Due to the lack of knowledge in the area several cellular mechanisms are being studied. Recent publications in the area have included the following studies.

Pezzali and colleagues published this year (2013) on a cohort of CRT recipients (n=101) who had been evaluated for beta adrenoceptor polymorphisms.(179) The group investigated the beta-1 Arg389Gly, beta-2 Arg16Gly, and beta-2 Gln27Glu ARs gene polymorphisms. The endpoint was the magnitude of left ventricular remodelling and correlations with appropriate ICD shocks. The Gln27Glu ARs gene polymorphism had higher rates of LV remodelling (P=0.0018). Gln27 homozygotes had a higher incidence of appropriate shocks for both ventricular fibrillation and tachycardia.

Clinical observational studies have documented certain patients experience reverse remodelling. Hence logically CRT in some individuals may have some effect on extracellular matrix turnover and the physiological pathways involved with this.

Marfella and colleagues analysed this and published in 2013.(180) Micro RNAs are non-coding RNAs which are linked to the regulation of cardiac structure and function. Due to the adverse cardiac remodelling, there may be dysregulation of the expression of micro RNAs.

The authors investigated the relationship between micro RNA expression, and LV reverse remodelling following CRT implantation.

A total of 81 patients made up the cohort. Micro RNA levels were measured in a healthy control group, age matched and disease matched (not for heart failure) and a heart failure population. At baseline, the HF population had a lower rate of expression of micro RNAs as compared to the healthy control group. (P<0.04). At 12 months 68 percent of the HF cohort (n=55) were classified as responders based on echocardiographic parameters. The levels of expression of certain micro RNAs were different between the responders and non-responders. The responders were characterised by higher expression of five miRNAs (MiRNA-26b-5p, miRNA-145-5p, miRNA-92a-3p, miRNA-30e-5p, and miRNA-29a-3p; P , 0.01 for all) as compared with non-responders. These micro RNAs have been linked to cardiac fibrosis and hypertrophy.

Hessel and co-workers investigated the effect of CRT on tissue matrix metalloproteinases, with particular attention to MMP-9.(181) This specific matrix metalloproteinase is felt to govern apoptosis and previously been found to be expressed in high levels in pathological disease states e.g. abdominal aortic aneurysms.

A series of 64 patients was followed up for six months and 72% of the cohort had LV remodelling. (>10 percent LVESV) This group had a significant reduction in circulating levels of MMP-9 (P=<0.01) and hence the suggestion is that reverse remodelling may be associated with an increased rate of extracellular matrix turnover.

Beyond the effect of specific pathways, CRT's effects have also been investigated on intracellular signalling.

It has been previously observed by Spragg and colleagues in 2003, that there was an imbalance between the expression of selective cardiac handling proteins and mitogen activated protein kinase.(182) The same group investigated this further in 2008, with the lead author being Chakir.(183) In the context of dyssynchronous contraction represented by LBBB on the surface electrocardiogram, the lateral wall showed an increase in p38 MAPK and $Ca^{2+}$-Calmodulin Kinase II activation and increased TNF-alpha which were both reversed with CRT.

Electrically myocytes when isolated from failing hearts suffer from prolonged action potentials.(184) This has been noted particularly in the lateral wall of the left ventricle, irrespective of aetiology.(185) CRT may shorten action potential duration in the lateral wall and therefore diminish the effect of prolonged action potentials in the lateral wall.

Another important mechanism noted in failing hearts is the abnormalities associated with calcium handling. Myocytes isolated from patients with heart failure demonstrate delays in the movement of intracellular calcium and altered intracellular kinetics. Beat to beat variation in calcium handling is influenced by both intracellular channels (L type $Ca^{2+}$ currents) and large scale $Ca^{2+}$ release through the sarcoplasmic reticulum by the phospholamban regulated SR Ca2+- ATPase. (SERCA 2A) CRT may restore normality to intracellular calcium movement and had some effect on regional variation.(186) However like most of the molecular field allied to the effects of CRT, the data is limited and the effect is not wholly understood nor characterised.

The effect on beta adrenoceptors has been discussed above, however beyond the cellular surface, abnormalities of G protein signalling allied to such receptors has also been documented.(187, 188) Analysis of adenylyl cyclase activity (cAMP) shows a reduction in patients with heart failure, CRT has been shown to upregulate cAMP levels.(186) Additional effects on G protein signalling have also been demonstrated with patients with CRT implants. G-proteins are inhibitory on the effects of beta adrenoceptor signalling. Pertussis toxin is inhibitory of G protein signalling, but when administered to myocytes following the application of CRT, had no effect.

The molecular, sub cellular and signalling fields with respect to CRT have been historically overlooked, but more attention is being paid to these mechanisms which underpin the macroscopic processes observed in some patients following CRT implantation. Further work is underway and much needed both in vivo studies and ex vivo with robust animal models which replicate human physiology. With the data thus far which has been published, it is clear that CRT does influence certain cellular pathways and expression of proteins.

## 1.11 Implementation of CRT

The body of evidence collected from the large randomised studies summarised above led to the rapid uptake of CRT within clinical guidelines in the UK, Europe and the United States.(22, 98)

All recommend CRT on the basis of the accrued evidence and suggest the consideration of implantation when the established selection criteria have been met. (LVEF <35 percent, QRS duration >120 milliseconds, optimal tolerated medical therapy and NYHA class II to IV therapy). However trial evidence does not reflect 'real-world' practice due to the inclusion criteria which often stipulate lack of co morbidity and younger age. Hence contemporary subgroups which are often clinically encountered are not represented in the literature e.g. the elderly, patients of female gender, those with co-morbidities (renal dysfunction, anaemia and diabetes mellitus) and those who have deteriorating left ventricular systolic function and have pre-existent pacing systems in situ. Hence since the uptake of CRT into the guidelines, several publications have released data from registries which actually reflect clinical practice. i.e. 'real world' practice.

British data is represented by the national audit of cardiac rhythm devices run by Heart Rhythm, United Kingdom (UK).(189) The most recent data is that from 2011 and primarily reflects number of CRT implants. The overall view is that CRT implantation rates have markedly increased from 2001 to 2011 but with significant country variation. See Figure 10.

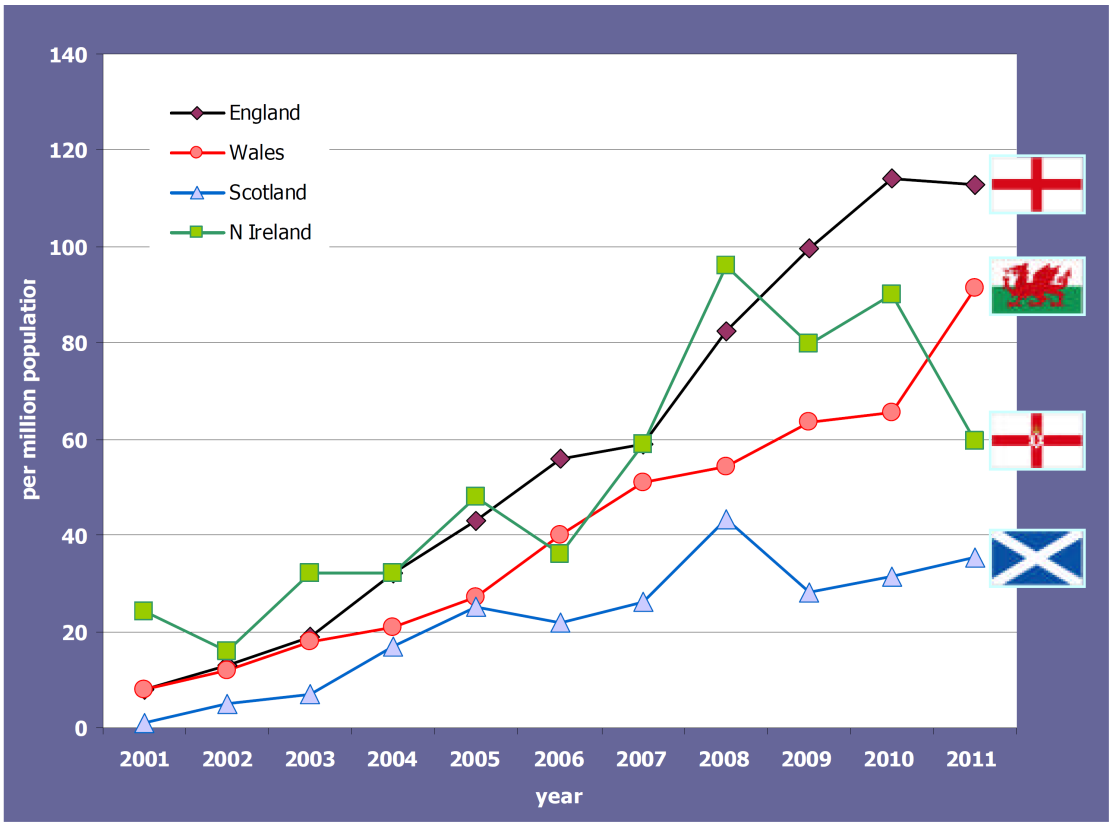



**Figure 10: Depicting rate of CRT implantation across the four individual countries which make up United Kingdom (England, Wales, Scotland and Northern Ireland). From UK National Audit of Heart Rhythm Devices(189)**

England has shown the largest increase in CRT implantation whereas the overall rate in Scotland has not increased over the same time period. The figures released by cardiac networks also demonstrate widespread geographical variability. The CRT implant rate varies in England from 70 per million in the North Trent Cardiac Network to a 180 per million in the Dorset Network. The mean is a 113 CRT implants per million (which is still under the target figure set by the British Society of Heart Failure and Heart Rhythm UK of 130 per million).

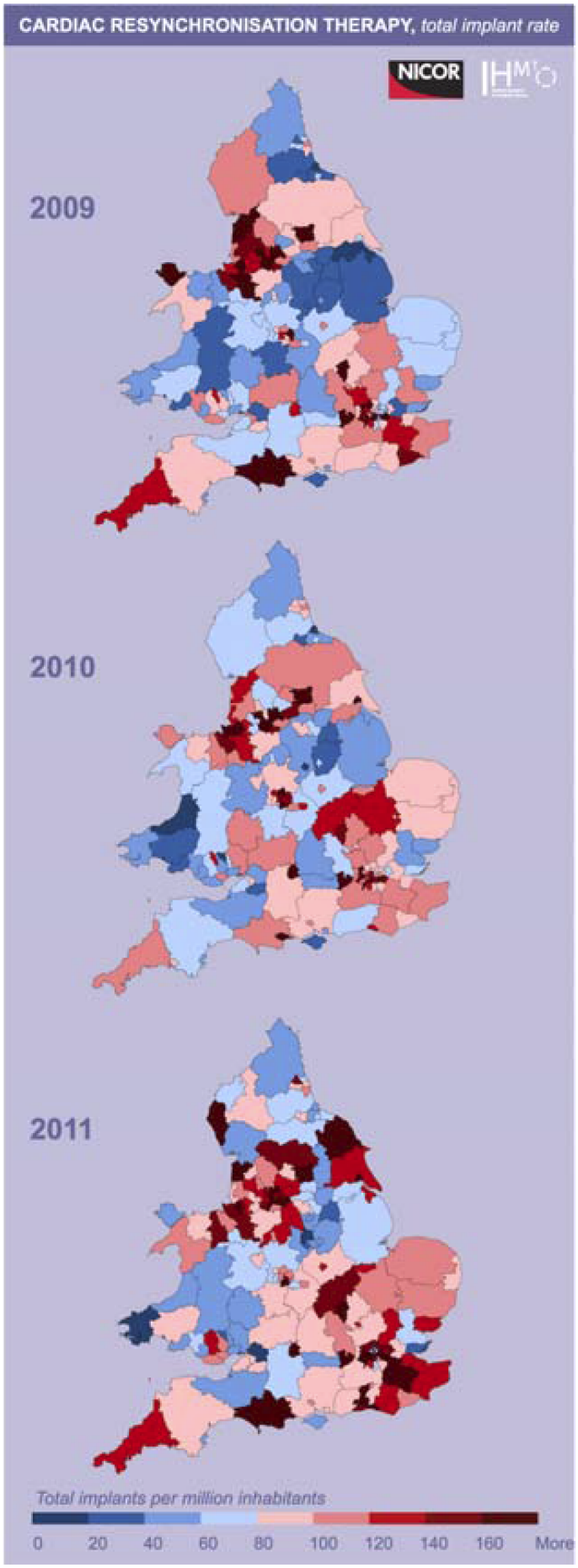



**Figure 11: Demonstrates geographical variation in CRT implant rates across England and Wales .From UK National Audit of Heart Rhythm Devices. Highest rates of implantation are represented by the darkest colours**

The increased numbers of CRT implants however have led to the UK becoming the 8th country in the European league table for CRT implantation. This was as compared to previous data which demonstrated the rate of CRT implant in the UK was lower than most of the rest of the Europe. In terms of indications, the data demonstrates that the majority (approximately 80 per cent) of implants fulfils criteria for CRT implantation and has prolonged QRS duration, reduced LVEF and are symptomatic. However there is a notable issue within the audit with regards to lack of data capture and there are significant amounts of missing data with regards to indications; with a rate of absent data of up to 60 percent. Hence conclusions regarding the validity of CRT implantations have to be interpreted cautiously.

The European experience with CRT has been documented by the European CRT survey chaired by Professor Dickstein and coordinated as a joint venture between the Heart Failure Association and European Heart Rhythm Association.(190) This was first published in 2009 and hence reflects the initial experience with CRT across the member countries of the European Society of Cardiology.

A total of 140 centres across 13 countries contributed data on 2638 patients. The median age of patients was 70 years of age (Interquartile range 62-76 years of age) and nearly a third (31 percent) of the cohort were aged >75 years of age. Prior to CRT implantation the mean LVEF was 27+/- 8 percent and the mean QRS duration was 157+/-32 milliseconds. The QRS duration was below 120 milliseconds in only 9 percent of cases. Approximately a quarter (26 percent) of the cohort underwent an upgrade of a preexistent pacing or ICD system to CRT capacity and 23 percent of the population had atrial fibrillation. Male patients of younger age with a prior ischaemic history were more likely to receive a CRT-D rather than CRT-P implant. The survey highlights regional variation in clinical practice and that the clinical use of CRT extended into areas with a paucity of literature e.g. the elderly, patients undergoing upgrade procedures with the addition of a LV lead and those with concomitant atrial fibrillation. All of these sub groups are under further investigation and require further clarification of the effects of CRT within these populations.

American data come from the ' Get with the Guidelines Programme' - a dedicated cardiac network of several hundred institutions spread across the continental United States. The programme was originally devised and supervised by the American Heart Association. The particular emphasis of the programme is to improve cardiovascular care via several

mechanisms, including guidelines, suggested clinical care bundles, recommendations, education and ongoing clinical audit.

Piccini and colleagues published on the most recent set of data in 2008 whereby they had analysed 33,898 patients from a period of 2005 to 2007.(191) 4201 patients were discharged with a CRT device in situ with 811 having received them as new implants on that admission. 10 percent of patients who received a CRT implant had a LVEF >35 percent. The survey documented widespread geographical variation and due to the structure of the American healthcare system patients attending tertiary academic centres were more likely to receive a CRT implant on that admission. The data also demonstrated significant rates of co morbidities - 10% of this cohort had a creatinine clearance of less than 35mls/min and 20% of patients had chronic obstructive pulmonary disease. Similar to other registry data described above, the American data indicates the extension of the application of CRT to other groups beyond those represented in the clinical trials.

# Chapter II:
# Aims and Hypotheses

## 2.1 Aims

The following aims will be tested within the four study chapters described later in the thesis.
1. To present the initial experience of a dedicated specialist heart failure pacing clinic.
2. To investigate whether the passage of patient with a CRT implant through a dedicated specialist heart failure pacing clinic results in higher rates of initiated and uptitrated evidence based therapies
3. Whether impedance cardiography is comparable to conventional echocardiographic methods of CRT device based optimisation
4. Whether impedance cardiography has sufficient reproducibility and reliability when compared to other methods of cardiac output monitoring in an intensive care/high dependency care setting.
5. Whether right ventricular dysfunction as assessed on cardiac magnetic resonance imaging prior to CRT implantation predicts clinical outcomes
6. Whether right ventricular dysfunction as assessed by cardiac magnetic resonance imaging prior to CRT implantation predicts left ventricular remodelling

## 2.2 Hypotheses

The following hypotheses will be tested within the study chapters and are presented below:
1. A dedicated specialised heart failure pacing clinic does result in increased doses of evidence based heart failure pharmacotherapies - 'Medical Optimisation'
2. Impedance Cardiography is comparable to conventional echocardiography for the adjustment of device based atrioventricular and ventriculo-ventricular delays - 'Device Optimisation'
3. Impedance Cardiography is a reproducible and reliable technique when assessing changes in haemodynamics in patients in intensive care following cardiac surgery
4. Right ventricular function as assessed by cardiac magnetic resonance imaging does predict clinical outcomes in patients undergoing cardiac resynchronisation therapy implantation
5. Right ventricular function as assessed by cardiac magnetic resonance imaging does predict the degree of left ventricular remodelling in patients undergoing cardiac resynchronisation therapy implantation

# Chapter III: General Methods

# General Methods

Within this thesis, the patients underwent a series of tests and questionnaires to ascertain their severity of HF. These included NYHA classification, Minnesota living with HF score, echocardiography, 6 minute walk test distance and venous blood sampling for serum uric acid levels and B-type natriuretic peptide. (BNP)

## 3.1 New York Heart Association Classification

The NYHA classification was devised to assess the patient's functional status.(192) Using a categorical system, the patient's ability to perform differing levels of physical activity is graded, usually by a physician. The symptoms have been previously been shown to correlate with the degree of LVSD and prognosis.(193, 194)

The grading system is described below:
NYHA I: No limitation in physical activity.
NYHA II: Slight limitation in physical activity
NYHA III: Marked limitation in physical activity
NYHA IV: Unable to carry out physical activity without discomfort. Symptoms at rest.

## Minnesota Living with Heart Failure Questionnaire (MLHFQ)

This is a 21 item questionnaire devised to assess physical symptoms of heart failure, psychological status and social aspects of a patient with heart failure.(195, 196) Each question is scored on a Likert scale from 0-5 and the total score is thus 105. A higher score indicates more symptoms and psychometric disturbance.(197) Conventionally it is used as a tool for documenting change in patient psychometric status over time. It has been used in several large randomised clinical trials involving drugs and cardiac pacing (including univentricular and bi ventricular systems).(198, 199) The original questionnaire was devised and validated within the United States, but has subsequently been validated and translated into several languages worldwide. Within the United Kingdom (UK), limited data are available but it has

been used as an assessment tool within several studies based within heart failure populations in the UK.(200, 201)

A copy of this questionnaire is included within the Appendix.

## Trans-Thoracic Echocardiography

Left Ventricular function was assessed by trans-thoracic echocardiography. (TTE) As described in the introduction, TTE has become a key part of the diagnostic and follow up process for patients with heart failure.

Its ease of use and widespread availability has meant that it is a routine examination for patients with heart failure. Using ultrasonic waves generated via a piezoelectric crystal, it is able to offer the ability to image the heart in real time. It does not involve radiation, nor invasive testing and is safe. It has been previously been demonstrated to be reproducible and enables the visualisation of intra-cardiac structures such as valves and chambers.

All echocardiography for this thesis was carried out by accredited trained professionals working in the Derek Gibson echocardiography laboratory at the Royal Brompton Hospital, London. All images were acquired either on Vivid 7 (General Electric, Andover, Massachusetts, US) or on iE33 (Phillips, Amsterdam, The Netherlands) with a multi-frequency transducer. The echocardiographer was blinded to the results of the other end point measures.

