STRAIN AND PACING STUDY:
THE EFFECT OF PACING ON THE MECHANICS OF CARDIAC STRAIN

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Abstract

Aims: Our aim was to find a strain-based echocardiographic measurement that could detect a difference in the LV function cardiac mechanics between paced and intrinsic conduction. The study assessed strain-based measurements to identify whether they could differentiate between RV apical and RVOT pacing when comparing paced beats to intrinsic beats.

Methods: An observational study was performed on echocardiographic data from twenty-seven subjects (75 ±9.2 years) who received permanent pacemaker systems, then a combined pacemaker check and echocardiogram peri-procedurally. These subjects had normal underlying cardiac structure and function. The group was separated into RVA (n = 12) and RVOT (n = 15) for sub-group comparison. Parameters were assessed twice for each subject; during intrinsic and paced conduction, heart rates were matched. The strain parameters analysed included global longitudinal strain (GLS), radial strain and strain rate, global circumferential strain and strain rate, rotational strain and strain rate. Dyssynchrony was assessed using TDI analysis and speckle tracking radial strain methods. Traditional echocardiographic measures of ejection fraction, LVOT VTI and cardiac output were analysed. Time measurements were made from the onset of the QRS to; systolic onset, cessation, strain and strain rate peaks, for analysis of dyssynchrony and the sequence of mechanical events during intrinsic conduction for comparison to paced conduction. Systolic duration was calculated to evaluate when in systole mechanical events occurred.

Results: GLS was sensitive to changes in cardiac mechanics with pacing compared to intrinsic conduction (GLS\textsubscript{paced} = -13.90 ±6.33% compared to GLS\textsubscript{intrinsic} = -16.31% ±3.92%, p 0.0359). The change in GLS was more
significant in the RVA sub-group (GLS\textsubscript{paced} = -12.93 ±4.53% compared to GLS\textsubscript{intrinsic} = -16.13% ±3.60%, p 0.0028), while GLS with RVOT pacing was similar to intrinsic conduction (GLS\textsubscript{paced} = -16.08 ±3.39% compared to GLS\textsubscript{intrinsic} = -16.08% ±4.28%, p 0.5989). None of the other strain-based parameters showed significant differences between paced and intrinsic beats. Dyssynchrony analysis was inconclusive, without significant difference between paced and intrinsic beats. QRS duration and cardiac axis altered with pacing in ways that have been well documented and reflect pacing lead site. Systole was temporally translated with pacing, occurring later, though this was unrelated to any increase in QRS duration. The significance of systole occurring later with pacing was unclear, though it is a definite mechanical change. There was no change in the sequence of cardiac events during systole.

**Conclusion:** GLS is sensitive to pacing induced changes in mechanics of LV function. GLS can differentiate between RVA and RVOT pacing, as RVOT pacing did not alter the cardiac mechanics as described by GLS. If these changes are observed in a longitudinal data series in patients with pacemakers, and predict deterioration in cardiac function, then they might be relevant to predict pacing-induced adverse events. If this were the case, then peri-procedural echocardiography could be used to determine when lead repositioning was required in this group.
Acknowledgements

Thank you to all those who in some way, shape or form have supported me. To my supervisors, Dr Peter Larsen, Dr Alexander Sasse and Dr Scott Harding, thank you for your kind support and encouragement.

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Scott, without your use of RVOT pacing, this research could not have happened. Knowing that I had the support of such an excellent pacing expert gave me confidence to reach out of my echocardiography comfort zone to learn more about the world of pacing.

To the cardiac physiology team at Wellington Hospital – a big thank you for putting up with me during one ultra-busy year. To the senior pacing staff thank you for answering all my questions about pacing implants and programming.

Saving the best for last, to my family, who have been there for me in new ways this year, when on multiple fronts I have been stretched beyond belief. For each of us 2012 has been a bigger year on the family front than any of us predicted; yet we’ve stuck together for the important bits and have reaped the benefits hard work can bring. Stephen, you have my heart and always will.
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<tr>
<td>2D</td>
<td>Two-dimensional</td>
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<tr>
<td>A-I</td>
<td>Anterior to inferior</td>
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<tr>
<td>A-paced</td>
<td>Paced from the atrial lead</td>
</tr>
<tr>
<td>ACE-1</td>
<td>Angiotensin converter enzyme inhibitor</td>
</tr>
<tr>
<td>A Dur</td>
<td>A wave duration – atrial wave of either MV inflow or Pvv inflow</td>
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<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
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<td>AFI</td>
<td>Automated function imaging – GE specific name for GLS analysis</td>
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<td>Alpha-b</td>
<td>Alpha blocker</td>
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<td>AoV</td>
<td>Aortic valve</td>
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<td>AP</td>
<td>Antero-posterior</td>
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<td>APLAX</td>
<td>Apical long axis</td>
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<td>ARB</td>
<td>Angiotensin receptor blocker</td>
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<tr>
<td>ASE</td>
<td>American Society of Echocardiography</td>
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<tr>
<td>AS-P</td>
<td>Antero-septal to posterior</td>
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<tr>
<td>ATO</td>
<td>Automated tissue optimisation</td>
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<tr>
<td>AV</td>
<td>Atrioventricular</td>
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<td>AV_GLS</td>
<td>Average global peak longitudinal strain</td>
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<td>AVN</td>
<td>Atrioventricular node disease</td>
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<tr>
<td>BB</td>
<td>Beta blocker</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>bpm</td>
<td>Beats per minute</td>
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<td>BT8, BT12</td>
<td>Break-through software levels for GE echocardiography machine</td>
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<td>CAD</td>
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<td>CCB</td>
<td>Calcium channel blocker</td>
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<td>CCDHB</td>
<td>Capital &amp; Coast District Health Board, Wellington Hospital</td>
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<td>CFM</td>
<td>Colour flow map or mapping</td>
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<tr>
<td>CHF</td>
<td>Congestive Heart Failure</td>
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<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<td>CRT-D</td>
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<td>CV</td>
<td>Chamber view, in conjunction with 2 or 4</td>
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<td>CW</td>
<td>Continuous wave</td>
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<td>DDD</td>
<td>Dual chamber pacing, sensing and inhibition</td>
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<td>DDP</td>
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<td>e.g.</td>
<td>Exempli gratia, example given</td>
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<td>eGFR</td>
<td>Glomerular Filtration Rate</td>
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<tr>
<td>fps</td>
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<td>GE</td>
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<td>GLS</td>
<td>Global longitudinal strain or average global peak longitudinal strain</td>
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<td>ICD</td>
<td>Implantable cardioverter defibrillator</td>
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<td>IRW</td>
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<td>IVRT</td>
<td>Iso-volumetric relaxation time</td>
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<td>IVS</td>
<td>Inter-ventricular septum</td>
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<td>LAD</td>
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LVOT VTI  Left ventricular outflow tract velocity time integral
LVPEP  LV pre-ejection period
M-Mode  Motion mode
MHz  Mega Hertz
MI  Myocardial infarction
mm  Millimeters
mm/s  Millimeters per second
MOD  Method of disks
msec, ms  Milliseconds
MV  Mitral valve
mV  Millivolts
MV dp/dt  MV change in pressure divided by change in time
MV E  Mitral valve early diastolic inflow wave
‘n’  Number, e.g. in a group or sub-group
PA  Postero-anterior
PCI  Percutaneous coronary intervention
PLAX  Parasternal long axis
PPM  Permanent pacemaker
PSAX  Parasternal short axis
PV D  Pulmonary venous diastolic wave
PV S  Pulmonary venous systolic wave
Pvv  Pulmonary veins or venous
PW  Pulse wave
PW-TDI  Pulse wave – Tissue Doppler imaging
RAD  Right axis deviation
RAO  Right anterior oblique
RBBB  Right bundle branch block
RS  Radial strain
RSR        Radial strain rate
RV         Right ventricle
RVA        Right ventricular apex or apical
RVOT       Right ventricular outflow tract
RVPEP      RV pre-ejection period
S-L        Septal to Lateral
SND        Sinus Node Disease
SPWMD      Septal to posterior wall motion delay
SR         Sinus rhythm
ST         Systolic time
SVC        Superior vena cava
TDI        Tissue Doppler imaging, synonymous with TVI
TGC        Transmission gain compensation
TSI        Tissue systolic imaging
TV         Tricuspid valve
TVI        Tissue velocity imaging, synonymous with TDI
V-paced    Ventricularly paced – paced by RV lead unless specified
VVI        Ventricular pacing, ventricular sensing, inhibited by intrinsic ventricular conduction
ΔPEP       Difference in pre-ejection periods of LV and RV
Introduction

Pacing from the RV more than 40% of the time is associated with greater incidence of adverse outcomes, including heart failure, hospitalizations and death (1). RV paced beats do not originate or necessarily travel along the normal cardiac conduction pathways; consequently a paced beat is likely to have a wider QRS complex. With paced beats altering the conduction pathway and activation sequence of ventricular myocardium, there are mechanical changes to the pattern of contraction, which over time may contribute to ventricular re-modeling and decreased LV function. In an effort to reduce adverse outcomes for those who require chronic RV pacing, the concept of pacing RV from different sites has developed.

When an ECG during pacing from the RVOT appears similar to intrinsically conducted ECG, some consider this a preferable pacing lead site (2). Yet narrow QRS complexes are seen in poorly functioning ventricles, so the meaning of a narrow QRS on its own is not the whole answer. As yet pacing from an RVOT lead position has not been definitively proven or accepted to provide any mechanical or clinical benefits compared to traditional RV apical pacing (3-6).

At CCDBH the pacing implanters practice both RVA and RVOT pacing lead site positioning. In 2010, echocardiograms were carried out on pacing implant patients to confirm the ejection fraction with pacing and during intrinsic conduction was the same.

Since that time, the Wellington echocardiography service has increased their appreciation and application of advanced echocardiographic analysis
measures of strain to consider using these advanced techniques to investigate the RV pacing lead site conundrum.

There are no established short-term echocardiography measurements that tell us that pacing from the RVOT is mechanically better than pacing from the RV apex. There are currently no prognostic indicators that show a difference with pacing compared to intrinsic rhythm. Finding a short-term measurement that is sensitive enough to detect differences between RVA pacing compared to other RV pacing sites is a step towards identifying if there is one group being put at more risk of pacing induced heart failure than another.

2D speckle tracking and tissue Doppler imaging allows measurements of mechanical dyssynchrony, strain, strain rate and relative timing of events throughout systole. Measurements during paced and intrinsic conduction could look for the possibility of:

• Dyssynchrony with pacing from different sites
• Changes in segmental or global peak values of the strains/strain rates with pacing from different sites
• Changes in the timing of the peak strain/strain rate or mechanical activities from QRS onset with pacing
• Changes in the sequential timing of mechanical activities

This thesis describes the findings of an observational study of previously recorded echocardiographic data on pacemaker patients. The study intended to use newer, sophisticated echocardiographic analyses that were expected to be measureable on existing data, and compare these strain-based echocardiographic measurements of LV function and contraction mechanics during intrinsic conduction when compared to paced conduction.
The observational study investigated whether:

- The advanced analyses could be successfully carried out
- Strain-based variables could show significant differences between intrinsic and paced conduction for the whole group, the RVA sub-group, the RVOT sub-group or between the two paced sub-groups.

As part of the methodology, the experience of performing echocardiograms on pacing implant patients within 24 hours post-procedure is described, as it had a specific set of peculiarities that needed to be overcome and were readily recalled during the data collation for this observational study.

Our aim was to find a measurement that was readily made and showed a reliably detected difference between pacing and intrinsic conduction; a measurement that changed significantly with RVA pacing and not with RVOT pacing, when compared to intrinsic conduction. We sought a measurement that would identify a significant difference in mechanical performance for one pacing lead site over another.

Longitudinal tracking of this variable may come to show association with pacing related adverse events, taking physicians a step closer to an evidence base for a pacing lead site that was associated with better long term outcomes.
Chapter One: Background

1 Role and Function of a Pacemaker

The function of a permanent pacemaker is to maintain chronotropic competence by delivering an electrical impulse directly to the heart, where a patient’s own intrinsic cardiac pacemaker cells and conduction system have been documented as failing to do so, either on a consistent or intermittent basis. Chronotropic incompetence may be described as a cardiac rhythm that is too slow or is unpredictable in its reliability, thereby failing to consistently maintain adequate cardiac rhythmicity needed for stable cardiac output. Pacemakers are highly effective at reducing morbidity and mortality in bradyarrhythmias, where intrinsic rhythms are too slow, or absent.

An adult pacemaker impulse generator is usually implanted under the skin in either a pre-pectoral or sub-muscular pocket in the left or right sub-clavicular region. The pacemaker ventricular lead is entered into the venous system via access to the subclavian or cephalic vein and advanced via the SVC into the RA and RV.

The tip of the pacemaker lead has a small electrode, which is capable of conducting an impulse from the generator into the adjacent myocardium. When this electrical stimulus from the pacemaker electrode exceeds the neighbouring cell thresholds, an action potential is generated and a wave of electrical excitation spreads across the myocardium initiating myocardial contraction.

The pacemaker lead tip is traditionally positioned within the RV apex, where it has a high chance of effective conduction and secure collocation with
myocardium, though other sites within RV have been used depending on pacing suitability and operator preference.

Pacemakers are programmable allowing their settings to be adjusted to suit each patient’s presenting rhythm and requirement for pacing. Pacemaker programming is always with regard to minimizing the time spent pacing. This approach serves the patient in two respects;

- Firstly by giving the normal conduction system opportunity to take control of electrical activation of the heart as much as possible in an effort to reduce the risk of pacing induced heart failure
- Secondly by preserving battery life, which defers as long as possible any requirement for pacemaker generator replacement

2 The Problem with Pacing

Chronic pacing can lead to ventricular re-modeling and impaired ventricular function, with a prolonged paced QRS being a predictor of developing congestive heart failure (7).

Paced electrical activation does not inherently follow the normal cardiac conduction pathway, hence a prolonged QRS >120msec, which may also be described as electrical dyssynchrony. The electrical activation of the myocardium dictates the mechanical activation of the ventricles. With paced beats, there are consequential changes in the ventricular mechanics, or contraction pattern, which in some cases may result in echocardiographically detectable mechanical dyssynchrony.

Pacing induced electrical and mechanical dyssynchrony and reduced LV performance may lead to adverse clinical consequences, especially in those
with reduced LV function prior to pacing (6). The mechanism of pacing induced heart failure is not fully understood, though there are a number of studies that attempt to identify underlying components or changes attributable to pacing (8, 9).

An animal study performed by Lee et al. in 1994 showed that pacing resulted in regional changes to tissue perfusion, while the perfusion and sympathetic innervation showed heterogeneity. Lee’s conclusion indicated that there were changes at cellular level with pacing and, “…abnormal activation of the ventricles”, that might, “…result in multiple abnormalities of cardiac function, which may ultimately affect clinical outcome.”(10).

Wang et al. found that after inducing heart failure in dogs by using rapid pacing their recovery was less satisfactory in the group with a prolonged QRS: this group was found to have greater echocardiographically assessed mechanical dyssynchrony alongside their electrical dyssynchrony. Wang’s group concluded that prolonged QRS had the potential to be a predictor of pacing induced heart failure (11).

Haemodynamic studies, during a variety of intrinsic and paced origins, have assessed short-term differences in systolic blood pressure, pulmonary capillary wedge pressure and cardiac output. The findings of these studies are consistent with the concept that electrical activation from different origins initiate different mechanical contraction patterns (1, 12-14). Haemodynamic studies are combined with echocardiographic measurements to correlate both sets of findings, as one means of validating echocardiographic measurements (15).
In clinical studies, RV pacing is associated with changes in a variety of physiological and clinical variables or their interactions, e.g. QRS duration, atrial fibrillation, AV and ventricular conduction, ventricular function, prior heart failure or infarct (7, 16). RV pacing more than 40% of the time is associated with a higher incidence of heart failure and AF (17, 18). There are studies that associate increased number of adverse affects with a higher burden of RV pacing (19). A case report by Fung et al. describes an extremely negative response to RV pacing and the subsequent dramatic improvement upon reducing the pacing burden (20).

Whatever the mechanism of pacing related adverse outcomes, studies continue to suggest RV pacing induces a degree of electrical and mechanical dyssynchrony, while in other studies, similar echocardiographic measurements of LV dysfunction and heart failure are found in patients without pacemakers (21-23).

In patients with severe brady-arrhythmias the need for pacing is undeniable, while there is increased appreciation that a chronic pacing burden increases risk of clinical deterioration. It is clinically relevant to pursue a measurement that can function as an early predictor of the adverse events associated with chronic pacing in the hope of identifying the risk group and attempting to mitigate their poorer long-term clinical outcomes.

### 3 Pacing Lead Site

Traditionally the RV pacing lead tip has been positioned in the RV apex, as an accessible and secure site for lead tip placement. Early commonly available pacing leads were fixed by passively hooking into place, dictating the need for a structure to hook onto, e.g. RV trabeculae, which are found in number in
the RV apex. The direction of the lead approach and the heavy trabeculae of the RV apex facilitate implanting an apical pacing lead.

Yet studies have shown RVA pacing causes prolonged QRS duration, and electrical and mechanical dyssynchrony (7, 23).

In an effort to simulate intrinsic conduction, the concept has developed to pace the heart in a way that might generate a narrower QRS complex, with the aim of creating less electrical and mechanical dyssynchrony. This concept became possible with development of pacemaker leads and systems.

3.1 Development of Pacemaker Systems
Pacemaker technology has progressed greatly since its inception. Much of the development has been of the device itself, with smaller componentry, longer lasting batteries and improved programmable algorithms.

As pacing more than 40% of the time is clinically detrimental (1), one approach to reducing the burden of ventricular pacing is to improve the pacemaker programming thereby mitigating patient risk of adverse pacing related outcomes. This has been addressed in part through development of pacemaker algorithms that allow intrinsic conduction to occur as often as is
safely possible to do so. However, the fact remains that even with this type of programming, some patients will require pacing more than 40% of the time.

Alongside pacemakers, their leads too have developed over the last 3 decades, with the first patents for active fixation leads being recorded in United States of America in August 1989. These active fixation leads were a different concept to the original passive fixation leads. Passive fixation leads appear similar to a grappling hook that can fix within the coarse RV trabeculae. Although the positioning of passive leads is fairly stable, they can become dislodged from the apex. The limitations of placing passive leads in some intra-cardiac sites lead to further development of active fixation leads.

Active fixation leads have a tiny screw that can be extended to literally screw into the myocardium (Figure 3A).

Active fixation leads opened the door to giving implanting physicians more options of how and where pacing leads might be sited. From the mid 1990s onwards, journal articles started to appear, reporting findings from using active fixation leads in routine practice and from different RV pacing sites (12-14, 26).
3.2 Alternative RV Pacing Sites

A variety of potential RV pacing locations have been described (5, 27, 28). These include RV mid septum, RVOT, high RVOT and the RV anterior free wall. Lieberman et al. defines high (infundibular) and low (outflow) septal positions, and high (infundibular) and low (outflow) free wall RVOT positions and their characteristic fluoroscopic and ECG findings (28).

These positions are intended to approach the region where the conduction system is anatomically situated. If myocardial cells adjacent to the cardiac conduction system could be activated by the electrical impulse from the pacemaker, then they may entrain the conduction system to produce an electrical excitation that traverses the bulk of the ventricles using much of the conduction system to activate the myocardium and so approximate an intrinsic conduction. It follows that the higher up in the ventricle, or the earlier in the conduction system, that entrainment could be achieved, the narrower the QRS complex and more similar to intrinsic conduction a beat
might be. Intuitively a narrower paced QRS complex might then result in less electrical and mechanical dyssynchrony.

The anterior free wall is not described as an optimal target for pacing lead site, though it is recognized as one of the locations that may be unintentionally accessed due to the limitations of fluoroscopy, ECG-related positioning and the orientation and anatomy of an individual’s heart relative to the direction of the lead approach (5).

Pacing lead positions have to meet achievable mechanical criteria; they need to be accessible for implant, return acceptable thresholds and be stable. The combination of these mechanical criteria combined with a narrow QRS, has lead to the most common alternative lead site found reported and advocated was the high RVOT lead site.

Pacing from the RVOT lead site produces ECGs with a shorter QRS duration than RVA pacing and RVOT lead sites return similar cardiac axis measurements to intrinsic conduction (7, 29). By contrast, ECGs seen with RVA lead placements have a wide QRS complex and resemble a LBBB pattern with a superior axis (30).

However, there are patients with poor LV function that have narrow QRS complexes, so improving QRS duration cannot be the complete answer to the optimal pacing lead site. Yet an increased paced QRS duration has been shown to be an indicator of decreasing LV function and heart failure (7). However, it is not yet clear whether a narrower QRS width as seen with RVOT pacing, is associated with fewer adverse outcomes than prolonged QRS width seen with RVA pacing.
There is ongoing debate as to whether RVOT pacing is offering the patient anything different or better than RVA pacing (3-5, 31).

The debate covers several concerns and limitations of studies comparing RVA and RVOT pacing to each other or to intrinsic conduction. These include:

- Inconsistent experimental methods across studies
- Generalised use of the term “septal” pacing, without specific differentiation of different non-apical pacing sites, particularly in earlier studies, making results from truly RVOT lead positions less clear
- Studies of inconsistent follow up durations, that may not be long enough in some instances to detect real changes, yet may be included in wider reviews of RVA to RVOT pacing
- Studies that rely on echocardiographic measurements that are not sensitive to small changes, e.g. volume estimation of LV ejection fraction
- The role and length of a wash-out or wash-in periods and whether they are necessary

A brief survey of two large implanting centres in New Zealand during October 2012, found that RV pacing leads were routinely implanted at the apex. This was confirmed from discussions with Fiona Riddell and Sharron Mathewson, Charge Cardiac Physiologists at Auckland and Christchurch District Health Boards respectively. Yet the implanting physicians at Wellington Hospital have a different opinion and a preference for RVOT pacing.

So RVOT pacing remains controversial.
3.3 Echocardiographic Input to a Pacing Conundrum

Just as pacing has progressed over time, so too have the measurement tools of echocardiography.

Some of the newer echocardiographic measurements of strain, strain rate and dyssynchrony are proving more sensitive to changes in myocardial mechanics than more traditional measurements, such as ejection fraction (32). Changes in strain are associated with LV dysfunction, heart failure hospitalisations and death, with studies suggesting longitudinal strain is a predictor of adverse cardiac events (22, 33).

The relative availability of echocardiography has lead to a multitude of studies that use echocardiographic measurements of reduced LV function to imply that heart failure is present or approaching, in a variety of pathologies (22, 33-35).

The echocardiographic analysis tools we used have been applied to patients with impaired LV contraction patterns, but have not been widely used to assess the consequences of pacing in patients with normal LV function. There is potential for strain, strain rate or dyssynchrony measurements of LV contraction patterns to show a deterioration with RVA or RVOT pacing, when compared to the contraction patterns of intrinsic conduction.

There are relatively few studies looking at the mechanical advantages of RVOT over RVA lead placements using advanced echocardiographic assessment tools. Long-term studies or specific data that looks at the effect of pacing on heart function frequently focus on ejection fraction (6, 36) or acute haemodynamic changes (13). In contrast, studies that use advanced echocardiographic tools to assess the effects of bi-ventricular pacing on
cardiac mechanics and trying to reduce dyssynchrony in this patient group through resynchronising ventricular contraction with bi-ventricular pacing are readily available (37-40).

We were interested in identifying an echocardiographic measurement that could reliably show, very early, that RVOT pacing is mechanically different to RVA pacing and that RVOT pacing is similar to intrinsic conduction. If echocardiography could show normal mechanical measurements of one pacing site over another, it could further contribute to the debate over whether pacing should be from the RVOT or the RVA.

If changes in longitudinal strain, strain rate or dyssynchrony could be detected early in paced patients, one of these measurements may also be a predictor of adverse events. Studies by Mignot et al. and Munk et al. suggest longitudinal strain, is predictive of adverse outcomes in patients with depressed LV function and ST elevation MI (22, 33). With an echocardiographic measurement that was predictive of adverse pacing related outcomes, this measurement could be optimised at implant to mitigate a patient’s long-term risk of the adverse events associated with chronic pacing.

So the underlying cardiac mechanics, as assessed by echocardiography, have not been definitively shown to be superior with RVOT pacing compared to RVA pacing.

4 Pacing and Echocardiography at Our Centre

There were two pacemaker-implanting physicians, and a pacing fellow during 2009/10 with varying preference for pacing lead site implantation.
From late 2009 and through 2010, echocardiograms were requested and performed on a number of patients who had received a pacemaker implant, as it became part of our routine clinical practice to confirm that patients who received a pacemaker implant retained their cardiac function with pacing and during intrinsic conduction, irrespective of their pacing lead site.

Routine comprehensive echocardiography at our centre includes an estimation of ejection fraction via biplane volumes and several other measurements that are outlined in more detail in the methods section. Since the pacing physiologist was conducting the post-implant pacemaker check simultaneously with the echocardiogram, there was opportunity to record ejection fraction both with pacing and during intrinsic conduction. By March 2010 the physicians were satisfied that the mixed pacemaker lead site was not disadvantaging their patients in terms of ejection fraction assessment.

5 Advent of a Strain and Pacing Study

Within the field of echocardiography, ejection fraction, as measured by biplane volumes, is understood to be a useful tool, though has limitations. Changes in ejection fraction are often seen later with disease progression or with moderate-to-severe disease: EF is accepted as being less sensitive for early or subtle changes in disease state. Echocardiography has developed other approaches to find earlier predictors of disease or progression of disease.

