Identifying patients at risk of pacemaker-related left ventricular systolic dysfunction using left ventricular mechanics

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Submitted in accordance with the requirement of the degree of

Doctor of Philosophy

The University of Leeds

Leeds Institute of Cardiovascular and Metabolic Medicine

School of Medicine

Submitted October 2024 for examination

Intellectual Property and Publication Statements:

The candidate confirms that the work submitted is her own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given where reference has been made to the work of others.

My contribution to the research outlined in this thesis, and the relevant research outputs:

Chapter 2: Literature review of advanced cardiac echocardiography measures in the assessment of dyssynchrony in people receiving pacing therapy

I performed and authored the literature review which was then reviewed and edited by Dr Maria Paton and Prof Dr Klaus Witte submitted for publication in the *Echo Research Practice* journal.

Chapter 4: The relationship of cardiovascular comorbidities and right ventricular pacing requirement: a cohort study

I performed analysis of a previously collected dataset. I undertook statistical coding and analysis. I also authored the abstract and the results manuscript, which is currently submitted for publication in *Europace* and have presented the preliminary findings as an oral presentation at the European Society of Cardiology Conference in Barcelona, Spain, in 2022.

Relevant publication:

Abdul Samad NH, Lowry JE, Cole CA, Straw S, Gierula J, Witte KK, Paton MF. Left ventricular dysfunction, heart failure, and mortality risk factors in de novo pacemaker recipients and those requiring pacemaker generator replacement. European Heart Journal. 2022 Oct 1;43(Supplement_2):544-712.

Chapter 5: Left ventricular mechanics in patients receiving right ventricular pacing: a retrospective analysis

I contributed to echocardiography image analysis, data collation, statistical coding and data analysis. I authored the abstract and presented the preliminary findings at the American Heart Association Conference in Philadelphia, United States in 2023. The full-text manuscript is currently in preparation for submission to *Echo Research and Practice*.

Relevant publication:

Abdul Samad NH, Straw S, Lowry JE, Gierula J, Witte KK, Paton MF, Leeds Institute of Cardiovascular and Metabolic Medicine. Myocardial Work-A Novel Approach to Investigate the Effects of Right Ventricular Apical Pacing on Left Ventricular Regional Work and Function. Circulation. 2023 Nov 7;148(Suppl_1): A18337

Chapter 6: Predicting left ventricular systolic dyssynchrony and adverse remodelling using measures of left ventricular mechanics

I co-ordinated the study and was responsible for the daily management of the study. My role included screening participants according to the inclusion and exclusion criteria, approaching potential participants, providing detailed explanations of the study, obtaining informed consent, and successfully recruiting patients. I also conducted diagnostic investigations and patient assessments, managed data collection, and performed image analysis and data analysis. This manuscript is being prepared for submission to the *European Heart journal – Cardiovascular imaging.*

Chapter 7: The effects of novel conduction system pacing compared to traditional right ventricular pacing on left ventricular mechanics

I co-ordinated and contributed to the study design, leading data collection, including patient recruitment, performing diagnostic investigations and ensuring appropriate patient matching by age and sex. I also performed statistical coding and data analysis. I co-authored the abstract, with preliminary findings accepted for presentation at the British Society of Echocardiography conference in Edinburgh, United Kingdom, in October 2024. I authored the results manuscript.

Assertion of moral rights:

The right of Nurul Abdul Samad to be identified as Author of this work has been asserted by her in accordance with the Copyright, Designs and Patents Act 1988.

Dedication

This thesis is lovingly dedicated to my parents and family – my late father, Abdul Samad whose memory continues to inspire me, and my mother, Hamimah, along with Firdaus, Siti, Aisyah, and Asyraf – who have been my constant source of strength throughout this challenging journey. Your endless support, love, and prayers have carried me through every step, and for that, I am forever grateful. I could not have achieved this without your encouragement and belief in me. This accomplishment is as much yours as it is mine. From the bottom of my heart, **thank you!**

Acknowledgement

I would like to extend my deepest and most sincere gratitude to my primary supervisor, Dr. Maria Paton. Being her first doctoral candidate was an honour beyond words, and I am profoundly grateful for the unwavering faith she has shown in me from the very beginning of this journey. Dr. Paton's exceptional guidance, tireless dedication, and thoughtful advice have been cornerstones of my academic and personal growth. Her remarkable passion for research and her commitment to excellence, especially in academic writing, have not only shaped the trajectory of my doctoral work but will continue to influence my future career in ways I will forever treasure. I feel truly fortunate to have had such a brilliant and caring mentor, and I will always be indebted to her for the wisdom and confidence she has instilled in me.

I am equally thankful for the invaluable support and encouragement of my co-supervisors, Prof. Dr. Klaus Witte, Dr. John Gierula, and Dr. Lynn McKeown. Their combined expertise, guidance, and constructive feedback were instrumental in refining my work and shaping it into what it is today. Each of them has played a crucial role in my academic development, and I could not have asked for a better supervisory team. Their presence, insight, and commitment have made this journey both intellectually fulfilling and personally rewarding. I am deeply appreciative of everything they have done to support me, and I consider myself incredibly fortunate to have had such a remarkable team of mentors.

Thank you also to my academic colleagues for sharing their thoughts, especially Dr Sam Straw, Dr Judith Lowry, and Dr Sam Relton, whose significant contributions to my research work have been both inspiring and necessary.

My doctoral research was conducted at the Cardiovascular Research Facility (CRF) at Leeds Teaching Hospitals, as part of the International PhD Academy of the Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM) programme. I would like to extend special thanks to Dr. Karen Porter and Dr. Piruthivi Sukumar for warmly welcoming me during my first

year in the programme, to Mrs. Julie Corrigan for her invaluable managerial support during my early days at CRF, and to Mrs. Patricia Sheridan for her exceptional administrative assistance with the research participants I recruited for this project. I am also deeply grateful to Miss Shumaila Ahmad and Miss Mathuri Partheban for being part of the research team. Their teamwork and support were immensely appreciated, and I must say I truly enjoyed working alongside them. A heartfelt thank you also to Ms. Charlotte Cole and Ms. Faye Jowsey for generously sharing their expertise in echocardiography, you have both been an inspiration to me in this field.

In 2020, when the world was being challenged by COVID-19, I was accepted into the Excellent Graduate Programme by Majlis Amanah Rakyat (MARA), a Malaysian government body, which went on to fund my doctoral degree for four years in the United Kingdom. Despite the difficult times, I was able to move across the globe, far from the place I used to call home, to make a new home. I couldn't have done this without the support of the dedicated MARA officers, whose kindness and assistance during that period were deeply appreciated.

Throughout my years in the UK, I received immense emotional support from my Malaysian peers who were on the same journey as me. I must acknowledge Dr. Ain Roshdan, Dr. Asila Mazlan, Dr. Dini Zupli, Dr. Hazwani Karim, Dr. Fikry Abdullah, Dr. Hanis Ghani, Dr. Fatinah Farid, Dr. Saira Banu, and Dr Kautsar Ramli who have always been my source of comfort whenever my days seemed impossible. Also, Dr. Rawan Abuzinadah and Dr. Nora Almulhim, my peers from the academy, I am deeply grateful to have gotten to know both of them. Thank you, my dear friends!

Of course, my sincere appreciation goes to the patients whose participation was the foundation of this research. Without their involvement, none of this would have been possible.

To everyone who has contributed to my journey but whom I am unable to mention individually, please know how truly grateful I am for your support.

Abstract

Right ventricular (RV) pacing (RVP) can lead to left ventricular (LV) remodelling and subsequently increased risk of heart failure hospitalisation (HFH) and mortality. Despite RV pacing avoidance programming now becoming commonplace, pacemaker patients remain at risk of pacing-related LV systolic dysfunction (LVSD). Alternative pacing strategies such as conduction system pacing (CSP) either through His Bundle or Left Bundle Branch area pacing (LBBAP) are available therapeutic options, but it remains unclear which patients should be targeted, and when.

Chapter 4 details an observational cohort study includes 514 patients who received their first pacemaker (new implant - NI) (2015-2017) and 510 patients who had pacemaker generator replacements (PGR) (2008-2011). Data was prospectively collected including clinical history, medication, echocardiographic and pacing measurements at baseline (6-week post procedure) and follow up (minimum of 12-month post procedure). Logistic regression identified a history of ischemic heart disease (IHD) and a ventricular pacing burden (VPB) over 80% as significant risk factors for LVSD, defined as an ejection fraction (LVEF) <50%. Cox proportional hazards models found that older age, the presence of atrial fibrillation (AF), LVEF <50%, and being at PGR were independent predictors of a composite outcome of time to HFH or all-cause mortality. This study highlights the complexity of managing pacemaker patients, emphasising the potential need for targeted screening and preventive strategies for those who require high VPB due to atrioventricular block (AVB), have a history of IHD, and multiple comorbidities, particularly at the time of first implant, and at pacemaker generator replacement.

Chapter 5 describes a retrospective analysis of 118 patients with AVB who received pacemaker therapy at two tertiary hospitals in Europe. Speckle tracking echocardiography and non-invasive brachial blood pressure measurements were used to calculate myocardial work (MW) measures using EchoPAC (version 206GEHealthcare Vingmed) software. Repeated

measures analysis from baseline (pre implant) to mid-term (0-6-week) and long-term (a minimum of 12-month) follow up post implant, demonstrated LVEF significantly and progressively reduce following RV pacing (RVP), leading to LVSD (defined as LVEF <50%) in 33 patients (28%) patients after a median long-term follow up of 454 (IQR:54-857) days. Advanced echocardiographic measures; global work index (GWI), global constructive work (GCW) and global wasted work (GWW) significantly reduced over time, with a statistically significant difference observed between those who preserved LVEF ≥50% at long-term follow-up, and those who did not (LVEF <50%), suggesting that MW measurements may help identify patients at risk of LVSD from RVP and guide the use of alternative pacing strategies such as CSP or cardiac resynchronisation therapy (CRT).