As per the American Society of Echocardiography guidelines, all LVEF measurements were calculated using the Biplane Simpson's technique.(202) This measured LVEF using a standardised format in the four chamber view and two chamber view. The accuracy of the measurement of LVEF is enhanced by choosing two planes which are perpendicular to each other. The measurement of LVEF via this technique is the suggested gold standard, however it is also recognised that there may be a reproducibility error with repeated measurement of such views.(203) Additionally, the echocardiographer also measured and recorded the left ventricular end systolic and end diastolic diameters. These were measured at rest, from the

cross sectional M- Mode recordings of the LV minor axis using the left parasternal long-axis view with the cursor at the tips of the mitral valve leaflets. The LV dimensions were taken at end-diastole and at end systole. The left atrial diameter was measured from the M-Mode recording from the left parasternal view at the level of the aortic valve.

During the routine echocardiographic study, co existent valvular disease was assessed. If mitral regurgitation was present, its severity was documented by using the colour Doppler of the regurgitant jet width at the level of the mitral valve. The regurgitant fraction was quantified using the recommendations from the American Society of Echocardiography for the assessment of valvular regurgitation.(204) Peak pulmonary artery pressure (PAP) was also recorded where possible. The technique was reliant on the patient having a degree of tricuspid regurgitation.

## 3.2 Six Minute Walk Test

The symptoms of heart failure are usually more severe on exertion. Symptoms such as shortness of breath and fatigue may not be prominent at rest or on minimal exertion but may be more apparent on mild – moderate exertion.

Exercise testing for patients with heart failure has been described over the past four decades. One option is to establish the patient's maximal oxygen ($MvO_2$) consumption via treadmill or ergonometric bicycle testing. Though it is a reproducible and reliable measure which is predictive of prognosis and the need for cardiac transplantation; it requires the use of trained personnel and complex equipment.

An alternative method which tests the patient's sub-maximal exercise tolerance in a standardised format is a six minute walk test. This was initially described in patients with respiratory disease; however two subsequent studies then described its application in patients with heart failure.(205-207) It was shown to be reproducible and reliable.(207)

It is also a prognostic marker in heart failure cohorts, and for patients undergoing implantation of cardiac resynchronisation therapy (CRT).(208-210) The 6 minute walk test has also been demonstrated to be able to predict long term mortality following CRT

implantation.(211) The data from Brugada's group indicates a pre CRT implantation six minute walking distance of 225m predicts long term mortality.
Within this thesis where used, the 6 MWT was performed according to one of its initial descriptions in patients with heart failure.(207) It was administered by two experienced observers familiar with the protocol. No encouragement was given to the patient during the 6 minutes. A walking track of twenty metres was marked out and the patients walked continuously from the start to the finish during the test period. Patients completed the course at their own pace. All tests were performed at least 2 hours after the administration of heart failure medication.

## 3.3 B-Type Natriuretic Peptide (BNP)

Previously described within the introduction, natriuretic peptides are released in response to myocardial stress. BNP is released by myocytes in response to raised ventricular filling pressures and volume overload. It should be noted that though BNP is specific for excluding heart failure, it has a limited sensitivity. BNP carries prognostic information for all aetiologies of heart failure and has been shown to be associated with adverse outcomes in patients undergoing CRT implantation.(212-214)

All BNP results quoted within this thesis, were collected and then subsequently analysed by the Department of Biochemistry, Royal Brompton Hospital, Royal Brompton & Harefield NHS Foundation Trust. A standardised assay was used for all samples. (Alere Triage BNP Assay, Alere Corporation, San Diego, California, US) All samples were processed on the same immunoassay system. (Beckman-Coulter Incorporated, Brea, California, US). The normal reference range for serum BNP for the duration of the studies performed within this thesis was <4 pmol/Litre.

## 3.4 Statistics

Statistical analysis was performed using SPSS version 19.0 for Microsoft Windows. (Chicago, IL) Continuous variables were expressed as a mean ± standard deviation (SD) and categorical variables were expressed as a percentage. Normally and non-normal distributed

variables were analysed with the appropriate statistical test depending on the statistical relationship under investigation. More complex statistics were performed under the supervision of a senior statistician. A p value $<0.05$ was deemed to be of statistical significance for all analyses.

# Chapter IV: A dedicated heart failure pacing clinic facilitates medical therapy optimisation in patients following Cardiac Resynchronisation Therapy

## 4.1 Introduction

Cardiac resynchronisation therapy (CRT) is a proven treatment in patients with symptomatic left ventricular systolic dysfunction (LVSD), on optimal tolerated medical therapy and a broad QRS duration.(22) It improves both morbidity and mortality in such patients.

Optimal medical therapy was an inclusion criterion for all trials with CRT. However there is a paucity of data in terms of medical therapy following CRT implantation. CRT, once implanted successfully, may improve haemodynamics, reduce central venous pressure, prevent symptomatic bradycardia and improve renal function.(99) All of these characteristics suggest that medical therapy following CRT implantation should be revisited.

Currently there are increasing numbers of CRT implants both in Europe and the United Kingdom (UK).(190) Due to limitations within healthcare infrastructure there is widespread geographical variation in the care of such patients following CRT implantation. The responsibility for uptitration or initiation of evidence based medical therapies may be devolved to a local general cardiologist, physician or primary care practitioner.

The aim of the present study was to present the initial experience of a dedicated specialist heart failure pacing clinic. We hypothesise that a dedicated service for these patients would lead to the improvement in both the initiation and uptitration of evidence based medical therapies for patients with heart failure.

## 4.2 Methods

### 4.2.1 Patient Selection & Management

A consecutive series of 148 patients who fulfilled standard criteria for implantation of CRT (Left Ventricular Ejection Fraction (LVEF) ≤ 35 percent, QRS duration >120ms in Left Bundle Branch Block Morphology (LBBB), NYHA Class III/IV or (II if they had a preceding decompensation episode in the last 12 months) were identified from the specialist heart failure pacing clinic at the Royal Brompton Hospital, London.(215) Prior to the consideration of CRT implantation, all patients had had efforts made for the uptitration of evidence based

pharmacotherapies. Patients were evaluated at baseline, one and six months post CRT implantation (Figure 12). Data were retrieved from hospital records, electronic, echocardiographic systems and the pacing records.

### 4.2.2 Medical Therapy

At every clinic visit, the patients' medication status was recorded. As per current guidance wherever possible; evidence based pharmacotherapy was uptitrated to target doses with monitoring of renal function and blood pressure.(10) Following CRT implantation, pharmacotherapies were reconsidered for initiation and where appropriate were started.

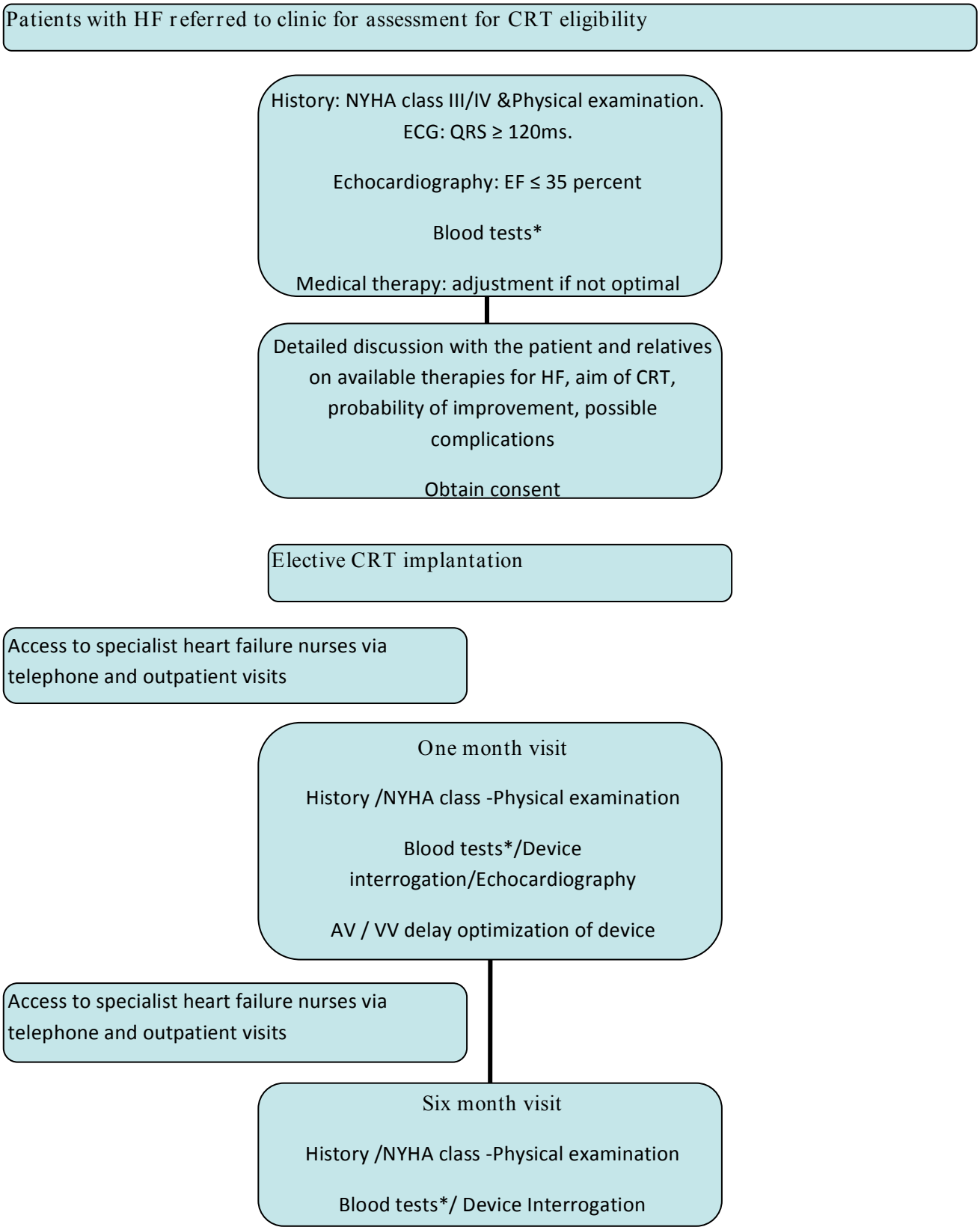



**Figure 12: Demonstrating Patient Pathway through the clinical protocol at baseline, 1 month and 6 month intervals. * Blood Tests = Venous blood sampling for full blood count, renal function and electrolytes and B-type natriuretic peptide.**

### 4.2.3 Device Implantation

All CRT implants were performed in a standardised manner. The left ventricular epicardial lead was implanted using established techniques into a lateral or postero-lateral branch of the coronary sinus. Right atrial and ventricular leads were implanted as per usual techniques. The type of CRT device implanted (i.e. CRT-P or CRT-D) was determined by the patient's clinical characteristics. The final lead position was confirmed by peri-procedural fluoroscopy and chest radiography 24 hours post procedure.

### 4.2.4 Echocardiography

All patients underwent transthoracic echocardiography at baseline, one and six month's clinic visits.

Echocardiography was performed by accredited cardiac physiologists using either GE (Vivid 7,GE Vingmed Ultrasound AS, Horten, Norway) or Philips (iE33; Philips Ultrasound, Bothell, WA) systems.

Standardised 2D and Doppler echocardiography were performed on each individual at baseline, one and six month visits. Cardiac dimensions, the presence of valvular pathology and left atrial size were all recorded. LVEF was calculated using Biplane Simpson's technique. At the one month visit, all patients underwent atrio-ventricular (AV) and ventriculo-ventricular (VV) optimisation using previously reported methodologies.(135)

### 4.2.5 Patient Education

Specialist heart failure nurses (HFSN) provided patient education with regards to aetiology, medical and device based therapy and psychosocial support. Between clinical visits, patients were encouraged to contact the HFSN team to discuss further physical or psychosocial issues.

### 4.2.6 Ethics

The study was ethically approved by the hospital ethics committee. (05/Q0404/121) The study complied with the principles of the Declaration of Helsinki.

### 4.2.7 Statistical Analysis

Statistical analysis was performed using SPSS version 19.0 for Microsoft Windows. (Chicago, IL) Continuous variables were expressed as a mean ± standard deviation (SD) and categorical variables were expressed as a percentage. Differences in variables at months 1 and 6 as compared to baseline were tested by Student's paired t-test for normally distributed variables or by Wilcoxon sign test for non-normally distributed ones. Differences between different groups were tested either by the Student's t-test or the Mann-Whitney test for normally and non-normally distributed variables, respectively. Chi-square test was used for comparison between categorical variables. Related categorical variables were compared using the McNemar test. A p value <0.05 was deemed to be of statistical significance for all analyses. Data were censored in the case of absence of follow up data or death or heart failure hospitalisation prior to the scheduled clinic visits.

## 4.3 Results

### 4.3.1 Demographics

The baseline demographics for the cohort are described in Table 3. Mean age at CRT implantation was 67 ± 13 years, with n= 42 (28 percent) of the cohort aged greater than 75 years old. The majority of the cohort were male; n=118 (79 percent) and received CRT-D implants n=114 (76 percent). Prior to CRT implantation the mean QRS duration was 164±29 milliseconds, mean LVEF 25± 7 percent and mean NYHA classification 2.9 ± 0.6.

### 4.3.2 Medical Therapy

Heart failure pharmacotherapy rates are described in Table 4. The rate of beta blocker (BB) prescription rose from 69 percent at baseline to 83 percent at 6 months (p=0.004). The numbers of patients on ≥50 percent of target dose (TD) rose from 32 percent to 61 percent at six months (p<0.0001). Angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers (ACEI/ARB) prescription rose from 91 percent at baseline, to 96 percent at one month following CRT implantation and 98 percent at six months following implantation. (p=0.06) There was a reduction in the prescription rate of loop diuretics and digoxin from 82 percent to 77 percent (p=0.42) and 18 percent to 13 percent (p=0.77). The rate of

anticoagulation with warfarin rose over the 6 month period from 30 percent at baseline to 42 percent at six months (p=0.001).

### 4.3.3 Change in clinical and echocardiographic variables

Changes in clinical and echocardiographic variables are demonstrated in Table 4. NYHA class improved both as a continuous and categorical variable. Initial mean NYHA class was 2.9±0.6 which improved to 1.9±0.8 at six months ($p<0.0001$). LVEF also rose significantly over the six months from 25±7 percent to 33±12 percent ($p<0.0001$). All patients had levels of >92 percent of biventricular pacing at initial follow up.

### 4.3.4 Follow Up

The series included 148 patients at baseline, however a total of 126 (85 percent) patients attended one month and 136 (92 percent) attended six month appointments respectively. All bar a solitary patient survived to the six month clinic appointment. All patients were followed up in general heart failure clinics following discharge from the structured CRT clinic protocol. Following a median follow up period of 41.8 months (Interquartile range 20 months to 58.1 months), 36 (24 percent) of the cohort had died.

## 4.4 Discussion

This study demonstrates that a structured heart failure pacing clinic model can facilitate the initiation and uptitration of evidence based pharmacotherapies. The rates of ACEI/ARB, BB and warfarin prescription rose during the initial six months following CRT implantation.

Current national and international guidance recommend CRT is only considered in symptomatic individuals with a broad QRS duration who are on optimal medical therapy.(11, 22) However there are very limited data available in the post implant cohorts. A recent document issued by the European Heart Rhythm Association (EHRA) and the American Heart Rhythm Society (HRS) suggests that heart failure pharmacotherapies should be uptitrated in the post CRT implant. However this is a consensus view agreed upon by leading cardiologists and electrophysiologists in the field. The consensus statement points out that

there is lack of data in this area and the need for further investigation.(99) Prior to implantation the rates of BB and ACEI/ARB usage were 72 percent and 85 percent respectively in CARE-HF, 68 percent and 89 percent in COMPANION and 96 percent for both in REVERSE.(5, 6, 96) However registry data demonstrate a lower rate of prescription. The European CRT survey describes clinical practice in relation to 2438 implants across thirteen European countries. The data showed that 84 percent of the cohort were on BB and 91 percent were on ACEI/ARB at the time of discharge. US data shows similar trends with a rate of ACEI/ARB usage in the IMPROVE-HF cohort of 79 percent.(216)

The reasons behind suboptimal levels of heart failure pharmacotherapies are varied. These include adverse physiological effects; beta antagonist mediated symptomatic bradycardia, ACEi/ARB mediated deterioration in renal function and orthostatic hypotension. These potential effects on physiology may be addressed by CRT. A functioning bi-ventricular system will prevent symptomatic bradycardia. CRT may also improve renal function in some patients. The exact mechanisms for this remain unclear but may be due either to an increase in renal perfusion or a reduction in central venous pressure.(217) Ultimately the potential effects of CRT mean that a previously trialled medication which was not tolerated should be reconsidered following successful CRT implantation.

This study adds to the currently limited data which exist for medical therapies following CRT implantation. Within this study which focussed on a specialist heart failure pacing clinic model, supervised by consultant cardiologists with expertise in heart failure and device management, the rates of evidence based therapies rose at 6 months following CRT implantation. The rate of absolute BB usage rose from 69 percent to 83 percent at 6 months. (See Figure 13) ($p=0.004$) The amount of patients on greater than 50 percent of target dose also rose over the same time period from 32 percent to 61 percent ($p<0.0001$). Though non-significant the rates of ACEI/ARB usage also rose over the six month period; from 91 percent to 98 percent. The lack of significance reflects the high rate of ACEI/ARB usage at baseline. The rates of digoxin and loop diuretics initially fell ($p<0.001$) but then rose subsequently by six months. This may be explained by an initial beneficial effect of CRT in terms of symptomatic response. However six months following CRT implantation it may be that the initial positive effects have receded or higher rates of atrial fibrillation have been detected. The rate of warfarin usage also rose significantly within the cohort over six months from 30 percent to 42 percent ($p=0.001$). Left ventricular systolic dysfunction is an established risk

factor for thrombo-embolic stroke within patients with atrial fibrillation.(218) Modern CRT devices are sophisticated and are capable of storing prolonged periods of rhythm data. Hence following implantation an active CRT device with accompanying device interrogation may detect higher rates of atrial arrhythmias. Once documented, patients should be considered for anticoagulation to minimise their thrombo-embolic risk.(219)

Limited data exists with patients in the post CRT period and medical therapy. Mullens and colleagues have presented the experience in 75 patients via a dedicated CRT clinic.(149) Using a structured clinical protocol, the authors identified 24 percent of patients at the time of implantation were not on evidence based pharmacotherapies. Altman and colleagues describe the experiences of a differing clinical protocol located within another tertiary centre in the United States.(150) Within this observational study, a potential area of identifiable improvement was the prescription of HF pharmacotherapies.

Current guidance suggests that uptitration of pharmacotherapies should be performed in all patients with LVSD. This includes patients undergoing CRT implantation, particularly as they are both symptomatic and have severe levels of LVSD. The studies performed with these agents suggest that patients should be uptitrated to target doses. Limited trial data exists for such suggestions, but clinical data are more suggestive that those patients who remain on suboptimal doses, especially those at less than <50 percent target dose have adverse clinical outcomes.(220) Due to these statistical relationships and as per current guidelines, HF therapies were uptitrated to target doses in this population.

## 4.5 Limitations

This study represents the initial experience of a specialist heart failure pacing clinic model located within a tertiary centre within the United Kingdom. Hence the referrals for consideration for device therapy were from secondary care and not primary care. This may have led to referral bias. However the demographics of the cohort are consistent with other clinical registry data within the field.

It is a single centre study with relatively low numbers of patients. The study is retrospective in design and hence the data utilised within it reflects that of a clinical service. In terms of

echocardiography, a number of accredited professionals carried out imaging studies and hence no appropriate measures of variance can be performed. Although the doses of prescribed HF pharmacotherapies were recorded, there were no measures of concordance. Hence it is assumed patients were compliant with the recommendations for concordance.

This study is a cohort study with no control group, but without a structured protocol and clinical recovery it is more unlikely that primary care follow up would have achieved an uptitration in pharmacotherapies.

The study lacked an un-paced control group, the study of whom is no longer possible with the approved guidelines for the implementation of CRT exist. Such a group would offer a control group in which to compare effect.