LV diastology has evolved to detect earlier deterioration of cardiac disease; it has been particularly useful in improving understanding of symptomatic patients with heart failure and preserved ejection fraction. Strain analysis is an advanced tool developed to assess tissue deformation or tissue
“deformability” and is showing increasing usefulness in quantifying LV systolic compliance in a number of clinical situations.

Diastology assessment, tissue velocity imaging and strain analysis via TVI and 2D speckle tracking have developed within echocardiography to address the need to detect and understand clinical and sub-clinical changes that might be useful early prognostic indicators.

During 2011, the clinicians within the echocardiography service at Wellington Cardiology were interested in broadening their use and application of the echocardiography analysis tools that were available on their existing echocardiography equipment. The question was asked whether strain analysis might be able to detect subtle changes caused by pacing, that ejection fraction could not. Echocardiographic data was already stored for a number of patients that had received a pacemaker implant and it was hoped this could be further analysed.

It was considered that the existing echocardiographic data should be of sufficient technical quality to apply the advanced analysis tools, as our echocardiographers are expected to routinely provide 2D echocardiographic image quality to the standard that is necessary for strain analysis.

At the time the extra clinical work of echocardiograms on pacemaker implant patients was carried out, I was usually the most available echocardiographer. Having performed the majority of the post-implant echocardiograms, the opportunity arose to become more closely involved with further analysis of the echocardiographic data through this body of work.
Ethical approval was sought and granted for an observational study on the existing echocardiographic data, with the expectation that a study would look more closely at the cardiac mechanics and synchronicity of contraction during intrinsic and paced conduction. Should there be detectable differences in cardiac mechanics or synchronicity of contraction via tissue velocity imaging or speckle tracking analysis, this information could further inform the discussion as to whether one pacing lead site was mechanically superior to the other.

6 Explaining Strain, Strain Rate and Dyssynchrony

Strain is defined in physics as the magnitude of a deformation, equal to the change in dimension of a deformed object divided by its original dimension. The heart is a 3-dimensional structure, with LV contraction being a complex process of tissue changing shape, which is well described in an article by Geyer et al. (41). The Geyer article describes how tissue deformation occurs in different directions; radial, circumferential and longitudinal dimensions. Strain in radial, circumferential and longitudinal dimensions is expressed as a percentage. In addition there is a rotational direction that may be considered, which is expressed in degrees.

\[
Strain = \frac{\Delta d}{d}
\]

Equation 1 Strain

How fast that strain changes can be measured and is a reflection on the health of the underlying structures. Faster changes in strain are consistent with healthier functioning muscle. Strain rate is expressed in 1/s.

\[
Strain \ Rate = \frac{(\Delta d/d)}{\text{sec}}
\]

Equation 2 Strain Rate
So strain is essentially tissue deformation – a change in shape and strain rate is how fast that change happens.

Dyssynchrony may be defined as occurring at different times. A normal LV can be seen to contract synchronously: timing of peak systolic strain measured in each of 6 basal segments occurs simultaneously. This can be shown with an echocardiogram using two approaches:

- Tissue Doppler velocity imaging with sampling of opposing segments
- 2D Strain analysis using speckle tracking

Timing differences are in milliseconds and changes can be very small; detecting discernible, repeatable and meaningful differences can be difficult. The two approaches have their advantages and disadvantages. TVI PW Doppler gives better temporal resolution than strain analysis. However, strain analysis segments are usually larger than TVI sample volumes, so speckle tracking is more likely to interrogate relevant myocardium.

To relate dyssynchrony to pacing, a simple metaphor may help. Should someone try to poke us with an object, we deform ourselves to try to avoid it; if the aim is low towards our left foot, we might lift that foot followed by stepping rightwards; if the aim is higher towards our left side, we might shift our torso immediately, followed by stepping rightwards to regain balance. In both instances our shape has changed and ended up in a similar position – rightward to where we started. The concept is similar to when a pacing impulse strikes, the adjacent tissues are affected to respond earlier than those more distant. The difference in tissue response caused by two different impulse sites may mean that strain or timing of peak strain is altered in a way that can be differentiated by echocardiographic measurement.
Summary and Hypothesis for the Observational Study of Strain and Pacing

In the absence of a definitive evidence base, the pacing practitioners are still divided locally, nationally and internationally as to whether there is a superior RV pacing lead site associated with reduced incidence of pacing induced heart failure. In part the problem is related to the absence of an accessible objective measure of cardiac function that is repeatable, meaningful, robust and reliable; a measure that can discern between pacing from one site compared to another.

Our aim was to establish that we could analyse existing echocardiographic data with newer measurement tools to find an echocardiographic measurement that was sensitive to pacing and show meaningful, detectable differences between RVA and RVOT pacing compared to intrinsic beats.

As part of this thesis we will outline the methods related to recording a comprehensive echocardiogram on patients who have just had a pacemaker implants.

Our hypothesis is that RV pacing alters LV contraction mechanics compared to intrinsic conduction mechanics in a way that will be measureable with strain-based echocardiographic tools.

The questions we will attempt to address in this study of patients who have a pacemaker implant are:

- Do echocardiographic measures of LV performance differ for paced beats compared to intrinsic beats?
• Do these echocardiographic measures of LV performance differ when the RV is paced from the apex compared to the RVOT?
• Are these echocardiographic measures with pacing from RVA or RVOT similar to intrinsic beats?
Chapter Two: Methods

1 Introduction

Chronic pacing more than 40% of the time is associated with heart failure. The concept of pacing induced heart failure has lead pacing implanters to place pacemaker leads in different parts of the RV in an attempt to reduce the incidence of pacing related heart failure.

Without a definitive evidence base that non-apical pacing is mechanically any better than apical pacing, the pacing world is still divided locally, nationally and internationally over the best location within RV to site a pacemaker lead.

The purposes of this thesis are twofold:

- To describe the methods of overcoming the specific issues related to recording a comprehensive echocardiogram on patients who have just had a pacemaker implant
- Write up of an ethically approved observational research project that applied advanced echocardiographic analysis to the existing echocardiographic data gathered as part of routine clinical practice on a group of pacemaker patients

2 Hypothesis

The observational study was designed to test the hypothesis that RV pacing alters LV mechanics of contraction compared to intrinsic conduction, in a way that will be measureable with strain-based echocardiographic tools.

Our study applied strain-based echocardiographic analysis to existing echocardiographic data from patients who had received a pacemaker implant,
to investigate whether there were differences in LV contraction patterns with paced beats compared to intrinsic beats.

Where an echocardiographic measure of LV performance could detect changes in cardiac mechanics with pacing, we ascertained whether it could differentiate between RVA and RVOT pacing. A strain-based measurement that could differentiate between RVA and RVOT pacing might show changes in contraction mechanics with RVA pacing compared to intrinsic conduction, yet show no significant difference between the contraction mechanics of RVOT pacing compared to intrinsic conduction.

In this way it might be shown that RVOT pacing more closely mirrors intrinsic LV contraction mechanics than does RV apical pacing.

Literature is not completely clear which echocardiographic measures of cardiac mechanics consistently return reliable results, though frequently published studies indicate that strain analysis and dyssynchrony i.e. timing of strain peaks in different cardiac segments might be useful (18, 42, 43). We analysed a variety of strain and dyssynchrony variables, to assess whether there were pacing induced detectable differences in timing of LV segmental contraction or LV mechanics.

3 Study Design

3.1 Observational Study Design

The study aimed to find up to 40 new pacemaker patients, male or female, who had presented with a Class I or II pacemaker indications according to published guidelines (44). Patients may have presented either acutely from primary care or emergency services, or from the community as an outpatient. Patients would have followed the existing clinical pathway for pacemaker
implantation and received a standard transthoracic echocardiogram post pacemaker implantation pre-discharge.

Records were reviewed for pacemaker implant patients who had received an echocardiogram pre-discharge, during which echocardiographic data was recorded while paced and in intrinsic rhythm. Furthermore, where echocardiographic data was present and gathered during both pacing and intrinsic conduction, the patients who met inclusion and exclusion criteria became subjects of the observational study.

There was a mixed preference of pacemaker lead implant site at the time of the study, so it was expected the groups would be naturally similarly sized.

The pacemaker implant work-up and post implant echocardiogram would provide characteristics of a subject, including clinical information that would allow application of inclusion/exclusion criteria as outlined in Section 4.2.

3.2 Observational Study Outline

Figure 5 is the initial template for the observational data collection of patient demographics, pacemaker implant indication, device type, baseline ECG characteristics and cardiac comorbidities.

Figure 5 gives list of the echocardiogram images in an abbreviated-format and the base data that should be present when assessing patients for inclusion in the study. As well as the base echocardiogram data, it refers to some of the calculations and advanced tools that might be applied to the data wherever possible. The echocardiographic data abbreviations in Figure 5 are standardly used at the centre where the study took place and are likely to be recognizable to
those who work in echocardiography. Full descriptions are in the list of abbreviations.

The echocardiography criteria, listed in Figure 5 Original Data Collection Outline, permitted two key things:

- Screening the patient for any unknown underlying cardiac pathology that might exclude them from the study
- Offline measurement and analysis of both standard routine echocardiographic data and application of advanced analysis tools

The study outline in Figure 5 notes recording of relevant pacing data, including the method of the paced conduction part of the initial data collection. This data was available from the hard copy pacemaker file kept routinely on pacemaker patients at our centre. There was no record of blood pressure at the time of echocardiogram, so the Tau constant was not calculable.
Study Outline RV Pacing & LV Dyssynchrony

Echo / Pacemaker Study:
RV Lead Position and its Influence on LV contraction patterns

Patient Criteria

Age:
Type of Pacemaker:
Indication for PM:
Cardiac comorbidities:
Baseline ECG characteristics:

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<th>Echo Criteria</th>
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<td>2 CV</td>
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<td>APLAX</td>
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<td>PSAX</td>
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<td>PLAX &amp; LVOT</td>
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<td>FPS &gt; 50 ms</td>
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<td><strong>TDI:</strong></td>
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<td>4 CV</td>
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<td>PW-TDI septal (E’)</td>
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<td><strong>M-Mode:</strong></td>
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<td><strong>Doppler:</strong></td>
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<td>RVOT-PW</td>
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<td>LVOT-PW and CW</td>
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<td>Trans-mitral PW</td>
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<td><strong>Colour-Doppler</strong></td>
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<td>TV</td>
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<td>Isovolumic relaxation time constant (Tau)</td>
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<td>ST, ADur, E/A, PV S, PV D, IVRT, E’, E/E’</td>
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<tr>
<td>SPWMD, LVPEP, RVPEP, MV dp/dt, TDI (S-L, A-I, AS-P; Yu-Index), TSI</td>
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<td><strong>Strain:</strong></td>
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<td>1 AFI</td>
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<td>2 Radial and circumferential Strain</td>
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<td>3 Timing of peak contraction</td>
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<td>4 Area under the curve</td>
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<td>12 lead ECG with different pacing modalities</td>
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<td>Pacemaker Settings:</td>
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<td>SR or atrial rhythm</td>
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<td>SR, short AV, V paced (or A paced, short AV, V paced)</td>
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Figure 5 Original Data Collection Outline
In addition to a post pacemaker implant echocardiogram, patients routinely undergo:

- 12-lead ECG recorded at standard paper speed of 25 mm/s and gain of 10mm/mV pre and post implant. The post implant ECG is recorded during pacing.
- Pacemaker check by a cardiac physiologist, checking electrical parameters to ensure satisfactory functioning of the pacemaker and pacing leads and appropriate programming
- Chest X-ray in PA and lateral projections to check for complications and lead positioning and stability

A post implant chest X-ray is primarily conducted to screen for potential complications of pacemaker implantation such as pneumothorax, with the benefit for this observational study of being a secondary means of confirming pacemaker lead tip position, apart from the procedure related fluoroscopy.

Where pacemaker implantation occurred in the morning, the initial echocardiographic assessment would normally take place in the afternoon. Where pacemaker implantation occurred in the afternoon, the initial echocardiographic assessment occurred as soon as feasible the next day to allow for timely patient discharge. For a number of reasons during the time period of the study, not all pacemaker implant patients received echocardiograms prior to discharge, limiting the numbers available to include in the study.

To achieve the echocardiogram post implant, an appropriately skilled and available cardiac sonographer or cardiology registrar would undertake the echocardiogram while the pacing cardiac physiologist was performing the pacemaker check. The pacing physiologist would ascertain when pacing and
intrinsic conduction was occurring during the echocardiogram, so ejection fraction was assessed appropriately for each conduction state. Finally, the pacing physiologist would ensure the pacemaker settings were appropriate for the patient’s bradyarrhythmia management and pacemaker battery preservation.

4 Subjects

4.1 Location
The observational study data was of patients that received pacemaker implant at Wellington Hospital, and their clinical data that was recorded as part of the normal service provision by the Cardiology Department at Wellington Hospital, Capital & Coast District Health Board.

The Wellington Cardiology Department has a pacemaker and Implantable Cardioverter Defibrillator (ICD) service that is supported by a dedicated team of Cardiologists and Cardiac Physiologists who provide a full pacemaker and cardiac device implant and follow up service. The implant service is a regional service, covering most of the lower North Island. During the time period records were reviewed, the pacemaker implant catchment area, included patients from Wanganui and Wairarapa, and complex device implantation for Mid Central (Palmerston North) & Nelson Marlborough District Health Boards.

4.2 Subjects
Potential subjects were those that presented with a typical pacemaker indication between 1st March 2010 and 30th November 2010.

In 2010, as part of normal clinical practice and where practicable, pacing implant patients received an echocardiogram at the time of their post implant
check, to review their ejection fraction with pacing and during intrinsic conduction.

Patients suitable for enrolment as part of the observational study were those that received a combination echocardiogram and pacemaker check, having met inclusion and exclusion criteria. This was ascertained from review of peri-implant clinical examination notes and confirmed by echocardiography.

4.2.1 Inclusion Criteria

Standard pacing indication may be considered as a brady-arrhythmia that is a chronotropically incompetent rhythm and is unable of consistently sustaining cardiac output.

Typical pacemaker indications that were considered for inclusion were:

- Mobitz 2
- Extreme sinus bradycardia
- Tachy-brady syndrome
- Sick sinus syndrome
- Sinus arrest

This list is not exhaustive, but indicative of the type of patients that would be considered eligible for pacemaker implant (44).

To be included, subjects must have received a combination echocardiogram and pacemaker check during admission for their first pacemaker implant.

4.2.2 Exclusion Criteria

Patients with any of the following were excluded:

- No or incomplete echocardiographic data during the post implant, pre-discharge echocardiogram
- QRS complex > 130msec on standard 12-lead ECG
• Significant comorbidity
• Reduced LV function with LVEF < 40% as measured by echocardiography estimation of ejection fraction, using the modified Simpson’s biplane volumes method(45)
• Cardiac valve disease – stenosis or regurgitation graded as moderate or greater by echocardiography(46) or valve replacement
• Documented episode of acute coronary syndrome within the last month
• LV hypertrophy where IVS ≥12mm
• Chronic atrial fibrillation – though regular HR AF may be considered

A normal QRS width was important, so conduction abnormalities indicated by increased QRS width and their consequent effect on LV contraction patterns could be excluded.

Normal LV wall thickness was necessary to exclude those with a potential for underlying abnormal myocardium and hence abnormal myocardial mechanics.

Those with coronary artery disease were not automatically excluded unless they had a reduced resting ejection fraction or obvious regional wall motion abnormalities. As echocardiograms are done at rest, patients with ischaemic heart disease, and without recent ACS, could potentially be included.

Subjects with valve disease or replacement impacts on myocardial mechanics in ways yet to be quantified, so were not suitable to study here.

Regular heart rates should reduce the impact of increased or decreased pre-loading conditions, to give more consistent results generally when comparing
intrinsic and paced states at similar heart rates. As longitudinal strain analysis is assessed from three views that must have similar heart rates, it cannot be readily calculated with highly variable AF.

4.3 Recruitment
This was a single centre observational study. Recruitment was from review of records for patients that received pacemaker implantation between 1st March 2010 and 30th November 2010. The 9-month period was expected to give a patient group size of up to 40 echocardiograms for further analysis.

Clinical examination as part of the normal pacemaker implant pathway identified whether the patient met the initial inclusion criteria and some of the exclusion criteria, e.g. significant co-morbidities, recent ACS, hypertension.

The peri-implant echocardiographic assessment confirmed the absence of underlying cardiac pathology that met exclusion criteria.

More thorough data analysis was performed on the remaining group of pacemaker patients that met inclusion criteria and had adequate echocardiographic information keep them in the study.

4.3.1 Sample Size
The available number of pacemaker patients and the proportion that received a combination pacemaker check and echocardiogram largely dictated the sample size. Other studies by Yoshikawa et al. and Leong et al. (8, 39) used intrinsically conducting controls or directly compared different pacing sites enrolled 56 and 58 subjects respectively. A study size of 30 to 40 was considered to be adequate to detect any trends and if it returned useful information could be a pilot to justify a larger prospective study.
The study was retrospectively powered based on the differences we detected in global longitudinal strain with paced and intrinsic beats. To calculate power, there were two sets of normal subject data that could be referenced, those of Marwick et al. (47) and those of Dalen et al. (48).

Marwick has normal values for GLS at -18.6 ± 5.1 regardless of age and gender. Dalen has normal values for those older than 60 years for males as -15.9 ± 2.4 and for females as 15.6 ±2.3. We calculated the power of our study using Marwick’s normal values and Dalen’s normal values for males > 60 years. We used the sample size relevant to group powered at significance level of 0.05 and the actual differences detected with GLS – which was >17% difference.

The study power with Marwick’s normals was 100% for the whole group and 97% for the RVA group. The study power with Dalen’s normals, which were much closer to our starting GLS, was 99% for the whole group and 98% for the RVA group.

It was calculated using Marwick’s normal values that to detect a 15% difference in mean GLS, using a population mean of -18.6, standard deviation of 5.1, and an 80% power, the required sample size was 27.

4.4 Ethics

Ethics approval was requested and granted by the Central Region Ethics Committee on 23rd May 2012. This approval was for an observational study to further analyse existing data from the echocardiogram and pacing implant and follow up data that was gathered as part of routine clinical practice.
5 Instrumentation/Materials

5.1 Pacemaker Implants

Pacing leads have either active or passive fixation mechanisms for attaching the lead to the RV wall. Septal leads are routinely active fixation leads. Apical leads are commonly active fixation leads, though may be passive fixation leads at the implanters discretion.

Pulse generators typically in use at the time our subjects received their pacemakers, were Biotronik Entovis and Philos II, Boston Scientific Altrua, Medtronic Sensia and Advisa. All devices are familiar to our cardiac physiology service, who routinely programme and check them at follow up.

Existing practice is for pacemaker implantation to be performed with the patient in the fasting state and receiving conscious sedation for the procedure. The pacing leads are inserted via either the right or left cephalic or axillary veins.

RV lead site is routinely confirmed during the procedure using fluoroscopy in 40° RAO, 40° LAO and AP projections and a V1 ECG lead. Where the V1 lead shows positive, it is indicative of apical lead placement; where V1 lead shows biphasic or negative, it is indicative of a RVOT lead placement.

Pacing lead placement is made at the implanting physicians’ discretion to either an apical or septal position. Where RVOT site is intended it is acknowledged this site may not always be achieved even with optimal x-ray and ECG site confirmation. The term RVOT pacing was chosen and used for the non-apical pacing group, to contrast clearly with RVA pacing site or data and convey an intended non-apical, high septal pacing site.
Where there was a rightward orientation of the RV pacing lead tip in the AP and RAO projections, an apical position was considered identified.

![Fluoroscopic criteria for pacemaker lead position](image)

*Figure 6 Fluoroscopic criteria for pacemaker lead position,*

*Retrieved from, “Accuracy of Fluoroscopic and Electrocardiographic Criteria for Pacemaker Lead Implantation by Comparison with Three-Dimensional Echocardiography” by Margulescu et al. JASE July 2012 (30)*

Where there was rightward orientation of the lead tip in the LAO projection a septal lead site was considered identified.

We used ECG axis and peri-implant fluoroscopy or x-ray to verify pacing lead position. There is known variation in septal lead placement as described by Margulescu et al. (30) where they used 3D echocardiography to confirm true septal lead placement and agreement between ECG, fluoroscopy and 3D echocardiography.

### 5.2 Pacemaker Lead Systems

An understanding of pacemaker systems and their basic concepts is useful for gathering and analyzing the paced and intrinsic echocardiographic data.

Pacemaker lead systems may consist of one, two or three leads attached to a pulse generator. Pacemakers included in this study were either single or double lead systems. Three lead systems, or bi-ventricular pacemakers, were not part of this study.
At our centre, single chamber atrial lead systems are rarely implanted, as atrial leads are more prone to higher failure rates from becoming dislodged and an atrial system does not provide sufficient rhythm support, should disease of the conduction system progress. For our purposes then, a single chamber pacemaker lead system refers to a ventricular lead placed in the RV. Hence a single chamber pacemaker refers to a single ventricular lead system.

A single chamber pacemaker may be chosen for patients with intermittent failure of their native conduction system. Where there is sinus node disease with intact AV conduction, a single chamber pacemaker may still be implanted, where only a low rate of pacing is expected or the rate-responsiveness, that a dual chamber pacing system permits, is not required.

A dual chamber pacemaker has two leads, one in the RA, the other in the RV. The likelihood of chronic RV pacing, and a patient’s requirement for activity related rate-response, are indicators for choosing a dual chamber pacemaker. In addition, a dual chamber pacemaker may sometimes be implanted where there is intact AV conduction, as a safeguard against atrial lead failure or progression of cardiac conduction system disease to include the AV node.

An atrial lead is useful for rhythms where the rate-responsiveness can be largely controlled by intrinsic sinus node activity. Atrial electrical activity results in atrial depolarization and contraction, which manifests itself as a ‘p’ wave on a surface 12-lead ECG. With dual chamber pacemakers, the atrial electrical activity can be sensed and is marked on the e-gram of the pacemaker programmer as paced or sensed – the latter indicating intrinsic sinus node conduction. Firing of the sinus node usually sets the atrial rate and where the AV node and the conduction network function is intact, it will set the consequent ventricular rate.
Where there is inadequate firing of the sinus node, the dual chamber
pacemaker will detect/sense the failure to electrically activate the atria via the
atrial lead, and after a programmed time, will provide an impulse to the atria
to initiate atrial contraction. This impulse will result in atrial depolarization,
which similarly to intrinsic conduction, will show as a ‘p’ wave on a 12-lead
ECG.

Similarly the ventricular lead can sense and pace activity in the RV. The
ventricular lead is timed to deliver an impulse at a set time after the atrial
electrical activity is sensed or paced by the pacemaker. After waiting for an
appropriate (programmed) time interval the pacemaker will sense whether
there has been any intrinsic ventricular electrical activity. Where no
ventricular impulse is sensed, the pacemaker will provide a pulse to the
ventricles via the RV lead. Firing of the ventricular lead only occurs after the
programmed AV delay. This AV delay simulates the natural delay seen as the
PR segment on an ECG.

Dual chamber pacemakers typical nominal values for AV delay are set to
180msec, though may be higher to give adequate opportunity for intrinsic
ventricular conduction. Similarly, the AV delay can be shortened if required
to force pacing or ensure there is ventricular “capture” i.e. that the pacemaker
pulse will result in ventricular depolarisation.

Shortening the AV delay creates the opportunity for a normally conducted
signal passing through the AV node to catch up to the paced ventricular
signal; the two electrical activation signals can fuse, giving rise to an
inconsistent ventricular activation and contraction profile. A pacing
physiologist would monitor for fusion of the ventricular activation signals
throughout the collection of the paced echocardiographic data.
It is worth noting that pacing spikes are frequently not visible on the surface ECG when bipolar pacing leads are in use. Bipolar pacing lead only require small voltages to conduct current between low resistance for the two very close poles at the distal end of a pacing lead. The small voltages are not reliably detected at the skin surface by the superior frequency response of a diagnostic ECG. The lower frequency response of a monitoring ECG, as used by an echocardiograph, makes it impossible to differentiate between paced and sensed ‘p’ wave activation. Similarly a monitoring ECG will not be able to differentiate between paced and intrinsic ventricular activation, unless there is a significant change in morphology with pacing, as seen with apical lead placement.

Dual chamber pacemakers are frequently the system of choice at Wellington Hospital for patients with sinus node dysfunction of one type or another, or where there is AV node or disease of the lower conduction network. The echocardiograph’s monitoring ECG of a patient with a dual chamber system may appear very similar to a patient without a pacemaker at all. At echocardiography, a programmer is recommended to identify paced from intrinsic conduction for certainty of the means of conduction.

5.3 Echocardiography Equipment & Software

Echocardiograms were carried out using a GE Vivid 7 Echopac (application software version 7.0.6). Imaging for all echocardiograms was with a Matrix 4S probe 1.5 – 3.5 MHz, with harmonic imaging frequency range of 1.9/2.0MHz to 1.5/3.0MHz.

All echocardiograms were stored to a networked GE Image Vault (system software version 3.0.2), allowing analysis and measurements to be made offline accessing the image archive via a Vivid 7 or a GE Echopac review
station. All components were running BT08 software at the time of data collection. Data analysis took place after the review station software was upgraded to BT12, application software version 112.0.6.

During the period of the study, the echocardiography system software was upgraded from BT08 through several levels to BT12. The industry representatives provided assurance that the data would not be manipulated any differently for strain analysis.