This led to a prospective study enrolling 145 patients with AVB who received pacemaker therapy between July 2022 and August 2024 at a single tertiary hospital in the UK, detailed in chapter 6. Participants were evaluated at four time points: pre-implant, pre-discharge, 6 weeks after implant, and 6 months after implant. Of these, 90 participants were included for a repeated measure analysis from baseline (pre-implant) to acute (0-6 weeks) to mid-term (6 months) post implantation. LVEF remained stable over time with no significant changes in LV volumes. However, advanced echocardiographic measures; global longitudinal strain (GLS), global work index (GWI), global constructive work (GCW) and septal myocardial work index (MWIs) significantly declined throughout follow-up. Multivariate regression analysis demonstrated age and VPB were associated with adverse LV remodelling, defined as a composite outcome of an increase in left ventricular end systolic volume index (LVESVi) ≥15% and a reduction in LVEF ≤10%, whilst a history of IHD and MWI_S measures were not statistically associated. These results suggests that although MWI_S measures measurably declined over time, perhaps indicating MW measures can detect more subtle changes in LV remodelling, it may not predict adverse remodelling prior to pacemaker implantation.

Finally, a pilot study was conducted to compare mechanical dyssynchrony between two pacing strategies (CSP and RVP) using echocardiographic measures of MW, detailed in chapter 7. Of 145 patients with AVB who received a pacemaker between October 2022 and October 2024, 17 patients received CSP, of which 10 had sufficient available images for analysis. These 10 CSP patients were aged, and sex matched to 10 patients receiving RVP to allow a comparative analysis. Repeated measures (ANOVA) with Bonferroni correction demonstrated GWI, GWW GWE and MWI_S measures were significantly different between CSP and RVP groups from baseline to acute (0-6 weeks) and mid-term (6 months) follow-up post implantation. CSP patients demonstrated a better maintenance of regional LV work compared to patients receiving RVP, potentially offering mechanistic insights into the effects of novel pacing strategies on LV mechanics.

In summary, while VPB is a significant factor, it is not the only predictor of LVSD, HFH, and mortality among pacemaker recipients. My studies highlight key characteristics including a history of IHD and comorbidities of those at risk. MW measurements show promise to detect signs of adverse LV remodelling earlier than traditional echocardiographic measures, with CSP demonstrating superior preservation of regional LV function compared to RVP. The observed changes in MW, particularly in the septal region, suggest its potential for guiding pacing strategies and thus improving patient outcomes. However, these findings indicate that, while MW provides valuable insights, further research is necessary to fully validate its clinical utility.

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Chapter 1 Evolution of pacemaker technology: a review

1.1 Introduction to the history of pacemaker technology

Implantable pacemaker therapy for bradycardia is recommended, effective, and safe according to clinical guidelines from the National Institute of Health and Care Excellence (NICE, 2005), the European Society of Cardiology (ESC) (Members et al., 2013) and the American College of Cardiology and American Heart Association (AHA) (Members et al., 2008). Pacemakers are a common type of cardiac device therapy, with their history dating back to the first successful human implantation in 1958 (Larsson et al., 2003, Jeffrey and Parsonnet, 1998, Aquilina, 2006). Arne Larsson was a 43-year-old Swedish man suffering from complete Atrioventricular (AV) block and severe Stokes-Adam attacks. His wife, in a desperate search for a solution, discovered ongoing research in Stockholm, Sweden, aimed at developing a heart-stimulating device. Despite the lack of human-testing, Dr Rune Elmqvist, an engineer who invented the first self-contained pacemaker, and Dr Åke Senning, a cardiologist, performed the open thoracotomy implantation on Mr. Larsson. Although the first fully implantable pacemaker utilising nickel-cadmium batteries required frequent transcutaneous recharging, and lasted only 3 hours, Mr. Larsson's remarkable response spurred subsequent advancements in pacemaker technology. Over his lifetime, which continued until the age of 86 in 2001, Mr. Larsson received nearly 30 pacemakers, each playing a role in extending his survival and improving his quality of life. His journey serves as a testament of the profound impact of medical innovation and the ongoing need for research and development in this field (Larsson et al., 2003). **Figure 1.1** shows a picture of Dr Elmqvist (left), and Dr Senning (centre) with their first patient Mr. Larsson, proudly displaying an early pacemaker model at a cardiology conference (Circulation, 2007)

Six decades have passed, and the advancements in pacemaker technology have led to smaller, more efficient devices with enhanced programming capabilities, allowing for personalised therapy delivery (Haddad et al., 2006, Hopps, 1981, Mond, 1999, Irnich et al., 1978, Reynolds et al., 2016, Tjong and Reddy, 2017, Bhatia and El-Chami, 2018, Defaye et al., 2023). Additionally, pacing leads have developed in stability and safety, and now allow for more physiological positioning allowing optimised therapy efficacy (Padala and Ellenbogen, 2020, Vijayaraman et al., 2017, Vijayaraman et al., 2015). Looking ahead, future directions in pacemaker technology aim to integrate artificial intelligence (Hung et al., 2024, Leclercq et al., 2022) , enhance biocompatibility (Cingolani et al., 2018, Bussooa et al., 2018, Lu et al., 2023), and integrate personalised therapy approaches (Paton et al., 2021, Gierula et al., 2014, Gierula et al., 2018), promising continuous advancements in managing cardiac conduction disease.

Figure 1.1 Dr. Elmqvist (left), and Dr Senning (centre) with their first patient Mr. Larsson, proudly displaying an early pacemaker model at a cardiology conference (taken from Circulation, European Perspectives, 2007).

1.2 Advancement in pacemaker technology

The artificial pacemaker system, comprising a pacemaker generator and a single or multiple pacing leads, has become the gold standard in managing cardiac conduction diseases (McDonagh et al., 2021, Members et al., 2008, Tracy et al., 2012, NICE, 2005, Members et al., 2013, Glikson et al., 2022). Over the years, significant advancements have been made in each of these components, addressing early limitations such as short pacemaker battery life, lead dislodgment, and material degradation, leading to modern pacemakers that offer increased battery longevity, stability and safety.

1.2.1 Pacemaker generator

The pacemaker generator serves as the core component of implantable pacemakers, providing the necessary power and control for cardiac pacing. Early generators were bulky external devices (Furman and Schwedel, 1959), serving as temporary solutions rather than internal implantable devices (Larsson et al., 2003, Aquilina, 2006). The early generator relied heavily on external electrical support and were typically attached to the patient body via external wires (Furman and Schwedel, 1959).

The obvious limitation of Elmqvist-Senning pacemaker devices was their short battery life, which prompted the industry to develop nuclear-powered pacemakers ((Larsson et al., 2003, Jeffrey and Parsonnet, 1998). In 1960, one of the first successful implantable pacemakers in the United States, developed by Chardack, an American engineer, and Greatbatch, a cardiac surgeon, was powered by plutonium (nuclear-powered) and could last for more than 30 years, though it initially only provided fixed or asynchronous pacing (Jeffrey and Parsonnet, 1998, Aquilina, 2006). However, nuclear-powered pacemakers posed significant challenges, particularly regarding the safe disposal of used cells. Plutonium can be fatal even with low concentrations, making it impractical for widespread commercial use. Despite their extraordinary longevity, nuclear-based pacemakers were eventually replaced by next-

generation devices utilising lithium-based batteries and enhanced software algorithms. In 1968, lithium-iodine batteries were developed by the Catalyst Research Group and became the mainstream technology when licensed to, and refined by, Greatbatch in 1973 (Aquilina, 2006, Jeffrey and Parsonnet, 1998). Lithium batteries were ideal for implantable pacemakers due to their long life, low current drain, and stable voltage characteristics (Lau, 2017, Mallela et al., 2004). Unlike alkaline cells, lithium cells exhibit a 10% loss of capacity over 5 years and are kinetically stable, producing no gas and allowing hermetic sealing (Mallela et al., 2004). The predictable terminal voltage decay enables anticipation of battery end-of-life during routine follow-up (Mallela et al., 2004). With a potential lifespan exceeding 10 years, lower production costs, and smaller size, lithium-iodine batteries became the preferred choice for pacemaker manufacturers.

These later generations of pacemakers introduced synchronous pacing capabilities, allowing the device to sense intrinsic heart rhythms and provide pacing only when needed, also improving device longevity (Cingolani et al., 2018). Due to their improved safety profile, lithium-based batteries have become the standard material for modern pacemakers (Cingolani et al., 2018, Mallela et al., 2004, Lau, 2017)

Further advancements in design and materials eventually led to the development of smaller, implantable pacemakers, roughly the size of a pocket watch, which provided patients with greater comfort and mobility (Cingolani et al., 2018). The introduction of leadless pacemakers in 2015, miniaturised to a size comparable to a large pill, further reduced device size from 1958 as shown in **Figure 1.2.** The risk of lead complications can now be avoided by using leadless pacing, which can be reliably and safely be used in the context of previous device complications (Bhatia and El-Chami, 2018, Tjong and Reddy, 2017)

Figure 1.2 The evolution of pacemakers from the 1958 (left) to the present day, showcasing a leadless pacemaker (right) with battery longevity ranging from a few months in early models to over ten years in current models. (Image courtesy of National University Heart Centre Singapore).

1.2.2 Pacing lead

An essential component of implantable transvenous pacemaker systems are the pacing leads. They perform the function of supplying the cardiac muscle with electrical impulses. Pacing leads were originally bare, stainless-steel wire, and were implanted under general anaesthetic with surgical thoracotomy (Aquilina, 2006). The quality of the pacing leads has since significantly improved, offering solutions to issues like high battery-drain, fracture rates, dislodgments, electromagnetic interference, inflammation and infection (Nelson, 1993, Aquilina, 2006). The primary parts of the pacing lead are the connector, conductor, insulation materials, electrodes, and a fixation mechanism, which secures the lead within the heart tissue and can be achieved either by a small, retractable helix that screws directly into the myocardium or by a flexible, tined anchor that grips the heart tissue in a less invasive manner

1.2.2.1 Pacing lead connector

The pacemaker lead connector attaches the lead placed in the heart to the pacemaker generator. To accurately send pacing signals, the connector must provide a secure and robust electrical connection. It usually consists of a series of contacts and a locking mechanism to ensure a secure attachment and prevent any dislodgement or loosening that could interfere with the device's performance {Nelson, G. D., 1993; Aquilina, Oscar, 2006; Jeffrey, Kirk, 1998}. Modern lead connectors are intended to be interchangeable with standardised connector systems, such as IS-1 or DF-4, to facilitate replacement or upgrades (Aquilina, 2006, Nelson, 1993, Furman and Schwedel, 1959, Jeffrey and Parsonnet, 1998). They are constructed of biocompatible materials that resist corrosion and deterioration over time, ensuring the longevity and safety of the pacemaker system (Nelson, 1993, Aquilina, 2006, Jeffrey and Parsonnet, 1998). **Figure 1.3** shows an IS1 right atrium (RA) lead and IS1 right ventricular (RV) lead aligned before insertion into a pacemaker.