## 4.6 Conclusion

This study describes a dedicated heart failure pacing clinic protocol for the uptitration of evidence based HF pharmacotherapy following CRT implantation. The initial results presented within the study are suggestive that such an approach with subsequent uptitration and initiation of pharmacotherapies may represent one model of care for such patients this as compared to the tendency to maintain current dosages in conventional practice. Further prospective work needs to be carried out in this area to determine whether uptitration of pharmacotherapies in patients following CRT translates into improved clinical outcomes.

| | *Patients n=148* |
|---|---|
| Age (years) | 67±13 |
| Age >75 years (%) | 42(28) |
| Gender (M/F) (%) | 118(79)/30(21) |
| Left ventricular ejection fraction (%) | 25±7 |
| NYHA class (mean +/- SD) | 2.9±0.6 |
| NYHA II (%) | 26(17) |
| NYHA III (%) | 94(64) |
| NYHA IV (%) | 28(19) |
| Ischemic aetiology (%) | 75(50) |
| CRT-D/P (%) | 114(76)/36(24) |
| Diabetes mellitus (%) | 34(23) |
| Hypertension (%) | 35(23) |
| Baseline rhythm (%) | |
| Sinus rhythm | 98(67) |
| Atrial fibrillation/atrial flutter | 37(25) |
| Paced | 5(3) |
| Complete heart block | 8(5) |
| QRS duration (ms) (Mean +/- SD) | 164±29 |
| Systolic BP (mmHg) (Mean+/- SD) | 117±19 |
| Diastolic BP (mmHg) (Mean +/-SD) | 70±15 |

**Table 4:Baseline demographics; NYHA; New York Heart Association Classification; CRT-D; Cardiac Resynchronisation Therapy and Defibrillator; CRT-P; Cardiac Resynchronisation Therapy and Pacemaker; BP; Blood Pressure**

| | Baseline | Month 1 | P value* | Month 6 | P value* |
|---|---|---|---|---|---|
| NYHA class | 2.9±0.6 | 2.0±0.6 | **<0.0001** | 1.9±0.8 | **<0.0001** |
| LVEF % | 25±7.0 | 31±12 | **<0.0001** | 33±12 | **<0.0001** |
| LVEDD (cm) | 6.7±1.0 | 6.4±1.0 | **0.042** | 6.6±1.1 | 0.380 |
| Systolic BP (mmHg) | 117±19 | 118±22 | 0.421 | 116±19 | 0.896 |
| Diastolic BP (mmHg) | 69±12 | 72±10 | 0.133 | 70±11 | 0.526 |
| Haemoglobin (mg/dL) | 13.0±1.6 | 13.1±1.4 | 0.499 | 13.2±1.4 | 0.303 |
| Urea (mmol/L) | 10.2±5.7 | 10.4±6.1 | 0.886 | 10.4±5.1 | 0.878 |
| Creatinine (µmol/L) | 122±47 | 118±45.7 | 0.529 | 119±39 | 0.701 |
| BNP (pmol/L) | 135±150 | 112±151 | 0.301 | 110±92 | 0.091 |
| AV delay (ms) | 128±25 | 124±36 | 0.302 | 126±28 | 0.570 |
| B blockers % | 69 | 79 | 0.078 | 83 | **0.004** |
| ≥50% TD | 32 | 37 | 0.180 | 61 | **<0.001** |
| ACEi/ARBs % | 91 | 96 | 0.344 | 98 | 0.065 |
| ≥50% TD | 71 | 76 | 0.263 | 82 | 0.185 |
| Aldosterone antagonist % | 60 | 65 | 1.000 | 66 | 0.824 |
| Digoxin % | 18 | 4 | **<0.001** | 13 | 0.424 |
| Loop diuretic % | 82 | 35 | **<0.001** | 77 | 0.774 |
| Thiazide % | 8 | 4 | 0.289 | 11 | 0.18 |
| Warfarin % | 30 | 34 | 0.454 | 42 | **0.001** |

**Table 5:Changes in echocardiographic and clinical variables over 6 months. NYHA (New York Heart Association); LVEF (Left Ventricular Ejection fraction); LVEDD (Left-Ventricular End-diastolic Diameter); BP (Blood Pressure); BNP (B type Natriuretic Peptide); AV (Atrio-ventricular); TD (Target Dose)* p values represent paired T tests comparing values at follow up with baseline**

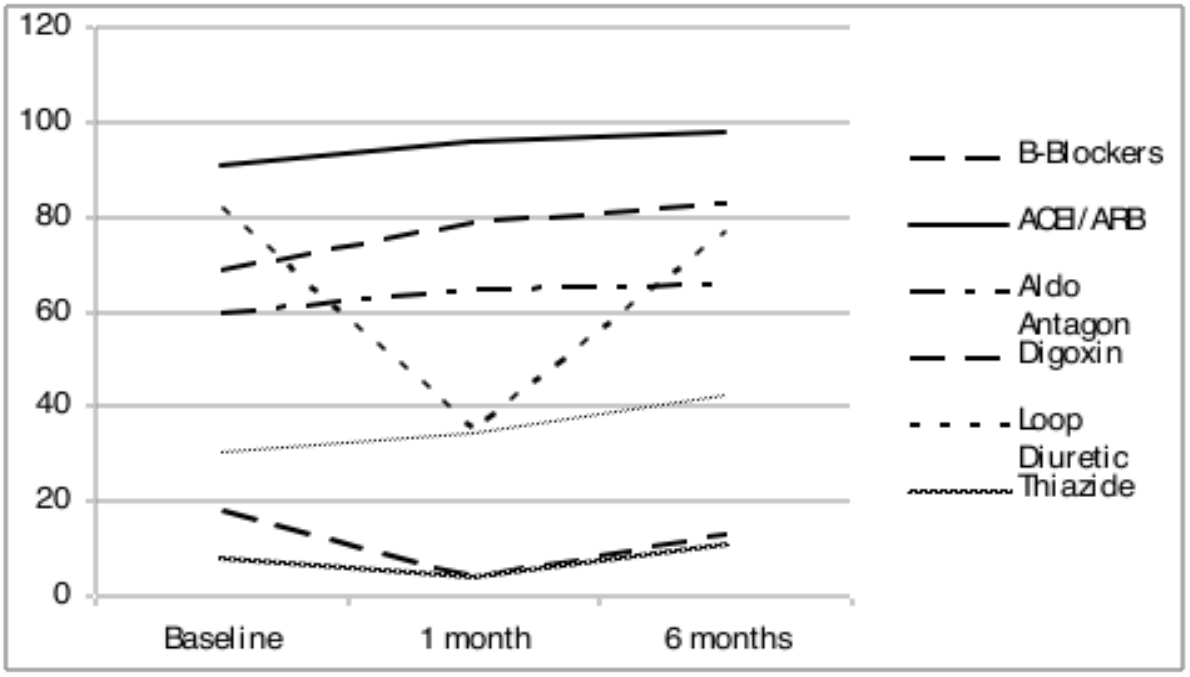



**Figure 13:Demonstrates changes in heart failure pharmacotherapies within the cohort over the 6 month period.**

# Chapter V: Haemodynamic Optimisation of Cardiac Resynchronisation Therapy - optCRT Study

## 5.1 Introduction

Cardiac Resynchronisation Therapy (CRT) is an established device based treatment for patients with symptomatic left ventricular systolic dysfunction, a broad QRS duration and on optimal tolerated medical therapy.(10) Despite documented beneficial effects upon morbidity and mortality, a minority of recipients do not derive the anticipated clinical benefit.

Previous explanations for such lack of benefit have included left ventricular dyssynchrony, position of left ventricular lead, age, impairment of renal function and the extent and distribution of myocardial scar.(121, 212, 221) The most recent guidance in the area is from the European Society of Cardiology, published in 2013. This suggests that all patients who fail to improve clinically following CRT implantation should be considered for device based optimisation i.e. adjustment of the atrioventricular (AV) and ventriculo-ventricular (VV) intervals.(22)

Both the rationale behind adjustment of AV and VV intervals and potential methods of optimisation have been covered in depth in Chapter I- Introduction. Amongst the non invasive techniques, impedance cardiography has been previously studied. Tse and colleagues in 2003, evaluated the role of impedance cardiography (ICG) in six individuals. ICG was used to optimise the AV delay, the results were then compared to those derived from transthoracic echocardiography. A range of values was evaluated and the optimal AV interval was identical in 5/6 patients (83 percent) (222) Braun and colleagues analysed data from a larger series published in 2005. Using 24 patients, the optimal AV delay was again evaluated using ICG and conventional echocardiographic methods. In terms of the identification of optimal AV delay there was a degree of positive correlation between the two methods. ($r=0.74$; $p<0.001$).(223) Heinroth, in 2007, also evaluated the performance of ICG in the optimisation of AV and VV intervals in 46 patients undergoing CRT implantation. Mean cardiac output rose from baseline following ICG optimised AV and VV intervals to 4.86+ 1.1L/min ($P=0.05$).(224) This pilot study was devised to compare non-invasive cardiac output monitoring (NICCOMO) based optimisation versus echocardiographic techniques on non-subjective symptomatic endpoints including 6 minute walk test distance, B type natriuretic peptide and quality of life scores in a non-inferiority trial design.(225)

## 5.2 Methods

### 5.2.1 Setting and Patient Population

Between January 2010 and April 2012, 44 patients were assessed for inclusion within this study. All potential participants within the study were identified from the dedicated heart failure pacing clinic within the institution. The institution was a tertiary university teaching hospital within London, United Kingdom.

All patients fulfilled contemporary guidance for the implantation of CRT.(215) This included optimal tolerated heart failure pharmacotherapy, broad QRS duration on surface electrocardiogram (>120 milliseconds, preferably in left bundle branch block morphology (LBBB)), a left ventricular ejection fraction (LVEF) of <35 percent and the presence of symptoms (New York Heart Association (NYHA) grade II-IV).

The study gained ethical approval from the local ethics committee (05/Q0404/121). The study protocol complied with the Declaration of Helsinki and all participants gave fully informed written consent.

### 5.2.2 Study Protocol

Paired data was collected for all study participants. Patients were optimised either via echocardiographic techniques (trans-mitral velocity time integral (VTI) and left ventricular outflow tract VTI) or by optimisation with the NICCOMO device. CRT devices were optimised at one month and paired data was collected at one and three months on clinical, echocardiographic, biochemical and functional indices. The study CONSORT diagram is demonstrated in Figure 14.

The primary endpoint for the study was a comparison of 6 minute walk test (6MWT) difference; secondary endpoints were NYHA class, Minnesota living with Heart Failure (MHLHFQ) scores, B-type natriuretic peptide levels and LVEF.

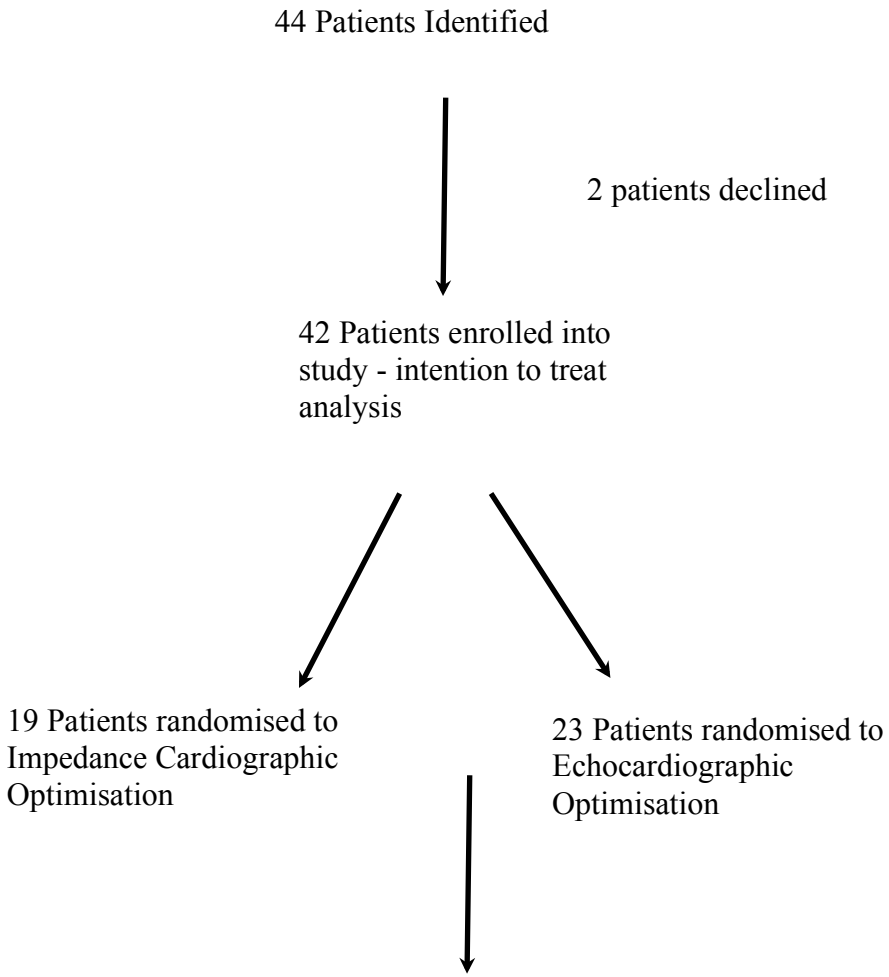



**Figure 14: CONSORT trial flow diagram depicting recruitment and patient pathway through the study**

### 5.2.3 Cardiac Resynchronisation Therapy Implantation

All patients received CRT implants in a standardised manner by a single experienced consultant operator (Dr Rakesh Sharma, Consultant Cardiologist and MD Supervisor). A selection of leads and generator boxes were used from the major manufacturers of CRT devices. All permitted alteration of both AV and VV intervals. A lateral or postero-lateral venous tributary of the greater cardiac vein was selected wherever possible. The final left ventricular lead position was confirmed in the catheter laboratory in multiple planes using fluoroscopy. Chest radiography was performed the following day in both posterior-anterior

and lateral views. All left ventricular leads were implanted successfully and there were no lead displacements within this cohort.

### 5.2.4 NICOMMO Device

The commercially available NICOMMO device (Medis, GmbH Ilmenau, Germany) was used to perform biosensor mediated impedance cardiography (ICG). Four surface electrodes were placed in the configuration demonstrated in Figure 15. Following the administration of small amounts of alternating current and using the algorithmic interpretation of Ohm's law, ICG can calculate bioreactive impedance using the pulsed blood volume in the ascending aorta.
The NICCOMO device can calculate cardiac output, cardiac index, stroke volume and systemic vascular resistance over a twenty beat cycle and has been previously validated.(226)

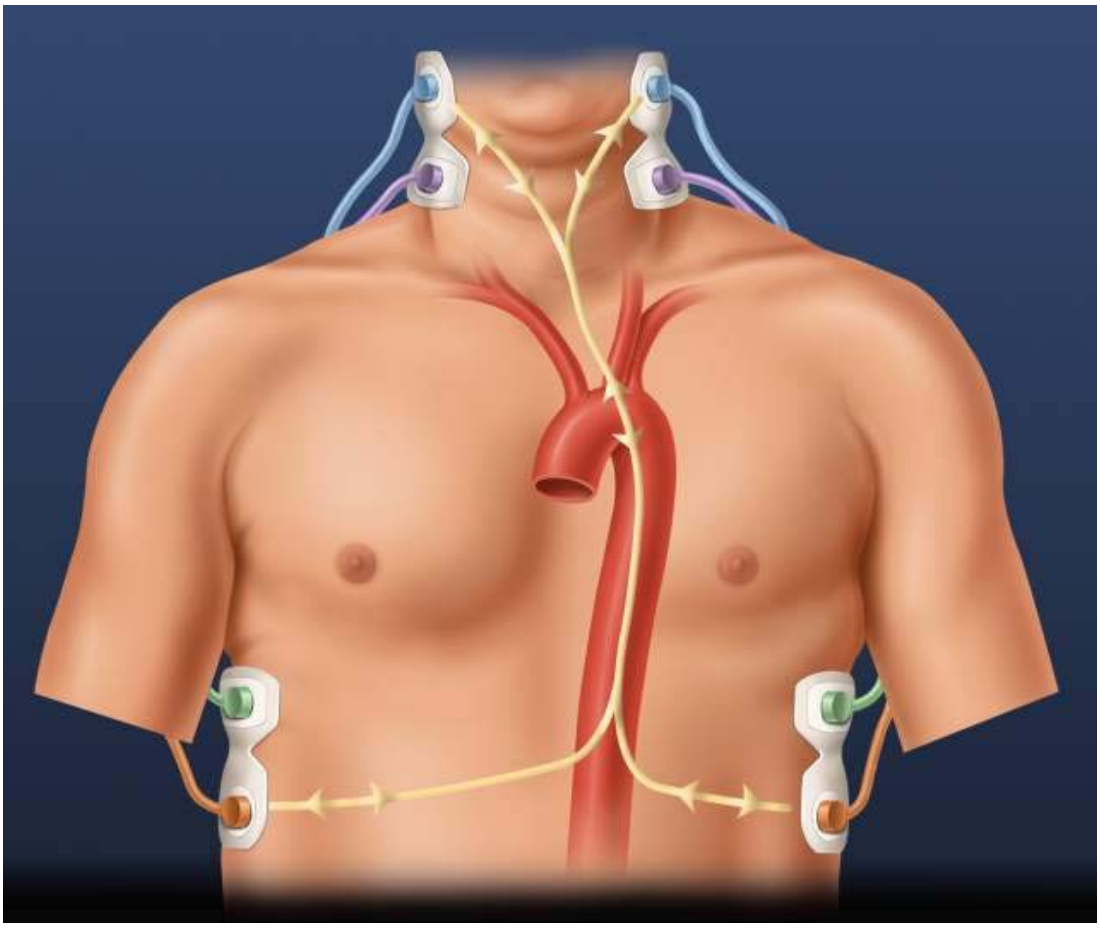


**Figure 15: Demonstrates the configuration of surface electrodes for a recording using the NICCOMO device**

### 5.2.5 Optimisation Procedure

Patients were randomised to either echocardiographic or NICCOMO based optimisation via a randomisation protocol. Due to physical limitations, patients and the investigator could not be blinded to the method of optimisation and hence the study was performed as a randomised non blinded study.

For both forms of optimisation, a range of AV delays was assessed (80 milliseconds to 200 milliseconds) and a range of VV delays also tested. (Right Ventricle Pre-Excited +60 milliseconds to Left Ventricle Pre-Excited +60 milliseconds). Prior to recording any measurements, a minute was allowed to elapse. All recordings took place in a quietened room with the patient recumbent. For patients in atrial fibrillation only the VV delay was optimised. For all patients wherever possible AV delay was performed first. The pacing mode for all participants was placed in DDD mode at 70 beats per minute except for those patients in atrial fibrillation who were placed in VVI mode at 70 beats per minute.

### 5.2.6 Echocardiography Optimisation

To guide the adjustment of AV and VV delays the previously described techniques of transmitral VTI and LVOT VTI were used.(135, 227) The ideal AV delay was identified by the maximal transmitral VTI and E/A wave morphology. The A wave was reviewed for potential truncation and encroachment into diastole. The ideal VV delay was identified by the maximal LVOT VTI.

### 5.2.7 NICOMMO (Impedance Cardiography) Optimisation

All patients receiving an ICG optimisation did so after a period of rest within the room for 10 minutes. This was to minimise any external stimuli which may have induced sympathetic activation.
After each change in pacing mode, the ICG module would self analyse 20 consecutive beats and calculate a mean cardiac output. The ideal AV and VV delays were those with the maximal cardiac output. No further echocardiography was performed within these patients to optimise their pacing systems.

### 5.2.8 Echocardiography

Routine 2-D and Doppler echocardiography were performed on all study participants at one month and three month intervals. All echocardiography was performed with commercially available systems (Vivid 7, General Electric Healthcare, Milwaukee, WA, US or ie33 Philips Medical Systems, Bothell, WA, US). Left ventricular measurements including dimensions, volumes and ejection fraction were all recorded as per the American Society of Echocardiography guidelines.(202) The Biplane Simpson's technique was used to calculate all LVEF.

### 5.2.9 Statistical Analysis

All statistical analysis was performed using SPSS version 20 (Integrated Business Machines Corporation, Armont, NY, US). Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as a number and percentage.