After upgrade to BT12, several data sets were re-run to confirm assurances that the numbers returned for longitudinal and radial strain analysis were the same. It was evident, that although the previously selected stored loops were accessible, the cardiac cycle and region of interest needed to be re-selected to run any strain analysis. As there was the intention to review any available 6-month longitudinal data on the initial subject group, having them measured by different software versions created the potential for differences that would need to be quantified. As I was in the data analysis phase, the dyssynchrony analysis was still to complete and there was still the occasional need to verify some of the previously measured data.

Consequently, the decision was made to re-measure all the strain parameters using the upgraded software, when the dyssynchrony analysis was made. The originally chosen loops had been stored, so the ROIs were re-set for these loops, hastening the process a little. Pleasingly, the newer strain algorithm was able to better track regions; so all segments had favourable tracking for strain analysis. Radial strain has only been released as a research tool and as such is not available as a clinical application on the echocardiographs. Consequently, all
radial strain analysis was made from the networked review station with the enabled radial strain research tool.

Automated Function Imaging (AFI) for longitudinal strain analysis could be run from either an echocardiography machine or the review station. AFI was not part of standard clinical echocardiography practice at the time of echocardiogram data collection and with the added problem of having to re-analyse AFI after the software upgrade, all study subjects AFI was measured from a review station.

6 Data Collection

6.1 Data Collection Points

The group of patients that received an implant in 2010 was accessed from logbooks and electronic cardiology departmental records of all implant procedures.

We were able to access echocardiography database and pacemaker files where data was recorded from any combination echocardiogram and pacing checks that occurred either post implant, prior to discharge and/or at approximately 6 months post implant.

Patients’ clinical records were reviewed to collect and confirm correct demographic data, study eligibility. Where patients were suitable subjects, a data collection template was completed. In addition to the echocardiogram and pacing files, the type of patient records review included internal electronic health records, blood tests, ECGs and X-rays.
Pacemaker patients at Wellington hospital have a departmental pacemaker file, which contained printed programming data and notes from the combined echocardiogram and pacemaker check.

We reviewed 12-lead ECG data recorded in paced and intrinsic rhythm around the time of the pacemaker implant. These ECGs were part of normal documentation during the admission for pacemaker implant. Basic monitoring ECG data is recorded with echocardiogram study loops and also a useful reference.

Documentation of height and weight was found from pacemaker implant procedure notes.

6.2 Patient Group Data Collection

A list was collated from the pacing implant database, of patients who received a new pacemaker implant between 1st March 2010 and 30th November 2010. This group was cross-referenced with the echocardiography database to establish the subset of patients who had received an echocardiogram during the time of their admission for pacemaker implant.

For each patient that had an echocardiogram, the echocardiography report was reviewed to see if they met inclusion criteria. If an echocardiography report was normal, a brief review of the echocardiogram images was made to identify whether there was adequate echocardiographic information to perform strain and dyssynchrony analysis.

Prior to completing any substantial echocardiographic analysis, a patient information template completed, to ensure patients met all criteria. When patients were found suitable subjects for study, the relevant clinical
information regarding their pacing implant was collated (See Figure 7 Patient Information Template).

The ECG and pacing data were found in the patient pacemaker, cardiology or main hospital files.

Demographic and clinical data were extracted from medical records to complete the patient information template for study patients for later description of group characteristics. Data of interest related to their status at the time of pacemaker implant. Clinical and demographic data recorded included:

- Age, gender, smoking status, height, weight
- Cardiovascular disease or major risk factors including; previous MI, CAD, PCI, valve disease or other vascular disease, hypercholesterolaemia or diabetes
- Blood pressure status
- Current or recent CHF, ACS or atrial tachycardias
- Renal function status
- Lung function status
- Smoking status
- Current medications, including calcium channel blockers (non-dihydropyridine or dihydropyridine), beta blockers, angiotensin converter enzyme inhibitors, ARBs, loops diuretics, bendrofluorizide, alpha blockers, statins and aspirin
Date of imaging | NHI | Age
---|---|---
Pacing indication

**Device**

*Please circle*

| | Single chamber | Dual chamber |
---|---|---|
RV Lead position

*please circle*

| | Apical | RVOT |
---|---|---|
| | (posterior tip deflection LAO 40; neg/ biphasic paced QRS vector on 12-lead ECG limb lead 1) |

**Inclusion criteria**

1. Standard pacing indication
   
2. Likely adequate echo information for advanced analysis
   
**Exclusion criteria**

1. Left ventricular systolic impairment (LVEF) < 40%
   
2. Significant valvular disease (≥ moderate)
   
3. Acute Coronary Syndrome within one month
   
4. Significant left ventricular hypertrophy (IVS > 12mm)
   
5. Permanent atrial fibrillation
   
6. Unwillingness or inability to comply with study requirements.
   
7. QRS width > 130ms
   
8. Significant comorbidity

**At the time of imaging**

**Rhythm** (?sinus, ?Mobitz, ?A paced) ....................

*Intrinsic ventricular rhythm

*Please circle:*

| | As Vs | Ap Vs |
---|---|---|
| | | |

Ventricular rate (bpm) ...... AV interval (ms) (ie PR interval) ......

QRS duration (ms) ...........

*Paced rhythm

*Please circle:*

| | As Vp | Ap Vp | Vp (VVI) |
---|---|---|---|
| | | | |

Ventricular rate ............ AV interval (ms) (ie PR interval) ............

QRS duration (ms) ........... % V pacing (at 6/12 visit) ............

**NOTES**

- please attach a 12-lead ECG of intrinsic ventricular activity AND one of paced ventricular activity *representative of the rhythm during ECHO imaging*

- ensure that “paced” ventricular complexes are truly paced and not fused. If any doubt, please V-pace in VVI mode.

*Figure 7 Patient Information Template*
Checking the quality of stored echocardiogram cine loops and the presence of pacing and intrinsic conduction, echocardiographic information were the key factors to identifying the study group. A template was designed and referenced to ensure the large majority of required echocardiographic data for strain and dyssynchrony analysis would be present (See Figure 8 Echocardiography Protocol Guidelines). There were several reasons why echocardiograms were not possible on everyone who received a pacing implant and these are outlined later in the methods (See Section 8.1: Patient and Staff Availability and Section 8.2: Echocardiogram Patient Positioning and Scanning Considerations).

7 Strain and Pacing Study Protocol

Subjects for the observational research study needed to have echocardiography data that was of sufficient technical quality to perform strain, strain rate and dyssynchrony analysis. The stored echocardiogram ideally should have contained all of the information outlined in the Echocardiographic Protocol Guideline (Figure 8). Where only a small amount of information was not recorded, analysis was still be attempted.

It was established that at the time of echocardiogram, the pacing and echocardiography physiologists had not been routinely told where the pacing lead was positioned. However, during the echocardiogram the pacing lead was usually seen and the likelihood of an apical or septal position was often indicated via imaging and ECG recording. As the data strain and dyssynchrony analysis occurred offline at a later date, any knowledge of pacing lead position during the echocardiogram was not considered to affect or influence data analysis or results.
### Echo Protocol

**SAPS – Strain and Pacing Study**

#### BASELINE

**PACE MAKER:** Native Rhythm

<table>
<thead>
<tr>
<th>Parasternal:</th>
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<tbody>
<tr>
<td>PLAX &amp; LVOT</td>
<td>2D</td>
<td>once</td>
</tr>
<tr>
<td>LV: PLAX</td>
<td>M-mode</td>
<td>once</td>
</tr>
<tr>
<td>PSAX</td>
<td>2D</td>
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<table>
<thead>
<tr>
<th>Apical:</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>4 CV</td>
<td>2D</td>
<td>all 2D with frame rate &gt; 50 fps</td>
</tr>
<tr>
<td>4 CV</td>
<td>TDI</td>
<td></td>
</tr>
<tr>
<td>E' MV-PW</td>
<td>PW-TDI</td>
<td>Doppler</td>
</tr>
<tr>
<td>2 CV</td>
<td>2D</td>
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<td>2 CV</td>
<td>TDI</td>
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<tr>
<td>APLAX</td>
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<tr>
<td>APLAX</td>
<td>TDI</td>
<td></td>
</tr>
<tr>
<td>LVOT-PW and CW</td>
<td>Doppler</td>
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</table>

**Screening on echo:**

- MV: Colour-Doppler once
- AoV: Colour-Doppler once
- TV: Colour-Doppler once
- RVSP: Doppler once
- PSAX – RVOT/PA: Doppler once
- RVOT-PW: Doppler once

#### PACED CONDUCTION

**PACE MAKER:** DDD / VVI pacing at similar rate to intrinsic conduction

<table>
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<tr>
<th>Parasternal:</th>
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<tr>
<td>PSAX</td>
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<td>E' MV-PW</td>
<td>PW-TDI</td>
<td>Doppler</td>
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<tr>
<td>2 CV</td>
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<td>2 CV</td>
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<td>APLAX</td>
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<tr>
<td>LVOT-PW and CW</td>
<td>Doppler</td>
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**Figure 8 Echocardiography Protocol Guideline**
A 12 lead ECG recorded during intrinsic conduction and paced conduction for each participant as part of their inpatient stay was collated and reviewed for QRS duration and cardiac axis, the latter for confirmation of pacing lead position.

Relevant pacemaker information about the leads, pacemaker type, RV pacing lead site, pacemaker indication, pacemaker generator and lead configuration and settings were tabulated with patient information for each subject.

8 Practicalities of Recording Post Pacing Implant

Echocardiogram Data

During 2010, the echocardiograms for post implant patients were a new workload to fit into the existing clinical work. With the natural time constraint of planned patient discharge, it meant there was not always an available echocardiographer or pacing physiologist to perform the combined pacing check with echocardiogram prior to discharge. Consequently, there was a proportion of pacemaker implant patients that did not receive an echocardiogram and could not be included in the study.

8.1 Patient and Staff Availability

Patients had their pacemaker implant procedure in the Pacing Laboratory of the Interventional Suite on Level 2 in Radiology at Wellington Hospital. Elective day case procedures are usually done as a morning list. The immediate post-procedure care for day cases took place in the Interventional Recovery ward (IRW) adjacent to the Pacing Lab; patients would be discharged from the IRW later that day if all had gone well.

When patients presented acutely, their post-implant care was in the cardiac ward on Level 6 of the Wellington Regional Hospital, from where they were
discharged after an appropriate recovery time. Alternatively, acute implant patients from a nearby secondary hospital might be held briefly in the IRW prior to transfer back to the cardiac ward at their presenting hospital for post-implant care and discharge.

Acute or elective patients implanted in the afternoon were usually kept overnight in ward 6 South, with discharge the next morning where appropriate.

Consequently patients were only available for echocardiography for a short time and may be in a choice of several locations. The echocardiogram was seen as desirable, but not essential prior to discharge.

Although elective pacemaker implants are scheduled ahead of time, due to acute demand, their planned implant may need to be deferred. Inevitably, implant patients could not be identified to the echocardiography service until the pacemaker implant had occurred and accommodating the echocardiogram was then prioritized alongside the acute inpatient echocardiogram demand, to be done where possible.

Once a pacemaker implant patient was identified to the echocardiography service, the patient location and availability could be assessed. This information was used to clarify whether pacing technologist and echocardiographer could both be available for a combined pacing check and echocardiogram, prior to patient discharge. There was usually only one echocardiographer available to accommodate the extra workload, due to having a mixed management and clinical workload. Consequently, a single operator performed nearly all the echocardiograms in our study.
At Wellington Cardiology, we have a rostered “Pacing Cover” duty to accommodate daily unplanned or acute pacing work. This staff member could usually be accessed to support the combined echocardiogram and pacing check when the patient and echocardiographer were available.

The combined pacing check and echocardiogram was not to impact on the discharge or transfer of the pacemaker implant patient. Normal fluctuation of acute demands on both echocardiography and pacing services meant occasions where both physiologists were not available at the same time. In these instances, the pre-discharge pacemaker check took precedence and the combined pacemaker check and echocardiogram did not occur.

Consequently, not all patients with a typical pacemaker indication received echocardiograms in the post-implant period prior to discharge or transfer, reducing the number of patients available to study.

### 8.2 Echocardiogram Patient Positioning and Scanning Considerations

Echocardiograms are routinely performed with patients in the left lateral decubitus position. Adopting this position brings the heart to the front of the chest and reduces the amount of the ultrasound attenuation due to air in the lobes of the left lung.

Typically the patient’s left arm is raised away from their body with the elbow at shoulder height or above and resting against the bed; the arm elevation opens the intercostal spaces. This position more reliably permits an acoustic window large enough for effective ultrasound transmission. A good acoustic window is essential to facilitate adequate reflected ultrasound (echo) to show the underlying cardiac structures. At our centre it is common practice to raise
the end of the echocardiography bed to approximately 30°. See Figure 9
Normal Echocardiography position.

Optimal patient positioning is critical to collection of echocardiographic images of good technical quality in a timely manner.

For patients who have just had a pacemaker implant, the standard echocardiography position as described above is not usually achievable for several reasons. As part of conducting this study, it was evident that a specific approach to echocardiography in the post-implant patient had developed to enable a comprehensive echocardiogram to take place.

Post pacemaker implant, patients are instructed to keep below the shoulder the arm on the side of the pacemaker implant. Raising the affected arm in the post implant period risks dislodging the pacemaker lead before endothelialisation of the pacemaker lead tip can provide more permanent fixation of the lead tip in a stable position. So the arm on the side of pacemaker implant must be kept down.

Pacemaker patients have a wound over their pacemaker implant site. Pacemakers are usually situated in the sub-clavicular region on the side of the patient’s non-dominant hand for maximal patient functionality in the recovery period. As the majority of people are right handed, the most common side for the pacemaker to be implanted is their left side, so they are asked to restrict motion of the left arm to below shoulder height.

As previously outlined, the typical echocardiography optimal position is lying on the left shoulder, creating some immediate difficulties when carrying
out echocardiograms on this patient group, both in terms of arm positioning and pain from lying on their left shoulder.

Patient wound dressings are generally out of the way of the acoustic window positions for standard echocardiography. However, there are areas of tenderness around the wound site that the echocardiographer needs to be mindful of. A clear, sealing, adhesive dressing is often used over the main dressing at our centre and this dressing may extend into one of the areas for scanning.

So echocardiography in patients immediately post implant presented a unique set of problems to overcome for safe, comfortable and effective image acquisition.

Very early on in the clinical echocardiography work associated with these patients a modified patient position for echocardiography was developed. Instead of the head end of the bed being at a 30° elevation, it was raised maximally, to approximately 85°, achieving a near sitting patient position. Having patients in a more upright position took pressure off their left shoulder, particularly important if this was the location of their pacemaker wound site.

From the seated position, a patient could be encouraged to lean forward and rotate their shoulders leftward as far as they comfortably could, to simulate a more left lateral decubitus position. Patients would be offered pillows to supported their head and right shoulder to stabilize their position to a point of comfort for the duration of the echocardiographic assessment.
This modified patient position was reported to improve patient comfort and allow access to adequate parasternal window in most patients.

Opening the intercostal spaces is useful for both parasternal and apical imaging windows. Where more open intercostal spaces might be necessary to improve imaging windows, the patient would be encouraged to bring their left arm forwards in a controlled and supported fashion to the least extended position that allowed acoustic window access. The patient’s left hand and forearm could then lie across their abdomen, with their elbow away from their side so the sonographer could access an apical or parasternal window underneath the patient’s arm. See Figure 10 Modified Echocardiography position, with rotated shoulders and left elbow away from side. Although the sonographer reported this was awkward at times, it was considered the only feasible solution for image acquisition in some instances.

Of note, it was important for the sonographer to directly assist and support the patient’s left arm movement, as often a patient’s natural inclination is to be helpful, which meant they would attempt to elevate their left arm – forgetting the new post implant instructions to restrict arm movements to below shoulder height.
The pacemaker programmer header was usually taped in place for the duration of the echocardiogram. There was some record of interference from
the header, though this did not significantly impact on the ability to store suitable echocardiographic data at the time, nor did it interfere with images later used for dyssynchrony and strain analysis.

Mitigating risk of pacemaker lead dislodgement and maintaining patient comfort were considered the priorities when attempting to perform all combination pacemaker and echocardiogram studies.

8.3 Infection Control
Immediate post implant echocardiograms were frequently carried out wearing gloves, for infection control purposes. Aquasonic gel proved to be an excellent medium for removing residual iodine solution from the patient’s skin and was subsequently difficult for the sonographer to remove from their hands after the echocardiogram, further motivating use of gloves.

Transducers were wiped down immediately after use to prevent iodine staining.
All bedding was changed and transducer and ECG leads wiped down with a damp soapy cloth at the end of each study, to remove residual iodine from the transducer. The room was aired to remove the iodine smell from the room as much as possible in preparation for the next echocardiography patient.

8.4 Paced Conduction vs. Intrinsic Conduction
From the monitoring ECG on the echocardiograph the echocardiographer could not always differentiate whether beats were paced or intrinsic. As the clinical question for these echocardiograms was to look for a difference in ejection fraction during intrinsic conduction compared with paced conduction, it was important to know how contraction was initiated.
During a combination pacemaker check and echocardiogram, the ECG would be monitored on the pacemaker programmer using both ECG leads and the programmer header placed over the pacemaker. The pacemaker programmer could then detect the pacemaker function and display the pacemaker activity alongside a surface ECG to indicate whether each QRS complex was paced, sensed or a fusion of a pacemaker impulse and the heart’s own electrical activity.

The pacing physiologist could monitor for fused beats during an echocardiogram and advise the echocardiographer of their occurrence to clearly identify the source of electrical activity whilst echocardiographic data was being recorded. The echocardiographer could then appreciate which were the paced beats on the echocardiograph’s monitoring ECG and annotate stored echocardiographic data as being paced or intrinsic conduction.

Where necessary, to overcome intrinsic ventricular conduction pacemaker settings would be safely adjusted in a controlled manner, according to the individual patient’s underlying rhythm and intrinsic conduction system’s activity level while echocardiographic images were collected as quickly as possible.

### 8.4.1 Approaches to sustaining paced or intrinsic rhythm

The echocardiogram to assess ejection fraction during paced and intrinsic conduction was to have very similar rates for both rhythms, since stroke volume and hence ejection fraction, varies with heart rate.

The method for sustaining pacing or intrinsic conduction while echocardiographic images were stored would depend on the patient’s underlying rhythm and their implanted pacemaker system.
The international code of VVI indicates the pacemaker is programmed to pace in the ventricle, sense in the ventricle and is inhibited from delivering a pacing impulse when intrinsic ventricular activation is sensed. The DDD code represents the programming is set to dual chamber (RA & RV) pace, sense or inhibit.

To understand how pacing can be sustained, an understanding of the underlying rhythms is useful, alongside the understanding of how the pacemaker can work.

The subjects in our study were recorded as having their pacing or intrinsic conduction captured or sustained in the following ways.

Sinus Node Disease Patients with dual chamber pacemaker:

- Patients have an intermittent problem with their sinus node firing
- Resting heart rate would be expected to be in the normal range for resting sinus rhythm much of the time
- Sinus node would usually fire often enough to capture intrinsic echocardiographic data without altering the pacemaker settings as the pacemaker sensed atrial electrical activity and subsequent ventricular electrical activity, so would be inhibited and remain silent
- Ventricular pacing could be promoted by shortening the length of time to wait, after atrial electrical activity was sensed/paced, to deliver a ventricular impulse, i.e. shortening the AV delay.
- Where fusion of pacemaker and intrinsic activation occurred, further shortening of the AV delay might have occurred. If fusion was still present, VVI rates slightly faster than the sinus rate would usually ensure paced ventricular activity
- Where intrinsic ventricular activation did not occur after atrial electrical activity due to extreme first-degree heart block, the two approaches were to (a) increase the AV delay to encourage intrinsic
ventricular activation to occur or (b) programme to VVI 35bpm and allow an intrinsic junctional rhythm to occur (See section 5.2 Pacemaker Lead Systems)

![Figure 11 Sinus pause](http://www.rnceus.com/ekg/ekgsar.html)


**Sinus Node Disease Patients with single chamber pacemaker:**
- Similar to dual chamber approach for intrinsic rhythm echocardiographic data
- To capture paced echocardiographic data recording, ventricular pacing was in VVI mode, with a paced rate slightly faster than the intrinsic sinus

**Atrioventricular Node Disease Patients with Second Degree Heart Blocks:**
- The pacemaker implant may be a single or dual chamber pacemaker system e.g. with Mobitz Type 2.

![Figure 12 Mobitz Type 2](http://www.mauvila.com/images/Mobitz2_1.gif)

Retrieved from [http://www.mauvila.com/images/Mobitz2_1.gif](http://www.mauvila.com/images/Mobitz2_1.gif) (50)

- Intrinsic echocardiographic data was gained without altering pacemaker settings for second-degree heart blocks
• Where there was insufficient intrinsic atrial activity, the pacemaker would be allowed to pace the atria, with the ventricular conduction being either paced or intrinsic as required

• Dual chamber systems could have their AV delay reduced to promote pacing at the same sinus rate: if fusing occurred, VVI pacing might be used

• Single chamber systems were programmed to a VVI rate slightly higher than the patient’s intrinsic ventricular rate. The rate would be as close to intrinsic as possible to override the resting heart rate.

Atrioventricular Node Disease Patients with Complete Heart Block:

• The pacemaker implant was a dual chamber pacemaker system

• VVI mode was used at ventricular rate just faster than the intrinsic ventricular rate. With CHB, the sinus rate is significantly faster than the ventricular rate so a-sense, v-pace mode would give a much faster paced ventricular rate than intrinsic

• Intrinsic rates were sustained by VVI rate below the intrinsic junctional rate, e.g. VVI 35 bpm

• Paced rates were sustained by programming VVI at a rate slightly faster than the intrinsic junctional rate, e.g. VVI 40 bpm

![Figure 13 Complete Heart Block](http://ontariomedic.ca/wordpress/wp-content/uploads/2011/04/3rdDegreeHeartBlock1.jpg)

9 Echocardiographic Data Recordings

All echocardiographic images were recorded using a phased array, Matrix 4S probe with frequency range 1.5 – 3.8 MHz and a footprint of 18 x 24 mm.
Available harmonic imaging frequencies range from 1.5/3.0 MHz to 2.0/4.0 MHz, available fundamental imaging frequencies range from 2.0 MHz – 3.8 MHz (See Section 5.3 Echocardiography Equipment & Software).

9.1 2D Image Data Acquisition and Optimization

2D image optimization is essential to the usefulness of the data for offline analysis with advanced echocardiography tools. Inadequate imaging quality would render the speckle tracking approach useless. For clinical work at our centre, all aspects of 2D imaging optimization are routinely considered when storing echocardiographic images as offline analysis is frequently applied by reviewing cardiologists or senior echocardiographers.