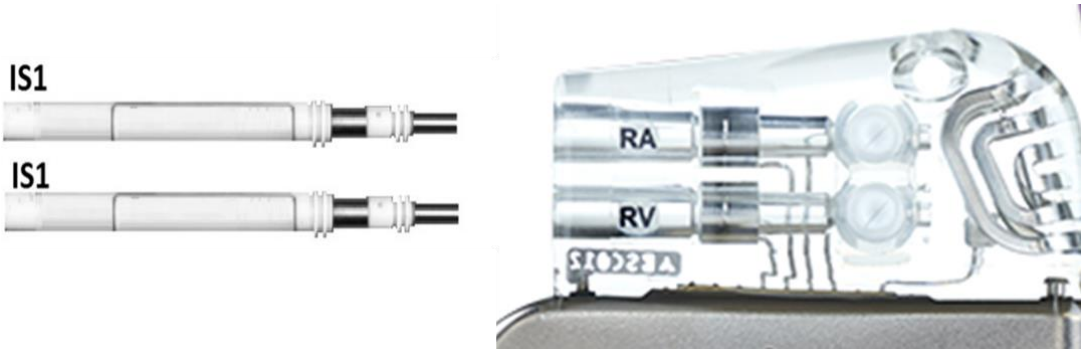


Figure 1.3 Schematic showing IS1 right atrium (RA) lead, IS1 right ventricular (RV) lead aligned before insertion into a pacemaker

1.2.2.2 Pacing lead conductor and insulation materials

In a cardiac pacing lead, the conductor and insulation play distinct yet complementary roles in ensuring the reliable and safe delivery of electrical signals to the heart. While the conductor serves as the pathway for transmitting electrical impulses, the insulation acts as a protective barrier, preventing unintended electrical contact with surrounding tissues (Jeffrey and Parsonnet, 1998, Nelson, 1993, Aquilina, 2006). Together, these components form a critical system that enables precise pacing therapy while minimising the risk of complication.

Early on, Teflon or polyethylene insulation were used for insulation, but these materials were quickly replaced by silicone and polyurethane due to their superior properties (Nelson, 1993, Aquilina, 2006, Janik et al., 2014, Szycher, 2013). Although silicone rubber has low tensile, elongation, and tear strength, it is ideal in terms of safety, inertness, and biostability, therefore, it was necessary to increase insulation thickness in order to minimise silicone insulation failure (Aquilina, 2006, Jeffrey and Parsonnet, 1998, Nelson, 1993, Warrick et al., 1979, Colas and Curtis, 2004). In 1980s, tougher silicone was introduced, which helped to enhance tensile,

elongation, and tear strength (Aquilina, 2006, Jeffrey and Parsonnet, 1998, Nelson, 1993, Colas and Curtis, 2004, Warrick et al., 1979). In the late 1970s, polyurethane, a polymer that demonstrated significantly greater tensile strength as well as higher elongation and tear strength than silicone was introduced (Sweesy et al., 1992, Phillips et al., 1986, Beck et al., 2010b). Although polyurethane allows thin insulation without jeopardising safety, it faced challenges when issues of degradation and stress-cracking were discovered in some of its applications (Chawla et al., 1988). Thicker insulations and stress-relieving techniques have been used to reduce stress-cracking (Jenney et al., 2005). According to preliminary research, a hybrid coating consisting of silicone and polyurethane might offer better durability (Jenney et al., 2005). This hybrid material has been shown to offer superior abrasion resistance and long-term durability, addressing common issues such as lead failure and insulation degradation. A prospective long-term studies indicate over 95% reliability, minimising mechanical failure and insulation abrasion in pacing and defibrillator systems (Cairns et al., 2014). Nevertheless, while long-term data show promising reliability, continued monitoring is crucial, as real-world performance over time can reveal challenges not evident in early studies of novel lead designs.

1.2.2.3 Pacing lead electrodes

The correct electrode tip can offer ideal impedance with a minimal and consistent pacing threshold. High impedance allows for pacing with less energy, resulting in a longer-lasting generator (Mond et al., 1988, Mond, 1999). A small surface area is preferred for high impedance due to the inverse relationship between electrode surface and impedance (Schuchert and Kuck, 1991). Older pacing lead electrode tips had a smooth metal surface in a round spherical shape, while newer versions use a combination of wire filament mesh, microsphere coatings, and microscopic pores to create a textured surface that is uneven and increases surface area (Beck et al., 2010a). Subsequent designs feature a further increased

surface area to preserve low sensing impedance, while still incorporating a small outer region to uphold high pacing impedance (Beck et al., 2010a)

In the 1960s, the use of bare metal electrodes came to an end due to their inconsistent corrosion resistance (Beck et al., 2010a). Subsequently, porous electrodes were used in their stead; they had lower tendency to dislodge but showed large increases in capture thresholds (Hirshorn et al., 1983). By the 1980s, cobalt, chromium, and nickel alloy elgiloy were used more often (Beck et al., 2010a). However, elgiloy was eventually discontinued due to its inferior threshold, polarisation, and corrosion properties (Beck et al., 2010a). In more recent years, the use of titanium, iridium, and vitreous carbon in various combinations increased (Mond et al., 1988, Mond, 1999). These materials have demonstrated minimal polarisation losses and low pacing thresholds.

In 1983, a significant advancement was made with the introduction of steroid-eluting cathodes by Stokes and Timmis addressing inflammation issues and scarring at the site where the lead is implanted, which can compromise its performance (Mond et al., 2014, Mond and Stokes, 1992). Additionally, there have been multiple comparative studies supporting the benefit of steroid-eluting electrodes in achieving low chronic pacing thresholds (Mond et al., 1988, Ellenbogen et al., 1999, Singarayar et al., 2005, Crossley et al., 1995, Mond and Stokes, 1996). Current steroid-eluting electrodes approach ideal performance with high pacing impedances of roughly 600 to 1,500 ohms (Ω), and low stable pacing threshold of less than 0.8-volt (V) at 0.3 milliseconds (ms) maximum (Beck et al., 2010a).

1.2.2.4 Pacing lead fixation

The method by which leads are secured within the heart is known as lead fixation. The frequency of lead dislodgment has significantly decreased with advancements in fixation techniques. Lead fixation can be accomplished either passively or actively. Passive fixation involves entangling tines in cardiac trabeculations, whilst active fixation utilising deployed

helix-screw. Although passive fixation is comparable to active fixation in long-term stability, active fixation leads provide greater flexibility in selecting the implant site and facilitate easier lead retrieval (Kistler et al., 2006, Ellenbogen et al., 2003, Hidden-Lucet et al., 2000).

In **Figure 1.4**, passive fixation and active fixation are depicted, illustrating different methods by which the leads are secured to the heart muscle for optimal electrical conduction. **Figure 1.4 (A)** shows a passive fixation lead. The lead has small flexible tines at its distal end, designed to become entangled within the natural trabeculations of the heart muscle. Trabeculations are the ridged, lattice-like structures lining the inner surfaces of the heart chambers, particularly prominent in the ventricles. Once the lead is positioned inside the heart, the tines engage with these trabeculations, holding the lead securely in place. This method relies on the heart's natural anatomy to stabilise the lead, and no mechanical attachment to the tissue is required. Passive fixation leads are effective but may be more suited for locations where the trabeculations are well-developed, such as in the right ventricle.

Figure 1.4 (B) illustrates an active fixation lead, which features a small helix or screw at its tip. Unlike passive fixation, the active fixation lead is actively screwed into the heart muscle. The helix is extended from the lead tip and rotated during implantation, effectively anchoring the lead directly into the myocardium. This method provides firm mechanical attachment, ensuring that the lead remains stable even in areas of the heart that lack the natural trabeculations. Active fixation leads offer more precise control over placement and are often used in the right atrium or areas where trabeculations are less pronounced.

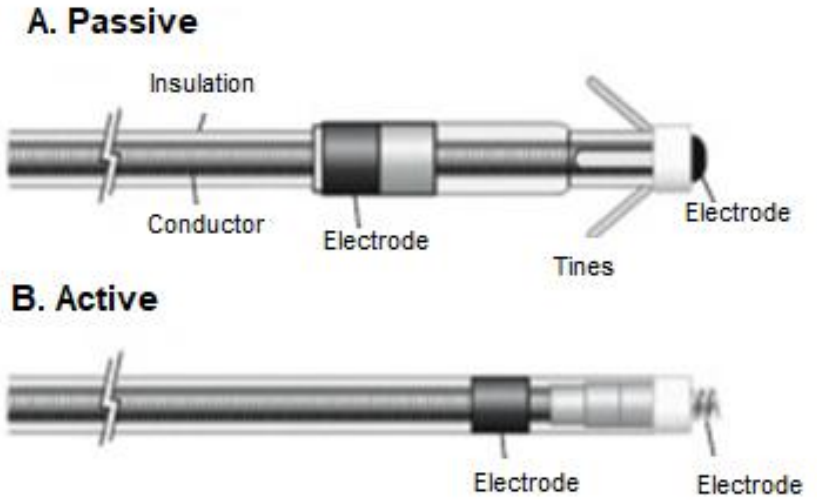


Figure 1.4 (A) Image of passive fixation lead; small fixation tines get tangled in the trabeculations of the heart muscle, (B) Image of active fixation lead; small helix-screwed on the heart muscle

1.2.2.5 Pacing lead polarity

Bipolar leads are generally preferred because they reduce the risk of extra-cardiac stimulation, myopotential over-sensing, far-field signals, and electromagnetic interference (Nielsen et al., 1985, Secemsky et al., 1982, Mulpuru et al., 2017). Initially, bipolar leads were more complex and had higher fracture rates compared to unipolar leads (Abler et al., 1992, Breivik et al., 1997). However, improvements in their design have enhanced their reliability, making them comparable to unipolar leads (Breivik et al., 1983). Additionally, modern generators now include software that can detect lead fractures (indicated by very high pacing impedance) and are able to automatically switch from bipolar to unipolar pacing (Breivik et al., 1983). With reduced fracture rates and advanced safety features, bipolar leads have become standard in nearly all endocardial pacing systems.