Differences in continuous variables were tested by the Student's paired t –test for normally distributed variables. Differences between groups were tested by the Student's t-test or the Mann-Whitney U test for normally and non-normally distributed variables respectively. Fisher's exact test was used for comparisons between categorical variables. For all analysis a p value $<0.05$ was deemed statistically significant.

### 5.2.10 Power Calculation

From a previous dataset of patients who have undergone CRT through the dedicated heart failure pacing clinic the mean 6MWT was 242m with a standard deviation of 82m. To detect a clinically significant difference of twenty five percent between the two groups with a power of 80 percent and a significance level of 5 percent we would require a sample size of 41 patients in each group. This number of patients would also be sufficient to demonstrate that the ICG method of optimisation is non inferior to that of echocardiographic optimisation.

## 5.3 Results

### 5.3.1 Baseline Demographics

A total of 44 patients were approached to participate in the study; 2 patients declined participation due to geographical distance from the institution. Hence 42 patients were enrolled. A solitary patient declined to return for follow up but was included in analysis on an intention to treat basis.

Pre- CRT implantation characteristics are demonstrated in Table 5. Study baseline characteristics are demonstrated in Table 6. The population prior to CRT implantation had a mean LVEF of 27.7 ± 7.8 percent, with a mean QRS duration of 156.5 ± 24.5 milliseconds. The rate of medical therapy in the cohort prior to CRT implantation was 33 (79 percent) on ACEI/ARB, 24 (57 percent) on beta blocker and 19 (45 percent) on an aldosterone antagonist.

At baseline there were no significant differences between the group of patients who underwent echocardiographic and impedance cardiographic optimisation save for uric acid levels.

| ***Characteristic*** | All Patients (n=42) |
|---|---|
| NYHA | 2.6 ± 0.8 |
| ACEI/ARB n (%) | 33 (79%) |
| >50% TD ACEI/ARB n (%) | 18 (43%) |
| β-Blockers | 24 (57%) |
| >50%TD β- Blockers n (%) | 10 (24%) |
| Aldosterone Antagonists n (%) | 19 (45%) |
| Loop Diuretics n (%) | 31 (73%) |
| Systolic Blood Pressure (mmHg) | 117.3 ± 21.8 |
| Diastolic Blood Pressure (mmHg) | 69.2 ± 11.7 |
| Left Ventricular Ejection Fraction (%) | 27.7 ± 7.8 |
| Left Ventricular End Diastolic Diameter (centimetres) | 6.3 ± 0.8 |
| **QRS duration** | 156.5 ± 24.3 |

**Table 6: Pre implantation baseline characteristics of the optCRT study population**

| *Characteristic* | *All Patients (n=42)* | *TTE Optimisation (n=23)* | *ICG Optimisation (n=19)* |
|---|---|---|---|
| Age (Years) | 66.7±12 | 66.4 ± 10.4 | 67.3 ± 14.1 |
| NYHA | 1.8 ± 0.6 | 2.0 ± 0.6 | 1.7 ± 0.7 |
| ACEI/ARB n (%) | 40 (95) | 23 (100) | 18 (95) |
| >50% TD ACEI/ARB n (%) | 26 (62) | 17 (74) | 12 (63) |
| β-Blockers | 37 (88) | 21 (91) | 16 (84) |
| >50%TD β- Blockers n (%) | 14 (33) | 6 (26) | 7 (39) |
| Aldosterone Antagonists n (%) | 24 (57) | 16 (70) | 8 (42) |
| Loop Diuretics n (%) | 29 (69) | 16 (70) | 13 (68) |
| Dilated Cardiomyopathy n (%) | 24 (57) | 12 (52) | 12 (61) |
| Ischaemic Cardiomyopathy n (%) | 18 (43) | 11 (48) | 7 (39) |
| Diabetes Mellitus n (%) | 9 (21) | 7 (30) | 2 (10) |
| Hypertension n (%) | 7 (17) | 5 (22) | 2 (10) |
| Sinus Rhythm n (%) | 31 (74) | 18 (78) | 13 (69) |
| Atrial Fibrillation n (%) | 11 (26) | 5 (22) | 6 (32) |
| Systolic Blood Pressure (mmHg) | 117.1 ± 18.5 | 113.2 ± 16.5 | 121.4 ± 20.7 |
| Diastolic Blood Pressure (mmHg) | 71.9 ± 12.5 | 72.7 ± 12.2 | 70.1 ± 12.8 |
| Haemoglobin (g/Dl) | 12.6 ±1.7 | 12.4 ± 1.9 | 12.8 ± 1.3 |
| Urea (mmol/L) | 9.4± 4.6 | 9.6 ± 3.9 | 9.2 ± 5.4 |
| Creatinine (mmol/L) | 105.2 ± 40.0 | 104.6 ± 31.5 | 106.8 ± 50 |
| B-Type Natriuretic Peptide (ρmol/L) | 105.9 ± 119.3 | 127.8 ± 114.8 | 85.6 ± 125.4 |
| Uric Acid (μmol/L) | 427.6 ± 136.5 | 472.9 ± 114.1 | 380.6 ± 148.4 |
| 6 Minute Walk Test (Metres) | 307.6 ± 106.3 | 304.7 ± 114.3 | 310.1 ± 99.7 |
| Left Ventricular Ejection Fraction (%) | 33.6 ± 10.1 | 31.9 ± 9.6 | 35.2 ± 10.9 |
| Left Ventricular End Diastolic Diameter (centimetres) | 6.1 ± 0.9 | 6.2 ± 0.9 | 6.0 ± 0.9 |

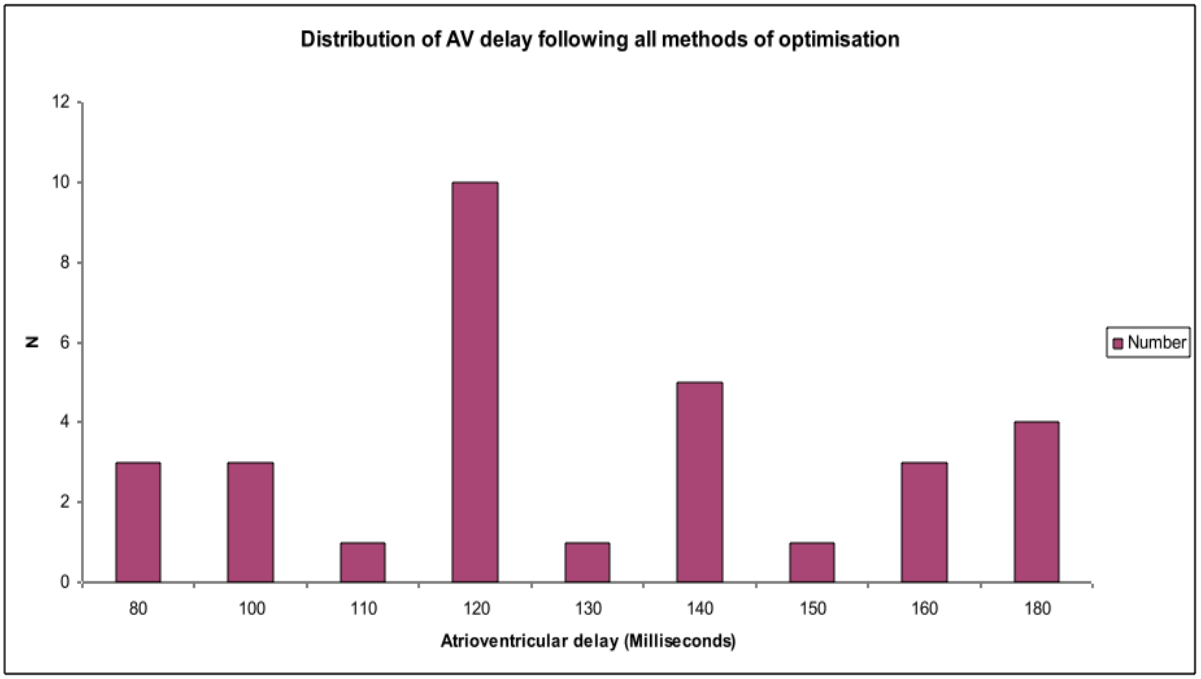
**Table 7: Baseline Entry of Study Characteristics (1 Month following implantation of cardiac resynchronisation therapy); TTE; Trans thoracic echocardiogram; ICG; Impedance Cardiography; NYHA; New York Heart Association; TD; Target Dose**

| *Variable* | *TTE Baseline* | *TTE FU* | *P Value* | *ICG Baseline* | *ICG FU* | *P Value* |
|---|---|---|---|---|---|---|
| BNP (ρmol/L) | 127.8 ± 114.8 | 120.7 ± 162.3 | P=0.95 | 85.6 ± 125.4 | 55.2 ± 54.3 | P=0.27 |
| 6 MWT (metres) | 304.7 ± 114.3 | 349.2 ± 101.2 | P=0.23 | 310.1 ± 99.7 | 365.2 ± 100.4 | P=0.15 |
| NYHA | 2.0 ± 0.6 | 1.9 ± 0.7 | P=0.49 | 1.7 ± 0.7 | 1.7 ± 0.6 | P=0.57 |
| LVEF (%) | 31.9 ± 9.6 | 32.7 ± 10.5 | P=0.56 | 35.2 ± 10.9 | 39.1 ± 11.8 | P=0.14 |
| LVEDD (cm) | 6.2 ± 0.9 | 6.2 ± 0.9 | P=0.98 | 6.0 ± 0.9 | 5.9 ± 1.0 | P=0.62 |
| LVESD (cm) | 5.2 ± 1.0 | 5.3 ± 0.9 | P=0.78 | 4.9 ± 1.1 | 4.9 ± 1.2 | P=0.77 |
| MLHFQ | 44.2 ± 25.3 | 37.4 ± 19.2 | P=0.23 | 28.4 ± 23.3 | 28.9 ± 29.5 | P=0.96 |
| Urate (μmol/L) | 472.9 ± 114.1 | 462.8 ± 115.7 | P=0.87 | 380.6 ± 148.4 | 394.7 ± 102.7 | P=0.72 |

**Table 8: Demonstrates the study endpoints for patients undergoing echo and impedance cardiography guided optimisation of the CRT device, BNP; B-Type Natriuretic Peptide; 6MWT; 6 Minute Walk Test; NYHA; New York Heart Association; LVEF; Left Ventricular Ejection Fraction; LVEDD; Left Ventricular End –Diastolic Dimension; LVESD; Left Ventricular End Systolic Dimension; MLHFQ; Minnesota Living with Heart Failure Questionnaire**

### 5.3.2 Optimal AV and VV delays

Within the cohort, 28 (90 percent) of eligible patients (i.e. those not in atrial fibrillation) had a change in AV delay from baseline. In 10 patients (32 percent) the optimal delay was 120 milliseconds For VV delay 26 (66 percent) of patients had an adjustment of their delay with the majority resulting in the optimal delay of simultaneous depolarisation. These are demonstrated in Figure 16: Demonstrate spread of atrioventricular and ventriculo-ventricular delays within the optCRT cohort using either echocardiographic or impedance cardiography methods of optimisation.



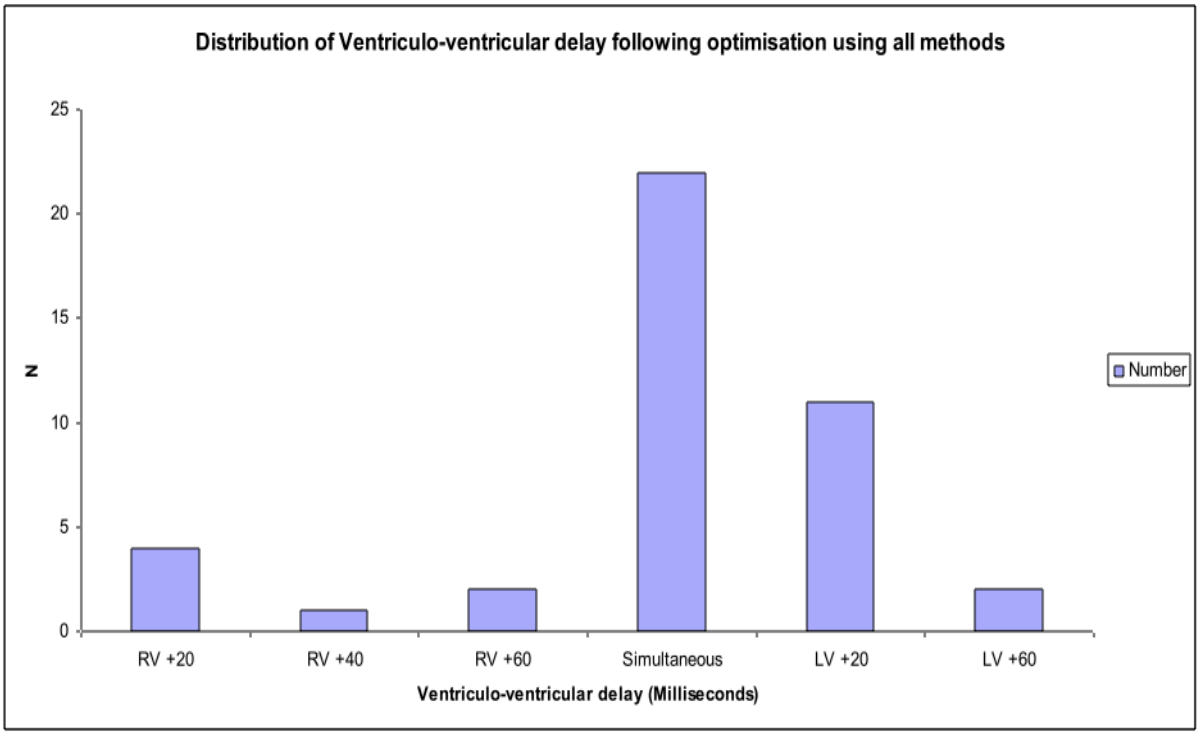




**Figure 16: Demonstrate spread of atrioventricular and ventriculo-ventricular delays within the optCRT cohort using either echocardiographic or impedance cardiography methods of optimisation**

## 5.4 Discussion

The study does not demonstrate a significant difference between an echocardiographic optimisation process as compared to using impedance cardiography. This relationship was confirmed for both primary and secondary endpoints i.e. functional (6MWT distance), mechanical (LVEF), neurohormonal markers (BNP, Urate) and symptomatic assessments. (NYHA, MQLHF)

The reasons behind these findings are varied. The study was originally conceived as a pilot study with a randomised, non blinded non inferiority study. However due to difficulties with patient recruitment and the initial purchase of the equipment, the study is underpowered. In terms of trial design the study had follow up visits at three months. However it is recognised within the literature that CRT may take up to six months to exert its effects on functional and mechanistic endpoints.(22) Though others have documented a rapid response in terms of symptoms, the other beneficial effects of CRT seem to take longer to become apparent. Hence if the study was repeated with larger numbers of individuals, it may be worthwhile to extend the follow up period to that over six months.

The population enrolled within the study were all recruited from the institution's dedicated heart failure pacing clinic. The institution is a tertiary university teaching hospital based in London and hence its patient load reflects a mixture of referrals from primary or secondary care. The majority (53 percent) of the population within this study had a non-ischaemic aetiology. All patients had CRT implanted on the basis of current guidance.(215) At their enrolement visit i.e. one month following CRT implantation, the rates of medical therapy were comparable to that of other studies with CRT and registry data. (ACEI/ARB -90 percent, β-Blocker -88 percent, Mineralocorticoid Receptor Antagonists -57 percent).(190) Following whichever method of optimisation that was performed (See Figure 16) there was a wide range of AV delays and VV delays identified as the optimal settings. The majority of patients had a change in their AV delay as compared to factory settings. (90 percent) and two thirds (66 percent) of patients had changes in their VV delays as compared to implantation intervals.

The study was equivocal in terms of endpoints. The primary pre-specified endpoint was the 6 minute walk test distance. Though the mean 6 MWT distance rose in both arms (349.2 ± 101.2, 365.2 ± 100.4 (echocardiographic and ICG respectively), none of these results demonstrated statistical significance. There was also a reduction in both groups in NYHA class and plasma BNP concentrations. Again these did not achieve statistical significance. Interestingly there was also little improvement neither in mechanical variables including LVEF, LVEDD nor in symptom score questionnaires. (Minnesota Living with Heart Failure Questionnaire)

There are several potential explanations for these results. Firstly the study is underpowered and this due to problems with recruitment. Though Figure 5 demonstrates high rates of agreement to participate in the study, there was a delay in securing ethical approval, purchasing the NICOMMO device and subsequent technical issues. All of this reduced study recruitment. A number of single centre studies have published data which demonstrates CRT may take anything up to 6 months to fully exert its beneficial effects.(102, 228) Hence this may explain the lack of positive remodelling in patients included within this study. Previous work has demonstrated that measures of left ventricular systolic function e.g. LVEF do not necessarily correlate with symptoms.(229) This is supported by a reduction in symptomatic classification as compared to lack of improvement in mechanical endpoints.

The introductory chapter summarises potential methods of optimisation – however the commonest methods of optimisation are echocardiographic based. This requires intensive labour, appropriate levels of skill and technology and therefore incurs significant cost. The other major criticism of echocardiographic measures is that raised by PROSPECT in terms of reproducibility and repeatability of complex echocardiographic methodology. PROSPECT evaluated numerous complex echocardiographic markers of dyssynchrony on a mass scale (all of which had been proven in smaller single centre studies) and demonstrated poor reproducibility.(103) Another issue is that resting echocardiographic alteration of the CRT device intervals does not take into account day to day variability of loading conditions, nor the effect of physical exertion on transmitral flow and subsequent left ventricular physiology.

Previous groups have therefore looked at device based algorithms for device 'self-optimisation'. The belief was that device based algorithms would monitor intrathoracic impedance or other biometric data and then adjust AV intervals accordingly. Two studies have published using device based protocols for optimisation. SMART-AV™ evaluated a three armed randomised, non-blinded study in 1014 participants randomised to a fixed AV delay of 120 milliseconds, SMART-AV CRT based adjustment of AV delay or echocardiographic adjustment of AV delay.(126) The study used the Smart Delay ™ sensing algorithm which was embedded in the CRT device as manufactured by Boston Scientific Corporation. (Natick, MA, US). Alternatively quickOPT™ is another device based algorithm in a different manufacturer which evaluated frequent optimisation versus echocardiography (FREEDOM Study).(127) In this study, 1580 patients were studied and the primary endpoint was a worsening in a heart failure composite endpoint. Secondary endpoints included cardiovascular hospitalisation and all-cause mortality. The results were equivocal and did not demonstrate any clear superiority in terms of clinical endpoints nor outcome.

With the lack of consensus derived from the literature with regards to echocardiography and device based methods of optimisation, others proposed impedance cardiography as an alternative. There is a paucity of literature within this area and few trials to date have been published evaluating optimisation via ICG techniques and clinical endpoints. Khan and colleagues in 2011 demonstrated in 203 patients, that ICG based optimisation was superior to standardised factory settings at six months in terms of symptoms (lower NYHA class), quality of life scores and echocardiographic setting.(146) However this study made a direct comparison to a randomised arm with no device optimisation and ICG optimisation. There was no comparison between ICG and echocardiographic methods of optimisation.

Another major critique of optimisation however it is performed is the lack of longer term clinical endpoints including heart failure hospitalisation and mortality. Though studies are underway to investigate this relationship there is no published evidence in either observational or randomised formats.

## 5.5 Limitations

This was a small non randomised observational study performed in a tertiary centre within the United Kingdom. Hence caution has to be exercised in terms of extrapolating the results to other populations and also in interpretation of its findings. As stated within the methods section, the study utilised resting measures of cardiac output and transmitral and trans aortic flow these may not correlate with those obtained following exertion and would represent another area of investigation. As per the institutional protocol and previous published literature AV delay was optimised followed by VV delay. This may not be correct and further work needs to be done to investigate whether this methodology is correct in terms of interval adjustment.