2D image optimization for all acoustic-imaging windows includes attention to:

- Patient position simulating a left lateral decubitus position with arm raised (See Section 8.2 Echocardiogram Patient Positioning and Scanning Considerations)
- Transducer position relative to incident angle to heart, with orientation marker standardly directed in the standard orientation for each of the imaging windows(52)
- Correct alignment to the relevant standardly described long axis, short axis, 4Chamber or 2Chamber planes through the heart (52)
- Frequency – transmit frequency for fundamental imaging and both transmit and receive frequencies for harmonic imaging, such that imaging penetration is optimised without significant compromise of resolution. Frequency is kept as high as possible to obtain adequate 2D image quality without compromising frame rate, so routine images could be expected to meet the protocol guidelines of frame rate >50fps
• Depth – adjusted to include all relevant structures for a particular view or measurement. May be reduced at times to show better the region of interest

![Figure 14 Apical 4C optimised for LV endocardial borders](image)

• Sector Width – set to include relevant structures with a small additional margin, to keep frame rate as high as possible. Typical settings are 70 degree sector angle

• Transmit Power – set to comply with principle of using as low power as reasonably achievable. Typical transmit power is -2dB, though where necessary to achieve adequate echocardiogram intensity transmit power may be increased to -1dB or 0dB

• Focal point corrected for each window, such that focal zone and hence lateral resolution is optimised through the region of most relevant interest to the view or measurement being recorded

• TGC – Time Gain Compensation – this function allows receive gain from specified depth range bands to be increased or decreased independently of each other. Used in conjunction with overall gain to
have blood pools return no echo (blackness or echo free) and similar tissue types to return similar intensity of echoes

- **Gain** – receive gain setting for overall image. 2D image was optimised to show black chambers. Chosen gain setting is interactive with TGCs, which alter the receive gain from different depths. Typical average TGC settings are mid range, with the gain control increased or decreased to permit mid-range TGC control alignment and hence maximizing available range variability

- **Frame rate** – where specified by the echocardiography protocol guideline the frame rate was > 50 fps. Frame rate generally refers to the acceptable frame rate for 2D imaging without additional scanning modes e.g. PW Doppler or CFM. There were no CFM measurements essential for the echocardiographic study, so no CFM frame rates were stated in the protocol guideline. For AFI measurement, optimal frame rate is between 50 – 70 fps (47) for good tracking sensitivity

- **Frame Rate rotary control** – a GE specific control used in position 1,2 or 3 to increase resolution of an image by increasing the packet size of the transmitted ultrasound pulse. A setting of ‘3’ uses the smallest packet size returning the highest frame rate; a setting of ‘1’ uses the largest packet size, with a lower frame rate, though will give improved resolution. In our routine clinical practice, standard 2D frame rates are expected to be above 50 Hz for routine 2D imaging

- **Colour Maps** – all images were recorded using a grey scale map. All grey scale and 2D colour maps are post-processed algorithms applied to the raw data as per individual preference for displaying images. They do not affect the quality of the stored echocardiographic data

- **Compress** – baseline is just above mid level, though may be increased for good echocardiography reflectors and reduced for poor echocardiographic reflectors – where the term ‘reflector’ refers to the
acoustic characteristic of the patients individual chest configuration.
Compress affects the contrast of a 2D image by limiting the number of shades of grey that echocardiograms are categorized into according to the intensity of each received echo signal

- **Reject** – kept at low setting to include as much data as possible in the image. Reject controls the amount of low-level intensity echoes that are displayed in the image. Too many low-level echoes gives an image full of noise, too few low-level intensity echoes gives images that are missing relevant low intensity echocardiographic information. It is preferred to keep the reject level low and utilize other 2D optimization techniques and tools to improve image quality, to avoid the risk of removing relevant data from the image

- **Dynamic Range** – kept at above mid level. This control sets the range of ultrasound frequencies that will be analysed for display. The 2D image contrast is affected as this control is adjusted, though it is different to the compress tool, which also affects the apparent contrast. Too low a dynamic range reduces the number of frequencies that are then categorized between the available shades of grey; too high a dynamic range increases the number of frequencies that are divided up across the available shades of grey. Where dynamic range is too high, there is too much information in the image which then appears too noisy, with echo-free regions of the blood pools likely to return noise echoes

- **DDP** – data dependent processing, a GE specific algorithm for temporal smoothing processing that is designed to reduce low level noise without significantly affecting the motion of significant tissue structures. This is a persistence control, so is kept to minimal levels, so moving structures are not adversely affected and can be temporally resolved
• Tilt – sector angulation – sector tilt may be used where transducer manipulation cannot bring relevant structures into the region of interest without widening the imaging

• UD Clarity – GE specific algorithm for processing echocardiogram signals. Designed to smooth the tissue appearance without altering the tissue resolution, it is for personal preference of appearance – which is to use it on very low setting

• Adaptive reject – a GE specific algorithm for reducing near field haze and blood pool artifact without diluting tissue appearance of moving structures. Adaptive reject was used minimally, as from experience it has little useful effect on image quality over and above other 2D optimization approaches and tools

• Contour – an edge enhancement control, which was not altered from preset probe default settings typically adopted at our centre. When applied at higher settings it returns images that appear hard, so is often a personal preference setting or used with difficult reflectors to give improved hardness of contrast. Routinely it is used minimally, with other 2D optimization approaches and tools being preferred

• Diff On/Off – GE specific control to reduce reverberation artifacts. More effective for young thin body configurations. In practice, there are very few patients that this control is noticeably effective for, so it is used infrequently in favour of other 2D optimization approaches and tools

• ATO – automated tissue optimization – is a GE specific algorithm, the following was the fullest definition, which could be found publicly, of how ATO works. ATO provides an automatic optimization of the 2D image by creating a histogram of the data in the scanning field’s region of interest or sector and applies up to the full 256 shades of grey available to enhance the contrast of the 2D image (53). The ATO
function can be applied to live scanning or stored images retrospectively. This control is frequently used in routine echocardiography work at our centre. It does not affect frame rate and is left on where it is seen to visibly improve the 2D image

- Thermal and mechanical indices are a function of the imaging settings and transmit power; effectively, where the image settings are optimised for high frame rate and the transmit power is kept to a minimum; the thermal and mechanical indices will be correspondingly at acceptable levels. Cardiac ultrasound has the additional advantage of a moving blood pool, so the potential theoretical risks of mechanical heating of tissue and cavitation are mitigated by the effective constant cooling from the moving blood pool both around and through the myocardium

- Cine loop length for standard image storage is a single cardiac cycle in most instances, though for apical images for volume calculation and PSAX of LV it is routine clinical practice to store cine loops of several cardiac cycles.

Since strain analysis was not performed at the time of the echocardiogram, it could not be known definitively whether the 2D images would be of sufficient quality to perform 2D speckle tracking strain analysis until the offline analysis phase of the study. However, routine image optimization techniques and the standard practice of paying attention to frame rate, heart rate, ECG triggering and ensuring all relevant structures are within the region of interest, meant we had good reason to expect the stored loops would be of suitable quality for speckle tracking strain analysis.

Cine loops lengths containing multiple cardiac cycles are preferred for strain analysis. The longer loops increase the chance of at least one cardiac cycle
within the loop being suitable for strain analysis, but are not essential. Where a single cycle cine loop is of sufficient quality it can contain all the required elements necessary for strain analysis.

9.2 Doppler Data Acquisition and Optimization

Doppler information is collected in a number of formats. Several Doppler formats are referenced in the study protocol as follows:

- Colour Flow Mapping (CFM)
- Pulse wave (PW) Doppler
- Continuous wave (CW) Doppler
- Tissue Velocity Imaging (TVI) – GE specific term, more generally referred to as Tissue Doppler Imaging (TDI)

Typically, where the best 2D window is obtained, the optimal window for all Doppler formats will be there too. The relevant Doppler format is applied with consideration of sample alignment to relevant flows. Consequently, the optimization techniques for Doppler data are the same in principle to that outlined for 2D optimization.

After optimizing the underlying 2D window before entering Doppler modes, there is usually further optimization of Doppler information, pertaining to the particular Doppler mode applied.

9.2.1 CFM Optimization

The best CFM occurs in the best 2D windows, so optimization for 2D as described returns good CFM. Additional specific CFM optimization usually relates to gain and scale, which were adjusted as per typical clinical practice to illustrate presence or absence of abnormal flow patterns at the valves.
9.2.2 PW Spectral Doppler Optimization (52)

Where PW spectral Doppler traces are stored for measurement, our normal optimization practice includes attention to:

- Cursor alignment – usually aligned to the centre of an expected laminar flow and as parallel to the flow as possible. For alignment with the MV inflow, the inflow itself is aligned with the centre of the sector, with the longest apical 4-Chamber view achievable tilted through the two AV valves, without inclusion of any of the LVOT. The basal lateral LV wall is usually nearly parallel to the incident line of the cursor. For LV outflow, the cursor is aligned parallel to the LVOT from the APLAX or apical 4C view. For RV outflow, the cursor is aligned to the RVOT in the PSAX view.

- Sample volume size – usually set at 2mm for most traces, though may be reduced to 1mm sample volume size for MV inflow or increased to 3mm for LVOT flow.

- Sample volume position – For MV inflow SV position in the apical 4-Chamber view is at the tips of the open MV leaflets with recording of traces at end expiration apnoea. For LVOT and RVOT traces, the SV is placed proximal to the relevant semi-lunar valve so that the Doppler noise of the valve closing-click was detected. For pulmonary venous trace the SV is placed within the pulmonary vein beyond the level of the opening to avoid being in the LA.

- Scale and Baseline – optimised together, so that the positive or negative flow profile of interest is at least a half to two thirds of the available spectral trace.

- Sweep speed – this is adjustable in post-processing, so storing at slower sweep speed allows more cycles to be stored, spectral Doppler traces are typically stored at 66cm/sec, while off line measurement of time intervals are routinely measured at higher sweep speeds.
(See Figure 15 PW of MV inflow optimised cursor alignment and SV position with spectral trace)

![Figure 15 PW of MV inflow optimised cursor alignment and SV position with spectral trace](image.png)

### 9.2.3 CW Spectral Doppler Optimization

CW Doppler optimization was similar to PW Doppler optimization with the exception of controls relating to sample volume. In place of sample volume position, the focal distance of the CW beam was placed at the level of the flow of interest.

Similarly as explained for 2D optimization, for CW and PW Doppler the compress, reject, frequency, frame rate, power, active mode gain, and low velocity reject controls were all set to enhance the trace to improve accuracy of measurement and good signal definition with all relevant data included while minimizing visualization of noise.
9.2.4 Tissue Velocity Imaging (TVI) Optimization

TVI is essentially PW Doppler with a large, colour coded sample volume, similar to CFM, though with a velocity scale, filtering and colour flow map suitable for tissue velocities. TVI base settings display the lower velocity, higher intensity signals of muscle motion; compared to the higher velocity, lower intensity signals of blood flow that is shown by CFM.

TVI may be acquired in two formats; TVI imaging with PW spectral Doppler mode added or live TVI overlaying the 2D image.

The TVI PW spectral Doppler format uses a sample volume that displays the range of frequencies detected within the sample volume. These signals will show the bandwidth of velocities occurring within the sample volume. Once stored, the loop holds the information from the sampled sites. If there is no
stored PW sampling of TVI, the bandwidth of velocities cannot be generated later. TVI PW spectral information is usually used for diastology analysis. TVI imaging mode is usually analysed offline by placing sample volume areas over regions of interest within the myocardium (Q-Analysis). The information is graphically displayed as a line that represents the average velocity within the ROI. In this way the timing of the peak velocity of contraction in opposing walls is compared for dyssynchrony assessment. Dyssynchrony may be most simply defined as a time delay between the peak velocities of systolic myocardial contraction in opposing walls. If there is no stored 2D TVI imaging loop this information cannot be generated or analysed later.

Where TVI imaging loops were stored, these were analysed to look for dyssynchrony.

![Figure 17 Optimised 2D Ap4C TVI images in diastole and systole](image)

Optimization of stored TVI imaging loops is typically with attention to:

- All of the points outlined above for 2D image optimisation
- TVI region of interest covering the basal and mid walls of LV and RV
- Scale – left at default setting, with Nyquist set by underlying 2D with TVI
- Baseline – centred, so positive and negative scales are equal
- Frame rate – left at default settings resulting from 2D image with TVI
• Invert – not used, so appearance of TVI colour scheme is standardised
• Simultaneous – not routinely used. It allows image duplication so two images are displayed; one with the TVI overlying 2D, one without. “Simultaneous” is on optional tool that is allows for operator personal preference and does not alter the quality of the stored image or the way they can be handled in post-processing
• Dual Focus – not routinely used, since temporal resolution would be compromised by consequential decreasing frame rate
• TVI visible – allows TVI data to be stored with a 2D image, while suppressing it during live scanning. This control is not typically used during routine data storage
• Colour Maps – routinely kept as the default colour map for consistency

All other TVI controls are left at machine defaults for routine TVI imaging. These included:

• Compress – the TVI colour bar may be adjusted by altering the colour compression
• Reject – similarly to other modes, trade-name for low velocity filtering
• Threshold – the 2D grey scale intensity is the reference for the colour scale so colour threshold is set with respect to grey scale
• Transparency – alters how transparent the TVI colour is to allow for improved visibility of the underlying 2D image
• Frequency – transmit frequency for TVI imaging and can be controlled separately to the 2D transmit frequency. Lower frequency provides greater penetration though at the expense of sensitivity and vice versa
• Lateral Averaging – looks at data along the same lateral data lines and averages them. Lateral resolution is reduced with higher settings of lateral averaging, so it is kept at lower levels
• Radial Averaging – looks at data along the same radial data lines and averages them. Higher settings of radial averaging will reduce radial resolution, so it is kept at lower levels

As per user manual recommendations for TVI imaging, default presets were used to provide optimum performance with minimum adjustment. The user manual indicates the Nyquist limit may be adjusted by reducing the scale to minimise variance or quantification noise, though this control is not routinely altered from preset values in our practice. Altering these controls are more relevant to optimising TVI Q-Analysis of strain.

TSI mode is not routinely used for image storage though can be useful to look at timing of peak velocities in wall segments during live scanning. If required, TSI can be switched on when post-processing TVI imaging loops.

10 Electrical Timing References

Electrical data reviewed came from standard 12 lead ECGs, pacemaker programmer printouts or readings, and echocardiograph’s monitoring ECGs.

Standard 12 lead ECGs are recorded at 25 m/s paper speed, calibrated to 1mV per cm. Frequency response is routinely set to the standard diagnostic range...
0.05Hz – 150Hz. ECGs were recorded on GE Mac5500 ECG machines with algorithmic analysis that could calculate QRS duration and axis.

QRS duration is known to increase with pacing and was recorded to check if pacing induced changes in duration were related to any identifiable mechanical changes in contraction.

A single monitoring ECG lead is used throughout an echocardiogram and is a necessary reference during paced and intrinsic rhythm. All Q-Analysis of 2D strain and TVI imaging and Automated Function Imaging are referenced from the ECG marker.

During analysis, it was evident there was significant variability in where on the QRS the echocardiograph’s algorithm placed the ECG marker. The ECG in Figure 19 shows a QRS with an exaggerated scale, to illustrate how the ECG marker position might vary and is not consistently placed at any of the following points:

- Onset of the QRS
- Peak of the major deflection
- First occurrence of a pre-determined slope steepness within the QRS
- First positive or negative deflection of pre-determined slope steepness
The echocardiographic ECG is the reference point for all time related measurements, so consideration of the QRS and the automated ECG marking was important for all timing related analyses.

QRS duration and morphology would affect where the echocardiograph’s ECG marker is placed within the QRS complex. For example, an intrinsic QRS complex might be marked near the QRS onset, while for the paced QRS it might be marked towards the end of the QRS. In extreme this could be more than 100msec as QRS durations for our subjects ranged from 74ms to 193ms. To avoid adding error, the onset of the QRS was used as the reference point for intrinsic and paced ECGs, wherever possible. If the QRS onset could not be manually marked, the time difference between QRS onset and ECG marker was taken into account when analyzing results.
Figure 20 ECG marker near QRS onset in right image and at QRS peak in same patient with pacing

For each subject manual measurements were made, during paced and intrinsic beats, from the onset of the QRS to the:

- ECG marker (Figure 21, measurements 1 & 2)
- Onset of flow through the aortic valve (Figure 21, measurements 3 & 4)
- Peak velocity of flow through the aortic valve (Figure 21, measurements 5 & 6)
- Cessation of flow through the aortic valve (see AVC line placement)

Figure 21 Auto ECG marker - measurements of QRS onset to ECG marker for correct time referencing
These additional timing interval measurements allowed accurate relative comparison of mechanical, electrical and haemodynamic events by using QRS onset as the single consistent reference point for timing.

Where the echocardiography software permitted, the ECG marker could be adjusted to the onset of the QRS. Placement was best done by eye, as a repeatable point could be chosen. This approach was used with 2D strain analysis as shown in Figures 22 and 23, which illustrate analysis of the same radial strain loop before and after the yellow ECG markers are adjusted.

![Figure 22 Radial Strain Graph - ECG marker automatically positioned](image)
In Figures 22 and 23 the AVC line is shown in the same place (yellow arrow), but moves with the QRS marker so has been adjusted independently to the correct time measured from the LVOT PW spectral Doppler in Figure 23.

During 2D strain analysis, the AVC line was adjusted to the value measured from the CW Doppler trace of aortic valve closure for correct identification of the end of systole. The 2D strain graph allowed AVC line placement within 6msec of the time measured from the CW Doppler trace.

Placement of the AVC line clearly identified the period of time in which to look for the peak systolic strain and strain rates, as it delineated (a) systolic peaks from peaks occurring immediately post-systolic and (b) the end-systolic point to measure where slopes continued to rise at the end of systole, similar to AFI end systolic strain measurement.
With 2D imaging, the start and end of cine loops can be adjusted, though this does not necessarily affect the QRS marker position. Upon entering the AFI measurement process, ECG marker adjustment is not permitted. For AFI results, the placement and measurement of the AVC line for “Event Timing” value is automatically made with reference to the QRS marker.

Figure 24 illustrates AVC line placement, though actual caliper placement should be at the extreme right edge of the drawn red line.

With understanding of AVC referencing and variability of automated QRS marker placement, loops for AFI were chosen for 2D quality and importantly for similarity in the QRS marking for the Doppler trace used for Event Timing AVC measurement. Prior to running AFI, the AVC value used for AFI calculation was verified as being equal to the time measured from the QRS onset to the cessation of systolic flow, less the time from QRS onset to the QRS
marker. In this way, end systole was the same for all strain analysis as it was referenced to exactly the same AVC point.

For each subject, there were two AVC times measured, one for each of the AFI calculations made for intrinsic and paced conduction.

Since the event timing AVC measurement is part of the AFI calculations, it is not specifically reported in the results chapter. The true timing of the aortic valve closure, with respect to the QRS onset, is reported in the results tables and used to calculate the timing and duration of systole.

The ECG marker is the point drift compensation of 2D strain analysis is applied. Drift compensation essentially forces the strain lines to cross zero at the ECG marker points. This adjusts the peak values and their timing slightly, as can be seen in Figures 25 & 26. Drift compensation is also referred to in Section 11.2.2 Q-Analysis – 2D Strain.

Figure 25 Radial Strain Analysis - without drift compensation (QRS markers adjusted)
The AVC lines in Figures 25 and 26 have not been adjusted to the correct time, so peaks should not be interpreted as being systolic or post-systolic. The only change is the drift compensation on/off – scale adjustments are automated to this point. The radial strain map (lower left) in Figure 26 appears ‘redder’ than in Figure 25, reflecting the lower range of peak values with drift compensation on, hence displaying a tighter range of peak values at a similar time.

In summary, measuring from a point within the QRS was considered an inaccurate method of relating timing of events. Instead, onset of QRS was referenced for time related measurements based on:

- Inability of the echocardiograph’s ECG algorithm to consistently detect the same point within QRS complexes of the same morphology
- Range of QRS durations with pacing and intrinsic conduction
- Variability in QRS morphology between pacing and intrinsic conduction for some subjects
- Having a consistent end point for systole for all strain analysis
- Applying drift compensation to a consistent point for strain analysis
With all measurements referenced to the onset of the QRS, more reliable comparisons could be made when relating mechanical events to systole and assessing dyssynchrony.

11 Offline Echocardiographic Data Measurement and Analysis

Routine and advanced echocardiography measurements were attempted on 27 subjects.

Refer to Section 9.1 2D Image Data Acquisition and Optimization and Section 9.2 Doppler Data Acquisition and Optimization for description of general approach to image optimization as part of clinical practice and for offline analysis.

Refer to Section 10 Electrical Timing References for ECG adjustments required for analysis and referencing of strain, strain rate and AFI.

Routine/established parameters measurement method is with reference to relevant ASE guidelines as reported in the text, *Echocardiography: the Normal Examination and Echocardiographic Measurements* (52).

11.1 Routine Echocardiography Measurements

Routine echocardiography measurements were attempted on all subjects; Table 1 lists these measurements.
Table 1 Routine Echocardiography Measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>During Intrinsic Rhythm</th>
<th>During Paced Rhythm</th>
<th>Calculations</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVOT diameter</td>
<td>Yes</td>
<td>No</td>
<td>Stroke volume, Cardiac Output</td>
</tr>
<tr>
<td>LVEDD/LVESD</td>
<td>Yes</td>
<td>No</td>
<td>Fractional Shortening</td>
</tr>
<tr>
<td>IVSD/LVPWD</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>LVPEP</td>
<td>Yes</td>
<td>Yes</td>
<td>ΔPEP</td>
</tr>
<tr>
<td>RVPEP</td>
<td>Yes</td>
<td>No paced data</td>
<td>ΔPEP – no paced data</td>
</tr>
<tr>
<td>LVEDV/LVESV</td>
<td>Yes</td>
<td>Yes</td>
<td>LVEF Bi-Plane MOD</td>
</tr>
<tr>
<td>Aortic diameter</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>PV peak velocity</td>
<td>Yes</td>
<td>No paced data</td>
<td></td>
</tr>
<tr>
<td>LA size</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>RA size</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>LVOT velocity</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>LVOT VTI</td>
<td>Yes</td>
<td>Yes</td>
<td>Stroke Volume, Cardiac Output</td>
</tr>
<tr>
<td>MV E velocity</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>TR peak velocity</td>
<td>Yes</td>
<td>No</td>
<td>RVSP Estimation</td>
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<tr>
<td>HR</td>
<td>Yes</td>
<td>Yes</td>
<td>Cardiac Output</td>
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</table>

Qualitative and semi-quantitative analyses were attempted routinely on all subjects as part of checking for inclusion and exclusion criteria. See Table 2

Table 2 Routine Qualitative and Semi-Qualitative Assessments

<table>
<thead>
<tr>
<th>Assessment</th>
<th>During Intrinsic Rhythm</th>
<th>During Paced Rhythm</th>
<th>Multiple views for all 2D &amp; CFM assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>Yes</td>
<td>No</td>
<td>2D valve motion, CFM</td>
</tr>
<tr>
<td>MR</td>
<td>Yes</td>
<td>No</td>
<td>CFM area of MR, CW spectral intensity</td>
</tr>
<tr>
<td>AS</td>
<td>Yes</td>
<td>No</td>
<td>2D valve motion, CFM, Aortic CW velocity</td>
</tr>
<tr>
<td>AR</td>
<td>Yes</td>
<td>No</td>
<td>CFM</td>
</tr>
<tr>
<td>TR/TS</td>
<td>Yes</td>
<td>No</td>
<td>2D valve motion, CFM</td>
</tr>
<tr>
<td>RV size and function</td>
<td>Yes</td>
<td>No</td>
<td>2D appearance relative to measured chambers</td>
</tr>
<tr>
<td>LV function and regional wall motion abnormalities</td>
<td>Yes</td>
<td>Yes</td>
<td>2D appearance of LV wall motion, MOD BiPlane EF</td>
</tr>
</tbody>
</table>

11.2 Strain, Strain Rate & Related Timing Measurements

Analysis of strain, strain rate and dyssynchrony were via the following methods:
• Automated Function Imaging (AFI) – 2D speckle tracking of longitudinal strain, using 3 apical views
• Q-Analysis of 2D Strain using speckle tracking of segments in the radial, circumferential and rotational planes
• Q-Analysis of TVI image loops of the apical views to assess for any wall motion delays between pairs of segments at the basal and mid walls in three apical views

Table 3 Measurements of Strain and Strain related timings, lists the measurements made on intrinsic and paced data sets to assess strains, strain rates, and their relationship to systole, and the synchronicity of contraction as assessed through differential timing of peak values. Results tables are matched to the list of variables below.

Table 3 Measurements of Strain and Strain related timings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Abbreviation +/- calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of QRS to machine place ECG timing marker</td>
<td>R-QRS marker</td>
</tr>
<tr>
<td>Time from onset QRS to onset of LVOT outflow</td>
<td>R-AVO</td>
</tr>
<tr>
<td>Time from onset QRS to peak LVOT velocity</td>
<td>R-LVOT pk v</td>
</tr>
<tr>
<td>Time from onset QRS to cessation of LVOT outflow</td>
<td>R-AVC</td>
</tr>
<tr>
<td>Systolic Duration</td>
<td>Sys Dur, (R-AVC) – (R-AVO)</td>
</tr>
<tr>
<td>Percentage of systolic duration when LVOT velocity peaks</td>
<td>LVOT pk v % Sys, (R-LVOT pk v – R-AVO)/Sys Dur(%)</td>
</tr>
<tr>
<td>AVO/AVC with respect to onset of QRS (for Event Timing as part of AFI)</td>
<td>R-QRS marker + AVC = R-AVC</td>
</tr>
<tr>
<td>Average Global Longitudinal Peak Strain</td>
<td>Av_GLS, Av_GLPS or GLS</td>
</tr>
<tr>
<td>Radial Strain values: Peak for 6 segments and average of peaks</td>
<td>RS, RS Avg Pk S</td>
</tr>
<tr>
<td>Radial Strain timing: Onset of QRS to each segment peak value, noting latest, earliest, average and maximal delay between peaks</td>
<td>RS LS - latest segment, RS ES - earliest segment, Avg RS time, RS LS – ES</td>
</tr>
<tr>
<td>Variable</td>
<td>Abbreviation +/- calculation</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Percentage of systolic duration when Radial Strain peaks</td>
<td>RS % Sys, (RS Avg RS time – R-AVO)/Sys Dur%(%))</td>
</tr>
<tr>
<td>Radial Strain Rate: Peak value of 6 segments</td>
<td>RSR</td>
</tr>
<tr>
<td>Radial Strain Rate timing: QRS onset to RSR peak for 6 segments</td>
<td>R-RSR pk</td>
</tr>
<tr>
<td>Percentage of systolic duration when Radial Strain Rate Peaks</td>
<td>RSR % Sys, (R-RSR pk – R-AVO)/Sys Dur%(%)</td>
</tr>
<tr>
<td>Circumferential Strain: Global peak value</td>
<td>G CS</td>
</tr>
<tr>
<td>Circumferential Strain Timing: QRS onset to global peak value</td>
<td>R-GCSpk</td>
</tr>
<tr>
<td>Percentage of systolic duration when Circumferential Strain Peaks</td>
<td>G CS % Sys, (R-GCS pk – R-AVO)/Sys Dur%(%)</td>
</tr>
<tr>
<td>Circumferential Strain Rate: Global peak value</td>
<td>G CSR</td>
</tr>
<tr>
<td>Circumferential Strain Rate Timing: QRS onset to CSR global peak value</td>
<td>R-G CSR pk</td>
</tr>
<tr>
<td>Percentage of systolic duration when Circumferential Strain Rate peaks</td>
<td>G CSR % Sys, (R-G CSR pk – R-AVO)/Sys Dur%(%)</td>
</tr>
<tr>
<td>Rotational Strain: Global peak value</td>
<td>G Rot</td>
</tr>
<tr>
<td>Rotational Strain Timing: QRS onset to global Rotational Strain peak</td>
<td>R-G Rot pk</td>
</tr>
<tr>
<td>Rotational Strain Timing: Onset of QRS to global peak value</td>
<td>R-G Rot pk</td>
</tr>
<tr>
<td>Rotational Strain Rate: Global peak value</td>
<td>G RotR</td>
</tr>
<tr>
<td>Rotational Strain Rate Timing: Onset of QRS to global peak value</td>
<td>R-G RotR pk</td>
</tr>
<tr>
<td>Percentage of systolic duration when Rotational Strain Rate peaks</td>
<td>G Rot R % Sys, (R-G RotR pk – R-AVO)/Sys Dur%(%)</td>
</tr>
<tr>
<td>Wall motion delay TVI: Time differential between opposing wall segments</td>
<td>TDI Av Septal-Lateral Delay, (Ant-post delay + Antlat-inferosep delay + Antsept-inferolat delay)/3</td>
</tr>
</tbody>
</table>

**Table 3 continued**

### 11.2.1 Automated Function Imaging – for longitudinal strain

AFI requires apical images from the 4-Chamber, long axis and 2-Chamber planes that must include all of the LV wall mass within the sector width throughout the cardiac cycle.
Selection of a specific cardiac cycle within a chosen cine loop is possible, although the automated function will default to the second cardiac cycle unless another cycle is manually chosen.