In Figure 1.5, the diagrams depict two types of pacemaker lead configurations. Figure 1.5 **(A)** represents a unipolar system. In this setup, the lead tip functions as the cathode (the negatively charged electrode), and the pacemaker device itself serves as the anode (the positively charged electrode). Electrical impulses are generated by the pacemaker and sent through the lead to the tip, which is implanted in the heart muscle. The current then flows from the cathode (lead tip) through the heart muscle and back to the anode (pacemaker casing), completing the circuit.

In the unipolar system, since the pacemaker body functions as the anode, the distance between the cathode (at the lead tip) and anode is larger, which can lead to a broader, more diffuse electrical field. This configuration, while effective, may sometimes be more susceptible to external interference (such as from muscle contractions or electromagnetic fields) due to the larger electrical field generated by the system (Gross et al., 1992, Wranicz et al., 2003, Swerdlow et al., 2011) Additionally, patients with unipolar systems might occasionally notice muscle twitching near the pacemaker site because of this wider electrical field and the inclusion of the pectoralis muscle in the circuit.

Figure 1.5 (B) shows a bipolar system, which differs from the unipolar system by having both the cathode and anode located on the lead itself. Specifically, the lead tip remains the cathode, while a proximal ring located slightly behind the lead tip functions as the anode. In this configuration, the electrical impulse travels only a short distance from the cathode at the tip of the lead to the anode on the same lead creating a much more localised and focused electrical circuit within the heart tissue.

Since the pacemaker is not part of the electrical circuit in a bipolar system, the electrical field is smaller and more confined to the immediate area around the lead, which significantly reduces the risk of interference from external sources. Bipolar systems are often preferred

because of this greater immunity to interference, and they tend to cause fewer extraneous effects, such as muscle twitching, compared to unipolar systems.

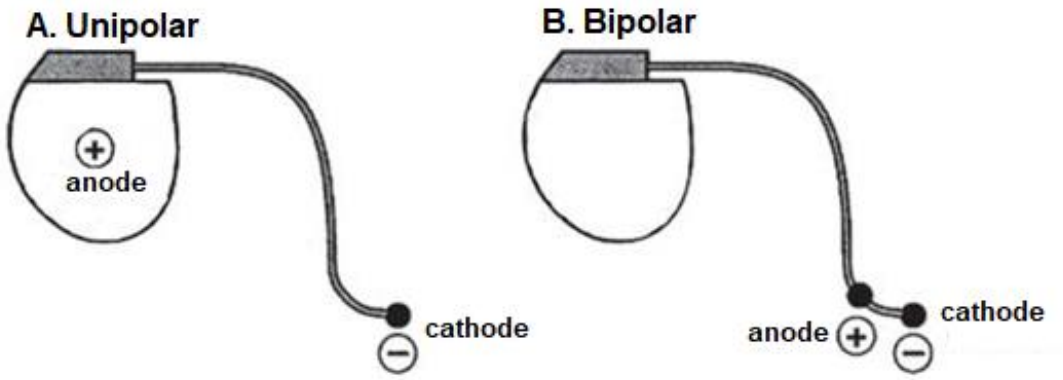


Figure 1.5 (A) Unipolar system; the lead tip is the cathode and the pacemaker is anode, (B) Bipolar system; the lead tip is the cathode and the proximal ring is the anode.

1.2.3 Methods of pacing

To date, pacing the myocardium through a lead fixed in the right ventricle is the most common method of pacing. Methods available to artificially pace the heart can be categorised depending on the aim, pacing area, heart chamber, sensing and response to the pacemaker. Typically, pacing methods involve the use of epicardial leads or endocardial leads (transvenous pacing).

1.2.3.1 Epicardial leads

Epicardial leads are typically used in cases where transvenous leads are impractical or high risk, such as paediatric patients with smaller vessels, those with congenital heart defects, or

when there are issues accessing the venous system (Warnes et al., 2008, Berul and Cecchin, 2003, Silvetti et al., 2013, Cohen et al., 2001)

This approach requires a surgical procedure, as depicted in **Figure 1.6 (A)** where the epicardial leads for pacing are surgically implanted on the outer surface of the heart (the epicardium).

The successful placement of the leads and the device can be confirmed through imaging, as shown in **Figure 1.6 (B)** where the image presents a post-implantation chest X-ray evidencing the placement of a pacemaker with epicardial leads. This X-ray provides a frontal view of the chest, revealing both the pacemaker device and the leads that have been surgically implanted on the outer surface of the heart (the epicardium). The pacemaker device is clearly visible in the lower right region of the chest (usually secured near the abdominal area). The device appears as a radiopaque (bright white) object, with its smooth, rounded shape indicating the pulse generator, which houses the battery and controls the pacing function. It is placed subcutaneously below the skin where it can be easily accessed for replacement.

From the pacemaker, two distinct bipolar leads can be seen extending toward the heart. These leads follow a path along the chest wall and are positioned on the surface of the heart, not inside the heart chambers as with endocardial leads. The X-ray confirms that the leads are placed on the epicardium, with no visible signs of displacement or complications such as fractures or migration of the leads. The position of the leads is consistent with the surgical implantation via the thoracotomy window, as depicted in **Figure 1.6 (A).**

Overall, the X-ray demonstrates proper positioning of the pacemaker and the epicardial leads, showing a typical postoperative view for a patient who has undergone epicardial lead placement for pacing. The clear visibility of the device and leads allows clinicians to assess the success of the procedure by confirming lead placement, and to monitor for potential complications post-surgery.

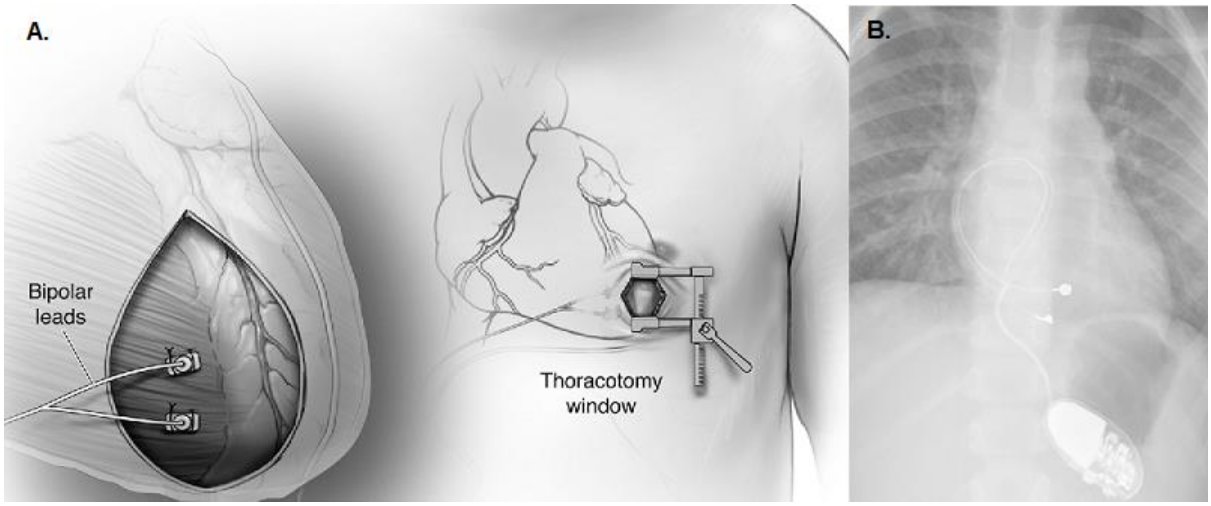


Figure 1.6 (A) Illustration of open thoracotomy window exposing the heart, and a bipolar lead sutured onto epicardium of the right ventricle of the heart. (B) Chest x-ray showing an epicardial lead implanted in a patient, pacemaker was placed into the abdominal pocket.

Epicardial leads are constructed to endure the continual motion and contraction of the heart. These leads, made of flexible materials and insulated wires, reduce the possibility of breakage or dislodgement, ensuring a strong connection between the pacemaker generator and the myocardium (Takeuchi and Tomizawa, 2013). Because of their durability, they are ideal for young children, patients with right-to-left cardiac shunts, and individuals who do not have access to the heart chambers for pacing purposes (Khairy et al., 2006, Glikson et al., 2021b, Burger et al., 2020)

Despite advances with newer insulation materials, bipolarity, and steroid elution in attempts to improve their longevity (Cutler et al., 1997), epicardial leads also present their own set of challenges; lead dislodgement is less common with epicardial leads because they are sutured to the heart, although it can still occur, especially in patients with substantial cardiac movement or those undergoing subsequent procedures. Dislodgement can cause pacing failure and frequently demands another surgical treatment to relocate or replace the lead; the surgical process itself poses risks not seen with endocardial leads, such as haemorrhage and infection;

infection at the surgical site or within the heart tissue (pericarditis or myocarditis) can also occur, all potentially hindering efficacy and recovery (Takeuchi and Tomizawa, 2013, Fortescue et al., 2004, Nelson-McMillan et al., 2016, Iguidbashian et al., 2024).

Mechanical difficulties with epicardial leads may also develop over time. Despite their flexible design, continual heart movement can result in lead breakage, insulation failure, or, in rare cases, erosion into the heart's tissues (Horenstein et al., 2003, Ector et al., 2006, Brady Peter et al., 1998). Insulation degradation can lead to electrical faults such as short circuits or loss of pacing, requiring lead replacement (Swerdlow et al., 2020). Lead erosion through the myocardial or pericardium, while uncommon, can result in serious consequences such as cardiac tamponade (Moazzami et al., 2017, Aryana et al., 2020).

Given these risks and the need for surgical intervention, endocardial leads are widely used, particularly in adult patients who can tolerate transvenous access, however, epicardial leads remains an important alternative in patients with congenital heart disease and tricuspid valve problems in whom RV access can be impossible.

1.2.3.2 Endocardial leads

The transitioning from epicardial approach to endocardial approach in the late 1960s represents significant advancement with the procedure moving away from a surgical intervention to a minimally invasive transvenous procedure (Jeffrey and Parsonnet, 1998, Stokes, 1990). In **Figure 1.7**, endocardial leads, as shown in **Figure 1.7 (A**), are commonly used for pacing because they are inserted through veins (such as the subclavian or cephalic) and do not require open surgery on the heart itself. Fluoroscopic and electrocardiographic guidance is used during the procedure to ensure correct positioning of the lead, typically in the right atrium and right ventricle. This method is less invasive than epicardial lead placement and is often preferred in adult patients or those with suitable venous access.