All patients were reviewed and recruited to the study, four weeks after CRT implantation. This differs to other studies of optimisation. This represents institutional policy and that the left ventricular lead is both functional and embedded with no changes in thresholds and impedances. However the differing time frames denoted within this study may not have been sufficient to capture a positive effect from CRT implantation and optimisation. The study is underpowered and thus statistical relationships obtained from this protocol require a correctly powered study to formally investigate the hypothesis in more robust fashion.

Lastly the study did not contain a control arm, with patients who had undergone CRT implantation and received no device optimisation. To truly evaluate the clinical effects of any optimisation intervention this would be necessary to evaluate the added effect of the change.

## 5.6 Conclusions

This study on the basis of its recruitment demonstrated no difference between an echocardiographic based or impedance cardiographic based method of optimisation on functional, symptomatic and mechanical endpoints over a follow up period of three months. Despite its limitations, it is one of only a few studies which compares two different methods of optimisation. Clearly a larger study is needed to further clarify this relationship and the current study's findings. It is noteworthy though that the population within this study had higher rates of heart failure pharmacotherapy as compared to baseline and that whichever method of optimisation was selected resulted in significant changes in AV and VV delay.

A larger multi-centre robust study is needed with multiple comparative methodologies with prespecified hard clinical endpoints which reflect the course of heart failure patients e.g. heart failure decompensation, major arrhythmic occurrence and death. It is only with such data and rigorous scientific evaluation that the community will be able to draw more formative conclusions.

# Chapter VI: Right Ventricular Dysfunction and its clinical importance in patients with Cardiac Resynchronisation Therapy

## 6.1 Introduction

Cardiac Resynchronisation Therapy (CRT) has become an established therapy for selected patients with symptomatic left ventricular systolic dysfunction.(22) However a number of patients as described in Chapter I do not obtain a symptomatic benefit. This is despite the current well recognised recommendations for patient selection for CRT devices. Furthermore this means that a number of patients are undergoing device implantation without acute clinical improvement, though as previously discussed there may be longer term effects on heart failure hospitalisation, progression of disease and mortality.

The definition of CRT response has been discussed in the introductory chapter. This remains controversial with no consensus. From a mechanical standpoint; studies have demonstrated that CRT may invoke left ventricular (LV) remodelling in certain patients, following implantation.(230)

Previous studies evaluating right ventricular (RV) function in such circumstances have used echocardiography and radionuclide imaging.(231-233) However the RV is anatomically complex and its structural geometry poses major challenges for cardiac imaging.(234) Cardiac Magnetic Resonance Imaging (CMR) has the ability to image the right ventricle throughout the cardiac cycle leading to a more robust and validated assessment of RV function.(23) The inter-observer variability in a validatory study performed in healthy subjects was 6.3 percent for end diastolic volumes (EDV), 8.6 percent for end systolic volumes (ESV), 7 percent for stroke volume (SV), 4.4 percent for ejection fraction (EF), and 7.8 percent for right ventricular mass (RVM). Intra-observer variability was 3.6 percent for EDV, 6.5 percent for ESV, 5.9 percent for SV, 4 percent for EF, and 5.7 percent for RVM.

The aim of this study was to investigate the impact of RV function, as assessed by CMR within patients undergoing CRT on clinical outcomes.

## 6.2 Methods

### 6.2.1 Study Population

A consecutive series of 60 patients was identified from the specialist heart failure pacing clinic at the Royal Brompton Hospital, London. All participants fulfilled contemporary criteria for CRT implantation.(215) 1. New York Heart Association Class III –IV, 2. QRSd >120 ms on surface electrocardiogram (ECG), 3. LVEF ≤ 35 percent by trans thoracic echocardiography) and on optimal tolerated evidence based medical therapy. Additionally all study participants had had a CMR study at most 3 months prior to CRT implantation.

The study period ran between January 2005 and March 2010.

Prior to CRT implantation, baseline demographical data was recorded, including aetiology of heart failure, symptomatic status, medication use, ECG data (including QRSd and rhythm). The data was obtained from the patient's medical records and electronic records.

The study involved a local review of patient medical records, therefore individual consent was not deemed necessary by the hospital Ethics Committee who approved the study.

### 6.2.2 Imaging

Cardiovascular magnetic resonance studies were performed in 1.5T Sonata or Avanto scanners (Siemens, Erlangen, Germany). A short-axis stack from atrio-ventricular level to the apex was acquired using a steady-state free-precession cine sequence (echo time 1.6 ms, repetition time 3.2 ms, flip angle 60°, slice thickness 7 mm with a 3 mm gap, acquisition time of 8-12 cardiac cycles) to quantify left and right ventricular volumes. Long-axis cines were also acquired to define the valve plane throughout the cardiac cycle. An inversion recovery gradient echo sequence was used 10 minutes after gadolinium injection (Magnevist® or Gadovist®, 0.1 mmol/kg) to assess myocardial scar. Inversion times were set to null the normal myocardium with images repeated in two stacks of identical short-axis planes but separate phase-encoding directions to exclude artefacts.
Left and right ventricular volumes were calculated using semi-automated software (CMR tools, Cardiovascular Imaging Solutions, London, UK) as previously described.(23, 24)

Epicardial and endocardial borders were traced in all short-axis images and the papillary muscles and trabeculations were delineated by thresholding of the blood pool. Tracking of the mitral and tricuspid valve was used to correct left and right ventricular volumes during systole. The resulting values were then indexed to body surface area and compared to reference values from a control population. Tricuspid annular plane systolic excursion (TAPSE) was measured from the 4-chamber view. RV dysfunction was defined as RVEF < 0.5 or TAPSE < 15 mm; severe RV dysfunction was defined as RVEF < 0.3 or TAPSE < 10 mm. Peak RV wall thickness was measured from the short-axis slices.

Valvular regurgitation was graded as mild (n=1), moderate (n=2) or severe (n=3) by blinded observers, based on the echocardiographic and CMR findings. LVEF was calculated by echocardiography using the Simpson's method from the 2-chamber and 4-chamber views. Pulmonary artery systolic pressure was determined by echocardiography using standard methodology.(235)

Assessment of late gadolinium enhancement (LGE) in the left or right ventricle was also interpreted by blinded observers. When present, the amount of LGE was quantified in a 16-segment model based on the "full width at half maximum" technique by customized analysis software (MRI-MASS, Medis, Leiden, the Netherlands)(236)

### 6.2.3 Outcomes

Every patient was followed up in a specialist heart failure clinic. At these appointments, evidence based heart failure pharmacotherapies were adjusted and optimized. No patient was lost to follow up.

The primary end point was a composite of all-cause mortality or an unplanned hospital admission for a major cardiovascular event. Only the first event was included for analytical purposes.

The secondary end point was an improvement in LVEF by ≥ 5 percent, 12 months after CRT implantation. This was assessed by trans thoracic echocardiography. (TTE)(237)

### 6.2.4 Statistical analysis

Results were analysed using SPSS software version 19.0 (SPSS Inc, Chicago, Illinois, US). Continuous variables were assessed for normal distribution and if normally distributed presented as a mean +/- standard deviation. If they were non normally distributed, they are presented as a median +/- interquartile range.

Two-tailed t-test and one-way ANOVA were used to compare normally distributed variables; Mann-Whitney test was used to compare non-normally distributed variables. Correlation with Pearson's or Spearman's methods was used as indicated.

Time-to-event analysis was performed using Cox's proportional hazard models. Logistic regression was used to evaluate the effects of CRT at 12 months. Multivariate analysis was performed on parameters that were significant on univariate analysis. A p value $<0.05$ was deemed to be statistically significant.

## 6.3 Results

### 6.3.1 Demographics

The baseline demographical data are presented in Table 8 . The mean age of the cohort was 65.3 +/- 12.5 years. The majority of the patients were male (76.7 percent). The principal aetiology within this study was previous ischaemic heart disease (48.3 percent) and the majority of patients were in sinus rhythm. (76.7 percent)
The mean heart rate prior to CRT was 76 +/- 15 beats per minute, the mean QRS duration on ECG was 156 +/- 21 ms. 95 percent of patients who had CRT implanted had left bundle branch block on their ECG. The median time between CMR study and CRT implantation was 6 days. Nearly all (93 percent) of the cohort received a biventricular-ICD (CRT-D).

| | |
|---|---|
| Age, years | 65.3 ± 12.5 |
| Male gender | 46 (76.7%) |
| Heart failure, aetiology | |
| Dilated cardiomyopathy | 27 (45.0%) |
| Ischaemic | 29 (48.3%) |
| Valvular | 3 (5.0%) |
| Congenital | 1 (1.7%) |
| Rhythm | |
| Sinus | 46 (76.7%) |
| Atrial fibrillation | 13 (21.7%) |
| Atrial flutter | 1 (1.7%) |
| Medication | |
| Beta-blockers | 43 (71.7%) |
| ACE inhibitors/ARB | 58 (96.7%) |
| Aldosterone antagonists | 39 (65.0%) |
| Loop diuretics | 52 (86.7%) |
| Digoxin | 12 (20.0%) |
| Aspirin | 23 (38.3%) |
| Warfarin | 19 (31.7%) |
| Statin | 30 (50.0%) |
| ECG | |
| QRS width (ms) | 156 ± 21 |
| Heart rate | |
| Beats per minute (bpm) | 76 ± 15 |
| Blood pressure | |
| Systolic (mmHg) | 120 ± 20 |
| Diastolic (mmHg) | 72 ± 13 |
| Left ventricle | |
| EDV (mL/$m^2$) | 169 ± 62 |
| ESV (mL/$m^2$) | 124 ± 55 |
| EF (%) | 27 ± 8 |
| Mass (g/$m^2$) | 113 ± 30 |
| Right ventricle | |
| EDV (mL/$m^2$) | 82 (65-123) |
| ESV (mL/$m^2$) | 38 (27-76) |
| EF (%) | 52 (37-62) |
| TAPSE (mm) | 13.5 ± 5.6 |
| Peak wall thickness (mm) | 3.6 ± 0.9 |
| Pulmonary artery pressure (mmHg) | 38.7 ± 8.7 |
| Late gadolinium enhancement | |
| Absent | 20 (33.3%) |
| Subendocardial | 19 (31.7%) |
| Subendocardial + mid-wall | 6 (10.0%) |
| Mid-wall | 15 (25.0%) |
| Right ventricle | 5 (8.3%) |

**Table 9: Data is presented as n (percent), mean ± SD, or median (25th - 75th percentile). NYHA = New York Heart Association; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; EDV = End-diastolic volume; ESV = End-systolic volume; EF = Ejection fraction; TAPSE = tricuspid annular plane systolic excursion.**

### 6.3.2 Right ventricle

The indexed volumes and RV ejection fraction were non normally distributed. They are presented as a median plus interquartile range.

The median end diastolic and end systolic volumes were 82 (65-123) mL/$m^2$ and 38 (27-76) mL/$m^2$, respectively. Right ventricular indexed end-diastolic volume was increased in 38 percent of patients, while the indexed end-systolic volume was increased in 53 percent of patients.(22) The median RVEF was 52 percent (IQR 37-62%), with 53 percent of patients having a RVEF ≥ 50 percent.

Mean Tricuspid Annular Plane Systolic Excursion (TAPSE) was 13.5 +/- 5.6 mm. If a standard echocardiographic definition of a normal TAPSE is applied than 40 percent of the population were within normal limits.(235)

The pulmonary artery systolic pressure (PAP) could be measured in 52 patients (87 percent). The mean PAP was 38.7 ± 8.7 mmHg, with 37 percent of patients having a PAP > 40 mmHg. Tricuspid regurgitation was seen in 57 percent of the patients, and was significant in 14 percent of patients (12 percent moderate, 2 percent severe). No significant pulmonary regurgitation was identified.

There was a moderate correlation of RVEF with TAPSE ($r=0.58$, $p<0.01$), and RVEF with LVEF ($r=0.41$, $p<0.01$). Severity of mitral regurgitation was associated with a higher PAP ($p=0.01$) and a lower RVEF ($p<0.01$). An inverse correlation was observed between RVEF and pulmonary artery pressure ($r= -0.37$, $p<0.01$), RV wall thickness ($r= -0.28$, $p=0.03$) and severity of tricuspid regurgitation ($p=0.03$). TAPSE was inversely related with RV wall thickness ($r= -0.29$, $p=0.03$), but not with pulmonary artery pressure ($r= -0.15$, $p=0.28$) or LVEF ($r= 0.09$, $p=0.48$).
RVEF was similar in patients with an ischaemic and non-ischaemic aetiology (46.9 ± 14.8 percent vs. 49.5 ± 18.9 percent, $p=0.56$), and in patients with atrial fibrillation (AF) compared to those in sinus rhythm (45.4 ± 14.9 percent vs. 49.2 ± 17.8 percent, $p=0.48$).

### 6.3.3 Myocardial fibrosis

All patients received concurrent gadolinium enhanced contrast media at the time of their CMR study. LV late gadolinium enhancement (LGE) was present in 66 percent of the group. Nineteen patients (31.7 percent) had subendocardial enhancement suggesting prior myocardial infarction, 15 patients (25.0 percent) had mid-wall enhancement pattern indicating fibrosis, and the remaining six patients (10.0 percent) had a mixed pattern of myocardial infarction and mid-wall fibrosis. Myocardial infarction was therefore present in 25 patients (41.7 percent): the septal wall was affected in 11 patients; the inferolateral wall was involved in 15 patients.

Right ventricular LGE was present in only five patients (8.3 percent). All these patients had coronary artery disease with inferior myocardial infarctions of the LV extending to the inferior free wall of the RV.

### 6.3.4 Follow-up

There was a median follow up period of 26.1 months (IQR 16.1 -39.3 months) following CRT implantation. Eighteen patients reached the primary study end point (13 unplanned cardiovascular hospitalisations (All for HF decompensation) and 11 deaths (8 cardiac, 3 non cardiac).

Atrial fibrillation and RV dysfunction emerged as the only predictors of the primary composite end-point on univariate analysis (See Table 10). Patients in atrial fibrillation or flutter had a HR of 2.6 (95 percent CI 1.02-6.84, p=0.047) for the primary end-point. For each 10 percent decrease in RVEF, the risk of the primary end-point increased by 40 percent (HR 0.96, 95 percent CI 0.94-0.99, p=0.006); for each 1 mm decrease in TAPSE, the risk of the primary end-point increased by 12 percent (HR 0.88, 95 percent CI 0.80-0.96, p=0.006). Patients were less likely to undergo LV remodelling if RV function was noted to be poor. Significantly impaired RV function, defined as a RVEF < 30 percent or a TAPSE < 10mm, was particularly associated with a low rate of LV remodelling with CRT (rates of 18.2 percent and 26.7 percent, respectively).

### 6.3.5 Improvement LVEF ≥ 5 Percent

The majority of patients (n=56 (93%)) completed one year of follow up. 27 (48%) of this sub group had an increase of more than 5% in LVEF. Two sets of parameters were associated with a failure of LV remodelling (as defined by <5% improvement in LVEF) from CRT on univariate analysis: (1) coronary artery disease, associated with myocardial infarction and amount of scar (myocardial fibrosis plus infarction), were predictors of a failure of remodelling to therapy; (2) right ventricular dysfunction (lower RVEF and TAPSE) and hypertrophy (thicker RV free wall). Myocardial infarction (OR 0.90, 95% CI 0.83-0.96, p=0.004) and RVEF (OR 1.05, 95% CI 1.01-1.09, p=0.01) were the only variables to remain significant on multivariate analysis. (See Table 11 + 12)

| | Events (n = 18) | No Events (n = 42) | HR | 95% CI | P value |
|---|---|---|---|---|---|
| Age (years) | 69.6 ± 11.9 | 63.3 ± 12.3 | 1.04 | 0.99-1.09 | 0.07 |
| Male gender | 14 (78%) | 32 (76%) | 1.14 | 0.37-3.46 | 0.82 |
| CAD | 10 (56%) | 17 (41%) | 1.73 | 0.68-4.38 | 0.25 |
| Atrial fibrillation | 6 (39%) | 8 (17%) | 2.63 | 1.02-6.84 | 0.047 |
| Heart rate (bpm) | 79.2 ± 19.4 | 74.1 ± 12.5 | 1.02 | 0.99-1.05 | 0.22 |
| SBP (mmHg) | 124 ± 22 | 118 ± 19 | 1.01 | 0.99-1.04 | 0.36 |
| QRS width (ms) | 151 ± 25 | 158 ± 21 | 0.99 | 0.96-1.01 | 0.23 |
| Left ventricle | | | | | |
| EDV index (mL/m$^2$) | 159 ± 54 | 173 ± 64 | 0.99 | 0.98-1.00 | 0.09 |
| ESV index (mL/m$^2$) | 120 ± 52 | 126 ± 56 | 0.99 | 0.98-1.00 | 0.19 |
| EF (%) | 26.9 ± 9.5 | 28.9 ± 7.6 | 1.00 | 0.94-1.06 | 0.93 |
| Mass index (g/m$^2$) | 106 ± 25 | 115 ± 32 | 0.98 | 0.97-1.00 | 0.08 |
| Mitral regurgitation | 1.3 ± 0.6 | 1.2 ± 0.8 | 1.33 | 0.73-2.44 | 0.35 |
| LGE | 13 (72%) | 27 (64%) | 1.57 | 0.50-3.98 | 0.51 |
| LGE (%) | 9.5 (0-20) | 3 (0-17) | 1.01 | 0.98-1.05 | 0.54 |
| Myocardial infarction | 9 (50%) | 16 (38%) | 1.57 | 0.62-3.95 | 0.34 |
| Right ventricle | | | | | |
| EDV index (mL/m$^2$) | 95 (76-138) | 77 (60-103) | 1.01 | 1.00-1.02 | 0.12 |
| ESV index (mL/m$^2$) | 52 (35-102) | 34 (21-66) | 1.01 | 1.00-1.02 | 0.06 |
| EF (%) | 39 (25-54) | 55 (43-66) | 0.96 | 0.94-0.99 | 0.006 |
| TAPSE (mm) | 11.0 ± 4.4 | 14.5 ± 5.9 | 0.88 | 0.80-0.96 | 0.006 |
| Wall thickness (mm) | 3.9 ± 1.0 | 3.5 ± 0.9 | 1.54 | 0.93-2.56 | 0.09 |
| PAP (mmHg) | 42.5 ± 8.3 | 37.5 ± 8.5 | 1.06 | 1.00-1.12 | 0.07 |

**Table 10: Univariate Analysis: Primary End Point (time to death from any cause and unplanned hospitalisation for a major cardiovascular event) Values are n (Percent), mean ± SD, or median (25th - 75th percentile). HR = hazard ratio; CI = confidence interval. CAD = Coronary artery disease; SBP = systolic blood pressure; LGE = late gadolinium enhancement; PAP = Pulmonary artery pressure.**

| Response | Response (n = 27) | No Response (n = 29) | OR | 95% CI | P value |
|---|---|---|---|---|---|
| Age | 64.0 ± 12.2 | 65.8 ± 12.2 | 0.99 | 0.95-1.03 | 0.58 |
| Male gender | 18 (67%) | 25 (86%) | 0.32 | 0.09-1.20 | 0.09 |
| CAD | 7 (26%) | 19 (66%) | 0.18 | 0.06-0.58 | 0.004 |
| Atrial fibrillation | 4 (15%) | 7 (24%) | 0.55 | 0.14-2.13 | 0.38 |
| Heart rate (bpm) | 76 ± 15 | 76 ± 16 | 1.00 | 0.97-1.04 | 0.89 |
| SBP (mmHg) | 120 ± 20 | 119 ± 19 | 1.00 | 0.98-1.03 | 0.76 |
| QRS width (ms) | 161 ± 21 | 150 ± 22 | 1.02 | 1.00-1.05 | 0.07 |
| Left ventricle | | | | | |
| EDV index (mL/m$^2$) | 156 ± 46 | 177 ± 71 | 0.99 | 0.98-1.00 | 0.19 |
| ESV index (mL/m$^2$) | 111 ± 40 | 133 ± 63 | 0.99 | 0.98-1.00 | 0.13 |
| EF (%) | 30.5 ± 8.5 | 26.5 ± 7.2 | 1.07 | 0.99-1.16 | 0.07 |
| Mass index (g/m$^2$) | 108 ± 26 | 118 ± 34 | 0.99 | 0.97-1.01 | 0.23 |
| Mitral regurgitation | 1.1 ± 0.6 | 1.3 ± 0.8 | 0.58 | 0.27-1.27 | 0.17 |
| LGE | 13 (48%) | 24 (83%) | 0.19 | 0.06-0.66 | 0.009 |
| LGE (%) | 0 (0-7) | 13 (3-22) | 0.91 | 0.85-0.97 | 0.005 |
| Myocardial infarction | 6 (22%) | 18 (62%) | 0.18 | 0.05-0.57 | 0.004 |
| Right ventricle | | | | | |
| EDV index (mL/m$^2$) | 77 (67-104) | 83 (61-139) | 0.99 | 0.98-1.01 | 0.28 |
| ESV index (mL/m$^2$) | 36 (23-54) | 40 (31-96) | 0.99 | 0.98-1.00 | 0.10 |
| EF (%) | 56 (45-63) | 44 (28-61) | 1.04 | 1.01-1.08 | 0.03 |
| TAPSE (mm) | 15.3 ± 5.8 | 11.8 ± 4.2 | 1.15 | 1.03-1.29 | 0.02 |
| Wall thickness (mm) | 3.3 ± 0.7 | 4.0 ± 1.0 | 0.42 | 0.21-0.84 | 0.02 |
| PAP (mmHg) | 36.9 ± 8.5 | 40.5 ± 9.0 | 0.95 | 0.89-1.02 | 0.16 |

**Table 11:Univariate Analysis Response to cardiac resynchronisation therapy (LVEF >5 Percent at one year). Values are n (Percent) and mean +/- standard deviation, or median +/- interquartile range. OR = Odds ratio, CI = Confidence Interval.**

| Response | Response (n = 27) | No Response (n = 29) | OR | 95% CI | P value |
|---|---|---|---|---|---|
| LGE (%) | 0 (0-7) | 13 (3-22) | 0.90 | 0.83-0.96 | 0.004 |
| RVEF (%) | 56 (45-63) | 44 (28-61) | 1.05 | 1.01-1.09 | 0.01 |

**Table 12 Multivariate Analysis of Response to Cardiac Resynchronisation Therapy (Improvement in LVEF >5% at one year)**

## 6.4 Discussion

The main findings of this study were that patients with impaired RV systolic function who undergo CRT are more likely to have a worse clinical outcome and are less likely to develop LV remodelling. RV systolic function has been demonstrated to be a marker of adverse prognosis within a range of cardiovascular disease.(238-240) The current study demonstrates that impaired RV function demonstrated by CMR imaging is associated with poorer clinical outcomes for such patients and less likelihood of LV reverse remodelling.