As part of cycle selection, close attention should be paid to four things:

- The position of the ECG marker for consistency
- Frame rate – which should ideally be the same for all three apical loops analysed and between 40 – 80 frames per second
- Heart rate – which ideally should be the same for all three apical loops for analysis, though a small degree of variability is tolerated by the semi-automated function
- The AVC value the calculation will use

Full description of AFI workflow is available from the user manual, so points included here are illustrative of the simplicity of making the measurement and where the user is required to make choices to aid the semi-automated quantitative AFI calculation.

There was a difference in AVO/AVC (event timing) between the paced and intrinsic states for each subject, so Event Timing was updated in the machine analysis page prior to running Automated Function Imaging (AFI) for paced and intrinsic data sets. See section 10 Electrical Timing References for explanation of how this was corrected for.

Event Timing is measured from the LVOT or Aortic Valve spectral Doppler traces as shown and the Aortic Valve Opening and Aortic Valve Closure points are marked. It is important that the AVC line is placed objectively in a repeatable manner for consistent measurement of AVC. The AVC measurement line was placed directly down the middle of the intense
“closing click” line that is seen at the end of forward flow. See Figure 24 AVC line placement (within closing valve click) for AFI

The AVC for AFI Event Timing is the time interval from the ECG marker to the AVC line placement on the CW Doppler trace. It is important that the timing marker on the ECG QRS complex occurs at a consistent point for all analysed traces i.e. the Doppler trace and the three measured apical cycles. This becomes critical when the reported peak longitudinal strain occurs at end systole, which is marked by the AVC line. Where there was variability in the QRS timing marker, only 2D loops and Doppler trace with similarly marked QRS timing were chosen for AFI.

After measuring the Event Timing, a 2D APLAX loop is chosen and the region of interest appointed.

Figure 27 AFI - ROI after initial point placement
Segment tracking is verified to reflect the underlying visible muscle motion. Where necessary, the ROI points may be repositioned and the tracking recalculated until tracking properly reflected muscle motion. This step can be repeated as many times as required. However, if tracking is likely to work, our experience was that it will usually work within the first 2-3 ROI adjustments; otherwise it may be quicker to abandon that cycle and choose another.

Figure 28 AFI Verification of Tracking

Approval of visible tracking is made, when satisfied of correct tracking of ventricular myocardium, to the exclusion of other structures, e.g., pericardium, valve leaflets. The AFI analysis programme will indicate whether there is good or bad computer tracking based on whether there are
enough speckles to detect and follow within each segment. The user must ascertain that the tracking is actually following the myocardial motion.

Where a segment is marked as tracking poorly the ROI points may be re-positioned again or another loop chosen as many times as required for machine approval.

Alternatively a red box and cross may be turned into a green box and tick by selecting it and overriding the machines estimation of good or bad tracking. For this study, bad machine tracking was not accepted, and ROI points were altered or different cycles chosen until a full set of machine-approved and user-approved tracking of segments could be achieved.

Figure 29 AFI Approved APLAX speckle tracking

So tracking approval is a twofold process of (a) Operator approval of visible tracking and (b) Machine approval of algorithm tracking.
At the end of APLAX tracking approval, the event timing method is selected, from a choice of manual, auto or “Event Timing”. The latter was always used, as it accessed the relevant AVC from the analysis data that was pre-selected for the correct intrinsic or paced AFI that was being calculated.

Next an Ap4C loop is chosen and ROI markers placed, followed by the tracking approval process as before.

![Figure 30 AFI Ap4C ROI and approval of tracking as for APLAX](image)

After approval, before the next view is chosen, other display formats can be chosen, though did not add to data analysis for this study, so are omitted.

![Figure 31 AFI Ap4C speckle tracking images in diastole and systole](image)

Finally an Ap2C loop is chosen and ROI point placement and recalculation, followed by tracking approval as before.
In any of the three apical images, when a segment struggles to detect enough speckles the first approach may be to adjust the ROI points of the poorly tracking segment. However, it was found that when the distal LV segments were not tracking well, dragging the basal segment markers away from the apex created a larger ROI for the distal segments and frequently improved distal segment tracking enough for machine approval.

Figure 32 AFI Ap2C ROI and approval of tracking

Upon approval of the tracking in the apical 2-chamber view, the results are presented in a graphical format and a circular map of the LV segments. The strain graphs must be further assessed for correct assignment of peak strain values. Each of the 18 segment lines, 6 within the three graphs, should be inspected.

Strain peaks are defined by an algorithm that is not always correct as preferred: in Figure 33 AFI Results - automatically assigned peaks where the red line for the anteroseptal base has a very early, positive designated peak.
Figure 33 AFI Results - automatically assigned peaks, note incorrect early peak (blue arrow)

Figure 34 AFI Results - APLAX red segment strain peak adjusted shows the red segment peak adjusted to a more correct negative systolic peak. This changes the polar map of the segmental strain values, where an asterisk denotes the adjusted segment. Once adjusted, there is no reset feature, so the loop must be re-analysed if original data is required.
Although there are a couple of other available formats for AFI, the set of graphs and bulls-eye are the most succinctly descriptive. The other displays were reviewed to confirm there was no specific timing or timing measurements that would add value to our AFI measurement.
A useful loop to store is the final loop created upon exiting the measurement package. The layout in Figure is indicative of the final AFI loop that may be stored. Choosing to store this loop facilitates later review, as AFI will run on the ROIs previously approved to re-create the same polar map and graphs. For this study, all AFI loops used for data analysis were stored.

![Figure 36 AFI final loop to store](image)

**11.2.2 Q-Analysis – 2D Strain**

Through the Q-Analysis programme, speckle tracking for strain analysis can be applied to PSAX data. User manuals describe the method of strain analysis, so this section focuses on our practical experience of using the strain module.

Analysis was of a PSAX loop at basal level. Typical optimization aims for as near a circular shape as possible at the LV bases, fully showing the endocardial border.
Examples of radial strain have been shown earlier, with regard to QRS marker adjustment and drift compensation. Other information available from the same data set was strain and strain rate in the circumferential and rotational planes.

On discussion with an industry expert, circumferential strain was recommended as potentially a more robust measurement than radial strain/strain rate, since the segmental data set has a wider range of motion in the circumferential plane than in the radial plane. Similarly strain rate was recommended, as it often returns a more cohesive signal than strain and may show a detectable change when related to timing of systolic events. Consequently global measures of circumferential strain and strain rate were included as part of data analysis. Global rotational strain and strain rate was reviewed for completeness, as these data were readily available alongside the radial and circumferential data.
Radial strain graph scale was adjusted for more accurate peak value measurement. QRS markers and AVC closure line were correctly placed, as previously described. Measurement of peak values and time from onset of QRS was recorded for each segment for radial strain. Peak systolic strain was taken as the greater of the systolic peak or end systolic value, where the strain peak occurred after aortic valve closure.
Although a results table was available, it was not used. The results for strain rates and some strains would have needed a lot of adjustment for the results table to be accurate. It was quicker to manually measure and record data.

Figure 39 Radial Strain Rate Results Table shows six peaks marked by the machine. Three peaks are marked during isovolumetric contraction time, while another three peaks are marked within the final set of systolic peaks. The final set of systolic peaks reflects the correct set to measure the peak positive systolic strain rate associated with systolic strain. However, with multiple peaks during systole and both large positive and negative peaks, strain rate was often found difficult to interpret.

In Figure 40 Rotational Strain; Global Average dotted line (blue arrow), the global measurement is indicated by the white dotted line. The peak value was readily measured from the global average for both strain and strain rate. Similarly, the multiple peaks seen on circumferential and rotational strain rate graphs are difficult to interpret, though global peak and time of global peak were more readily measureable.
Care was taken to review drift compensation for all strain analysis, as is recommended (32). Drift compensation affects both systolic and diastolic values, by applying a linear correction algorithm to the data such that at the point of QRS onset values are forced to cross the zero line. The example Figure 41 Circumferential Strain with drift compensation on (top) and off (bottom) illustrates a lot of drift relative to the values of the strain peaks. (Note scale not adjusted for measurement, but to show range of uncompensated drift values)
For comparison, see Section 10 Electrical Timing References in Figure 25 Radial Strain analysis - without drift compensation (adjusted QRS markers) and Figure 26 Radial Strain with drift compensation (adjusted QRS markers) where Figure 25 illustrates a tight range of strain graph lines when drift compensation is removed. For much of the analysis on the PSAX data sets, the uncompensated drift values were similar in size to the peak values. The relevance of drift compensation to interpretation of results is briefly explored in the discussion chapter.

11.2.3 Q-Analysis – Dyssynchrony Assessment

TVI imaging format may be observed by eye, but is difficult to interpret at normal heart rates, even where there is extreme abnormality. TSI mode illustrates delayed segments during live scanning, though gives relative peak timing and not an actual time the peaks are occurring, though this can be measured during post processing.

Mechanical dyssynchrony assessment was measured from by two methods:

- TVI Imaging Q-Analysis
- 2D Radial Strain timing of segment peaks

Dyssynchrony, using TVI imaging, was measured by comparing the time difference between opposing wall pairs for the 3 apical views. We sampled at the base and mid wall in each apical view, giving us (3 x 2) 6 pairs on which time differences were measured.

We used default sized sample volume ROIs. The 6 pairs were analysed for maximal delay from anterior to inferior walls, average anterior – inferior delay and absolute maximal delay between any pair.
The pairs were measured anterior to inferior, anteroseptal to inferolateral, anterolateral to inferoseptal for the maximal anterior – inferior delay and the average anterior to inferior delay. The time difference between pairs was measured as positive if the anterior, anteroseptal or anterolateral peaked first and negative if the posterior, inferolateral or anterolateral segment peaked first. The average difference of the 6 pairs was the reported wall motion delay.

Figure 42 Apical 4C Dyssynchrony; TVI Imaging SV placement (blue arrows)
Figure 43: Apical 2C Dyssynchrony; TVI Imaging SV placement
The second method of mechanical dyssynchrony assessment was measured from 2D speckle tracking of radial strain segments. In the PSAX view, the circle of the LV bases can be divided into 6 segments. Each segment has a percentage length change (or strain) and a time that the strain peaks, which are reported in a graphical format.

We measured the 6 radial strain segment peaks and times, with subsequent analysis of the following specific measurements:

- Time interval of QRS onset to each strain peak
- Latest segment to peak after QRS onset
- Earliest segment to peak after QRS onset
- Absolute maximal delay between latest and earliest segments
- Average time the 6 strain peaks occurred
- Value of the strain peak

All segment peaks were measured within systole as designated by the correct placement of the AVC line prior to measurement.
Figure 45 Radial Strain Peaks occurring synchronously

Figure 46 Radial Strain Peaks occurring at different times, maximal time delay (TD) marked

Retrieved from “Differences in left ventricular dyssynchrony between high septal pacing and apical pacing in patients with normal left ventricular systolic function”, by Yoshikawa et al. (39)
12 Statistical Analysis

Data are reported as mean ± standard deviation. We compared measures from intrinsic and paced beats for the whole group, and compared paced to intrinsic data for RVA and RVOT sub-groups. Comparisons were made using paired t-tests for normally distributed data and Wilcoxon rank sum test for matched pairs, where data was not normally distributed. Direct comparison of RVA to RVOT paced data means was with Mann-Whitney test for unmatched pairs. The significance of proportions within the group characteristics data was estimated using Fisher’s exact test or Chi Square test. Confidence intervals for testing were set at 95%. P values of <0.05 were considered statistically significant. Statistical tests were performed using GraphPad Prism 5.0.
Chapter Three: Results

1 Subject Recruitment

Subjects were taken from the group of patients who had received a pacemaker implant at Wellington Cardiology between 1st March 2010 and 30th November 2010. During that time, there were 175 patients who received pacemaker implant at Wellington Hospital.

Of these 175 patients, 132 were domiciled in the CCDHB region, of which 62 received echocardiograms. There were two patients that had brief echocardiograms specifically to review an acute emergent complications, so the content of the echocardiogram had been focused on addressing the higher clinical need rather than providing a comprehensive echocardiographic study. Reduced LV function and valve disease excluded another 21 patients from the list of potential subjects. From the 39 remaining, a further 12 were excluded based on increased QRS or no paced data for comparison or poor echocardiographic imaging windows.

There were 27 subjects suitable to include in the study.

Table 4 Study Subjects

<table>
<thead>
<tr>
<th>175 Pacemaker Implants at CCDHB 1/3/10 – 30/11/10</th>
</tr>
</thead>
<tbody>
<tr>
<td>132 Local Patients</td>
</tr>
<tr>
<td>62 Received Echocardiogram</td>
</tr>
<tr>
<td>35 Excluded</td>
</tr>
<tr>
<td>Subjects</td>
</tr>
<tr>
<td>27</td>
</tr>
</tbody>
</table>
Table 5 Study Subject Selection

<table>
<thead>
<tr>
<th>Applied Criteria</th>
<th>Number Excluded</th>
<th>Possible Subjects</th>
<th>Average Age (years)</th>
<th>Gender (Male)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacing Implants at CCDHB</td>
<td></td>
<td>175</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCDHB Domicile</td>
<td>41</td>
<td>132</td>
<td>75 ±10.7</td>
<td>60%</td>
</tr>
<tr>
<td>Received Echocardiogram</td>
<td>70</td>
<td>62</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Exclusion Criteria:

- Acute complications: 2 (60)
- LVEF < 50%: 12 (48)
- Valve Disease > mild: 9 (4 AVR, 1 AS, 4 MVD) (39)
- Poor Echocardiography Images: 4 (35)
- QRS > 130 msec: 4 (31)
- No Paced data: 4 (27)

Subjects for study: 27 (75 ±9.2) 67%

Table 5 confirms that the subject group was of similar age, with a similar percentage of males in the final group, compared to the initial group of pacemaker implant patients that the sample was drawn from.

Table 6 Pacemaker Indication, characterizes the pacing indications of the study group, separating subjects into two sub-groups;

- RVA group - the RV pacing lead fixed in the RV apex
- RVOT group – the RV pacing lead fixed somewhere other than the RV apex

The second group is referred to as the RVOT group, as the intention of the implanter was to position the RV lead in the RVOT, using fluoroscopy, ECG V1 lead characteristics, QRS duration and axis to confirm lead position(30, 36).

Table 6 Pacemaker Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>All</th>
<th>RVA</th>
<th>RVOT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrioventricular node disease</td>
<td>14</td>
<td>54%</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Sinus node disease*</td>
<td>11</td>
<td>41%</td>
<td>3</td>
<td>11%</td>
</tr>
<tr>
<td>Carotid Sinus Hypersensitivity</td>
<td>1</td>
<td>4%</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Implantable Cardioverter Defibrillator</td>
<td>1</td>
<td>4%</td>
<td>1</td>
<td>4%</td>
</tr>
</tbody>
</table>

27 100% 12 44% 15 56% 0.81

Includes one subject in the RVOT group with slow AF that had an ICD lead implanted
Using Fisher’s exact test for significant proportions
Atrioventricular node disease made up 54% of the whole group, with complete heart block 36% and Mobitz II 64% of this AVN group. The incidence of AVN disease was evenly spread between the RVA and RVOT groups.

The sinus node disease group includes sick sinus syndrome, sinus arrest, sinus bradycardia, tachy-brady syndrome and a fairly regular, slow AF.

There were two subjects with an Implantable Cardioverter Defibrillator. One was a new implant and in the RVA group. The other had a pacing indication as well as an ICD indication; this subject was in the RVOT group. All ICDs must have the ability to RV-pace as a safety precaution post shock delivery and although there was no clear pacing indication for one of these patients, they did have a pre-discharge echocardiogram during intrinsic and paced conduction; their data was included as normal control without a pacing indication. The results of these two subjects were tracked through the data analysis to confirm that their results fell within one standard deviation of the mean for normally distributed variables.

Although the total group number was small, there were a reasonable number of subjects in each sub-group, to continue with advanced analysis of the echocardiographic data. There was no significant difference in the proportion of AVN disease between the RVA and RVOT groups. There was a bias toward more sinus node disease in the RVOT group, though this was not statistically significant.
The pacemaker population can reasonably be expected to be older and predominantly male. This is consistent with our sample of subjects, where two thirds were male and mean age was 75 years.

There were a small number of patients with known coronary artery disease; one subject had a previous myocardial infarction and 2 had received PCI. In all cases, these subjects met the inclusion criteria, having normal LVEF.

Table 7 Subject Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>All (n=27)</th>
<th>RVA (n=12)</th>
<th>RVOT (n=15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75 ± 9.2</td>
<td>78 ± 7.0</td>
<td>74 ± 9.5</td>
<td>0.27</td>
</tr>
<tr>
<td>BSA</td>
<td>1.85 ±0.17</td>
<td>1.79 ±0.17</td>
<td>1.88 ±0.16</td>
<td>0.26</td>
</tr>
<tr>
<td>Incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
<td>67%</td>
<td>8</td>
<td>67%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5</td>
<td>19%</td>
<td>2</td>
<td>17%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>67%</td>
<td>10</td>
<td>83%</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>12</td>
<td>44%</td>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1</td>
<td>4%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Known CAD</td>
<td>5</td>
<td>19%</td>
<td>3</td>
<td>25%</td>
</tr>
<tr>
<td>PCI</td>
<td>2</td>
<td>7%</td>
<td>2</td>
<td>17%</td>
</tr>
<tr>
<td>Other Vascular disease</td>
<td>5</td>
<td>19%</td>
<td>3</td>
<td>25%</td>
</tr>
<tr>
<td>Prior Congestive Heart Failure</td>
<td>1</td>
<td>4%</td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td>eGFR &lt; 60</td>
<td>8</td>
<td>30%</td>
<td>5</td>
<td>42%</td>
</tr>
<tr>
<td>Ejection Fraction &lt; 40%</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Smoker</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Ex-Smoker</td>
<td>9</td>
<td>33%</td>
<td>6</td>
<td>50%</td>
</tr>
<tr>
<td>COPD</td>
<td>0</td>
<td>0%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>&quot;A&quot; Tachy</td>
<td>6</td>
<td>22%</td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td>Unrelated other medical findings</td>
<td>15</td>
<td>56%</td>
<td>8</td>
<td>67%</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>10</td>
<td>37%</td>
<td>5</td>
<td>42%</td>
</tr>
<tr>
<td>CCB (non-dihydro)</td>
<td>1</td>
<td>4%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>CCB (dihydro)</td>
<td>2</td>
<td>7%</td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td>ACE-i</td>
<td>7</td>
<td>26%</td>
<td>3</td>
<td>25%</td>
</tr>
<tr>
<td>ARB</td>
<td>3</td>
<td>11%</td>
<td>3</td>
<td>25%</td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>1</td>
<td>4%</td>
<td>1</td>
<td>8%</td>
</tr>
<tr>
<td>Bendrofluorizide</td>
<td>4</td>
<td>15%</td>
<td>2</td>
<td>17%</td>
</tr>
<tr>
<td>Alpha-b</td>
<td>4</td>
<td>15%</td>
<td>2</td>
<td>17%</td>
</tr>
<tr>
<td>Statin</td>
<td>13</td>
<td>48%</td>
<td>7</td>
<td>58%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>14</td>
<td>52%</td>
<td>7</td>
<td>58%</td>
</tr>
</tbody>
</table>

Using Fisher’s exact test for significant proportions
With the pacemaker population being predominantly elderly, subjects did have a level of other disease and were on appropriate medication for these diagnoses. Major cardiac pathology that might affect cardiac function and hence alter cardiac afterload, were excluded.

3 Pacing Lead Site Results

3.1 ECG Results

ECG results were taken from 12 lead ECGs where they were available. There were some subjects for whom the relevant 12 lead ECG could not be readily located. There were 3 subjects where an ECG could not be located for both the intrinsic and paced rhythms, while an additional fourth patient had no obvious 12 lead ECG in a verified paced rhythm. This is more a reflection on the paper-based notes system than whether or not these ECGs were recorded at the time of the pacing implant.

Table 8 Number of Subjects with available ECGs

<table>
<thead>
<tr>
<th>Group</th>
<th>Whole Group</th>
<th>RVA Group</th>
<th>RVOT Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic</td>
<td>24</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Paced</td>
<td>23</td>
<td>9</td>
<td>14</td>
</tr>
</tbody>
</table>

3.1.1 Cardiac Axis

Cardiac axis was assessed from intrinsic and paced 12 lead ECGs and results are part of routine confirmation of pacemaker lead site.

Apical pacing alters cardiac axis to consistently show left axis deviation with respect to intrinsic conduction and RVOT pacing. (Table 9) This is consistent with findings in other studies (2, 30, 36).
RVOT pacing altered cardiac axis, though the axis measurements ranged widely with RVOT pacing; see RVOT pacing lead site variability is referred to under the limitations section of the discussion.

### 3.1.2 QRS Duration

QRS duration was measured from 12 lead ECG. Results show both RVA and RVOT pacing increases QRS duration, though RVOT pacing appears to increase QRS duration by less than RVA pacing. There was no significant difference when comparing the QRS durations of the RVA and RVOT groups.

#### Table 10 QRS Duration

<table>
<thead>
<tr>
<th>QRS Duration</th>
<th>Intrinsic Conduction</th>
<th>Paced Conduction</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group*</td>
<td>104.1 ±21.06</td>
<td>147.9 ±28.02</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>RVA Group*</td>
<td>98.1 ±17.74</td>
<td>162.7 ±20.22</td>
<td>0.0001</td>
</tr>
<tr>
<td>RVOT Group*</td>
<td>108.3 ±22.82</td>
<td>138.4 ±28.80</td>
<td>0.0026</td>
</tr>
<tr>
<td>RVA compared to RVOT (both paced)*</td>
<td></td>
<td></td>
<td>0.0397</td>
</tr>
</tbody>
</table>

* Using paired t-tests' and unpaired t-test

### 3.2 Rhythms and Heart Rates

The paced heart rate was matched to the intrinsic heart rate for each subject, though there was a wide range in heart rates amongst subjects, with the range in HR from 35bpm –98bpm. There was no significant difference in the mean HR when comparing intrinsic to paced group and this finding carried
through to the sub-groups, with no significant difference in HR between intrinsic and paced conduction for the RVA or RVOT groups. See Table 11 Rhythms and Rates, which shows most patients had an underlying rhythm of sinus origin.

Table 11 Rhythms and Rates

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects in Sinus Rhythm (n)</th>
<th>Minimum Rate of Sinus origin (bpm)</th>
<th>Maximum Rate of Sinus origin (bpm)</th>
<th>Subjects in Junctional Rhythm (n)</th>
<th>Minimum Rate of Junctional Origin (bpm)</th>
<th>Maximum Rate of Junctional Origin (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Intrinsic</td>
<td>23</td>
<td>40</td>
<td>95</td>
<td>4</td>
<td>35</td>
<td>44</td>
</tr>
<tr>
<td>RVA – intrinsic</td>
<td>11</td>
<td>40</td>
<td>98</td>
<td>1</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>RVOT – intrinsic</td>
<td>12</td>
<td>50</td>
<td>80</td>
<td>3</td>
<td>35</td>
<td>44</td>
</tr>
</tbody>
</table>

4 Echocardiography Results

All 27 subjects that had echocardiographic data could be analysed with 2D speckle tracking strain and TVI analysis.

2D strain in radial, circumferential and rotational planes were analysed for all patients. There were 6 segments for each plane in the PSAX view.

Table 12 Number of AFI Segments Tracked

<table>
<thead>
<tr>
<th>AFI Number of Segments Tracked</th>
<th>Intrinsic Conduction</th>
<th>Paced Conduction</th>
<th>Subjects (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group</td>
<td>486</td>
<td>486</td>
<td>27</td>
</tr>
<tr>
<td>RVA Group</td>
<td>219</td>
<td>219</td>
<td>12</td>
</tr>
<tr>
<td>RVOT Group</td>
<td>270</td>
<td>270</td>
<td>15</td>
</tr>
</tbody>
</table>

2D strain in the longitudinal planes via automated function imaging was measured in all 27 subjects. AFI will calculate an average global longitudinal peak strain as long as 16 or more of the potential 18 segments can be tracked. With re-analysis of AFI after the BT12 software upgrade, all segments could be satisfactorily tracked.
Suitable parasternal short axis views for 2D strain analysis were found in all 27 subjects. The data from PSAX view is used for strain analysis in the radial, circumferential and rotational directions. Each strain/strain rate analysis segmented the LV bases into 6.