Figure 1.7 (B) shows the chest X-ray that provides a post-implantation view of an endocardial pacemaker lead in a dual chamber pacing system, showing both the pacemaker device and the leads that has been inserted into the heart chamber (right atrium and right ventricle). The X-ray is a frontal view of the chest, which allows visualisation of the key components of the implanted system. The pacemaker device is clearly visible in the upper right chest area. It is implanted just beneath the skin but outside the rib cage, appearing as a rectangular, bright white object. The pacemaker's location, just below the right clavicle, is typical in such procedures, and this is where the battery and pulse generator, responsible for pacing the heart are housed. Extending from the pacemaker, the lead wire is seen traveling into a retrosternal location.

The lead enters the subclavian vein, which is located beneath the collarbone, and then follows the natural path of the veins into the superior vena cava (SVC). From the SVC, the lead passes into the right side of the heart. On the X-ray, this lead is clearly visible as it passes into the right atrium and then further down into the right ventricle. The tip of the lead appears to be positioned at the right ventricular apex, the most common location for pacemaker leads to stimulate the heart muscle effectively.

The X-ray shows that the lead is well-positioned, with no signs of complications such as kinking, displacement, or breakage of the wire. Its path is clear and follows the expected trajectory from the pacemaker into the heart, confirming a successful implantation. The lungs appear darker in the background of the X-ray due to their lower density, while the diaphragm can be seen as a clear line at the base of the lungs, indicating normal positioning. Overall, this chest X-ray is a post-surgical confirmation of a properly placed pacemaker and endocardial lead.

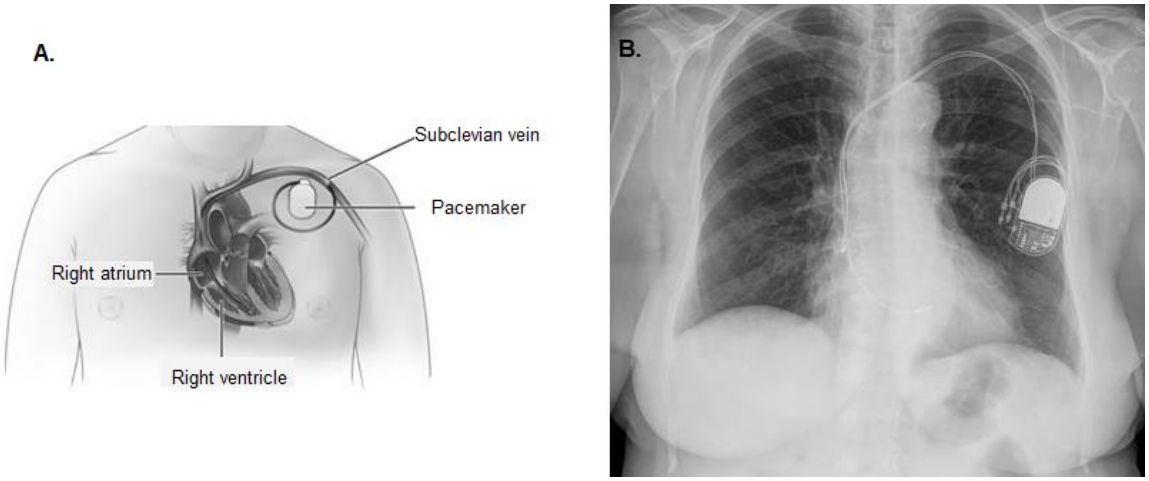


Figure 1.7 (A) Illustration of dual chamber pacemaker system using endocardial lead inserted through subclavian vein, implanted in right atrium and right ventricle. (B) Chest x-ray showing two endocardial leads implanted in a patient, pacemaker was placed into the pocket just above the pectoral fascia (subcutaneously) near the upper left chest.

The design of endocardial leads is to provide stable and reliable transmission of electrical impulses from the pacemaker generator to the myocardium. They are constructed with flexible materials and insulated wires to ensure optimal performance and minimise the risk of damage or dislodgement (Stokes, 1990).

The use of endocardial leads offers advantages such as reduced surgical morbidity, shorter recovery times, and improved patient comfort compared to epicardial leads (McLeod et al., 2010). Yet, there are a number of considerations when making the clinical decision of pacing access route. In patients with cardiovascular implantable electronic devices (CIEDs) approaching end-stage renal disease, transvenous access can be particularly challenging, as arteriovenous accesses created ipsilateral to the CIED have a higher primary failure rate, emphasising the need to favour contralateral access whenever possible (Barakat et al., 2000, Tan et al., 2013). Venous stenosis is a recognised complication following the implantation of pacemakers with studies showing that it occurs in 20% to 50% of patients (Stoney et al., 1976, Lickfett et al., 2004, Abu-El-Haija et al., 2015, Sticherling et al., 2001). While lead size was

initially considered a risk factor, recent small studies have shown no clear link. (Abu-El-Haija et al., 2015, Lickfett et al., 2004, Sticherling et al., 2001, Goto et al., 1998, Oginosawa et al., 2002). Other factors, such as the number of leads and the use of anticoagulation or antiplatelet therapy also require consideration (Barakat et al., 2000, Lickfett et al., 2004, Stoney et al., 1976, Mirowski et al., 1980, Abu-El-Haija et al., 2015).

Interaction with the tricuspid valve is another significant risk (Gelves-Meza et al., 2022). A study of 382 patients showed that tricuspid regurgitation (TR) increased by two or more grades in 10% of the cohort after device implantation, with 66% developing moderate TR and 37% having no prior TR (Lee et al., 2015). Additionally, 19.4% of patients experienced a smaller increase in TR severity (Lee et al., 2015). Endocardial leads also increased the risk of tricuspid valve endocarditis, a serious complication with high mortality (Sohail et al., 2008, Tarakji and Wilkoff, 2014, Nishimura et al., 2014). Despite their effectiveness, these risks highlight the need for careful management and monitoring.

1.2.3.3 Leadless pacing

Pacing leads, along with the requirement for a subcutaneous pocket for the generator, necessitate invasive procedures that increase patient morbidity, particularly through lead-related infections and failures (Tjong and Reddy, 2017). To address these issues, leadless pacemakers were introduced, with the first human implant performed in 2013 (Tjong and Reddy, 2017, Reddy et al., 2014, Reddy et al., 2015)

In **Figure 1.8**, the image displays a chest X-ray showing the placement of a leadless pacemaker inside the heart. Unlike traditional pacemaker systems that require leads and a generator pocket, the leadless pacemaker is a self-contained device that is directly implanted within the heart chamber itself, typically in the right ventricle.

In the X-ray, the leadless pacemaker is marked by a red circle to highlight its position within the heart. The device appears as a small, radiopaque object located inside the cardiac silhouette. The size and design of leadless pacemakers are significantly smaller compared to traditional pacemaker systems, and they resemble a small capsule, blending into the anatomical structure of the heart. Since the device is positioned inside the heart chamber, it directly stimulates the heart muscle without the need for pacing leads.

The implantation process for leadless pacemakers is minimally invasive. The device is inserted via a catheter, typically through a large vein, such as the femoral vein, and guided into the heart under imaging guidance. This approach offers a quicker recovery time for patients compared to traditional pacemaker implantation. Moreover, the absence of leads and a subcutaneous generator pocket reduces the risk of complications commonly associated with conventional systems, such as infection or lead fractures.

In summary, this chest X-ray demonstrates the presence of a leadless pacemaker, which represents a modern advancement in cardiac pacing technology by offering a simplified, minimally invasive solution that reduces the risks associated with traditional pacemaker systems.

Leadless pacemakers are though currently limited to a select group of patients (Boersma et al., 2022), despite their benefits in safety, efficacy, and patient outcomes are clear (El-Chami et al., 2019, Reynolds et al., 2016). This is because ongoing challenges continue, including long-term device retrieval and end-of-service management, but as the technology evolves, it promises to further advancement the field of cardiac pacing.

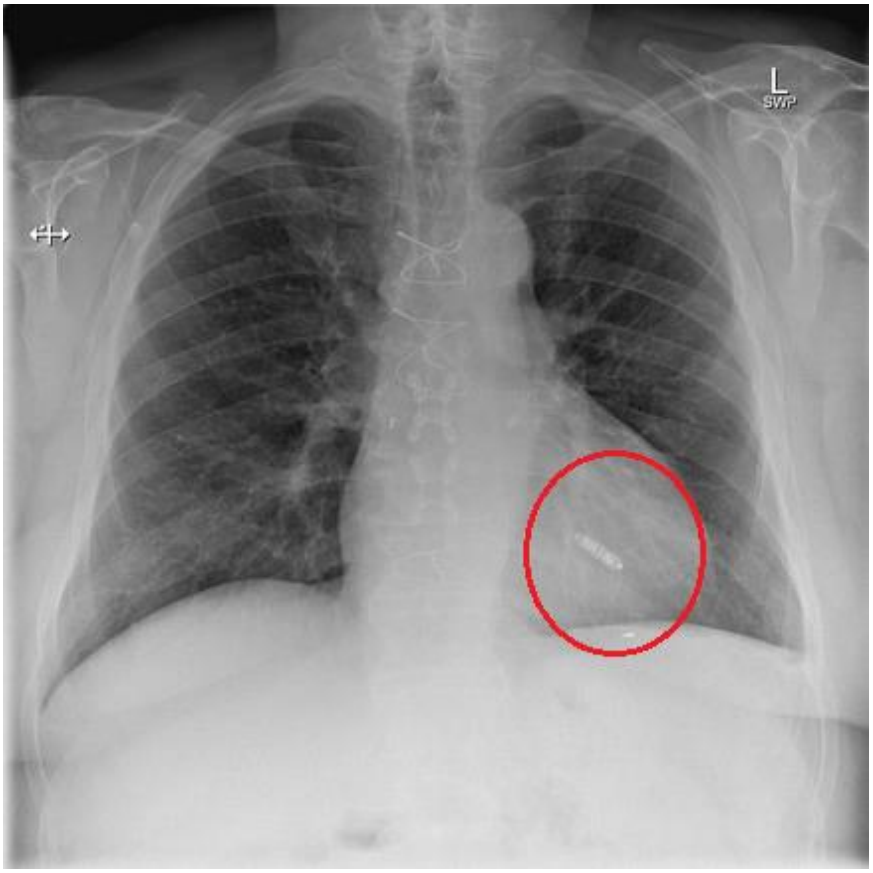


Figure 1.8 Chest x-ray showing a leadless pacemaker (marked in red circle) implanted in a patient.