The study participants fulfilled contemporary criteria for CRT implantation, despite this there was a heterogeneous distribution of RV systolic function. This is despite all having decreased LV systolic function, which is mandatory for the consideration of CRT implantation.
The mechanism of RV dysfunction may either be due to a bi-ventricular reduction in intrinsic contractility, or raised left ventricular end diastolic pressures and mitral regurgitation.

Poor RV function may reflect more extensive bi ventricular disease or pulmonary hypertension, which is less modifiable by CRT. It is notable within this cohort, an RVEF <30% indicated a failure to undergo reverse LV remodelling. This relationship needs further characterisation and investigation.

### 6.4.1 Previous work

Prior work has shown up to 20-40% of RV systolic pressure and volume load is dependent on LV contractility.(241) Left Bundle Branch Block (LBBB), may interfere with ventricular activation and induce mechanical dyssynchrony. Hence LBBB may have an adverse effect on biventricular function. The effects of CRT and right bundle branch block (RBBB) are contentious. A proportion of CRT recipients in the randomised controlled trials have had RBBB on the surface ECG. An earlier substudy from the MIRACLE trial found that RBBB in association with other conduction abnormality (left anterior or posterior fascicular block) did not prevent the positive effects of CRT as measured by symptomatic and quality of life endpoints.(242) However the more recent MADIT CRT substudy conflicted with this and found that RBBB had an increased association with mortality and morbidity.(108) The association between RBBB and adverse outcomes has also been demonstrated in large

registry data. The physiological effects of RBBB have been under investigated and more work is needed within the area. RBBB has been shown to induce an activation delay in the right ventricular free wall and CRT may improve LV activation but further cause extension of the RV free wall delay.(243) However the area has such limited data that more robust investigation of physiological mechanisms is needed.

Functional markers of RV function have been previously been evaluated within populations undergoing CRT. Field et al investigated RV function in an advanced heart failure population consisting of 77 patients. The authors used the Doppler derived myocardial performance index (MPI) as a predictor of the composite end point of death, transplantation and left ventricular assist devices.(231) A total of 28 patients achieved the primary end point over a median follow up period of 21 months. Worse RV function, as demonstrated by a higher RV MPI, was seen in those patients who reached the end point compared with those who did not (0.83 vs. 0.69, P =0.004). The highest tercile of RV MPI was associated with a 3.3-fold increased risk of poor outcome (95% CI 1.3e8.5). Each 0.1 unit increase in RV MPI was associated with a 16% increased risk (95% CI 8-26).

A smaller cohort study of 44 patients used echocardiographic indices of RV function (TAPSE and RVEF) to assess whether these were associated with LV reverse remodelling at six months (defined by >15% increase in LVESV). Severe RV dysfunction was defined as TAPSE < or =14 mm and the population was stratified into two groups based on baseline TAPSE < or = or > 14 mm. As compared to those with high TAPSE (n = 30), patients with low TAPSE (n = 14) were less likely to show LV reverse remodelling after CRT (76% vs 14%, P < 0.001).(232) Burri and co-workers, using radionuclide imaging also demonstrated within a study of 44 patients, that those with a lower RVEF at baseline, were less likely to improve in symptomatic status and LVEF following CRT implantation.(233) Following a median follow up period of 9 +/- 5 months, a RVEF <35% was associated with a failure in improvement in NYHA class (P=0.016) and also had a non-significant trend towards improvement in 6MWT distance and LVEF. (P<0.06).

Longer term data comes from a CARE-HF substudy. Using the original cohort of 813 patients enrolled into CARE-HF, 688 had a TAPSE recorded at the recruitment visit.(244) Out of these, 345 were randomised to CRT and the median follow up was 748 days (IQR 582 to 950 days). Patients with lower TAPSE measurements were more likely to have had an ischaemic

aetiology and higher rates of mortality. (P<0.001) However when the data was analysed by tercile CRT still proved to be effective. TAPSE was a predictor of events irrespective of CRT implantation.

### 6.4.2 Cardiac Magnetic Resonance

CMR was used as the gold-standard technique within this study. For the purposes of this study the reference marker was RVEF. Along with myocardial infarction, RVEF was an independent predictor of LV remodelling following CRT. Among an array of established prognostic markers in HF, RVEF and TAPSE emerged as the strongest predictors of events.

### 6.4.3 Tricuspid Annular Plane Systolic Excursion (TAPSE)

RVEF is a validated prognostic marker in cardio-pulmonary disease. However the right ventricle is a complex structure which cannot be modelled with simple geometric assumptions. It possesses radial, longitudinal and oblique fibres.(234) Hence measures other than EF have been suggested to describe RV systolic function. One such proposed by current imaging guidelines, is that of TAPSE.(235) An easily attainable and reproducible marker, it has been shown to be a predictor of adverse prognosis which is independent of symptomatic status and LV function.(245) Within this study TAPSE was also predictive of LV remodelling and clinical outcomes. Hence this is an alternative measure which may be able to be of clinical significance.

In this study, TAPSE not only identified which patients would respond to CRT, but also the patients more likely to have major adverse events. Thus, TAPSE may be used by CMR as an alternative to RVEF for assessing RV function pre CRT when the latter cannot be estimated.

### 6.4.4 Myocardial fibrosis

Cardiac magnetic resonance imaging, with the aid of concurrent gadolinium contrast can demonstrate myocardial scar or replacement fibrosis.(246) Late gadolinium enhancement has been shown to be a prognostic indicator in several disease states.(26, 27) The scar burden, location and extent have all been shown to be of clinical importance within populations with CRT.(247, 248) This study was not designed to evaluate LGE and CRT. On univariate analysis septal and lateral scar was associated with a reduced likelihood of remodelling. (OR 0.98, 95% CI 0.97-1.00, p=0.01; and OR 0.98, 95% CI 0.97-1.00, p=0.03, respectively), however on multivariate analysis the scar burden (determined by percentage of LGE mass) did not remain significant. A larger study specifically designed to investigate LGE, extent and distribution, is needed to clarify their relationship within patients with CRT.

### 6.4.5 Atrial fibrillation

Atrial Fibrillation was the other predictor of clinical outcomes besides RV dysfunction. This correlates with the findings of others, where AF has been shown to predict unfavourable clinical outcomes.(212)

AF with a fast ventricular rate, may compromise the delivery of biventricular pacing. A low level (<90%) of biventricular pacing may interfere with the beneficial effects from CRT.(249, 250) The rate control of patients within this study was satisfactory (Median 97%, IQR 91-99%); no patient underwent an atrioventricular nodal ablation.

### 6.4.6 Left Ventricular Remodelling

We assessed the role of RV dysfunction on LV remodelling after CRT as a secondary end-point. In keeping with previous work, response for this study was an improvement in LVEF ≥5% at 12 months. The remodelling rate observed was 48%, but still in accordance with the published literature.(160) Using this criterion, RV dysfunction predicted a failure of LV remodelling (RVEF (OR 1.05, 95% CI 1.01- 1.09, p = 0.01) thus supporting previous echocardiographic and radionuclide studies.(232, 233) Response to CRT was noted to be lower as RV function deteriorated. Poor RV function, defined as a RVEF < 30% or a TAPSE

< 10 mm, was associated with a particularly low response to CRT (response rates of 18.2% and 26.7%, respectively).

## 6.5 Limitations

This was a retrospective cohort study with a limited number of patients and events; which limits the point of the multivariate analyses.

All patients were scanned and clinically followed up at the Royal Brompton Hospital, London. This is a tertiary/quaternary heart failure referral service and hence the study cohort may not be representative of less selected heart failure cohorts.
All CMR scans were performed by the CMR unit on the site; this facilitated consistent CMR scanning protocols.

Historically the guidance from device manufacturers has been that CRT generators should not be exposed to magnetic resonance imaging this is due to the risk of electromagnetic interference. Hence within this study LV remodelling was documented using repeat trans thoracic echocardiography.

## 6.6 Conclusions

This study demonstrates that RV function has potential as a predictor of LV remodelling and clinical outcomes in patients following CRT implantation, when assessed by cardiac MR.

Conventional selection criteria focus on left ventricular disease and systolic performance, RV function may be a marker which is able to prognosticate adverse clinical outcomes for patients following CRT.

# Chapter VII: A pilot study to validate impedance cardiography (ICG) versus transthoracic echocardiography in patients in a cardio-thoracic intensive care setting

## 7.1 Introduction

As described previously, cardiac resynchronisation therapy (CRT) is an established treatment for symptomatic left ventricular systolic dysfunction, on optimal tolerated medical therapy with a broad QRS duration >120milliseconds on the surface electrocardiogram. One of the proposed mechanisms of CRT is to restore coordinated contractility without the expense of increased myocardial oxygen consumption.(41)

Within cardiac intensive care (cICU), the use of temporary epicardial pacing systems is common in the management of patients in the peri-operative period. Myocardial dyssynchrony has been previously demonstrated within patients in the peri-operative period.(251) CRT has become an established therapeutic option in the chronic setting; hence this has led to a renewed focus on temporary pacing within the intensive care setting. Historically this area is underrepresented within the literature.

Cardiac output monitoring within the cICU has been performed conventionally via invasive methods. This requires invasive instrumentation in potentially critically ill patients which exposes them to the risks of infection or bleeding. Hence alternative methods have been investigated for the non-invasive measurement of CO within the intensive care setting.

One such method which has been evaluated is the impedance cardiography (ICG) technique which relies on the calculation of intra-thoracic impedance via four surface electrodes and the application of a minute amount of direct current to the patient.

Using blood volume passing through the thoracic aorta and the electrical impedance the ICG technology is able to calculate various haemodynamic parameters. CO derived from ICG measurement has been previously evaluated within ITU patients and has been found to have adequate reproducibility and repeatability.(252, 253) One particular sub group in which it seemed to have strong correlation with traditional invasive techniques of CO measurement was within patients with septic shock which required vasopressors and organ support within an ITU setting.(254, 255)  ICG has also been previously been demonstrated to be of clinical use in the optimisation of permanent pacing systems. (both dual chamber and biventricular types)(146)

Utilising the knowledge of previous efficacy both within the field of pacemaker optimisation and CO monitoring within an intensive care setting – we proposed a pilot study to validate the ICG measure of CO versus those derived from transthoracic echocardiography (TTE) within patients in a CICU setting. The hypothesis of the study being that impedance cardiography reliably evaluates cardiac output in patients following cardiac surgery as compared to transthoracic echocardiography.

## 7.2 Methods

### 7.2.1 Patient Selection & Recruitment

Patients were identified from the pre-operative theatre lists published at the Royal Brompton Hospital, London. All potential study participants had to provide written informed consent and were given twenty-four hours to consider study participation. Due to the structure of the study protocol all potential participants had to have cardiac surgery and potentially temporary epicardial right atrial and right ventricular pacing leads connected to the Micro Pace 4580 temporary pacing box (Pace Medical Inc, Waltham, Massachusetts). Ethical approval was provided by the North West London Research Ethics Committee (REC) -1. (Study ID 11-LO-0131)

### 7.2.2 Setting

All study participants were identified prior to adult cardiac surgery and were approached only if they fulfilled inclusion criteria. If any exclusion criterion was deemed to apply – the patient was not approached. Following cardiac surgery the patients were transferred to the Doverdale Adult Intensive Care Unit at the Royal Brompton Hospital, London. All study measurements were either performed within the ITU or within the high dependency unit. (HDU). The exclusion criteria for the study are listed in Table 11.

### 7.2.3 Methodology

All participants were haemodynamically stable (defined by no change in ventilatory settings, oxygen requirements, change in filling pressures or change in inotrope requirements for > 30 minutes) prior to the alteration of pacing settings. All patients were also normothermic defined as temperature between 35.0 and 37.2 degrees Celsius. Prior to the recording of effect of different settings all epicardial leads were tested for electrical stability measured by thresholds.

Providing the above conditions had been met the patients then underwent the following pacing protocol.

A baseline recording was performed with a ventricular pacing rate set at 80 beats per minute (BPM) in the following configurations.

1. Atrial Sensed Pacing (AAI) - This was not performed in patients who had underlying high degree atrioventricular block. The patient was paced only from the Right Atrial Lead (RA) and a range of heart rates tested from 80 to 120 BPM in 10 beat intervals.

2. AV delay adjustment. The patient was placed in a dual chamber pacing and sensing mode (DDD) and the rate preset at 100 BPM. The AV delay was then adjusted between 80 and 200 milliseconds at 20 millisecond intervals.

3. Ventricular Sensed Pacing (VVI) - Right Ventricular Pacing Only. A range of heart rates was tested from 90 beats per minute to 120 beats per minute.

4. Dual Chamber Pacing (DDD) - Right Atrium (RA) to Right Ventricular (RV) pacing with fixed atrioventricular (AV) delay of 100 milliseconds. A range of heart rates was tested from 80 to 120 BPM in 10 BPM increments.

For all adjustments in pacing settings, a period of 30 seconds was allowed prior to the recording of cardiac output either via echocardiography or impedance cardiography. An average of 20 beats per setting was recorded.

### 7.2.4 Echocardiography

All transthoracic echocardiography was performed by a single operator with appropriate accreditation. All echocardiography was performed using a Philips IE33 system (Phillips Corporation, Andover, Massachusetts, US).

The left ventricular outflow tract (LVOT) diameter was measured from the parasternal long axis view in systole. The LVOT velocity time integral (VTI) was recorded from the apical 5 chamber view using pulsed wave Doppler.

Cardiac output was then derived from these settings using the following equation:

$$\textit{Cardiac Output} = \textit{Heart rate} * (\pi\ (\textit{LVOT diameter}/2)^2 * \textit{LVOT VTI}$$

### 7.2.5 Impedance Cardiography

All measurements were recorded using the NICCOMO ICG device (Medis, Medizinische Messtechnik GmbH). Four surface electrodes were placed in a standardised configuration as recommended by the manufacturer. The device then recorded the cardiac output by analyzing 20 consecutive beats over each setting.

### 7.2.6 Statistics

All analysis was performed using SPSS version 19 (International Business Machines Corp, Armonk, NY, US). Continuous variables were expressed as mean ± standard deviation (SD), categorical variables are expressed as percentages.

Analysis of the relationships between the two sets of derived variables was guided by an experienced statistician and regression equations were generated. A p value $<0.05$ was deemed as statistically significant.

## 7.3 Results

Baseline demographics for the study population are demonstrated in Table 12. In total six patients were recruited to the study. All had undergone aortic valve replacement. The majority of the cohort (n=4, 67 percent) were male and the baseline left ventricular ejection fraction (LVEF) was 57.3 ± 5.5 percent, the mean QRS duration on surface electrocardiogram at enrolment was 112 ± 35 milliseconds.

Due to the exclusion criteria all six participants were studied in the HDU setting rather than the intensive care setting. Most of the patients were not on any inotropes with a solitary patient being on low dose noradrenaline infusion (0.02 mcg/Kg/min).

### 7.3.1 AAI Pacing Mode

A full dataset for this pacing mode was only obtained on n=3 (50 percent) of the cohort this was due to the patient requesting termination of readings in one case and resting AV block or severe sinus bradycardia in the other two cases. Due to the lack of data for this modality further statistical evaluation did not proceed.

### 7.3.2 AV delay adjustment

A full dataset was captured for this pacing mode in n=5 (83 percent) participants. As proposed a range of AV delays was tested with a set heart rate of 100 beats per minute. The Bland Altman and Regression Graphs for these settings and the following settings are demonstrated in Figures 17 and 18.

### 7.3.3 VVI Pacing Mode

A full dataset was captured in this pacing mode for n=5 (83 percent) of participants.

### 7.3.4 DDD Pacing Mode

A full dataset was captured in all of the study participants in this pacing mode. (n=6, (100 percent).

## 7.4 Discussion

The study was conceived as a novel pilot study to evaluate the relationship between impedance cardiographic measurement of cardiac output versus a more standardised method in this case - transthoracic echocardiography.

Using a very limited number of patients (N=6), a dataset was obtained over different pacing configurations and heart rates. Therefore any conclusions drawn from the interpretation of such a dataset should be considered with caution. The findings may provoke further hypothesis generation for future studies but do not provide definitive conclusions.

Using the data from the VVI, DDD and AV delay pacing groups there is little agreement between the two methodologies in terms of recorded cardiac output especially in the VVI and DDD pacing groups. There is a tendency for the ICG to generate higher readings especially at higher heart rates. There is some degree of correlation in this dataset in terms of AV delay adjustment but this as stated above should not be viewed as strong. The scatter of such data which is demonstrated in the Bland Altman plots is wide and hence difficult to meaningfully interpret. This may reflect individual variability of the patient such as variability in left ventricular loading conditions or the technique recording the cardiac output. A Bland Altman plot also only demonstrates how well the method under evaluation (in this case ICG) performs as compared to the gold standard (again within this study- transthoracic echocardiography). It does not demonstrate the ability of ICG to evaluate a change in cardiac output. When reviewing the individual values and raw data this is demonstrated within these datasets.

Impedance cardiography calculates cardiac output via the measurement of pulsatile thoracic aortic blood flow. It assumes that thoracic fluid is negligible and hence relies on the mechanistic changes in aortic dimensions to generate cardiac output. By using the application of Ohm's Law to measure changes in voltage and impedance and it is able to translate these

into parameters of cardiac function. Several commercial systems are available and have been previously evaluated in intensive or critical care settings.(256, 257)

The gold standard of cardiac output monitoring as recommended by international guidelines in critical care settings is the thermodilution method using pulmonary artery catheters. Prior work has demonstrated that ICG is comparable to pulmonary artery catheters and CO measurement in such settings.(257) However this has not been an uniform finding and some groups have found poor correlation between the two methods.(258)

Within the critical care setting it has been used to evaluate patients with decompensated heart failure, septic shock and hypovolaemia following major insult e.g. trauma. However ICG has never been previously used to evaluate cardiac output monitoring in post-operative cardiac surgical patients and hence the prior literature is being extrapolated to this context.