Table 13 2D Strain & Strain Rate from PSAX data

<table>
<thead>
<tr>
<th>Segments Tracked</th>
<th>Intrinsic Conduction</th>
<th>Paced Conduction</th>
<th>Subjects (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group</td>
<td>162</td>
<td>162</td>
<td>27</td>
</tr>
<tr>
<td>RVA Group</td>
<td>72</td>
<td>72</td>
<td>12</td>
</tr>
<tr>
<td>RVOT Group</td>
<td>90</td>
<td>90</td>
<td>15</td>
</tr>
</tbody>
</table>

Results tabulated in Tables 14 – 17 use the same listed set of variables for each of the following comparisons:

- All subjects during intrinsic and paced conduction; Table 14
- RVA group; during intrinsic and paced conduction; Table 15
- RVOT group; during intrinsic and paced conduction; Table 16
- RVA paced group to RVOT paced group; Table 17

The data in each table are grouped into clusters of related information. Where measurements were used to calculate variables, the raw data was reported, where any significant variation may affect the calculated measurement. This allowed tracking of potential causative factors influencing calculated results.

Variables 1, 5 & 7 are perspectives of LV contraction effectiveness.

Variables 2 – 4 are used to accurately measure the duration of systole and accurately calculate how far after the QRS onset systole occurs.

Variables 8 & 9 are looking at how far through systole the peak velocity of LV blood flow occurs. This is equivalent to the timing of peak instantaneous pressure gradient between LV and aorta.
Variable 10 is the results of Automated Function Imaging (AFI) analysis and is reported as the average value of all the longitudinal strain peaks – the timing of these peaks cannot be measured in the same was as for other strain analysis.

Variables 11 – 19 from radial strain analysis looking at strain and strain rate peaks, timing of strain and strain rate peaks.

Variables 20 – 25 refer to global circumferential strain and strain rate peaks and where they occur in systole.

Variables 26 – 31 refer to global rotational strain, strain rate peaks and timing.

Variables 32-34 are results from Q Analysis of the TVI images from the three apical views.
Table 14 All Subjects during intrinsic and paced conduction

*Using paired t-tests and Wilcoxon signed rank test*

<table>
<thead>
<tr>
<th>#</th>
<th>Variable</th>
<th>All Intrinsic</th>
<th>All Paced</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>std dev</td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td>1</td>
<td>LVEF (%)</td>
<td>65.2</td>
<td>7.64</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>R-AVO (ms)</td>
<td>82.2</td>
<td>21.87</td>
<td>27</td>
</tr>
<tr>
<td>3</td>
<td>R-AVC (ms)</td>
<td>387.5</td>
<td>43.43</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Sys Dur (ms)</td>
<td>305.3</td>
<td>46.04</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>LVOT VTI (cm)</td>
<td>22.75</td>
<td>9.4</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>HR (bpm)</td>
<td>63.19</td>
<td>15.18</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>CO (l/min)</td>
<td>5.36</td>
<td>2.01</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>R-LVOT pk v (ms)</td>
<td>163.9</td>
<td>27.33</td>
<td>27</td>
</tr>
<tr>
<td>9</td>
<td>LVOT pk v %Sys (%)</td>
<td>27</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>10</td>
<td>Av_GLS (%)</td>
<td>-16.31</td>
<td>3.92</td>
<td>27</td>
</tr>
<tr>
<td>11</td>
<td>RS LS (ms)</td>
<td>328.7</td>
<td>76.29</td>
<td>27</td>
</tr>
<tr>
<td>12</td>
<td>RS ES (ms)</td>
<td>314.5</td>
<td>70.83</td>
<td>27</td>
</tr>
<tr>
<td>13</td>
<td>RS LS-ES (ms)</td>
<td>14.2</td>
<td>44.06</td>
<td>27</td>
</tr>
<tr>
<td>14</td>
<td>RS Avg Pk S (%)</td>
<td>36.22</td>
<td>23.36</td>
<td>27</td>
</tr>
<tr>
<td>15</td>
<td>Avg RS time (ms)</td>
<td>321.7</td>
<td>70.9</td>
<td>27</td>
</tr>
<tr>
<td>16</td>
<td>RS % Sys (%)</td>
<td>78.4</td>
<td>20.9</td>
<td>27</td>
</tr>
<tr>
<td>17</td>
<td>RSR (1/s)</td>
<td>3.42</td>
<td>2.07</td>
<td>27</td>
</tr>
<tr>
<td>18</td>
<td>R-RSR pk (ms)</td>
<td>229.6</td>
<td>71.13</td>
<td>27</td>
</tr>
<tr>
<td>19</td>
<td>RSR % Sys (%)</td>
<td>49.9</td>
<td>21.1</td>
<td>27</td>
</tr>
<tr>
<td>20</td>
<td>G CS (%)</td>
<td>-8.38</td>
<td>11.63</td>
<td>27</td>
</tr>
<tr>
<td>21</td>
<td>R-GCS pk (ms)</td>
<td>353.0</td>
<td>53.70</td>
<td>27</td>
</tr>
<tr>
<td>22</td>
<td>G CS % Sys (%)</td>
<td>88.9</td>
<td>15.1</td>
<td>27</td>
</tr>
<tr>
<td>23</td>
<td>G CSR (1/s)</td>
<td>-0.61</td>
<td>1.04</td>
<td>26</td>
</tr>
<tr>
<td>24</td>
<td>R-G CSR pk (ms)</td>
<td>220.8</td>
<td>68.37</td>
<td>26</td>
</tr>
<tr>
<td>25</td>
<td>G CSR % Sys (%)</td>
<td>43.3</td>
<td>25.0</td>
<td>27</td>
</tr>
<tr>
<td>26</td>
<td>G Rot (°)</td>
<td>3.70</td>
<td>6.89</td>
<td>27</td>
</tr>
<tr>
<td>27</td>
<td>R-G Rot pk (ms)</td>
<td>299.0</td>
<td>81.33</td>
<td>27</td>
</tr>
<tr>
<td>28</td>
<td>G Rot % Sys (%)</td>
<td>71.7</td>
<td>24.6</td>
<td>27</td>
</tr>
<tr>
<td>29</td>
<td>G RotR (°/s)</td>
<td>13.06</td>
<td>75.15</td>
<td>27</td>
</tr>
<tr>
<td>30</td>
<td>R-G RotR Pk (ms)</td>
<td>245.5</td>
<td>95.71</td>
<td>27</td>
</tr>
<tr>
<td>31</td>
<td>G Rot R % Sys (%)</td>
<td>52.9</td>
<td>28.8</td>
<td>27</td>
</tr>
<tr>
<td>32</td>
<td>TDI Av Septal-Lateral Delay (ms)</td>
<td>0.97</td>
<td>13.81</td>
<td>27</td>
</tr>
<tr>
<td>33</td>
<td>TDI Max Delay (ms)</td>
<td>-0.87</td>
<td>45.50</td>
<td>27</td>
</tr>
<tr>
<td>34</td>
<td>TDI Max (absolute) Delay (ms)</td>
<td>38.33</td>
<td>23.35</td>
<td>27</td>
</tr>
</tbody>
</table>
Table 15 RVA Group during intrinsic and paced conduction

Using paired t-tests and *Wilcoxon signed rank test

<table>
<thead>
<tr>
<th>#</th>
<th>Variable</th>
<th>RVA Group - Intrinsic</th>
<th>RVA Group - Paced</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LVEF (%)</td>
<td>Mean: 67.2, std dev: 9.54</td>
<td>n: 12, Mean: 67.7, std dev: 7.01, n: 12, p: 0.83</td>
</tr>
<tr>
<td>2</td>
<td>R-AVO (ms)</td>
<td>Mean: 78.07, std dev: 13.64</td>
<td>n: 12, Mean: 114.8, std dev: 23.63, n: 12, p: 0.0005</td>
</tr>
<tr>
<td>3</td>
<td>R-AVC (ms)</td>
<td>Mean: 384.3, std dev: 51.71</td>
<td>n: 12, Mean: 406.1, std dev: 53.05, n: 12, p: 0.06</td>
</tr>
<tr>
<td>4</td>
<td>Sys Dur (ms)</td>
<td>Mean: 306.2, std dev: 58.66</td>
<td>n: 12, Mean: 288.1, std dev: 51.81, n: 12, p: 0.15</td>
</tr>
<tr>
<td>5</td>
<td>LVOT VTI (cm)</td>
<td>Mean: 20.61, std dev: 7.64</td>
<td>n: 12, Mean: 18.80, std dev: 2.92, n: 12, p: 0.26</td>
</tr>
<tr>
<td>6</td>
<td>HR (bpm)</td>
<td>Mean: 66.42, std dev: 17.53</td>
<td>n: 12, Mean: 64.75, std dev: 17.04, n: 12, p: 0.34</td>
</tr>
<tr>
<td>7</td>
<td>CO (l/min)</td>
<td>Mean: 5.09, std dev: 1.79</td>
<td>n: 12, Mean: 4.72, std dev: 1.71, n: 12, p: 0.35</td>
</tr>
<tr>
<td>8</td>
<td>R-LVOT pk v (ms)</td>
<td>Mean: 164.4, std dev: 22.36</td>
<td>n: 12, Mean: 196.6, std dev: 32.82, n: 12, p: 0.0015</td>
</tr>
<tr>
<td>9</td>
<td>LVOT pk v %Sys (%)</td>
<td>Mean: 28.2, std dev: 5.8</td>
<td>n: 12, Mean: 28.0, std dev: 7.5, n: 12, p: 0.88</td>
</tr>
<tr>
<td>10</td>
<td>Av_GLS (%)</td>
<td>Mean: -16.13, std dev: 3.60</td>
<td>n: 12, Mean: -12.93, std dev: 4.53, n: 12, p: 0.0028</td>
</tr>
<tr>
<td>11</td>
<td>RS LS (ms)</td>
<td>Mean: 327.3, std dev: 88.16</td>
<td>n: 12, Mean: 347.7, std dev: 95.00, n: 12, p: 0.44</td>
</tr>
<tr>
<td>12</td>
<td>RS ES (ms)</td>
<td>Mean: 299.3, std dev: 72.62</td>
<td>n: 12, Mean: 333.6, std dev: 89.01, n: 12, p: 0.26</td>
</tr>
<tr>
<td>13</td>
<td>RS LS-ES (ms)</td>
<td>Mean: 28.08, std dev: 63.97</td>
<td>n: 12, Mean: 14.08, std dev: 18.77, n: 12, p: 0.39</td>
</tr>
<tr>
<td>14</td>
<td>RS Avg Pk S (%)</td>
<td>Mean: 40.17, std dev: 26.91</td>
<td>n: 12, Mean: 30.00, std dev: 26.67, n: 12, p: 0.17</td>
</tr>
<tr>
<td>15</td>
<td>Avg RS time (ms)</td>
<td>Mean: 314.0, std dev: 75.66</td>
<td>n: 12, Mean: 339.3, std dev: 92.67, n: 12, p: 0.34</td>
</tr>
<tr>
<td>16</td>
<td>RS % Sys (%)</td>
<td>Mean: 76.5, std dev: 22.2</td>
<td>n: 12, Mean: 76.13, std dev: 26.1, n: 12, p: 0.97</td>
</tr>
<tr>
<td>17</td>
<td>RSR (1/s)</td>
<td>Mean: 3.87, std dev: 1.92</td>
<td>n: 12, Mean: 2.90, std dev: 1.45, n: 12, p: 0.0131</td>
</tr>
<tr>
<td>18</td>
<td>R-RSR pk (ms)</td>
<td>Mean: 191.8, std dev: 42.71</td>
<td>n: 12, Mean: 254.0, std dev: 90.46, n: 12, p: 0.0411</td>
</tr>
<tr>
<td>19</td>
<td>RSR % Sys (%)</td>
<td>Mean: 38.5, std dev: 16.39</td>
<td>n: 12, Mean: 44.6, std dev: 21.36, n: 12, p: 0.42</td>
</tr>
<tr>
<td>20</td>
<td>G CS (%)</td>
<td>Mean: -7.17, std dev: 11.29</td>
<td>n: 12, Mean: -4.75, std dev: 13.37, n: 12, p: 0.64</td>
</tr>
<tr>
<td>21</td>
<td>R-GCS pk (ms)</td>
<td>Mean: 342.2, std dev: 64.52</td>
<td>n: 12, Mean: 384.3, std dev: 60.42, n: 12, p: 0.0345</td>
</tr>
<tr>
<td>22</td>
<td>G CS % Sys (%)</td>
<td>Mean: 86.2, std dev: 18.7</td>
<td>n: 12, Mean: 92.9, std dev: 16.2, n: 12, p: 0.25</td>
</tr>
<tr>
<td>23</td>
<td>G CSR (1/s)</td>
<td>Mean: -0.58, std dev: 1.09</td>
<td>n: 11, Mean: -0.46, std dev: 1.25, n: 12, p: 0.92</td>
</tr>
<tr>
<td>24</td>
<td>R-G CSR pk (ms)</td>
<td>Mean: 200.1, std dev: 66.40</td>
<td>n: 11, Mean: 216.3, std dev: 41.89, n: 11, p: 0.55</td>
</tr>
<tr>
<td>25</td>
<td>G CSR % Sys (%)</td>
<td>Mean: 41.1, std dev: 23.0</td>
<td>n: 11, Mean: 33.0, std dev: 16.4, n: 11, p: 0.42</td>
</tr>
<tr>
<td>26</td>
<td>G Rot (°)</td>
<td>Mean: 1.87, std dev: 6.51</td>
<td>n: 12, Mean: 1.82, std dev: 7.29, n: 12, p: 0.98</td>
</tr>
<tr>
<td>27</td>
<td>R-G Rot pk (ms)</td>
<td>Mean: 279.3, std dev: 93.65</td>
<td>n: 12, Mean: 313.7, std dev: 112.9, n: 12, p: 0.0349</td>
</tr>
<tr>
<td>28</td>
<td>G Rot % Sys (%)</td>
<td>Mean: 63.9, std dev: 31.6</td>
<td>n: 12, Mean: 67.2, std dev: 36.0, n: 12, p: 0.53</td>
</tr>
<tr>
<td>29</td>
<td>G RotR (°/s)</td>
<td>Mean: -13.97, std dev: 68.52</td>
<td>n: 12, Mean: 33.12, std dev: 87.10, n: 12, p: 0.090</td>
</tr>
<tr>
<td>30</td>
<td>R-G RotR Pk (ms)</td>
<td>Mean: 244.6, std dev: 80.68</td>
<td>n: 12, Mean: 266.1, std dev: 99.54, n: 12, p: 0.60</td>
</tr>
<tr>
<td>31</td>
<td>G Rot R % Sys (%)</td>
<td>Mean: 54.0, std dev: 24.3</td>
<td>n: 12, Mean: 50.3, std dev: 33.5, n: 12, p: 0.79</td>
</tr>
<tr>
<td>32</td>
<td>TDI Av Septal-Lateral Delay (ms)</td>
<td>Mean: 0.27, std dev: 10.31</td>
<td>n: 12, Mean: 4.17, std dev: 11.80, n: 12, p: 0.46</td>
</tr>
<tr>
<td>33</td>
<td>TDI Max Delay (ms)</td>
<td>Mean: 35.93, std dev: 23.69</td>
<td>n: 12, Mean: 39.63, std dev: 20.92, n: 12, p: 0.37*</td>
</tr>
<tr>
<td>34</td>
<td>TDI Max (absolute) Delay (ms)</td>
<td>Mean: -3.70, std dev: 44.16</td>
<td>n: 12, Mean: 14.97, std dev: 43.66, n: 12, p: 0.70*</td>
</tr>
</tbody>
</table>
Table 16 RVOT Group during intrinsic and paced conduction

*Using paired t-tests and *Wilcoxon signed rank test

<table>
<thead>
<tr>
<th>#</th>
<th>Variable</th>
<th>RVOT Group – Intrinsic</th>
<th>RVOT Group – Paced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>std dev</td>
</tr>
<tr>
<td>1</td>
<td>LVEF (%)</td>
<td>63.6</td>
<td>5.53</td>
</tr>
<tr>
<td>2</td>
<td>R-AVO (ms)</td>
<td>85.43</td>
<td>26.76</td>
</tr>
<tr>
<td>3</td>
<td>R-AVC (ms)</td>
<td>390.0</td>
<td>37.24</td>
</tr>
<tr>
<td>4</td>
<td>Sys Dur (ms)</td>
<td>304.5</td>
<td>35.11</td>
</tr>
<tr>
<td>5</td>
<td>LVOT VTI (cm)</td>
<td>24.46</td>
<td>10.56</td>
</tr>
<tr>
<td>6</td>
<td>HR (bpm)</td>
<td>60.60</td>
<td>13.05</td>
</tr>
<tr>
<td>7</td>
<td>CO (l/min)</td>
<td>5.59</td>
<td>2.21</td>
</tr>
<tr>
<td>8</td>
<td>R-LVOT pk v (ms)</td>
<td>163.6</td>
<td>31.53</td>
</tr>
<tr>
<td>9</td>
<td>LVOT pk v %Sys (%)</td>
<td>26.0</td>
<td>4.3</td>
</tr>
<tr>
<td>10</td>
<td>Av_GLS (%)</td>
<td>-16.08</td>
<td>4.28</td>
</tr>
<tr>
<td>11</td>
<td>RS LS (ms)</td>
<td>329.9</td>
<td>68.54</td>
</tr>
<tr>
<td>12</td>
<td>RS ES (ms)</td>
<td>326.7</td>
<td>69.38</td>
</tr>
<tr>
<td>13</td>
<td>RS LS-ES (ms)</td>
<td>3.13</td>
<td>9.72</td>
</tr>
<tr>
<td>14</td>
<td>RS Avg Pk S (%)</td>
<td>33.07</td>
<td>20.51</td>
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<tr>
<td>15</td>
<td>Avg RS time (ms)</td>
<td>327.8</td>
<td>68.90</td>
</tr>
<tr>
<td>16</td>
<td>RS % Sys (%)</td>
<td>80.0</td>
<td>20.4</td>
</tr>
<tr>
<td>17</td>
<td>RSR (1/s)</td>
<td>3.06</td>
<td>2.28</td>
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<td>18</td>
<td>R-RSR pk (ms)</td>
<td>259.9</td>
<td>75.85</td>
</tr>
<tr>
<td>19</td>
<td>RSR % Sys (%)</td>
<td>57.2</td>
<td>21.3</td>
</tr>
<tr>
<td>20</td>
<td>G CS (%)</td>
<td>-9.34</td>
<td>12.19</td>
</tr>
<tr>
<td>21</td>
<td>R-GCS pk (ms)</td>
<td>351.7</td>
<td>43.62</td>
</tr>
<tr>
<td>22</td>
<td>G CS % Sys (%)</td>
<td>91.0</td>
<td>11.6</td>
</tr>
<tr>
<td>23</td>
<td>G CSR (1/s)</td>
<td>-0.63</td>
<td>1.04</td>
</tr>
<tr>
<td>24</td>
<td>R-G CSR pk (ms)</td>
<td>236.0</td>
<td>67.92</td>
</tr>
<tr>
<td>25</td>
<td>G CSR % Sys (%)</td>
<td>49.5</td>
<td>19.4</td>
</tr>
<tr>
<td>26</td>
<td>G Rot (°)</td>
<td>5.17</td>
<td>1.04</td>
</tr>
<tr>
<td>27</td>
<td>R-G Rot pk (ms)</td>
<td>322.0</td>
<td>64.2</td>
</tr>
<tr>
<td>28</td>
<td>G Rot % Sys (%)</td>
<td>78.0</td>
<td>16.9</td>
</tr>
<tr>
<td>29</td>
<td>G RotR (°/s)</td>
<td>34.68</td>
<td>72.32</td>
</tr>
<tr>
<td>30</td>
<td>R-G RotR Pk (ms)</td>
<td>246.3</td>
<td>109.1</td>
</tr>
<tr>
<td>31</td>
<td>G Rot R % Sys (%)</td>
<td>52.0</td>
<td>32.8</td>
</tr>
<tr>
<td>32</td>
<td>TDI Av Septal-Lateral Delay (ms)</td>
<td>1.53</td>
<td>16.43</td>
</tr>
<tr>
<td>33</td>
<td>TDI Max Delay (ms)</td>
<td>1.39</td>
<td>47.96</td>
</tr>
<tr>
<td>34</td>
<td>TDI Max (absolute) Delay (ms)</td>
<td>40.26</td>
<td>23.79</td>
</tr>
</tbody>
</table>
Table 17 RVA paced compared to RVOT paced

*Using paired t-tests and *Wilcoxon signed rank test*

<table>
<thead>
<tr>
<th>#</th>
<th>Variable</th>
<th>RVA Group – Paced</th>
<th>RVOT Group – Paced</th>
<th>n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LVEF (%)</td>
<td>67.7</td>
<td>7.01</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R-AVO (ms)</td>
<td>114.8</td>
<td>23.63</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R-AVC (ms)</td>
<td>406.1</td>
<td>53.05</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Sys Dur (ms)</td>
<td>288.1</td>
<td>51.81</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>LVOT VTI (cm)</td>
<td>18.80</td>
<td>2.92</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>HR (bpm)</td>
<td>64.75</td>
<td>17.04</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>CO (l/min)</td>
<td>4.72</td>
<td>1.71</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>R-LVOT pk v (ms)</td>
<td>196.6</td>
<td>32.82</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>LVOT pk v %Sys (%)</td>
<td>28.0</td>
<td>7.5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Av_GLS (%)</td>
<td>-12.93</td>
<td>4.53</td>
<td>12</td>
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<tr>
<td>11</td>
<td>RS LS (ms)</td>
<td>347.7</td>
<td>95.00</td>
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</tr>
<tr>
<td>12</td>
<td>RS ES (ms)</td>
<td>333.6</td>
<td>89.01</td>
<td>12</td>
<td></td>
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<tr>
<td>13</td>
<td>RS LS-ES (ms)</td>
<td>14.08</td>
<td>18.77</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>RS Avg Pk S (%)</td>
<td>30.00</td>
<td>26.67</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Avg RS time (ms)</td>
<td>339.3</td>
<td>92.67</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>RS % Sys (%)</td>
<td>76.13</td>
<td>26.1</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>RSR (1/s)</td>
<td>2.90</td>
<td>1.45</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>R-RSR pk (ms)</td>
<td>254.0</td>
<td>90.46</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>RSR % Sys (%)</td>
<td>44.6</td>
<td>21.4</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>G CS (%)</td>
<td>-4.75</td>
<td>13.37</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>R-GCSspk (ms)</td>
<td>383.5</td>
<td>63.32</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>G CS % Sys (%)</td>
<td>92.9</td>
<td>16.2</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>G CSR (1/s)</td>
<td>-0.46</td>
<td>1.25</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>R-G CSR pk (ms)</td>
<td>216.3</td>
<td>41.89</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>G CSR % Sys (%)</td>
<td>33.0</td>
<td>16.4</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>G Rot (°)</td>
<td>1.82</td>
<td>7.29</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>R-G Rot pk (ms)</td>
<td>313.7</td>
<td>112.9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>G Rot % Sys (%)</td>
<td>67.2</td>
<td>36.0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>G RotR (°/s)</td>
<td>33.12</td>
<td>87.10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>R-G RotR Pk (ms)</td>
<td>266.1</td>
<td>99.54</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>G Rot R % Sys (%)</td>
<td>50.3</td>
<td>33.5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>TDI Av Septal-Lateral Delay (ms)</td>
<td>4.17</td>
<td>11.80</td>
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<td>33</td>
<td>TDI Max Delay (ms)</td>
<td>39.63</td>
<td>20.92</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>TDI Max (absolute) Delay (ms)</td>
<td>14.97</td>
<td>43.66</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>
5 Systolic Events

Pacing appears to delay the opening and closing of the aortic valve. However, the systolic duration is not significantly different when paced for the whole group, or within the RVA or RVOT paced groups.

Table 18 shows that the opening of the aortic valve is consistently delayed, irrespective of the pacing lead site.

Table 18 R - AVO

<table>
<thead>
<tr>
<th>R – AVO (ms)</th>
<th>Intrinsic Mean ± std dev (ms)</th>
<th>Paced Mean ± std dev (ms)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group</td>
<td>82.2 ± 21.87</td>
<td>115.9 ± 26.28</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RVA Group</td>
<td>78.07 ± 13.64</td>
<td>114.8 ± 23.63</td>
<td>0.0005</td>
</tr>
<tr>
<td>RVOT Group</td>
<td>85.43 ± 26.76</td>
<td>114.2 ± 28.94</td>
<td>0.0002</td>
</tr>
<tr>
<td>RVA compared to RVOT (both paced)</td>
<td>85.43 ± 26.76</td>
<td>114.2 ± 28.94</td>
<td>0.7134</td>
</tr>
</tbody>
</table>

Using paired t-tests and unpaired t-tests

Table 19 shows that the systolic duration is not significantly changed with the delay in aortic valve opening.

Table 19 Systolic Duration

<table>
<thead>
<tr>
<th>Systolic Duration (ms)</th>
<th>Intrinsic Mean ± std dev (ms)</th>
<th>Paced Mean ± std dev (ms)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group</td>
<td>306.2 ± 58.66</td>
<td>295.2 ± 44.42</td>
<td>0.15</td>
</tr>
<tr>
<td>RVA Group</td>
<td>311 ± 58.92</td>
<td>288.1 ± 51.81</td>
<td>0.15</td>
</tr>
<tr>
<td>RVOT Group</td>
<td>304.5 ± 36.32</td>
<td>301.0 ± 38.42</td>
<td>0.66</td>
</tr>
<tr>
<td>RVA compared to RVOT (both paced)</td>
<td>304.5 ± 36.32</td>
<td>301.0 ± 38.42</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Using paired t-tests and unpaired t-tests

The timing of strains and strain rates peaked was measured with reference to the QRS onset. As haemodynamic flow was also referenced to QRS onset, the mechanical and haemodynamic activity could be related to each other to calculate how far through systole mechanical activity occurred. This was calculated for the following strains and strain rates:

- Radial
- Circumferential
- Rotational

Timing of longitudinal strain could not be readily measured on current equipment.
This was intended to look at whether the mechanical activity of strains and strain rates were linked in a consistently identifiable way to what was occurring electrically and haemodynamically to see if there was any significant difference caused by pacing.