1.2.4 Pacing lead position

The positioning of pacing leads within the heart is critical for maximising therapy efficacy and minimising complications. Traditionally, pacing leads were placed in the right ventricular (RV) apex due to its accessibility and stability, and the right atrial appendage (RAA). However, concerns about long-term adverse effects from RV apical (RVA) pacing have prompted exploration of alternative pacing sites, such as the RV septum (RVS), RV outflow tract (RVOT), His Bundle, and Left Bundle Branch Area Pacing (LBBAP). These alternative sites reflect a shift towards personalised pacing strategies tailored to individual patient anatomy and pathology.

1.2.4.1 RV apical

RV apical (RVA) pacing has been the most common site for lead placement due to its easy accessibility and stable lead positioning, however it is associated with potential adverse effects on LV function.

Studies in 12 patients with intact intrinsic conduction and no structural heart disease have evaluated the impact of RVA pacing on cardiac performance. Patients were randomised to 3 different pacing modes: atrial demand pacing (AAI), dual chamber pacing with dual chamber sensing and dual response (DDD) with maximum AV delay and ventricular demand pacing (VVI). This study demonstrated that those who programmed with AAI avoided the impairment of systolic LV function compared to those who programmed with DDD (at maximum AV delay) or VVI. The benefit was evidence by improved LVEF and enhanced hemodynamic at rest and during exercise. This study concluded that an abnormal activation with DDD or VVI led to delayed, uncoordinated LV contraction and LVEF (Rosenqvist et al., 1991, Leclercq et al., 1995).

The diastolic effects of RVA pacing have been more prominently observed in patients with reduced LVEF (Bedotto et al., 1990). In those with severe LVSD without conventional indications for pacing, the use of short AV delay DDD pacing with the lead positioned at the RVA was initially proposed as an adjunct therapy for advanced HF (Cowell et al., 1994) following evidence that optimised AV delay DDD pacing could improve LV filling and by addressing mechanical AV dyssynchrony, particularly in the left heart (Hochleitner et al., 1990). (Bedotto et al., 1990). This led to a huge enthusiasm for patients with non-ischaemic cardiomyopathy to undergo dual chamber pacemaker implantation.

Over the years, it has become clear that this is more harmful than optimised AV timing is beneficial. RVA pacing-related dyssynchrony can contribute to the progression of heart failure (HF), particularly in patients with reduced LV function, and studies have shown that long-term RVA pacing can lead to adverse ventricular remodelling, a reduction in LVEF, and increased risks of hospitalisation and mortality in HF patients (Auricchio et al., 1999, Gold et al., 1995, Linde et al., 1995, Sweeney et al., 2003, Lamas et al., 2002b, Toff et al., 2005) Therefore, the hypothesis that optimised dual chamber pacing can improve filling times, outweighing the detrimental effects of RVA pacing is no longer accepted.

Cardiac resynchronisation therapy (CRT), which involves pacing both ventricles to restore synchrony, has demonstrated significantly better outcomes in patients with HF and electrical dyssynchrony (Kindermann et al., 2006, Valls-Bertault et al., 2004, Baker et al., 2002, Leon et al., 2002, Cleland et al., 2005). CRT is now preferred over RVA pacing in patients with HF and intraventricular conduction delay (Tracy et al., 2012), whereas pacing for people with HF but without a bradycardia indication or conduction delayed is no longer carried out.

The acceptance that RVA pacing could worsen LV function has led to the exploration of alternative strategies such as the RV septal (RVS), RV outflow tract (RVOT), His bundle pacing (HBP), and left bundle branch area pacing (LBBAP). These alternative sites aim to

promote more physiological activation patterns and improved hemodynamic outcomes over RVA pacing, reflecting a shift towards personalised pacing strategies tailored to individual patient characteristics.

1.2.4.2 RV septal

Pacing at the RV septum offered the first alternative to the apical position **(Figure 1.9).** The RV septal position was hypothesised to form a more physiological ventricular activation and improve clinical outcomes, hence, positioning transvenous leads at the septum gained popularity for many years (Molina et al., 2014, Flevari et al., 2009). Nevertheless, a number of studies concluded no significant benefit in terms of clinical outcomes in septal pacing compared to apical pacing (Burri et al., 2007, Spath et al., 2019, Kypta et al., 2008, Domenichini et al., 2012, Leclercq et al., 2015).

One example was the study conducted by Burri et al (Burri et al., 2007). A total of 362 pacemaker recipients (RVS, n=157 vs. RVA, n=205) were divided into two groups based on the location of their pacing lead placement. Both groups demonstrated similar acute and chronic electrical parameters such as sensing, pacing thresholds, and lead impedance both at implantation and during the 24-month follow-up. Additionally, the risk of lead dislodgement was comparable between the two groups (2.5% for RVS vs. 3.9% for RVA, p=0.56). However, the study emphasised the need for multiple fluoroscopic views to ensure accurate lead placement at the RVS, raising concerns about increased radiation exposure. This additional fluoroscopy and procedure time could be avoided by placing the lead at the RVA, delivering similar electrical outcomes.

Subsequently, in a randomised, prospective, multicentre trial, 240 patients (age 74 ± 11 years, 67% male) with high-grade atrioventricular (AV) block requiring >90% ventricular pacing were

compared based on the location of their pacing lead placement (RVA versus RV high septal (RVHS). At the 2-year follow-up, both groups experienced a decline in LVEF, with RVA dropping from 57±9 % to 55±9 % (p=0.047) and RVHS decreasing from 56± 0 % to 54±10 % (p=0.0003); however, no significant difference in the intra-patient change in LVEF was observed between confirmed RVA and RVHS lead positions (p=0.43). Additionally, there were no significant differences in HFH, mortality rates, or AF burden between the groups. The study did highlight that the time required for lead placement was significantly longer for RVHS compared to RVA (70±25 vs. 56±24 min, p<0.0001), along with increased fluoroscopy times (11±7 vs. 5±4 min, p<0.0001). These findings indicate that RVHS pacing did not demonstrate a protective effect on LVEF compared to RVA pacing over two years, and the procedural complexities and radiation exposure associated with RVHS placement could be minimised by opting for the RVA approach (Kaye et al., 2015).

As a result, RV septal pacing was not widely adopted in clinical practice due to the persistent ease of implanting in the RV apex.

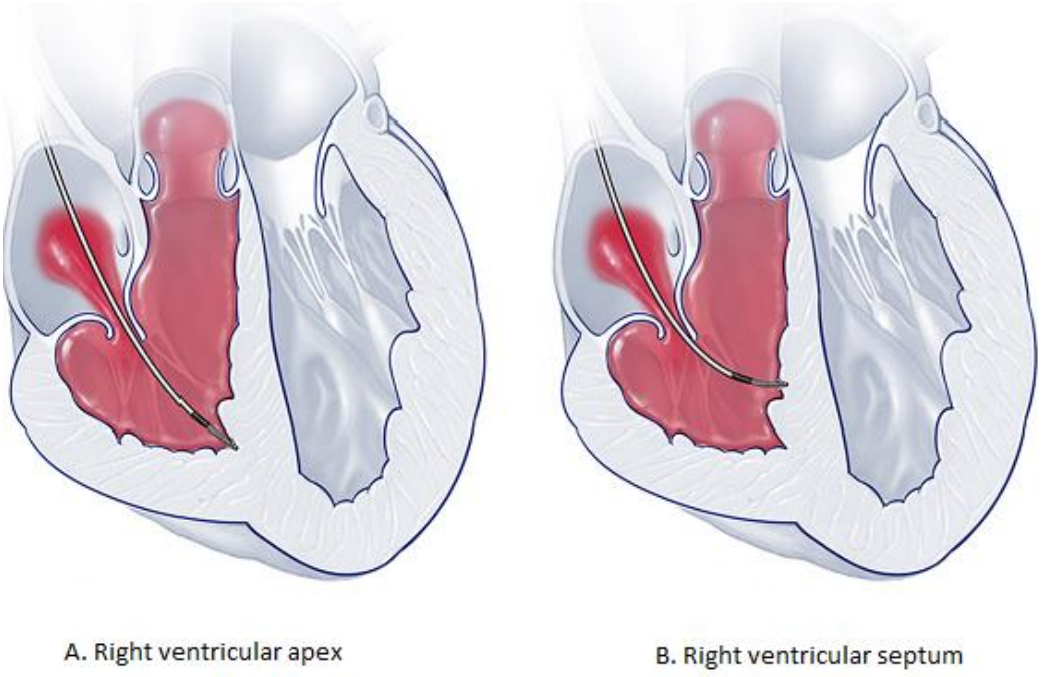


Figure 1.9 Transvenous pacing lead placement at (A) right ventricular apex versus (B) right ventricular septum

1.2.4.3 RV outflow tract

Another alternative site for lead placement was the RV outflow tract (RVOT). Although slightly more challenging to access, this site was hypothesised to have potential benefits based on an animal investigation that show pacing the RVOT could reduce the asynchrony of activation, subsequently minimising the decline in LV function by preventing myofibrillar disorder from occurring (Tse et al., 2002, Karpawich et al., 1991, Rosenqvist et al., 1996, Gong et al., 2009, ten Cate et al., 2008, Singh et al., 2015).

When examining patients with AV block, a study compared the long-term effects of RVA and RVOT pacing on myocardial function and perfusion showed similar outcomes, including LVEF (55 ± 3% vs. 55 ± 1%), myocardial perfusion defects (50% vs. 25%), and regional wall motion abnormalities (42% vs. 25%) ($p > 0.05$) (Tse et al., 2002). However, by 18 months, RVA pacing

resulted in significantly more myocardial perfusion defects (83% vs. 33%), regional wall motion abnormalities (75% vs. 33%), and a lower LVEF (47 ± 3% vs. 56 ± 1%) compared to RVOT pacing (all $p<0.05$). The study concludes that RVOT pacing preserves synchronous ventricular activation and prevents the long-term detrimental effects on myocardial perfusion and function associated with RVA pacing. However, it is important to consider the possibility that some of these observed changes could be due to artefact, particularly in imaging techniques such as thallium scintigraphy, which can sometimes yield false positives or be influenced by factors such as patient movement or suboptimal imaging conditions. Therefore, while the study presents compelling evidence of the adverse effects of RVA pacing, further investigation with additional controls for potential artefacts should be consider to confirm the clinical significance of these findings.