With regards to pacemaker optimisation, a few groups have previously compared its reproducibility to transthoracic echocardiography in permanent pacing systems and atrioventricular delay.(146) However the overall number so patients enrolled into such studies is small and though individual studies have demonstrated significant findings a larger multicentre study is needed. One of the largest studies recently published was that performed by Khan et al who evaluated the NICOM device (Cheetah Medical, Oregon, US) in 47 patients with cardiac resynchronisation therapy (CRT) implants.(145) Following CRT implantation, after a period of fourteen days, the optimal AV and ventriculo-ventricular delay was identified using the ICG device. The optimum AV delay determined by NICOM was confirmed by echocardiography in 40 of 47 patients (85 percent, $r = 0.89$, $P < 0.01$) and for VV delay in 39 of 47 patients (83 percent, $r = 0.89$, $P < 0.01$). In a longer term study the successful identification of AV delay when the NICOM device was used revealed a cohort who had higher rates of positive LV remodelling and clinical improvement following CRT implantation.(146)

All six patients within this study had undergone aortic valve replacement for aortic stenosis and had preserved left ventricular systolic function with a majority also having narrow QRS durations. Therefore this is a very different population to that of a patient with left ventricular systolic dysfunction and broad QRS duration being considered for CRT. There is no prior literature evaluating the physiological effects of temporary pacing in this population. There

have been a few limited trials investigating the effects of short term acute biventricular pacing in populations with significant levels of systolic dysfunction and dyssynchrony but the overall literature is extremely limited.(259, 260) Further work is much needed within this area to characterise the effect of pacing in the post operative period and its ability to assist in improving cardiac output.

## 7.5 Study Limitations

The study was conceived as a pilot study and therefore is most limited by its extremely small number of participants. All participants had had aortic valve surgery and hence the population is certainly not representative of other patients undergoing cardiac surgery e.g. mitral valve repair or replacement.

The study did not demonstrate a relationship between impedance cardiography and transthoracic echocardiography in terms of cardiac output measurement. However there is variation within every patient, to left ventricular systolic function, left ventricular outflow tract diameter, biochemistry, loading conditions and electrical conduction. A larger cohort would ensure any anomalous outliers in terms of these or other such variables would be controlled for.

Due to the exclusion criteria none of the patients were studied in the intensive care unit setting directly. Therefore we were unable to compare the relationship between ICG and invasive forms of cardiac output monitoring. Another small pilot study under such conditions would be necessary to investigate the relationship in this group of patients as compared to invasive measurement.

## 7.6 Conclusions

This small pilot study did not demonstrate a relationship in cardiac output measurement between impedance cardiography and transthoracic echocardiography in a cardiac surgical post-operative setting.

Impedance cardiography within this cohort had a tendency to record a higher cardiac output as compared to echocardiography.

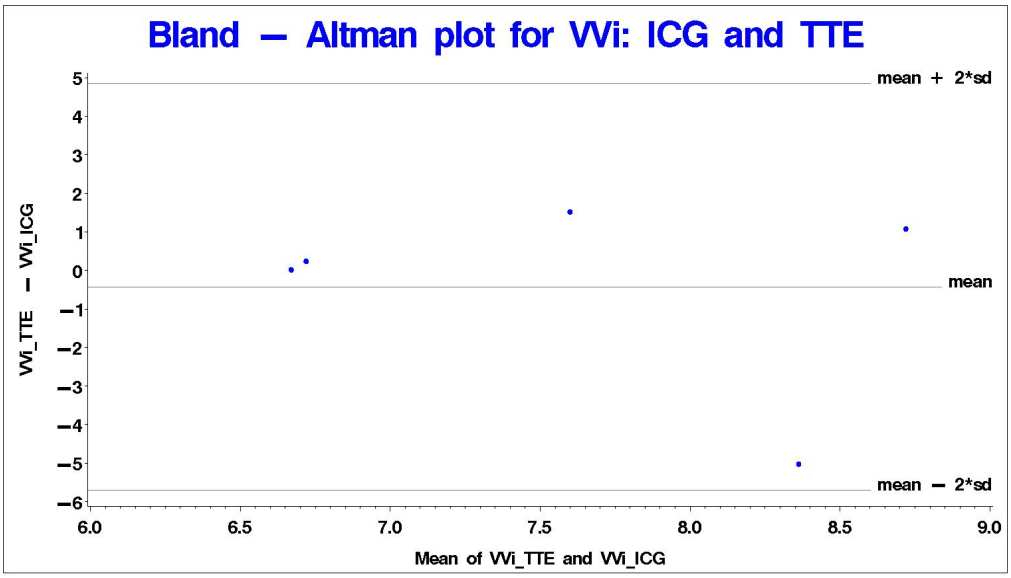
Overall alteration of pacing settings and modes within this cohort did result in changes in cardiac output. Further work is much needed within this area to further evaluate this effect. A larger study is needed to satisfactorily answer whether ICG can reliably assess cardiac output in this group of patients.

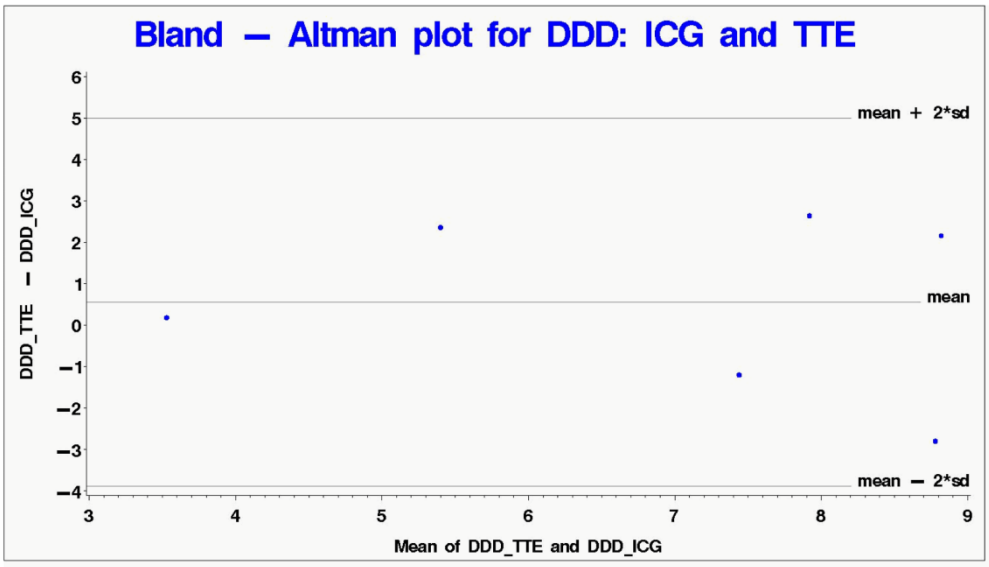
| |
|---|
| Persistent Atrial Arrhythmias (Atrial Fibrillation/ Atrial Flutter) |
| Clinical Deterioration prior to entry into study requiring more than three classes of inotropes |
| Serum pH <7.0 |
| Lactate >15 mmol/L |
| Severe renal dysfunction – (Serum Creatinine >200mmol/L or requiring renal replacement therapy) |
| The clinical necessity for a Left Ventricular Assist Device (LVAD) prior to recruitment into the study |
| Procedures performed on patients with congenital heart disease and/or involving the right ventricle |

**Table 13: Exclusion Criteria for Study**

| *Variable* | *Mean (Standard Deviation) unless specified* |
|---|---|
| Gender | Male =4 (67%), Female =2 (33%) |
| AVR | N=6 (100%) |
| pH | 7.41 = +/- 0.04 |
| Lactate (mmol/L) | 1.6+/- 0.9 |
| Haemoglobin (g/dL) | 9.9 +/- 0.6 |
| Urea (mmol/L) | 6.6+/- 2.0 |
| Creatinine (mmol/L) | 101 +/- 23.8 |
| Potassium (mmol/L) | 4.7+/- 0.5 |
| Sodium (mmol/L) | 139.5+/-2.9 |
| Magnesium (mmol/L) | 1.29+/-0.47 |
| QRS duration (ms) | 112+/-35.4 |
| PR interval (ms) | 195.6 +/- 97.8 |
| QT corrected (ms) | 454.6 +/- 46.6 |
| LV Ejection Fraction | 57.3 +/-5.5 |
| LVEDD (cm) | 4.5 +/- 0.5 |
| LA Diameter (cm) | 4.4+/- 0.8 |

**Table 14: Baseline Demographics of cohort; AVR; Aortic Valve Replacement; LVEDD – Left Ventricular End Diastolic Diameter; LA – Left Atrial Diameter**


Bland – Altman plot for Vvi: ICG and TTE
mean + 2*sd
mean
mean – 2*sd
Vvi_TTE – Vvi_ICG
Mean of Vvi_TTE and Vvi_ICG
5
4
3
2
1
0
−1
−2
−3
−4
−5
−6
6.0
6.5
7.0
7.5
8.0
8.5
9.0


Bland – Altman plot for DDD: ICG and TTE
mean + 2*sd
mean
mean – 2*sd
DDD_TTE – DDD_ICG
Mean of DDD_TTE and DDD_ICG
6
5
4
3
2
1
0
−1
−2
−3
−4
3
4
5
6
7
8
9

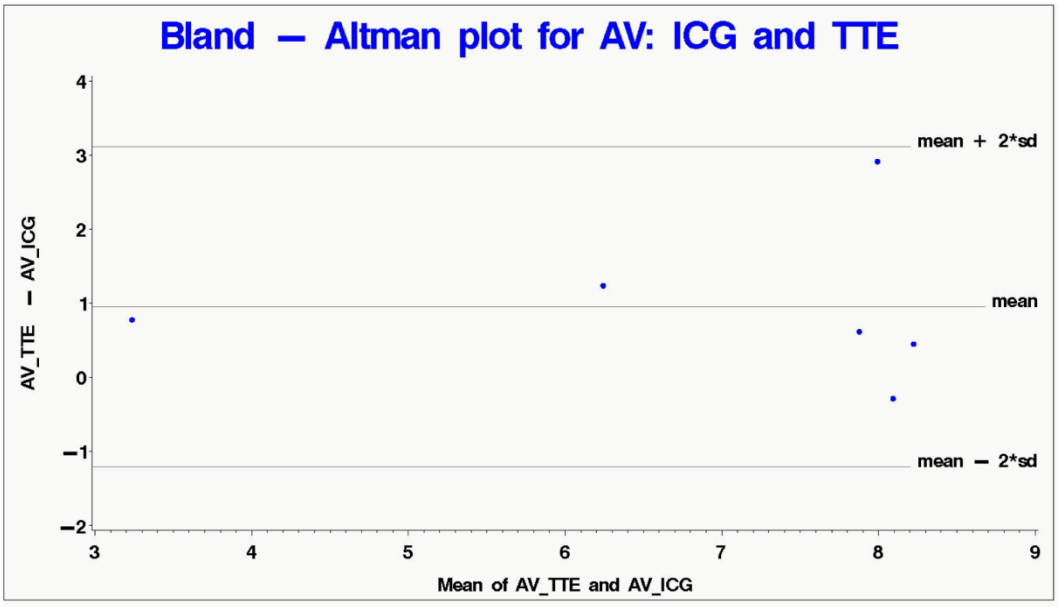
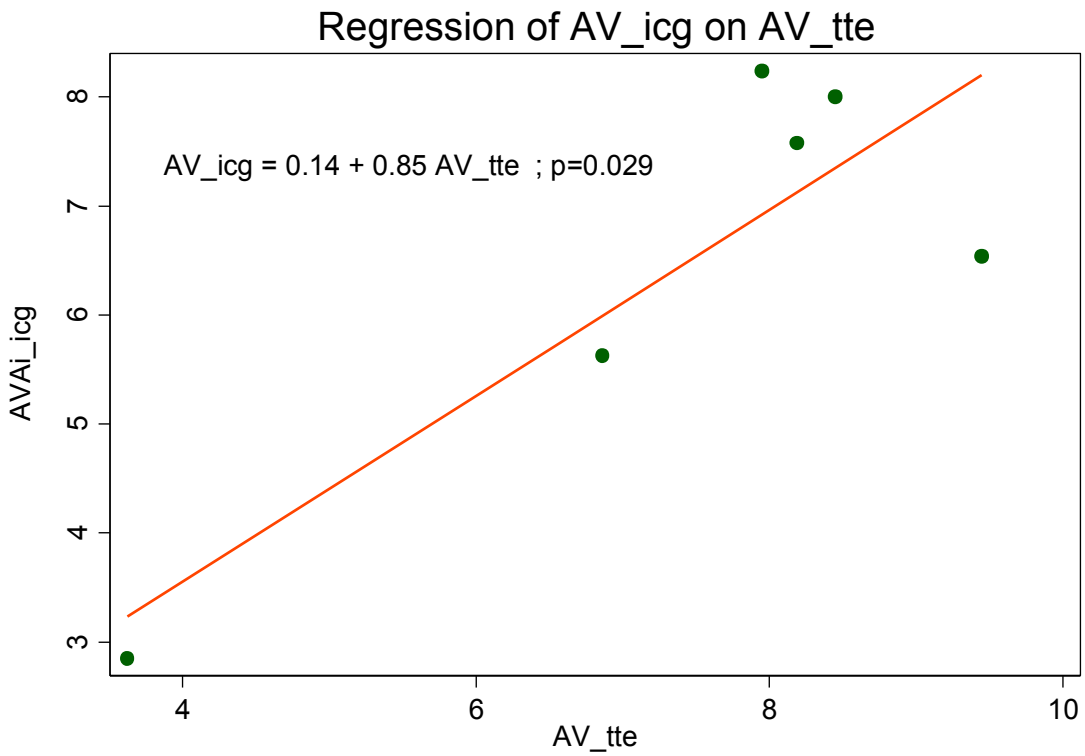
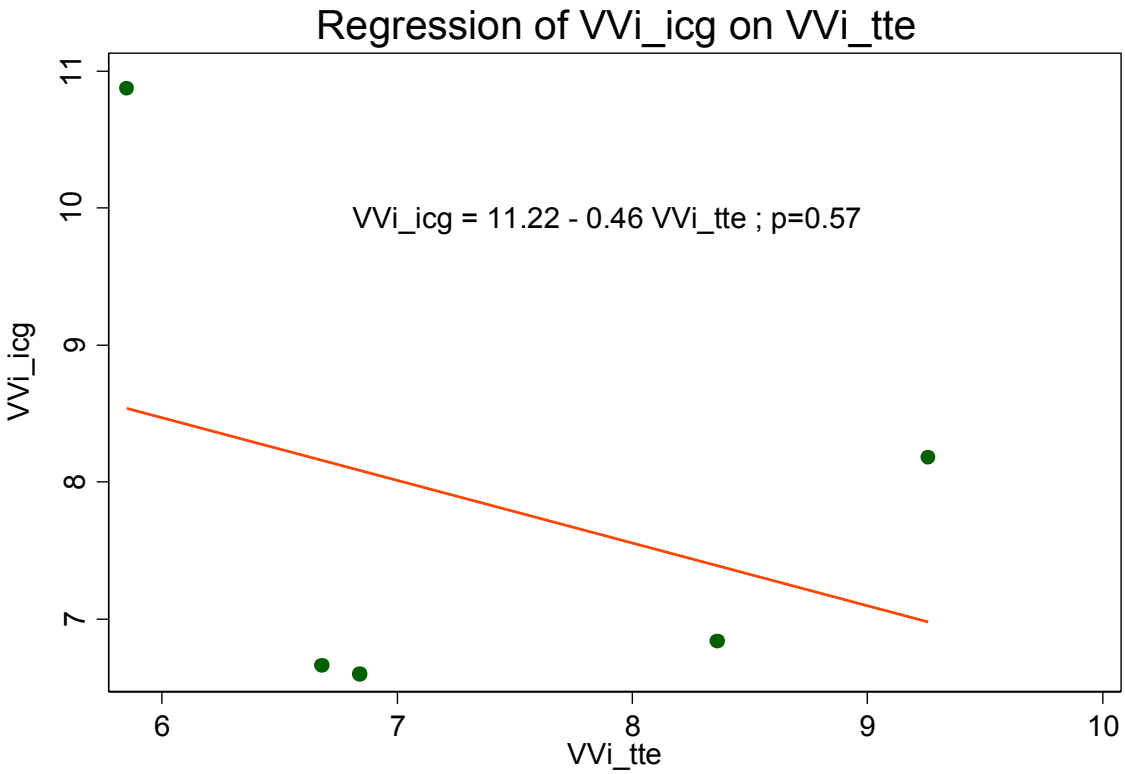



**Figure 17: Bland Altman Plots for the data from 6 paired samples with cardiac output calculated via transthoracic echocardiography versus impedance cardiography (NICOMMO device).The three figures represent different modes of pacing.**


Regression of AV_icg on AV_tte
AV_icg = 0.14 + 0.85 AV_tte ; p=0.029
AVAi_icg
AV_tte
3
4
5
6
7
8
4
6
8
10


Regression of VVi_icg on VVi_tte
VVi_icg = 11.22 - 0.46 VVi_tte ; p=0.57
VVi_icg
VVi_tte
7
8
9
10
11
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7
8
9
10

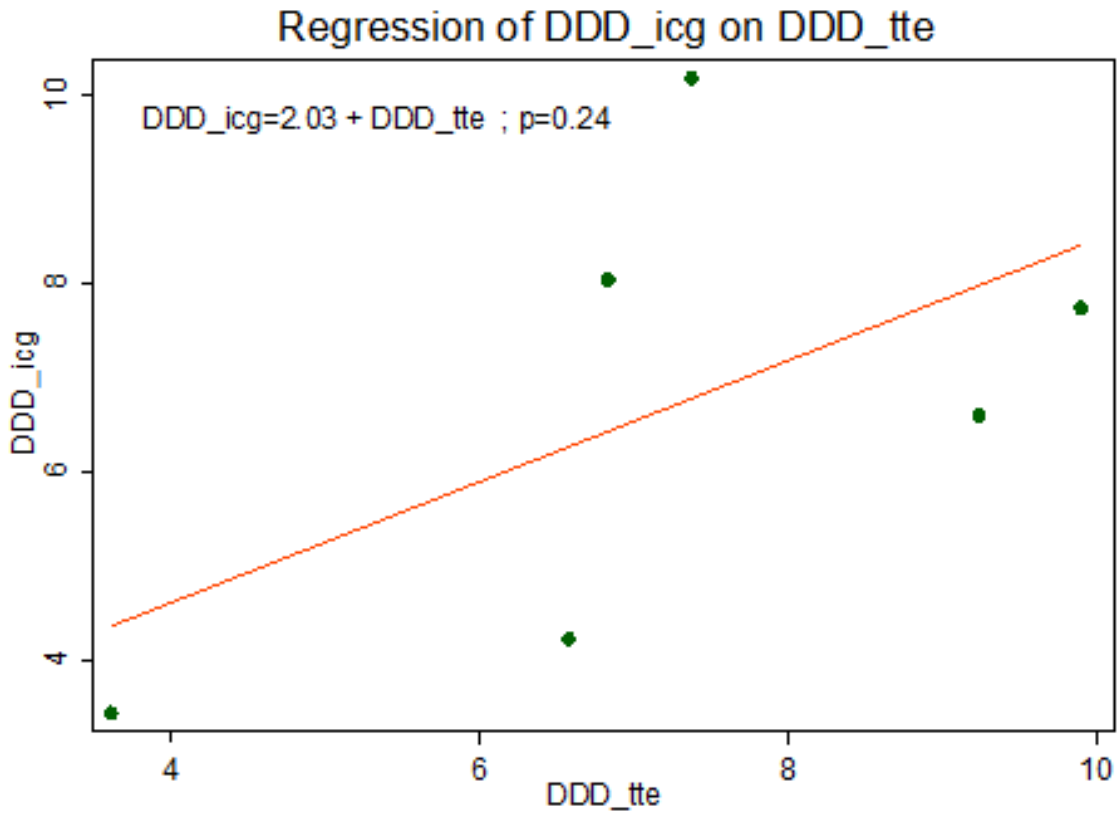


**Figure 18: Demonstrating the regression equation and Line of best fit.Demonstrates the above relationship in variable atrioventricular delays. Demonstrates the above relationship in VVI configuration pacing. Demonstrates the above relationship with DDD configuration pacing.**

# Chapter VIII: Discussion, Clinical Implications, Ideas for Future Research and Conclusions

## 8.1 Discussion

Cardiac Resynchronisation Therapy (CRT) is an established therapy for patients with specified selection criteria and symptomatic left ventricular systolic dysfunction. The associated literature within the field of CRT is vast. The thesis has explored some concepts within the area and the conclusions drawn are below.