Using data from Tables 14 – 17, Table 20 extracts the results for variables 9, 16, 19, 22, 25, 28 & 31 for closer comparison and understanding of the sequence of events.

Table 20 Timing of Systolic Strains & Strain Rates

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>RVA</th>
<th>RVOT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intrinsic</td>
<td>Paced</td>
<td>p</td>
</tr>
<tr>
<td>LVOT pk v % Sys (%)</td>
<td>27 ± 5.0</td>
<td>27 ± 12</td>
<td>0.52</td>
</tr>
<tr>
<td>G CSR % Sys (%)</td>
<td>43 ± 25.0</td>
<td>42 ± 19.1</td>
<td>0.88</td>
</tr>
<tr>
<td>RSR % Sys (%)</td>
<td>50 ± 21.1</td>
<td>45 ± 21.0</td>
<td>0.41</td>
</tr>
<tr>
<td>G Rot R % Sys (%)</td>
<td>53 ± 28.8</td>
<td>54 ± 24.8</td>
<td>0.91</td>
</tr>
<tr>
<td>G Rot % Sys (%)</td>
<td>72 ± 24.6</td>
<td>70 ± 30.9</td>
<td>0.77</td>
</tr>
<tr>
<td>RS % Sys (%)</td>
<td>78 ± 20.9</td>
<td>74 ± 26.2</td>
<td>0.48</td>
</tr>
<tr>
<td>G CS % Sys (%)</td>
<td>89 ± 15.1</td>
<td>89 ± 13.0</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Using paired t-tests and unpaired t-test

Table 20 shows that LVOT peak velocity occurs before the strains and the strain rates peak. As can be expected, the 3 strain rates peak before the 3 strains peak.

There is no significant difference between intrinsic and paced means for each variable in table 20. There is no significant difference between the timing of the 3 strain rates in each group and the 3 strains in each group. Pacing from RVA or RVOT did not give rise to any detectable change from intrinsic conduction timings either as a combined paced group or separate paced sub-groups.
6 Dyssynchrony Results

The results Tables 14 – 17 show there was no significant difference in any of the dyssynchrony measurements. This includes the septal-to-lateral time delays measured by radial strain peaks and TDI measurement. There is no significant difference at any level when comparing intrinsic to paced conduction for the whole group, or for the RVA and RVOT sub-groups.

The TDI paired peaks and the radial strain time differentials between the latest and earliest segments were used to assess for dyssynchrony. TDI peaks were used to calculate the absolute maximal delay in any direction, a maximal delay in the septal-to-lateral direction, and the average of the septal-to-lateral delays for the 6 measured pairs on each subject during intrinsic and then during paced conduction. Timing of longitudinal strain peaks is visible from graphic display, but is not readily measureable, so could not be used for dyssynchrony assessment.

For the whole group, the comparison of the average septal-lateral delay for intrinsic to paced data was the closest dyssynchrony measurement to being significant with \( p = 0.2235 \). The average septal-lateral delay for RVA-paced compared to the RVOT-paced was not significant, though was similar to the whole group comparison. From all of the TDI measurements and calculations of dyssynchrony we were not able to show any definite dyssynchrony.

There was no significant difference between the timing of average septal-to-lateral strain peaks, when comparing the average delay between the 3 basal and 3 mid wall pairs of segments; anterior-posterior, anteroseptal-posterolateral, anterolateral-inferoseptal.
The radial strain data was not able to detect any differences in patterns of contraction between paced and intrinsic conduction.

7 Potentially Significant Findings

Table 21 Analysis of significant differences, shows the results for any findings that suggest significant differences in any of the groups. These results may have come from sub-group or whole group analysis. Where significant differences were detected in the whole group, they were sought in one of the sub-groups for further relevance. Where the significant difference occurred in a sub-group, the relevant p value of the whole group was reviewed to see if the difference was strong enough to influence the whole group. Where there was a significant difference in both sub-group and whole group, the relevant p value in the second sub-group was reviewed to find a variable that was sensitive to pacing site.

Table 21 Analysis of significant differences

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>RVA</th>
<th>RVOT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intrinsic</td>
<td>Paced</td>
<td>p</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.2 ± 7.64</td>
<td>63.5 ± 7.63</td>
<td>0.19</td>
</tr>
<tr>
<td>Av_GLPS (%)</td>
<td>-16.31 ± 3.92</td>
<td>-13.9 ± 6.33</td>
<td>0.0359</td>
</tr>
<tr>
<td>RS Avg Pk S (%)</td>
<td>36.22 ± 23.36</td>
<td>26.63 ± 22.52</td>
<td>0.0550</td>
</tr>
<tr>
<td>RSR (1/s)</td>
<td>3.42 ± 2.07</td>
<td>2.75 ± 1.66</td>
<td>0.14</td>
</tr>
<tr>
<td>R-RSR pk (ms)</td>
<td>229.6 ± 71.13</td>
<td>250.9 ± 75.71</td>
<td>0.24</td>
</tr>
<tr>
<td>RSR %Sys (%)</td>
<td>49.9 ± 21.1</td>
<td>44.7 ± 21.0</td>
<td>0.41</td>
</tr>
<tr>
<td>R-GCS pk (ms)</td>
<td>353.0 ± 53.7</td>
<td>376.4 ± 44.9</td>
<td>0.0252</td>
</tr>
<tr>
<td>R-GRot pk (ms)</td>
<td>299.9 ± 81.33</td>
<td>323.0 ± 93.50</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Using paired t-tests and unpaired t-tests!

7.1.1 Ejection Fraction

LVEF does not change significantly for the whole group during pacing, though the results suggest the ejection fraction is decreased slightly with RVOT pacing.
7.1.2 Average Global Longitudinal Strain

Av_GLs (average global longitudinal strain) is subsequently referred to as global longitudinal strain (GLS) for convenience, though it should be noted that this measurement is an average of 18 segment peaks, rather than a single measure. GLS showed a significant difference between intrinsic and paced for the whole group. This significant difference was even stronger in the sub-group analysis, where the RVA paced result was significantly different to the RVA intrinsic result. There is no significant difference between paced and intrinsic result of GLS measurement in the RVOT group – pacing does not change GLS.

The GLS results are shown for the whole group, sub-groups and two paced groups in Figure 47 Graphical Comparison of Means

The GLS, measured using AFI, was a relatively easy measurement to make and could be readily extracted from standard apical views. All segments could be analysed (See Table 12 Number of AFI Segments Tracked)
Global Longitudinal Strain

All Intrinsic compared to All Paced  
RVA Paced compared to RVOT Paced

whole group

Pacing Lead Sub-Groups

Intrinsic compared to RVA Paced  
Intrinsic compared to RVOT Paced

Apical Pacing Lead Group  
RVOT Pacing Lead Group

Figure 47 Graphical Comparison of GLS means
7.1.3 Radial Strain Average Peak Strain
RS Avg Pk S trended towards a significant difference between intrinsic and paced conduction for whole group, though reviewing the comparison at the two sub-groups level this was not confirmed as being particular to either pacing lead site.

7.1.4 Radial Strain Rate
The mean RSR value appears to decrease with RV apical pacing, but when looking at the results across both sub-groups, the values are small and the standard deviations large compared to the mean. Of note, the intrinsic mean for the RVOT group is very near the paced mean for the RVA group, making it difficult to find any meaning in the RSR results.

Radial strain rate results for R-RSR peak and RSR % systole are related; timing of the peak from onset of the QRS is used to calculate how far through systole the peak occurs. Results suggest RSR occurs later after the onset of the QRS for the RVOT group. As previously described, when paced, the timing of systole after the onset of the QRS occurs later and the QRS width is increased. Consequently, these factors serve to normalize the timing of the RSR with respect to when in systole it occurs.

7.1.5 R – Global Circumferential Strain Peak value
R – GCS pk suggested there was a significant difference between intrinsic and paced beats for the whole group. Sub-group analysis confirms there is a significant difference in the RVA group, with results suggesting it takes longer to reach global circumferential strain peak with apical pacing. When reviewing the RVOT sub-group results for R-GCS pk, the mean value during pacing is larger than that of the RVA paced results, yet there is no significant difference due to the intrinsic RVOT mean being larger than the RVA intrinsic
mean value. As there appears to be no difference when in systole the GCS occurs, these results were not considered important.

7.1.6 R – Global Rotational Rate peak

R-G RotR results mirrored that of R-GCS pk with a significant difference for the RVA paced mean value compared to intrinsic mean value. However, there was no difference in when the G RotR peaked during systole. These results were not considered important.

8 Summary Of Results

There were 27 subjects whose echocardiographic data was analysed; strain analysis was possible on all subjects. The 27 subjects were made up of two subgroups: RVA lead position (11 subjects) and RVOT lead position (16 subjects).

There are two major aspects to our investigations:

- Timing of peaks
  - Relative to how far through systole they occur
  - Relative to other segments of LV (dyssynchrony)
- Value of peaks
  - Quantifying strain, strain rates

Pacing alters when systole takes place, causing it to occur further after the onset of the QRS than intrinsic conduction. However, it appears the timing of events during systole remain unchanged whether conduction is initiated by intrinsic or paced stimulation.

We could not reliably show dyssynchrony with either RVA or RVOT pacing from analysis of TVI analysis or radial strain or strain rate.
The most important changes are the effect RVA pacing has on Average Global Longitudinal Peak Strain. For the RVA group there is a significant difference in the GLS between paced and intrinsic beats (p = 0.0049), while the RVOT group showed no significant difference in GLS (p = 0.46) when comparing paced and intrinsic beats. The significant difference in the RVA sub-group is strong enough to influence the whole group; for the whole group there is a significant difference in GLS (p = 0.0359) between paced and intrinsic conduction.

When the GLS mean for RVA paced group is compared directly to RVOT paced group there is a significant difference (p = 0.0493).

**Table 22 GLS results**

<table>
<thead>
<tr>
<th>Av_GLS (%)</th>
<th>Intrinsic Mean ±sd (%)</th>
<th>Paced Mean ±sd (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Group</td>
<td>-16.31 ± 3.92</td>
<td>-13.9 ± 6.33</td>
<td>0.0359</td>
</tr>
<tr>
<td>RVA Group</td>
<td>-16.30 ± 3.73</td>
<td>-13.04 ± 4.74</td>
<td>0.0028</td>
</tr>
<tr>
<td>RVOT Group</td>
<td>-16.31 ± 4.18</td>
<td>-15.81 ± 3.44</td>
<td>0.5989</td>
</tr>
<tr>
<td>RVA &amp; RVOT</td>
<td></td>
<td></td>
<td>0.0493</td>
</tr>
</tbody>
</table>

*Using paired t-tests* and *unpaired t-test*.

GLS appears to be a measurement that is significantly altered by pacing from the apex compared to pacing from the RVOT.
Chapter Four: Discussion

1 Principal Findings

Global longitudinal strain (GLS) stood out from the multitude of strains, strain rates and mechanical synchrony assessments, as relatively easy to measure, sensitive, accessible and meaningful. Not only does GLS detect changes with pacing compared to intrinsic rhythm, it differentiates between the cardiac mechanics of RVA and RVOT pacing.

GLS is sensitive to mechanical changes in contraction that occur with apical pacing that are less evident with RVOT pacing.

In general, GLS tells us about the distance myocardial cells move or deform in systole, with respect to their original position or shape. Healthy myocardium is more compliant than impaired myocardium; so healthy myocardium will longitudinally shorten more than impaired myocardium. GLS is a negative value, reflecting the fact that myocardium is shortening; a lengthening strain would be a positive value, e.g. radial strain where LV myocardium thickens in the radial plain during systole.

GLS is expressed as a percentage; shortened length is relative to a starting length. A normal GLS value is -18% (47) while an example of an abnormal value is -12% or worse at -7%. An abnormal, or reduced value indicates less longitudinal shortening, and ventricles might be considered as moving less, be stiffer, or have reduced systolic compliance; the myocardium is less responsive to the electrical stimulation of a conducted beat.
For measurement of GLS, 18 segments of myocardium are analysed during systole to identify the more negative of two values: (a) peak strain during systole or (b) end-systolic strain peak. The timing of aortic valve closure defines the end of systole for GLS calculation, although some segments may continue to shorten after systole. As there is no addition to cardiac output from post-systolic strain motion, it is ignored for calculation of GLS. This phenomenon of post-systolic shortening is more often seen with impaired or dyssynchronous ventricles, so the use of end-systolic strain effectively serves to correctly reduce the calculated GLS of these ventricles. The peak strain of each segment is a mechanical response to that segment’s electrical activation. An average of the peak strain in the 18 segments gives a single value for GLS. Where the electrical activation sequence is altered, as occurs with pacing, the peak strain of some segments may be altered, changing the calculated GLS.

Our study showed myocardial response to electrical activation is dynamic and related to the site from which the electrical stimulation originated. The data sets during intrinsic conduction and paced conduction were stored within minutes or seconds of each other, with no particular washout period between intrinsic and paced conduction. We were able to show an immediate deterioration in GLS with RVA pacing. Less negative values of GLS are known to be present in heart failure and reduced LV function patients, so could be useful a measurement to follow.

With GLS able to assess the responsiveness of cardiac mechanics to electrical activation, we can start to study whether the GLS changes we observed with pacing:

• Are maintained over time
• Are permanent or reversible over time
• Continue to deteriorate over time
• Are predictive in any way of pacing induced heart failure
• Could be normalized at implant as a means of mitigating risk of pacing induced heart failure or AF

2 Results

Our aim was to analyse existing echocardiographic data with newer measurement tools to find an echocardiographic measurement that was sensitive to changes with pacing and show meaningful, detectable differences between RVA and RVOT pacing. The most useful echocardiographic measurements should be easily performed, repeatable and reliable.

2.1 What We Found

There was no doubt that a number of parameters during paced conduction were not the same during intrinsic conduction. There is a difference between paced and intrinsically conducted beats. It was not so easy to be confident about the differences between RVA and RVOT paced conduction for most of these parameters, with the one exception of GLS, which stood out as being sensitive to differences during RVA pacing, while detecting no significant change during RVOT pacing.

In our results, paced beats showed a number of differences compared to intrinsic beats. The main differences we found were:

• Less negative GLS
• Increased QRS duration
• Altered cardiac axis
• Later opening of the aortic valve (R-AVO)
• Later closure of the aortic valve (R-AVC)
• Later peaking of the LVOT velocity (R-LVOT pk v)
• Later global circumferential strain onset after QRS (R-GCS)
2.1.1 Less Negative GLS

Global longitudinal strain is a relative measure of myocardial shortening, so is a negative value. Values of GLS that are less negative (i.e. -12% is less negative than -16%) where there is less systolic myocardial shortening and indicative of less systolic myocardial strain.

Automated Function Imaging (AFI) assessment of GLS, showed a significant reduction in GLS with pacing, with paced GLS less negative than intrinsic GLS. The significance of the difference in GLS was stronger when looking at the RVA sub-group alone, while RVOT pacing did not alter longitudinal strain significantly when compared to intrinsic conduction. This finding is consistent with studies by Inoue et al. (37) and Delgado et al. (23).

Outlined above are some of the key potential directions of further research into the less negative values of GLS that we found with RVA pacing.

2D speckle tracking is not limited by angle dependency, so it has come to the fore for strain analysis, with all forms of strain becoming more widely researched. The research and clinical applications and indications for using speckle tracking strain analysis of longitudinal strain are increasing; studies using strain analysis are becoming easier to find and normal values are being reported for strain-based measurements, assisting with interpretation of our findings.

The differences we measured in GLS are large enough to have meaning. GLS measurements are reliable with little inter-observer variability as described in a study of normal subjects by Marwick et al. where the inter-observer variability was 0.24% mean difference in measurements, with 95% confidence intervals, i.e. a range of -18.5 to -18.7% (47). The difference in the mean GLS
was -3.2% between intrinsic and RVA paced beats and is enough to be a significant, and should not be dismissed as variability.

Our older and predominantly male subject group has a lower mean GLS than the mean normal GLS reported by Marwick et al. (47) though closer to age and sex matched normal GLS from the study by Dalen et al. (48). Marwick’s study group was a relatively small study (n =242) so might not have been as sensitive to age and sex related changes in GLS as Dalen’s larger (n = 1266) was, which differentiated on age and sex, finding that older males had reduced GLS compared to both younger and female subjects. As our group was older, mean age 75 ±9.2 years and two-thirds male, Dalen’s findings may provide an explanation for our mean GLS of -16.31%, being at the lower end of the normal range and an appropriate GLS starting point to detect pacing induced changes.

There are technical means of introducing variability in GLS that we tried to avoid. In Figure 4 of Delgado’s paper, an example of longitudinal strain illustrates reduced longitudinal strain and shows the AVC was 125ms shorter with pacing. Our study took particular care with QRS durations, QRS onset, ECG triggering and AVC timing, such that Delgado’s example of an AVC 125ms earlier with pacing conflicts with our results, which showed that pacing delayed systole with AVC occurring later.

The AVC line in AFI dictates where end systolic longitudinal strain peaks are measured. The worst that will occur with early AVC is for GLS end systolic peak to be calculated too early, lower on its slope, returning a lower peak value. The combination of HR effects as discussed above and AVC line placements may explain the less negative GLS paced mean and the consequent bigger difference between intrinsic and paced GLS that Delgado reports, compared to our study.
A study by Inoue et al. (54) used sex and age matched intrinsically conducting controls, i.e. subjects without a pacemaker. Inoue’s control group GLS was \(18.2 \pm 2.4\%\), similar to Delgado’s group; both have higher mean GLS than our group. Further inspection of Inoue’s group characteristics, may explain the difference in baseline GLS compared to ours. Inoue’s subject group was 58% female, while ours was 33% female – females have higher GLS according to Dalen’s study. Inoue excluded diabetics, while we did not. Nakai et al. (55) showed that GLS is reduced with diabetes, even in the sub-clinical stage.

Including diabetics, more males and older subjects could be reasonably expected to reduce our baseline GLS, compared to the studies by Delgado and Inoue. As our study paired subjects, we controlled for the presence of diabetes in the baseline group, so did not see the need to exclude diabetics.

As speckle tracking for strain analysis is a recent technique, it was important to ascertain its validity. 2D Speckle tracking has been validated against sonomicrometry and tagged magnetic resonance imaging (43, 56). The usefulness of global longitudinal strain in a variety of disease states is becoming evident; with the advent of many more published studies in the last 18 months.

### 2.1.2 Increased QRS Duration and Altered Cardiac Axis

In our study the RVA-paced QRS duration was longer than the RVOT-paced QRS duration, which was longer than the intrinsic QRS. These findings are consistent with other studies. The longer QRS duration with paced conduction is indicative of the change in electrical activation pattern of the heart.
It is generally accepted that QRS duration increases with pacing. In our study QRS duration was seen to increase less with RVOT pacing compared to RVA pacing, similar to findings by Victor et al., Stambler et al., and a meta-analysis of pacing studies by Shimony et al. (6, 36, 57). Pacing studies have been conducted on subjects with a variety of baseline intrinsic QRS durations, so some studies had longer QRS durations at baseline than ours. Our study began with normal QRS durations, indicative of our subjects having normal underlying LV structure and function. A study by Sweeney et al. (16) indicates that normal EF subjects have shorter QRS durations during pacing, than those with reduced EF and describes increased risk of heart failure hospitalization with increased QRS duration.

In our study, the RVA paced QRS duration was very similar to the RVOT paced QRS duration in Stambler’s study; our subjects had normal LVEF, while Stambler’s had reduced LVEF. This is consistent with findings described in Sweeney’s study that suggests normal EF subjects have shorter QRS duration in general than reduced EF subjects.

Cardiac axis, or vector is one of the tools used to confirm the position of the pacing lead and is expected to alter with pacing (2). The results for cardiac axis in our study were as expected for normal structure and function with intrinsic conduction and axis changes appropriate to RVA and RVOT pacing respectively.

However, it is evident from some studies, that within the RVOT pacing group, a degree of heterogeneity may make some results harder to interpret and return less significant differences.
2.1.3 Systolic Timing – Aortic valve Opening and Closure, peak LVOT velocity

We measured a significant difference in the onset of systole between the intrinsic and paced groups, with pacing delaying the onset of systole. However, the delay in systolic onset did not appear to be related to the degree of increase in QRS duration and this mechanical change could not be related to the electrical dyssynchrony as measured from QRS duration.

The R-AVO time during pacing for the RVA and the RVOT groups were within a millisecond of each other. Yet we found a significant difference in QRS duration between the two paced sub-groups, with RVA paced mean QRS duration being 25ms longer than the RVOT paced mean QRS duration. So QRS duration with pacing showed a difference between the two sub-groups, while systolic onset with pacing did not. So the mechanical change, evident by the delay of systole with pacing, could not be related to the electrical changes, evident with increased QRS duration.

The measurement of LV and RV pre-ejection periods to calculate a difference between the two is a measure of inter-ventricular dyssynchrony. The delay in onset of left-sided systole changes the LV pre-ejection period with pacing. Similarly pacing may alter the timing of RV pre-ejection period. How this affects the LV to RV pre-ejection period differential could not be assessed by this study, as there was no paced data for RVOT spectral PW Doppler.

Tops et al. assessed inter-ventricular dyssynchrony, reporting it to increase with pacing (58), implying that it was due to delayed activation of LV segments. However, upon review, it was not clear in any of the studies that look at inter-ventricular dyssynchrony, whether it was due to earlier pulmonary valve opening or later aortic valve opening, pacing or just a chance variable.
Bordachar et al. (59) found that although CRT might improve/reduce interventricular dyssynchrony, it did not correlate with any clinical benefits of CRT. The significance of our finding of delayed systole with pacing remains unclear.

The delay in opening of the aortic valve in our study is a clear mechanical change with pacing. It implies something is different about the way pacing induces myocardial contraction to create the driving pressure gradient that opens the aortic valve, but on its own, it is not evident that delaying systole has any deleterious effects.

The aortic valve closure occurred later with pacing along with the aortic valve opening, systole was effectively the same length during pacing as it was with intrinsic conduction. The timing of the peak instantaneous pressure gradient between LV and aorta, indicated by the timing of peak LVOT velocity (R-LVOT pk v) was delayed similarly to aortic valve opening and closure. When these three measurements were related, the peak LVOT velocity was reached at the same point in systole during both intrinsic and paced conduction. The timing of the LVOT peak velocity could then be considered as part of the whole translation in time of systole that paced conduction causes. The aortic valve opening, closure and peak velocity of the LVOT VTI are not specific to pacing site, with each of the of the three paced mean measurements ≤ 9ms different to its intrinsic pair.

So although the onset of systole was delayed, systolic duration was unchanged. There was no literature found reporting on the specific finding of unchanged systolic duration with pacing. It is difficult to interpret the finding that systole is delayed with pacing, as we were unable to relate it to other mechanical changes or pacing from a particular site.
Similarly to 2009, when the echocardiograms for this study were recorded, our current routine practice is to have a reliable and consistent ECG for triggering and measurement of all time related variables. This practice meant our data analysis of systolic event timing was accurate and our practice was confirmed as the recommended approach in the 2011 ESE/ASE Consensus Statement on Methodology and Indications (32).

The temporal translation of systole to occur later after QRS onset with pacing is a real mechanical change.

### 2.1.4 Timing and Sequence of Systolic Strain-Based Events

From our investigation into the activities of systole, pacing does not seem to alter the timing or sequence of mechanical events. Since there was an evident mechanical change in the timing of systole, we reviewed the timing of strain and strain rate peaks, with respect to QRS onset, to calculate how far through systole each event occurred, noting the sequence of events.

Using the QRS onset as the starting reference point, the sequence of mechanical contractile events was related to the haemodynamic events, via the PW Doppler of LVOT velocity profile. The time from QRS onset to LVOT VTI onset, peak and cessation were measured so the timing of these events, i.e. systole, could be accurately related to other events timed from the QRS onset.

Our results showed that despite the delay in systolic onset, the peak LVOT velocity, strain rate peaks and strain peaks occurred in the same sequence with intrinsic and paced conduction. There was no significant difference in any of the timing of the individual strain-based events either. So it would appear that pacing did not adversely affect the order of things or when they
happen within systole for our subjects. This was true for both the whole group and the sub-groups. Although interesting that systole is delayed with pacing, this part of our analysis did not reveal a useful measurement sensitive to changes with pacing.

There were no significant differences in the sequence of mechanical strain-based events with paced beats compared to intrinsic beats.

2.1.5 Timing of Global Circumferential Strain – R - GCS
The peak of the global circumferential strain after the onset of the QRS was found to have a significant difference between intrinsic and paced conduction, though overall analysis of GCS was not consistent enough between sub-groups to be relevant to our study.

R-GCS values are in the region of 350ms, while the most significant difference was only 24ms. Although the global circumferential strain line is designated by the machine’s algorithm using data from the six circumferential segments in the PSAX view, observation of the underlying segment graphs did not inspire confidence in the GCS peak measurement. The circumferential strain peaks were seen to vary a lot, with a degree of shift sometimes larger than the peak value. Drift compensation is discussed further on.

The R-GCS measurement with pacing was not specific to either sub-group, in that it was more significant for the whole group, so was not sensitive enough for the purposes we had.