In contrast, the Right Ventricular Outflow Tract Versus Apical Pacing (ROVA) trial (Stambler et al., 2002) failed to show a clear benefit of RVOT pacing. The study involved 103 pacemaker recipients with congestive HF, LV systolic dysfunction (LVSD) (LVEF ≤ 40%), and chronic atrial fibrillation (AF). It aimed to determine whether quality of life (QOL) improved more with RVOT pacing compared to RVA pacing over 3 months. The results indicated that QRS duration was significantly shorter during RVOT (167 ± 45 ms) than RVA pacing (180 ± 58 ms, $p< 0.0001$) at 6 months, the RVOT group had higher role-emotional QOL scores than the RVA group ($p=0.01$), but these differences were not significant at 9 months. Numerous previous studies have also shown inconsistent clinical outcomes in patients with RVOT pacing (Buckingham et al., 1997, Giudici et al., 1997, Schwaab et al., 1999, Victor et al., 1999), explaining why it has not been widely adopted in clinical practice.

A later study involved 96 consecutive patients with AVB whom were randomised into two groups (RVA vs. RVOT) further supported the hypothesis by demonstrates that while LV systolic asynchrony was significantly more pronounced in the RVA group than in the RVOT group ($p<0.05$), there were no significant differences with respect to the mean myocardial

systolic and early diastolic velocities, LVEF, LV end-diastolic and systolic volume in the both groups at 12 months of follow-up (Gong et al., 2009).

1.2.4.4 His bundle

Since the documentation that a septal lead position was not more physiologic and an apical lead position, other locations to provide treatment for bradycardia have been trialled with an increasing focus on pacing the left bundle branch or the His-Purkinje system directly. Pacing higher up the conduction system is likely to lead to more normal activation of the left and right ventricles.

In 2000, Deshmukh et al. (Deshmukh et al., 2000) made significant advancements in the field of persistent His bundle pacing (HBP) in humans. Their study concentrated on evaluating the feasibility and outcomes of HBP in 18 patients with chronic AF and dilated cardiomyopathy. The study reported acute pacing thresholds of 2.4 (±1.0) V at a pulse duration of 0.5ms. Significant structural improvements were observed, including reductions in LV end-diastolic dimension (LVEDD) (from 59±8mm to 52±6mm, $p \leq 0.01$) and LV end-systolic dimension (LVESD) (from 51 ± 10 mm to 43 ± 8 mm, $p<0.01$), an increase in fractional shortening (from 14±7% to 20±10%, $p=0.05$), and an improvement in LVEF (from 20±9% to 31±11%, $p<0.01$). Although these data suggest a positive outcome, they are limited to a small, selected patient sample.

Following this, between 2006 and 2011, several case reports and series emerged that applied HBP in broader clinical contexts (Barba-Pichardo et al., 2006, Vernooy et al., 2006, Zanon et al., 2008, Kronborg et al., 2011). These early observations and findings spurred further investigations into the efficacy of persistent HBP for patients requiring pacing and device-based heart failure therapy.

In the original study by Deshmukh et al. (Deshmukh et al., 2000) HBP achieved a success rate of approximately 66% in patients with cardiomyopathy using traditional pacing leads. Subsequent studies showed improved outcomes, with Zanon et al. (Zanon et al., 2006) reporting a 92% acute implant success rate in patients without underlying heart conditions, while Sharma et al. (Sharma et al., 2015) found an 80% success rate in a cohort of 94 unselected patients, including those with various heart conditions. As procedural experience has increased, the success of HBP capture has increased to around 90%, with procedural and fluoroscopy times comparable to that of RV pacing (Vijayaraman et al., 2018a). However, HBP continues to present challenges, exhibiting variable success rates ranging from 65% to 92% in less experienced centres, and requiring a significant learning curve with lesser sensing, higher thresholds and higher rates of pacing displacement (Keene et al., 2019, Bhatt et al., 2018, Dandamudi and Vijayaraman, 2016)

1.2.4.5 Left bundle branch area

As techniques and technology continue to evolve, recent research, utilising pacing via the left bundle branch area **(Figure 1.10)**, has demonstrated further haemodynamic benefits (Li et al., 2019, Huang et al., 2019), a reduction in the risk of complications compared to HBP, and increased ease of implantation, (Hua et al., 2020, Jastrzębski et al., 2022) **,** making it more likely to gain acceptance clinically.

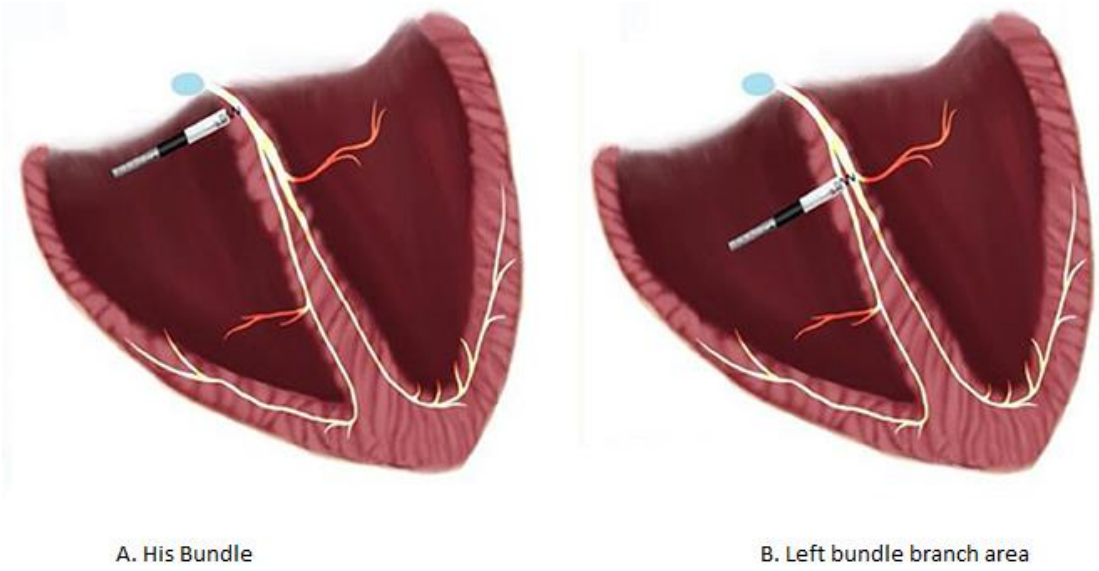


Figure 1.10 Transvenous pacing lead at (A) His bundle versus (B) left bundle branch area

An observational study (Sharma et al., 2022) compared clinical outcomes between LBBAP and RVP (n=703) in patients undergoing pacemaker implantation for bradycardia. Of these, 321 patients received LBBAP and 382 received RVP. The findings revealed that QRS duration in the LBBAP group remained similar to baseline and was significantly narrower than in the RVP group. Importantly, the primary composite outcome of all-cause mortality, HFH or upgrade to biventricular pacing, was significantly lower in the LBBAP group compared to the RVP group (10% vs. 23%; hazard ratio: 0.46). In patients with a VPB greater than 20%, LBBAP further reduced mortality (7.8% vs. 15%) and HFH (3.7% vs. 10.5%, respectively). These results suggest that LBBAP may provide better clinical outcomes, particularly for patients with higher RVP requirement, highlighting the significance of pacing site selection in managing patients requiring unavoidable ventricular pacing. However, the observed reduction in mortality should be interpreted with caution due to several inherent limitations.

First, as this was an observational study, the possibility of residual confounding cannot be excluded. Although statistical adjustments may account for known variables, unmeasured factors such as differences in baseline comorbidities, medical therapy, and functional status could have influenced the results. Second, selection bias remains a concern, as patients receiving LBBAP may have had a more favourable clinical profile compared to those who underwent RVP, which could have contributed to better outcomes independent of pacing modality.

While the physiological advantages of LBBAP in maintaining ventricular synchrony provide a plausible mechanistic explanation for improved outcomes, further validation through randomised controlled trials is necessary to confirm its survival benefit in this high-risk population.

While His-bundle pacing (HBP) is a physiological pacing method that directly activates the cardiac conduction system, maintaining the native synchrony of ventricular electrical activation and providing significant clinical benefits (Sharma et al., 2020, Abdelrahman et al., 2018), there are ongoing challenges, such as lower HBP success rates and higher, often unstable, His-bundle capture thresholds, particularly in patients with conduction system disorders (Vijayaraman et al., 2015, Chen et al., 2019).Further research confirms that LBBAP produces a narrow QRS duration, rapid left ventricular activation, stable low capture thresholds, and high implantation success rates.(Vijayaraman et al., 2019, Hou et al., 2019).

The PROTECT-HF (Physiological Vs Right Ventricular Pacing Outcome Trial Evaluated for Bradycardia Treatment) trial is currently underway, aiming to recruit 2,600 participants with LVEF >35% and indication for pacing (Whinnett, 2023). This trial comparing RVP with HBP or LBBAP could significantly influence practice by identifying which pacing strategy is preferable, though the requirement of RVP for patients with LVEF 36-49% is debated, as CRT may be the standard of care for this group (Glikson et al., 2021a, Kamalathasan et al., 2024).

1.2.5 Pacing programmability

Simultaneously, the industry is focused on minimising the detrimental outcomes associated with pacing through advancements in pacing programming technologies. The programming of pacemakers plays a vital role in optimising therapy delivery and patient outcomes. Different pacing modes, such as asynchronous pacing versus synchronous pacing, and pacing configurations in a single -chamber device (AAI or VVI) versus dual-chamber device (DDD), offer clinicians flexibility in tailoring therapy to individual patient needs. Advancement in rate-response algorithms and RV pacing avoidance algorithms have further improved pacing efficacy and patient quality of life (Gierula et al., 2018, Mcmeekin et al., 1990, Lau et al., 1988, Fearnot et al., 1986, Murakami et al., 2009, Gierula et al., 2014, Gillis et al., 2006, Boriani et al., 2014).