### 8.1.1 A structured clinical protocol for the care of patients following Cardiac Resynchronisation Therapy

Increasing numbers of patients throughout the westernised world and particularly the United Kingdom are undergoing CRT implantation.(189, 190) However the systems in terms of local and national healthcare infrastructure for the pre and after care of such patients remains heterogeneous and non-optimal.

There are limited data from the United States that dedicated heart failure pacing clinics may be one such model for patients with CRT implants.(149) The published data suggests that such clinics with structured protocols may be able to identify reasons behind the individual lack of clinical benefit such as the need for Atrio ventricular (AV) interval and Ventriculo-ventricular (VV) interval optimisation, the need for addressing co-morbidities such as anaemia and the need for review and up titration of concomitant evidence based pharmacotherapy. A large proportion of the patients who were not experiencing anticipated clinical benefit were on sub optimal evidence based pharmacotherapy.

Using data from the specialised heart failure pacing clinic at the Royal Brompton Hospital, London, I was able to demonstrate that a structured clinical approach to the follow up of such patients results in improved doses of HF pharmacotherapies.(220) This also agrees with data from other groups, whereby the period following CRT implantation may lead to favourable physiological conditions where HF therapies may be introduced or uptitrated. The pertinent longer term question is as to whether this results in improved outcome for such patients and

justifies the added expense of the introduction and maintenance of a specialised clinic. This would need further research into the area as described below.

### 8.1.2. Haemodynamic Optimisation of Cardiac Resynchronisation Therapy Study (optCRT)

A consecutive series of 44 patients was recruited prospectively and randomised to either echocardiographic guided optimisation or impedance cardiographic (ICG) optimisation. Using a primary endpoint of improvement 6MWT distance, both methods were shown to be equal. There were no differences on secondary endpoints within either arm.

The trial population was recruited from a single tertiary centre and was small. However the study is one of the largest in the field using ICG equipment. Although a larger study is needed to evaluate whether ICG is superior as compared to echo guided methods of adjustment of AV and VV intervals - it remains a viable alternative on the basis of this study.

Similar to others within studies based around the optimisation process, a notable majority of patients had alteration in their AV and VV intervals from the CRT implant baseline settings. Though the optimisation process has not been investigated in terms of impact on clinical outcomes, the data accrued from this study along with others is suggestive that it should be considered for all patients in the post implant period. Another point which was noted within this study and links to the findings described in chapter IV is that by evaluating patients systematically at preset time points following CRT implantation, this allows the review and uptitration of HF evidence based pharmacotherapies.

### 8.1.3 Right Ventricular Dysfunction predicts clinical outcomes in a population undergoing CRT

From analysing the previous literature and my own clinical experience during the research period, I noted that several patients seemed to have significant levels of right ventricular (RV) dysfunction prior to CRT implantation. Right ventricular dysfunction has long been recognised as an adverse prognosticator in populations with heart failure.
Right ventricular dysfunction has long been recognised as an adverse prognosticator in populations with heart failure.(234) Recent observational data from selected groups used echocardiography to measure parameters associated with right ventricular dysfunction including right ventricular fractional area change, myocardial performance index and tricuspid annular plane imaging.(245) Due to its complex geometrical anatomy, the right ventricle is difficult to visualise on echocardiography. A certain proportion of patients do not possess sufficient acoustic windows to permit accurate visualisation of the right ventricle let alone make accurate measurement of structure and function.

Hence using a cohort derived from the heart failure pacing clinic and who had undergone cardiac magnetic resonance imaging of their heart prior to CRT implantation, I was able to demonstrate that using a cut point of 15 millimetres for Tricuspid Annular Plane Systolic Excursion distance (TAPSE) and 50 % for Right Ventricular Ejection Fraction (RVEF) was associated with adverse clinical outcomes defined as a composite endpoint of heart failure hospitalisation and all cause mortality. A couple of further points of interest emerged from this study. Firstly there was a wide spread heterogeneity in RV function despite all patients fulfilling the necessity to possess a LVEF <35% for CRT implantation. Since the publication of the study included in this thesis, others have corroborated its findings using speckle tracking.(261) However the overall collection of data from various studies at this timepoint remains limited. Further work is needed to evaluate right ventricular dysfunction in a patient undergoing CRT implantation and whether it ultimately has a role in patient selection.

Secondly the use of cardiac magnetic resonance (CMR) in heart failure is expanding. Late gadolinium enhancement (LGE) has been demonstrated in several cohorts to be associated with adverse prognosis and increased morbidity. The position of LGE within the left ventricle and its location in relation to a contiguous LV lead has also been shown to carry adverse prognosis.(262) Thus the right ventricular data from this study also supports another purpose

of CMR within this group of patients. Ultimately all of these findings from CMR based studies have been performed on small cohorts, often single centre studies with non-randomised groups. Each finding need to be further characterised in larger prospective cohorts but in the longer term, a CMR study may become a part of the evaluation process for potential CRT recipients.

### 8.1.4 Optimisation of biventricular pacing in ITU setting (BiTU)

This study was conceived as a response to comments at the upgrade viva. It was designed as a validation pilot study for ICG equipment in the role of pacemaker optimisation in an alternative setting.

A series of 6 patients was recruited prospectively who were scheduled for cardiac surgery. All received epicardial pacing leads as part of their routine clinical care.
Following their transition from intensive care to the high dependency unit, the haemodynamic profiles in conjunction with echocardiographic assessment was performed at various heart rates and pacing modes. The findings were documented and the degree of correlation was investigated.

In conclusion there was some limited agreement between ICG equipment and echocardiographic measures - this was more so at lower heart rates. At certain levels of heart rate and pacing modes there was little correlation.

One point of note is that the optimal cardiac output for each patient differed significantly from their baseline setting in the post-operative period. This may be of some clinical benefit and a larger study with different protocol would be needed to answer this question.

## 8.2 Future Research

Cardiac Resynchronisation Therapy (CRT) has become an established therapy for heart failure over the last twenty years. Its transition from theory and initial pilot studies to large scale randomised controlled trials has been relatively rapid. It should be remembered as the CRT literature has expanded, medical therapy for heart failure has also improved with several large randomised trials reporting recently.

The evidence base has grown and there is clear evidence from various trials that CRT is effective at improving morbidity and mortality within selected populations of LVSD. However like any other technology, what is unknown is the ability of CRT to be beneficial in patients outside of the current evidence base. The current recommendations for a patient to be considered for a CRT device are broadly similar in terms of European and American guidelines (British guidelines are currently being revised).(22, 98) Currently this is a left ventricular ejection fraction (LVEF) of <35 percent, a surface QRS duration of >120 milliseconds on the electrocardiogram (ECG), optimal tolerated medical therapy and New York Heart Association (NYHA) class II to IV. However despite the number of trials and several thousand participants, it still unknown as to why a third of patients do not derive the clinical benefit anticipated prior to the procedure of CRT implantation. The reasons behind this are likely to be multifactorial. Each step of the process looking after a potential patient who is a CRT candidate is crucial and may have variation which ultimately impacts on the clinical experience and outcome for that individual.

Prior to CRT implantation, the patient should be assessed by a heart failure pacing specialist and suitability deemed by the guidelines and also clinical status. The decision to proceed to CRT implantation should be performed only once pharmacotherapy has been reviewed and co-morbidities addressed. The implantation stage of the procedure has become standardised with simplified transvenous techniques. However the left ventricular (LV) lead position and maybe the right ventricular lead (RV) is critical. Current fluoroscopic techniques preclude the on table demonstration of myocardial scar, but it is imperative that the LV lead avoids such regions and is placed where possible in a lateral or infero-lateral position.
Following successful implantation of CRT, the patient needs to have pacing checks, detailed imaging and frequent careful clinical supervision. The period of six months following CRT

implantation is an opportunity to review and uptitrate prognostic medication. They should also undergo optimisation of the AV and VV intervals.

Each of these steps has been evaluated in small single centre or limited multi centre studies. However none of these steps or processes has yet formed the basis for a larger randomised controlled trial. The other noteworthy development in the field is the ongoing technological development. Manufacturers of CRT are continuously refining generators and lead to improve performance. One such example is the development of a quadripolar left ventricular lead which is able to perform multi-site pacing via reconfiguration of pacing vectors.(263) Alternatively more sophisticated algorithms are becoming embedded into the device to monitor intra-thoracic impedance, pulmonary capillary wedge pressure. These tools when monitored, may allow the healthcare team looking after the patient to act and predict imminent decompensation.

The clinical trials have recruited and published with speed, several having been published over the last ten years. However though the clinical effectiveness of CRT is unquestionable, there are notable areas with a paucity of data including females, more elderly patients, patients with atrial fibrillation, patients with significant levels of co-morbidities, patients with heart failure from the ethnic minorities and patients undergoing ‘upgrade’ procedures from conventional dual chamber pacing and ICD systems. The rapid speed whereby CRT has become an established therapy for selected patients with heart failure means that to deny a patient the benefit of CRT is unethical. Therefore either data needs to be collected and published from observational studies or prespecified sub group analyses from the prospective randomised controlled trials. Both do exist but often give different results, which leads to debate in the sub area. Another alternative is to perform studies in geographical areas of the world with less exposure to CRT and thus compare the true effect of CRT versus modern heart failure therapy.

The boundaries described by the current recommendations are defined as a QRS duration>120 milliseconds and a LVEF <35 percent. Apart from the issues described above the other question facing the field is whether CRT would be effective in those patients which currently fall outside of the cut points. Some data exists from sub studies from large trial data that this may be the case but further larger randomised trials are underway in the area. The registry data that exists for the use of CRT highlights the expansion and use of CRT beyond

the guidelines.(190) Thus the areas I have described above need further clarification, thought and data to support such clinical extension of the technology. This is especially relevant in modern healthcare infrastructure, where the focus has shifted onto evidence based application of technology in association with the collection of clinical outcomes.

The ideas for future research on the basis of the studies presented within this thesis are:

A direct comparison of conventional ad hoc care of the patient with a CRT implant versus the structure approach described within chapter V. The primary endpoint would be the dose of evidence based pharmacotherapy.

The longer term follow up of patients described in hypothesis 1. Does this affect clinical outcome in terms of HF hospitalisation and mortality?

Optimisation using impedance cardiography versus echocardiographic guided optimisation in a prospective randomised study with symptomatic and clinical endpoints.

Optimisation of impedance cardiography should be performed at rest or on exercise- pilot study using a symptomatic endpoint

A long term multi centre prospective study observing all patients following CRT implantation and optimisation with endpoints being clinical outcomes. Patients would be randomised to different optimisation techniques

A prospective large cohort of patients randomised to CRT or medical therapy implantation on the basis of right ventricular dysfunction and current selection criteria and clinical endpoints

The reproducibility and repeatability of RV assessment using cardiac magnetic resonance imaging in patients with CRT implants – a validation study

A comparative study of CMR versus echocardiographic measures of RV function in a cohort of patients with CRT on a prespecified endpoint

A validation study of impedance cardiography versus echocardiographic monitoring of cardiac output in a cardiac intensive care setting

A validation study of impedance cardiography versus echocardiographic monitoring of cardiac output in a intensive care setting

Optimisation of AV intervals in patients in a cardiac intensive care setting improves clinical outcome

## 8.3 Clinical Implications

Having studied the field of cardiac resynchronisation therapy in more detail there are numerous potential clinical implications derived from the thesis and the studies contained within it.

The evidence base for CRT has steadily increased over the last fifteen years. The established indications are now non debatable but the boundaries for the application of CRT technology are under constant investigation. Logically the use of CRT needs to be evaluated in large rigorous randomised clinical studies in populations with narrow QRS durations, patients with milder forms of left ventricular systolic dysfunction and those with preserved left ventricular systolic function, rarer aetiologies such as infiltrative cardiomyopathy (sarcoidosis, haemachromatosis and amyloidosis) and a direct comparison of CRT-P vs CRT-D in structured trial format.

Apart from investigating the boundaries of technological application, further work needs to be performed in all aspects of the process for a patient undergoing CRT implantation.

Firstly patient selection needs to be investigated further and reliable prognosticators identified from larger data sets. The issue of cardiac imaging and its role in patient identification and evaluation of mechanical dyssynchrony needs careful thought and carefully constructed studies to evaluate whether such techniques justify costly equipment and healthcare resources in an environment of diminishing healthcare expenditure.

The actual implantation process for CRT has evolved over the last seven years but more sophisticated lead technology, wireless systems, more embedded algorithms which may aid the diagnostics and ongoing care of a patient with heart failure, and compatibility with cardiac magnetic resonance scanning.

In the post implant phase further investigation is badly needed in the field of optimisation with more attention paid to device and medical optimisation. Despite the extension of CRT to increasing number of patients - the residual problem of response remains poorly characterised and understood. A consensual definition is urgently needed which would permit further evaluation. In the longer term healthcare infrastructure also needs to be reviewed to cope with increasing numbers of patients with CRT implants in situ. Apart from dedicated heart failure pacing clinics, increasing numbers of CRT devices have a remote transmission capability and modern healthcare needs to evolve and investigate how best to employ such technology.

Concentrating on healthcare within the United Kingdom - there are numerous issues raised following further study and partly answered by some of the studies within this thesis. The current model of healthcare in the UK is a public funded system which covers the National Health Service. Within this framework control is delegated from the Department of Health to regional groups who then are responsible for clinical commissioning locally. However the UK along with all other major Western nations is currently in the midst of economic recession and has had major recent healthcare structural change. In the new commissioning environment it is currently unknown as to what will happen with regards to CRT implantation rates. This against the backdrop of a constant increase in CRT implantation rates across particularly England and Wales over the last ten years. Currently there is widespread geographical variation not only in CRT implant rates but also in the aftercare of such individuals. The study performed within this thesis (Chapter IV) which evaluated individuals passing through a dedicated heart failure pacing clinic demonstrated a clear improvement in the initiation and uptitration of evidence based pharmacotherapies. Though the study lacked a control group, the regional and local variation of patients with CRT implants means that many patients remain on sub optimal doses and medication following CRT implantation. This represents a potential lost opportunity to review HF medication.

Hence one possible implication from this thesis is to consider HF-pacing clinics with consultant cardiologists experienced in both heart failure and devices in a more widespread format. Whether this is worthwhile of further resource allocation and expense needs to be considered properly in a prospective study comparing patients passing through such clinics as compared to conventional care.

The most recent guidance has been issued by the ESC, this year.(22) The guidelines covering CRT are currently being revised by NICE and are awaited. Device based optimisation according to the current ESC guidance is now reserved for patients who are non-responders. Initial evidence relied on echocardiographic optimisation methods, however due to a limited literature these methods are under question. Numerous alternative methods including algorithmic and other non invasive methods now exist for device based optimisation. Chapter V presents an optimisation study using impedance cardiography.

With increasing numbers of patients with CRT implants in the UK, there is potential for the enhanced collection of clinical data. A national audit already exists for patients with heart failure and Cardiac Rhythm Devices by combining the two and recording clinical outcomes, this would ensure a large collection of data which could be analysed. An increased degree of cooperation between local, regional and national bodies would enhance the possibilities of meaningful research within the area and also ensure that the UK remains a suitable destination for large randomised studies in the field of CRT.

Ultimately the thesis has contributed small amounts of data to certain areas of this field, but in my own personal opinion further research is sorely needed to clarify this technology and all of its associated aspects. Cardiac resynchronisation therapy is now an established therapy but remains complex and with multiple questions which remain unanswered and needing further clarification.

## 8.4 Conclusion

This thesis has allowed me to investigate different aspects related to the management of patients with CRT implants. The literature for this area has mirrored clinical development and has increased rapidly.

However there are still many uncertainties with regards to management of patients following CRT implantation and why some derive a much greater clinical improvement than others.

The study chapters focussed on clinical protocol, optimisation and right ventricular dysfunction have demonstrated with small amounts of data the ability to improve on certain points in the pathway for the care of such patients. Right ventricular function is a prognostic marker and may be of use clinically in the longer term. A structured clinical protocol which thoroughly re-evaluates the patient following CRT implantation and permits medical optimisation is described in chapter IV. This may again be of some clinical merit and needs further exploration. The study performed on optimisation demonstrates that ICG is a viable option for CRT optimisation but its true effect needs further investigation. Similar to others, however it shows that optimisation does result in significant haemodynamic improvement in certain individuals.

The thesis chapters and other publications during my research time have shown that there gaps of knowledge deficiency which need further investigation but in the longer term may yield improved clinical benefits for the patient with CRT.

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# Appendix

# 9.1 Appendix I - Minnesota Living with Heart Failure Questionnaire

**MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE**

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

| Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by - | No | | | | Very Much |
|---|---|---|---|---|---|
| | Very Little | | | | |
| 1. Causing swelling in your ankles or legs? | 0 | 1 | 2 | 3 | 4 | 5 |
| 2. Making you sit or lie down to rest during the day? | 0 | 1 | 2 | 3 | 4 | 5 |
| 3. Making your walking about or climbing stairs difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 4. Making your working around the house or yard difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 5. Making your going places away from home difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 6. Making your sleeping well at night difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 7. Making your relating to or doing things with your friends or family difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 8. Making your working to earn a living difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 9. Making your recreational pastimes, sports or hobbies difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 10. Making your sexual activities difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 11. Making you eat less of the foods you like? | 0 | 1 | 2 | 3 | 4 | 5 |
| 12. Making you short of breath? | 0 | 1 | 2 | 3 | 4 | 5 |
| 13. Making you tired, fatigued, or low on energy? | 0 | 1 | 2 | 3 | 4 | 5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **14. Making you stay in a hospital?** | **0** | **1** | **2** | **3** | **4** | **5** |
| **15. Costing you money for medical care?** | **0** | **1** | **2** | **3** | **4** | **5** |
| **16. Giving you side effects from treatments?** | **0** | **1** | **2** | **3** | **4** | **5** |
| **17. Making you feel you are a burden to your family or friends?** | **0** | **1** | **2** | **3** | **4** | **5** |
| **18. Making you feel a loss of self-control in your life?** | **0** | **1** | **2** | **3** | **4** | **5** |
| **19. Making you worry?** | **0** | **1** | **2** | **3** | **4** | **5** |
| **20. Making it difficult for you to concentrate or remember things?** | **0** | **1** | **2** | **3** | **4** | **5** |
| **21. Making you feel depressed?** | **0** | **1** | **2** | **3** | **4** | **5** |

## 9.2 Appendix II - Further Publications

### OTHER PUBLICATIONS WHILST REGISTERED FOR THIS DEGREE

1 T M$^{c}$Donagh, **K Guha**. British society of heart failure meeting report, 2009. Expert Rev Cardiovasc Ther; 2010; Apr 8 (4):499-502.

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Sharma, JP Carpenter, SA Cook, MR Cowie, RG Assomull, DJ Pennell, SK Prasad. The Prevalence and Prognostic Significance of Right Ventricular Systolic Dysfunction in Non-Ischemic Dilated Cardiomyopathy. Circulation;2013;Aug 21 (Epub ahead of publication)

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**EDITORIALS**

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