2.2 What We Did Not Find
A number of parameters did not show any difference between paced and intrinsically conducted beats. The results that might have shown a significant difference, but did not, were:
• Ejection Fraction
• Dyssynchrony as assessed by TDI method
• Dyssynchrony as assessed by radial strain method
• Radial strain and strain rate changes
• Other strains and strain rates changes

2.2.1 LV Ejection Fraction & Cardiac Output

EF in our study was similar during paced and intrinsic conduction for the whole group (65% vs. 64%). LVEF was not significantly different for each of the paired sub-groups. Yet when RVA paced was compared to RVOT paced, the LVEF was significantly different and suggested that RVA pacing gives an improved LVEF compared to the RVOT pacing group (68% vs. 61%).

Upon closer inspection, the RVA sub-group had a mean LVEF (67%) with intrinsic conduction, higher than the RVOT sub-group (64%). The RVOT sub-group LVEF reduced insignificantly with pacing (61%), while the RVA sub-group LVEF increased insignificantly with pacing (68%). By having paired sub-groups, it avoided over-interpreting the RVA/RVOT comparison to mean something more than it should. Our LVEF findings are not definitive enough to address the aims of our study.

Studies have shown mixed findings for LVEF results, summarized in the review article by Shimony et al. (6). The meta-analysis of LVEF findings showed:

• RVA paced LVEF > RVOT paced LVEF for 3 studies
• RVOT paced LVEF > RVA paced LVEF for 5 studies
• LVEF same or ‘similar’ for another 6 studies
Shimony’s group clustered pacing sites into apical and non-apical and their analysis suggests that LVEF may be improved with non-apical pacing compared to RVA pacing, but only where LVEF is < 40% – 45% at baseline. Shimony’s report indicates that EF is not that helpful in assessing the affects of pacing where LVEF is normal at baseline. Shimony’s review does not tell us anything definitive about whether LVEF is any better with non-apical pacing compared to RVA pacing where LVEF is preserved.

Our group had normal LVEF at baseline, so would not be expected to show any important change in LVEF with pacing as a whole or for a sub-group. Our findings from direct comparison of the RVA and RVOT paced sub-groups gave a statistical difference, though it was not considered relevant to aims of our study. The spread of significance across the groups may give some explanation as to why studies directly comparing RVOT and RVA LVEF have mixed results for EF.

Shimony’s meta-analysis of the results for the simple measure of ejection fraction by echocardiography highlights one of the causes of controversy when comparing RVA to RVOT pacing. Although the EF difference in some of the studies was statistically significant, in other studies the changes in EF were too small to be significant. Yet haemodynamic studies by Ishikawa et al. (13), and more recently Lieberman et al. (60) show that pacing from RVA has a negative effect on ejection fraction compared to pacing from RVOT. The variation in findings makes LVEF and its accepted inter-observer variability of <10% makes it less suitable for our purposes.

Ishikawa et al. (13) reports a change in cardiac output and stroke volume with pacing. Although we measured SV, we did not focus on any difference in value due to the fact that the HRs for our subjects varied between 35bpm and
98bpm. With the inversely proportional relationship of stroke volume to HR for CO calculation, it was expected that SV would range widely. Instead CO means were compared, but there was no significant difference between paced and intrinsic conduction for the whole group or sub-groups.

2.2.2 Dyssynchrony Assessment by TDI method

We applied several calculation methods to the time differential data sets to assess whether there was any dyssynchrony from TDI Q Analysis. We reviewed the approaches used in other studies to ensure we were treating the data in a similar and comparable way. None of our three approaches returned any significant differences to indicate dyssynchrony.

Some specific approaches to dyssynchrony analysis are reported by Leong et al. (8) Yoshikawa et al. (39) and Liu et al. (61). Each study defines its own methodology for measuring dyssynchrony and although there is some degree of overlap, having different approaches complicates interpretation of dyssynchrony results. Some of these methods are quite involved and take additional operator manipulation or in Leong’s study calculation of a dyssynchrony index. These extra levels of calculation and manipulation make it more difficult to include TVI dyssynchrony measures in routine clinical practice.

We restricted our calculations to three straightforward approaches, as one of our aims was a measurement that was easily made and accessible:

- The absolute maximal delay in any direction during intrinsic conduction to compare to the absolute maximal delay in any direction during pacing.
- Comparison of the maximal delay in an anterior-inferior direction during intrinsic and paced conduction.
• Comparison of the average delay in an anterior-inferior direction during intrinsic and paced conduction

Although it might be relatively easy to create a TDI image for Q Analysis, converting these measurements into meaningful information is not necessarily straightforward.

Our experience was of TDI graphs that were not always as tidy as those used in illustrations. Peaks did not always occur within systole and as illustrated in Tops et al. paper (Figure 3, page 768) (62) these late peaks are post systolic, occurring after the aortic valve closure, though are sometimes used for dyssynchrony assessment. Once you go beyond the AVC, how far do you go in search of the correct peak? We chose to accurately measure and position the AVC line and to stay within systole

All our measurements of TDI peaks were within systole, to have a repeatable, simplified approach, in the same way that the semi-automated longitudinal strain takes end systolic peaks if the strain value is still rising. Our experience of TDI peaks included finding:

• Slow rising peaks too rounded to accurately measure timing of the peak
• Multiple peaks occurring within systole
• Peaks that were barely evident in systole at all
• Peaks occurring post aortic valve closure

Interpreting the TDI graphs for accurate measurement has a definite degree of subjectivity that may contribute to some of the variation in reported results.

We were not the only study to fail to find dyssynchrony with pacing from different sites. Leong et al. (8) found no dyssynchrony, while Cho et al. (63)
reported that there was no difference in TDI dyssynchrony “according to pacing site”.

2.2.3 Dyssynchrony Assessment by Radial Strain
Analysis of radial strain data used speckle tracking, but our results did not prove to be significant. We expected that looking at the peak strain and strain rate in the 6 radial segments might show a difference or delay between timing of peaks. This timing was carefully measured and calculations of maximal, minimal and average delays were used to try to detect dyssynchrony.

Although we did not find any useful data from radial strain assessment of dyssynchrony, other research applications with pacing have used radial strain dyssynchrony and we might have expected to see similar changes to other studies. Many of the articles were related to CRT response and not directly to RVA vs. RVOT pacing, though overlapped with our area of study.

From the articles using speckle tracking strain analysis or TDI to assess differences in pacing lead site, many focused on the electrical and mechanical dyssynchrony seen with reduced ventricular function. These articles often assessed the influence of bi-ventricular pacing on timing of peak strain segments to show improved electrical and/or mechanical dyssynchrony (42, 59, 64-69). Carrying out mechanical dyssynchrony assessment pre and post biventricular pacing therapy is one approach to identifying CRT-responders, prior to implant. While assessing changes with CRT, Yu et al. compared RVA pacing to CRT, but only to an apical pacing site (70). CRT patients will have reduced EF and are likely to have more pronounced mechanical dyssynchrony to begin with, whereas our study subjects had normal EF, without dyssynchrony.
Normally functioning hearts may not show the definitive dyssynchronous response to pacing that is seen with abnormally functioning hearts undergoing bi-ventricular pacing.

Yamano et al. (71) adopted a different approach to radial strain dyssynchrony assessment. Yamano’s group used a PSAX basal LV loop, placing PW Doppler sample pairs opposite to each other to look for timing of peak strain velocity. This approach is subject to operator sample placement. Yamano’s subjects all received their echocardiograms while in a supine position, which could orientate hearts slightly differently to the transducer, potentially making the strain sampling via this method less reproducible in clinical practice. As there were no other studies found using this technique, its reproducibility has not been shown.

2.2.4 Strain and Strain Rate Assessments
As well as dyssynchrony, 2D strain speckle tracking analysis was used to assess radial strain and strain rate. We found the mean radial strain values had large standard deviations, often similar to the mean value itself. Significant effort was spent assessing radial strain. Radial strain is still considered a research tool and not yet ready for clinical use and our findings only endorse that.

Although we were able to create tight, clean graphs of 2D radial strain rate, our values were fairly widely spread. Nevertheless, there is an inference from our results that the radial strain rate decreases with RVA pacing, while RVOT pacing does not effect a significant change. RVA intrinsic and paced conduction, radial strain means were 3.87/s and 2.90/s, respectively, with \( p = 0.0131 \), but these are small measurements and numbers, that did not translate to a significant result. The radial strain rate for RVOT intrinsic group was
3.06/s, so if this measurement stayed the same with pacing it could not be
differentiated from the RVA-paced mean radial strain rate. The RSR was not
able to differentiate between RVA and RVOT pacing, which limits its
usefulness and meaning for our purposes.

Circumferential and rotational strain and strain rates were all analysed,
though no significant results were found. We found with rotational strain and
strain rate, there was a mixture of clockwise and anti-clockwise rotation at
baseline, even before pacing loops were analysed to look for any change. All
loops analysed had anatomical markers that indicated they were the LV basal
section, so it might be expected rotation would occur in a single direction. We
were unable to reliably show this – hence the large standard deviations and
the positive and negative values for rotational mean values.

The Strain Rate Imaging webpage by Dr Asbjørn Støylen (72) outlines pitfalls
and insights into using strain analysis, including explanations of drift
compensation, affect of ROI width and drift smoothing. The latter alters strain
peak values, removing the ability to make conclusive findings from strain
values.

During all strain analysis of the PSAX LV basal image, we reviewed drift
compensation, as recommended (32), as a quality control measure. Drift gives
a surrogate for how credible the strain peaks values are. Although strain
graphs might look attractive, when drift compensation is removed and the
range of drift exceeds the value of the highest peak, less credence might be
given to a strain peak value.

Radial strain is one of the key methods to assess dyssynchrony so was a
significant part of our analysis. We briefly looked at circumferential and
rotational strains and strain rates. Shaw et al. (73) and Notomi et al. (74) and Bertoli et al. (75) worked with indices of radial strain, circumferential strain, rotation and torsion and whether they might have further application in other clinical situations.

Alongside our results of radial, circumferential strain and rotational strain, we noted the range of drift compensation. As the actual values are particular to a strain loop and their measured value is not fully understood, they are not reported in the results, though were reviewed as part of interpreting strain results. For the most part, the range of drift was minimal for strain rate. For strains, the drift was marked for radial, circumferential and rotational strains, which was one of the reasons only a global or average value was reported. Even then, the radial, circumferential and rotational strains were not found to be a significant result in our study.

3 The Study

3.1 Participants

Our study group was a selected sub-group of the regional and national pacemaker implant population in 2009. Based on current projected population data from Statistics NZ (76), the Wellington, Hutt, Wanganui and Wairarapa catchment area is approximately 750,000 people. From a survey in 2005, in a single year there were 275 pacemakers implanted per million people in New Zealand (77). In 2009 over 9 months in our catchment area there were 175 pacemaker implants, which equates to 275 implants per million. This means the volume of pacemaker implant patients we had to sample from was representative of the expected volume of pacemaker implants in NZ at that time. The subject sample size of 27 was more than 10% of the pacemaker
implant population available to us. So our sample size was of a reasonable proportion of the number available.

The study group was older and predominantly male, reflecting the typical characteristics of the larger group it was sampled from. The study group characteristics were similar to findings from an epidemiological study of pacemaker implants by Silverman et al. (78) confirming the type of characteristics you might expect in a pacemaker population.

All pacemaker indications for our subjects were consistent with standard international guidelines for implantation of cardiac devices (44).

### 3.2 Study Design

The study group of 27 patients was measured twice; once during intrinsic conduction and again during paced conduction. Other similar studies by Leong et al. (8) and Yoshikawa et al. (39) had 58 and 50 subjects respectively, conducting a single set of echocardiographic measurements per subject, while Ng et al. (79) had 55 subjects, including 17 with RVA pacing, 17 with RVOT pacing and 22 intrinsically conducting control subjects without pacemakers. The size of our study using paired samples equates to a similar size as these studies.

Studies often focus on direct comparisons of RVA vs. RVOT paced groups, with or without controls (8, 13, 39, 60, 79). Our study shows the benefits of having subjects as their own controls, since the differences between the two paced sub-groups can be subtler than shown via direct comparison between paced sub-groups. We were able to control for HR, age, sex, weight, all of which have been shown to be independent correlates of variation in strain, or GLS.
The difference in GLS was barely significant when directly comparing the two paced sub-groups (p=0.0493). Sub-group analysis made it apparent that the difference in GLS within the RVA sub-group alone was strong enough to influence the whole group and to show up against the RVOT group.

Conversely, there were other variables that were significantly different, or trended towards a significant difference, between the RVA and RVOT groups, but on closer analysis, could not be considered meaningful. The wide-ranging measurements seen with circumferential and rotational strains and the small changes in LVEF could be discounted after reviewing the combination of their significance within the sub- and whole groups.

There were few studies that used 2D speckle-tracking strain to look at differences in pacing from RVA vs. RVOT. Older studies used haemodynamics to detect differences and QRS duration, while more recent studies used echocardiography estimated EF and measures of TVI dyssynchrony. The study design by Victor et al. (80) had subjects implanted with two RV leads attached to the atrial and ventricular ports of a subject’s pacemaker. Subjects were 100% RVA paced for four months, and then switched to 100% RVOT paced for four months. CO measured from echocardiography using Doppler information and LVEF measured by radionuclide angiography. Although dyssynchrony with TVI was applied, strain analysis was not used in this study. Strain analysis might have shown the presence or absence of longitudinal changes in GLS.

In our study, there was no documented washout period prior to data collection for pacing or intrinsic conduction. The study by Victor et al. (36) was at the extreme end of using “washout” periods, using a month long washout period with 100% pacing. Delgado et al. (23) used a five-minute
period of overdrive pacing prior to collection of paced echocardiographic data. Yet there is no clear evidence to show a “washout” period is necessary, let alone how long this should be. It could be argued that the differences we detected are transient rather than sustained with pacing. This cannot be known until further research in this area is carried out on longitudinal data.

The paced and intrinsic echocardiographic data observed for our study was recorded at the same echocardiogram, without a “washout” period. Measureable changes can be attributed directly to activation by pacing, and not another mechanical, cellular or pathological process. We considered a measurement that could detect instant changes with pacing initiation would be practical for clinical use.

Some studies compared data from the same subject during intrinsic and paced rhythms during temporary pacing, but there were few studies that used both 2D strain analysis and permanent pacemakers (13, 60). Delgado’s study used echocardiography to look at mechanical changes with temporary pacing and was an early indication that longitudinal strain may alter with apical pacing. Delgado assessed the apical pacing site with comparison to baseline intrinsic data; there was no assessment of RVOT pacing. Inoue et al. (37) published a study in 2011 that was the most similar in design to our study. Inoue recruited 50 age and sex matched controls for 103 paced patients, split equally between RVA and RVOT sub-groups. Their findings are similar, with significant changes to GLS with RVA pacing.

### 3.3 Certainty of Pacing Lead Site

Our centre routinely uses ECG axis, V₁ and fluoroscopy results to confirm pacing lead site as apical or septal. The variation that we found in ECG axis is consistent with findings in a study by Mărgulescu et al. (30). Mărgulescu’s
study looked at agreement between RVOT pacing lead site positioning as denoted by EGG & fluoroscopy compared to 3D echocardiographic visualization of the pacing lead tip.

There are other studies that indicate RVOT pacing lead placement is not always what it seems (2, 30, 79). Implanting physicians can be sure that they have an apical pacing lead site, but the positioning of pacing leads in the RVOT does not appear so exact. There will be a degree of individual operator expertise to improve agreement with actual lead tip visualization, but lead tip visualization is not routine practice in the implant laboratory. It seems generally agreed that there is heterogeneity of RVOT pacing lead positions, which complicates the analysis of the effectiveness of RVOT pacing site when comparing studies.

In our study, all apical lead placements had left axis deviation during paced conduction, while the RVOT group had a mixture of normal axis (47%), right axis deviation (26%) and left axis deviation (26%). These findings are consistent with a degree of heterogeneity in RVOT lead placements that may vary from RV mid wall, to RVOT, to high RV anterior free-wall.

Although it is reasonable to accept that our RVOT group is likely to have some degree of heterogeneity of the actual lead site, the GLS results may give some insight into the amount of heterogeneity. The comparison of mean GLS during intrinsic and paced conduction for the RVOT group shows they are very similar, which might be expected with a minor degree of heterogeneous RVOT lead placement within the group.
3.4 Certainty of Paced vs. Intrinsic Echocardiographic Data

When reviewing the echocardiograms we were able to be sure which data was during paced or intrinsic rhythm due to annotation of the stored data at the time of the echocardiogram. This correlated with the notes and printouts made by the pacing physiologist at the time of the echocardiogram.

It transpired, one of the main reasons the 2D loops had been labeled was the realization by the sonographer performing the echocardiograms that the echocardiograph’s monitoring ECG could not reliably identify whether conduction was paced or intrinsic. This was important at the time the echocardiograms for the routine analysis and proved an essential aid to our study data analysis.

3.5 Controlling for Heart Rate

We controlled for heart rate by measuring data sets on the same patient during similar intrinsic and paced heart rates. Heart rate variability may affect strain-based measurements. The normal range defined by Marwick et al. (47) identifies HR, along with weight and blood pressure, as being independent correlates of strain that account for 26% of systolic strain variation.

As our groups were their own controls, this removed the age and weight factors. Pacing compared to intrinsic conduction may cause a minor degree of blood pressure variation, though was not considered to be great enough to contribute any major strain variation.

Our study can be compared to a study by Inoue et al. Inoue’s group controlled heart rates to be similar for control, RVA and RVOT groups (37). This was possible since Inoue’s subjects had sick sinus syndrome, and hence intact AV conduction. The subjects were programmed to AAI (atrially paced)
to obtain intrinsic ventricular conduction for baseline data and programmed to DDD mode with a reduced AV delay to obtain paced echocardiographic data at the same HR as intrinsic.

Our subjects had a mixture of sinus node disease and atrioventricular node disease, for which they received either a single or dual chamber pacemaker. Consequently there was not a single approach to obtaining paced rhythm for our group.

In Delgado’s study, echocardiographic assessment of longitudinal and short axis strain variables were made on data recorded during temporary RV apical pacing on 25 patients with structurally normal hearts (23). Delgado age and sex matched these 25 subjects with another 25 normal controls. The baseline echocardiographic measurements were made at mean HR = 69 ±14bpm, while for paced data the mean HR = 106 ±11bpm. So when Delgado’s study reported GLS as changing from -18.3% to -11.8% with pacing, this may be an exaggeration of the pacing induced changes compared to those we detected. HR may have influenced Delgado’s paced and intrinsic GLS results, while our results controlled for HR variation and are probably a more repeatable reflection of the degree of change with pacing.

The fact that we, like Inoue, showed reduced GLS in a mixed pacemaker indication group, makes it more likely for reduced GLS to be specific to RVA pacing, rather than potentially associated with either sinus node or atrioventricular node conduction pathology.
4 Limitations

This was an observational study, and not randomised to RVA or RVOT pacing. Nevertheless, there was a fairly even split between the two sub-groups. Within the sub-groups there did not appear to be any unexpected bias in patient characteristics, pacemaker indication or system type.

One of the major limitations of this study is the lack of longitudinal data. One of the key questions to study is what changes are maintained over time and whether they are able to be reversed or predictive of increased risk of poorer long-term outcomes. We have a measurement of altered cardiac mechanics at the beginning and the end, but further research is required to join these two points to show that those with reduced GLS at time of implant go on to have worse GLS, which is a measure present in heart failure patients.

Although the analysis for the observational study was blinded to whether the pacing lead was sited in the apex or elsewhere, this in reality is never the case. A sonographer experienced enough to make the analyses for this study would be expected to see the pacing lead during the echocardiogram and identify that there was a significant ECG axis change on the echocardiograph’s monitoring ECG. As many measurements required further manipulation statistical analysis or were semi-automated, we considered there was no bias introduced by the observer “un-blinding” themselves.

At the time the echocardiograms were taken, our routine practice was to maintain 2D frame rates as high as possible. This meant frame rates were often greater than 90 fps for the stored loops available for data analysis. Generally recommended frame rates for optimal 2D speckle tracking are 40-80 fps. While our data was tracked and analysed, the faster frame rates are
associated with reduced lateral resolution and with that a consequential angle dependence (43, 72). Longitudinal strain is less affected by lateral resolution than the other strain dimensions. The high frame rates may in part explain our experience of wide ranging values and drift for radial, circumferential and rotational strains. For the purposes of this study we did not analyse the radial strain data to ascertain whether the more curved segments reliant on lateral resolution were the ones that drifted or varied the most.

As might be expected, apical pacing was readily and reliably detected from the echocardiograph’s ECG, but septal pacing was not. For dual chamber systems, the pacing physiologist identified whether or not there was atrial pacing. We did not regard presence or absence of atrial pacing as important and did not note whether there was any atrial contraction or not. Subjects presenting with CHB would often have a high rate of sinus node activity, though unrelated to ventricular activation; these subjects were paced at a similar VVI rate to their junctional rate.

Where subjects had atrial contraction, from intrinsic or paced conduction, this was usually maintained for their paced data collection, via manipulating the AV delay. There were some patients with single chamber pacemakers that had atrial conduction, that were paced in VVI mode at similar ventricular rates as their inherent conduction. We did not record whether or not subjects had the preload volume contribution from atrial contraction, so cannot be sure of the effect this may have had on our results.

Pacing from RVA is straightforward to identify and be certain of position, with high correlation of actual position by 3D echocardiography. This is not the case with pacing from the RVOT. Although experienced implanting physicians will have a higher correlation of RVOT pacing lead actual site
confirmation, there is a degree of variability between intended pacing lead site and actual pacing lead site for RVOT positions, which may affect results in an un-quantified way. Our results of GLS being similar for RVOT intrinsic and paced conduction suggest there was only a minor degree of heterogeneity in actual RVOT lead position.

5 Recommendations

Like many recent studies, we have shown that GLS can be readily evaluated in the clinical setting. It is a quick adjunct to an echocardiogram, even when some of the more traditional echocardiographic parameters cannot be measured. There are an increasing number of papers expounding the value of GLS for predicting heart failure and outcomes in a number of clinical situations where LV performance is reduced. Paced patients may benefit from tracking GLS too: as paced patients are a group accepted to be at higher risk of outcomes related to reduced LV performance, tracking their GLS would detect the decreased LV performance, as it does for a range of pathologies.

From personal experience of training others, the learning curve for effective use of AFI is short. Mentoring in the early stages to learn the critical points is recommended to equip staff to use this reliable semi-automated strain measurement, which is likely to become an important clinical tool.

Frequent use of global longitudinal strain assessment is recommended for improved familiarity with its interpretation, uses, relevance, norms and nuances.

Echocardiography staff would benefit from having content regarding echocardiography in pacemaker patients included in their education
programmes. This would assist the echocardiographer to realize that with dual chamber or RVOT lead systems, they may not be able to reliably discern which beats are paced. All measurements obtained during pacing, particularly for GLS calculation, may be different to intrinsic conduction and care should be taken to correctly interpret and report these findings. Without a pacemaker technologist on hand equipped with a programmer, an echocardiographer must accept there will be times when their study on a patient with a pacemaker will be limited through not knowing the origin of conduction.

6 Further Research

Further research is required to show whether GLS changes with pacing from RVA are maintained over time, reversible or deteriorate and are associated with adverse outcomes.

A prospective study that randomised patients to RVA or RVOT pacing could take our initial findings further. Such a study could assess GLS changes with pacing in the acute stage and after a period of follow up, to give insight into the behavior of GLS over time. As the pacing burden is relevant to long-term outcomes, this should be recorded as part of this type of study, so any correlation with pacing-related adverse outcomes could be identified.

An adjunct to this observational study could identify whether any of the existing study subjects have received another echocardiogram at their six month follow up, to give opportunity to assess short-term follow up of GLS changes. There may be useful post implant data available on the subjects of our observational study, which could be analysed specifically focusing on GLS. One of the ways this data may add value is by showing whether GLS is
permanently or temporarily reduced. If at 6 months post-implant, where there has been significant degree of pacing, any changes in intrinsic or paced GLS may be markers of myocardial vulnerability. If the paced GLS had reduced, yet the intrinsic GLS was normal, a degree of reversibility to pacing-reduced GLS changes could be inferred. With our study having small numbers in the RVA arm, a prospective trial may serve to delineate this better.

Another approach would be to study existing pacemaker patients who are paced more than 40% and assess their GLS during paced conduction and if possible again during intrinsic conduction. This group could be compared to patients with existing pacemakers that had a low burden of pacing. Where there were measureable differences these would need to be looked at for other correlates, e.g. burden of pacing, other pathologies, to identify if their GLS changes were due to pacing in the first instance.

There is an association between heart failure and reduced GLS and it has been shown that where GLS < -7% it is consistent with significantly poorer outcomes (22). If GLS values with pacing were able to predict those vulnerable to heart failure from the onset of pacing, by assessing their early paced GLS, we could use GLS at implant to show pacing from a particular site had a predilection for HF outcomes vs. a site that did not, influencing the decision on where a pacing lead should be located.
7 Conclusions

We have shown that RV pacing alters cardiac mechanics in a way that echocardiography strain-based tools can detect.

Echocardiographic measures of LV performance differ for paced compared to intrinsic beats, with global longitudinal strain appearing to be the most reliable parameter that describes this.

Global longitudinal strain is significantly reduced with RV apical pacing and not significantly altered with RVOT pacing, when compared to global longitudinal strain during intrinsic conduction.

Global longitudinal strain is sensitive to mechanical changes in LV contraction patterns induced by RVA pacing, while RVOT pacing does not significantly alter cardiac mechanics as measured by global longitudinal strain.
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