1.2.5.1 Assynchronous pacing versus synchronous pacing

In the early days of cardiac pacing, pacemakers were known for their simple yet successful design, particularly throughout the 1950's and 1960's. The evolution of pacemaker technology is illustrated in Figure 1.1.1, showcasing the transition from early electronic devices in 1958 to modern advancements in 2016. Early pacemakers were large, used epicardial leads, and required open thoracotomy for implantation. In contrast, contemporary single-chamber and dual-chamber devices are significantly smaller, utilise endocardial leads, and can be implanted through minimally invasive techniques. Additionally, leadless pacemakers are now available, featuring a compact capsule that houses the battery, generator, and electrodes, allowing for percutaneous implantation via the femoral vein (**Figure 1.11**). While first-generation pacemakers offered only asynchronous (VOO) pacing, which delivered fixed electrical stimulation regardless of the heart's intrinsic activity, modern devices provide synchronous and on-demand (VVI/DDD) pacing options (Aquilina, 2006)**.** The primary objective was to ensure consistent stimulation, often at outputs well beyond what was necessary. As inventor Wilson Greatbatch noted, this approach prioritised basic functionality

over battery efficiency, setting the framework for later developments in synchronous pacing devices that would improve adaptability and patient outcomes (Jeffrey and Parsonnet, 1998, Curtis, 2010).

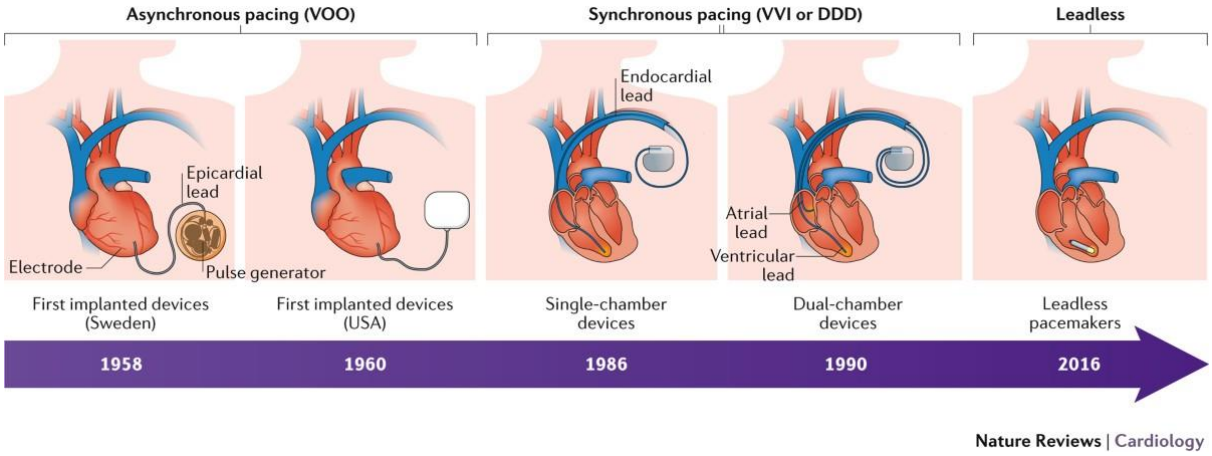


Figure 1.11 The evolution of pacemaker technology is illustrated, showcasing the transition from early electronic devices to modern advancements from 1958 to 2016.

1.2.5.2 Single-chamber pacing (VVI) versus dual-chamber pacing (DDD)

Clinicians have been interested in restoring the haemodynamic benefits of functional synchronisation between the atrium and ventricle from the early days of long-term pacing. It was debated for years before becoming a major topic of interest in the 1980s (Jeffrey and Parsonnet, 1998). Nevertheless, dual chamber pacing maintaining atrioventricular (AV) synchrony was a radical breakthrough, similar to transvenous pacing in the 1960s, because it provided a step change in the pacing modes available. Despite increased interest in pacing as a treatment for sick sinus syndrome, and the hypothesis that sustaining AV sequential pacing was appropriate, dual chamber pacemakers were limited to patients with heart block due to the expense (Ibrahim et al., 1995). Previously, the dual chamber pulse generator was

large and drained increased power from its batteries compared to the single chamber pacing and pulse generator (Aquilina, 2006). Additionally, the risk of atrial lead failure and dislodgement were also an issue and in people with sick sinus syndrome, these often become irrelevant when intermittent AF becomes permanent (Ibrahim et al., 1995, Nielsen et al., 2011, Luria et al., 2007, Witt et al., 2016).

With innovations in technology, modern dual-chamber devices provide better programming options alongside more reliable pacing system components, minimising the risk of lead failures. In addition, clinicians often encounter the need to adjust pacing modes due to atrial arrhythmias. A careful assessment of patients who may only require a single-chamber pacemaker is crucial to prevent potential complications, and ultimately, the choice between single and dual-chamber pacemakers should be made with consideration of both the benefits and the individual patient's circumstances.

1.2.5.3 Rate-response

Rate-responsive pacing was introduced in the late 20th century to address the limitations of early pacemakers which provided fixed rate of pacing regardless of the patient's activity level or physiological needs (Fearnot et al., 1986). Although early pacemakers could restore heart rhythm, they could not adapt to the body's demand, particularly during physical activity, resulting in inadequate output and limited exercise capacity. The recognition of this as a limitation led into the development of sensors that monitor various parameters, including activity, heart rate, respiratory rate, and QT interval as ways to try and identify patient activity and allow measured heart rate adaption (Beyersdorf et al., 1986).

An early study assessed the activity-sensing rate-responsive pacemaker in 15 patients, demonstrated that it significantly increased treadmill exercise time compared to constant-rate pacing (mean ± SD: 8.0 ± 3.3 minutes vs. 5.4 ± 2.3 minutes; $p < 0.01$), but did not respond

effectively to non-movement-related activities or changes in treadmill gradient, indicating the need for further refinement (Lau et al., 1988).

Later, a randomised study compared four modern rate-responsive pacing modes in 22 patients (aged 18 to 81) with high-grade atrioventricular block (AVB) and chronotropic incompetence, using a double-blind crossover design. Results showed that the dual chamber universal rate-responsive mode (DDDR) was preferred by 59% of patients and was objectively superior, with longer exercise treadmill time ($p < 0.01$) and greater cardiac output at rest ($p = 0.006$) compared to the ventricular demand rate-responsive mode (VVIR), which was the least acceptable and showed significant under-responses to mental stress and staircase ascent. No significant differences in echocardiographic parameters were found across pacing modes, but those who preferred DDDR experienced a 22% increase in stroke volume in DDD mode compared to only 2% in VVIR mode ($p = 0.03$), indicating that DDDR is superior both objectively and subjectively to other pacing modes (Sulke et al., 1991).

Patients with chronotropic incompetence and a pacing requirement can benefit significantly from rate-response pacing, permitting an enhancement in cardiac output during periods of increased activity. Even patients with VVI pacing see improvements, although they lack the benefits of A-V synchrony. At higher heart rates, A-V synchrony becomes less critical, as the increased pacing rate itself drives better cardiac output (Mcmeekin et al., 1990). However, for patients with compromised heart function, maintaining A-V synchrony remains important to provide active filling during shortened diastolic periods. (Lau et al., 1990, Lau et al., 1988).

Innovations in pacing technology, particularly rate-responsive features in programmable pacemakers, can enhance the quality of life for patients with sick sinus syndrome. A new algorithm, known as the regional effective slope quantity, isolates the autonomic nervous system signal, leading to a normalised parameter called the ventricular inotropic parameter, which reflects autonomic nervous system activity. Multi-centre studies demonstrated that this

new algorithm in patients with AVB closely correlated pacing rates with spontaneous sinus rates, and positive patient-reported outcomes indicated effective cardiovascular control (Schaldach et al., 1992).

Additionally, a study involving 131 chronotropic incompetent patients compared pacing rate adaptation using closed-loop stimulation (CLS) versus accelerometer sensor (AS) following pacemaker implantation. Results showed that CLS produced a significantly higher heart rate during mental stress (3.0 ± 9.2 bpm; P = 0.004) compared to AS, while both modes improved walking distance similarly. Patients preferred CLS over AS, with twice as many selecting it ($p<0.01$), indicating greater sensitivity of CLS to mental stress (Coenen et al., 2008).

1.2.5.4 RV pacing avoidance algorithm

Many studies have highlighted the detrimental effects of RVP on cardiac function, leading to one of the most recent paradigms shifts in pacing with the introduction of RV pacing avoidance algorithms. The MOST trial (Lamas et al., 2002b), which studied dual-chamber pacing in patients with sinus node dysfunction (SND), found that a high VPB (>40%) was associated with a 2.5-fold increased risk of HFH and AF. Similarly, the DAVID trial in people with HF demonstrated that in patients with standard indications for ICD therapy but no need for cardiac pacing, dual-chamber pacing (DDDR-70) led to worse outcomes compared with ventricular backup pacing (VVI-40). The trial reported a higher rate of death or HFH in the DDDR group, reinforcing the negative impact of unnecessary RV pacing, (Wilkoff et al., 2002).These findings spurred the development of algorithms designed to reduce VPB.

Results from a pivotal trial indicate that dual-chamber minimal ventricular pacing reduced the risk of persistent atrial fibrillation (AF) by 40%, highlighting the benefits of minimising right ventricular pacing (RVP) for improved outcomes in patients with sinus-node disease (Sweeney et al., 2007). Early studies, such as the PREVENT trial (KOLB et al., 2011) showed modest reductions in VPB using enhanced automatic AV search hysteresis. However, it was

not fully effective in significantly reducing VPB, especially in patients who did not require frequent ventricular pacing. Subsequently, the SafeR trial (DAVY et al., 2012) achieved more substantial improvements, reducing unnecessary RVP to 4.5% compared to 37.9% with conventional pacing modes, without compromising atrial function. This demonstrated the potential for selective pacing in patients with SND.

Most recently, a cohort study further reinforced these conclusions, demonstrating that reprogramming pacemakers to reduce VPB led to a 6% improvement in LVEF over six months, with no adverse effects on patient quality of life or exercise capacity (Gierula et al., 2014), followed by a randomised controlled trial following the same pacing protocol (Paton et al., 2021). These studies also found reducing RVP led to improved systolic LV function, suggesting that RVP not only contributes to the risk of HF but that this can be mitigated through optimised programming.

These studies confirm that reducing unnecessary RVP is essential for improving cardiac outcomes, especially in patients with compromised heart function. Furthermore, the findings indicate that RV pacing avoidance is safe and effective across diverse patient populations. Therefore, clinicians should prioritise RV pacing avoidance in their programming strategies to mitigate the risk of LVSD in pacing populations. However, the challenge remains for patients requiring unavoidable RV pacing, where alternative pacing strategies should be considered.

1.3 Future directions of pacemaker technology

The first pacemakers were little more than a battery and a timer. They lacked sensing capabilities, had a fixed pacing rate, and could not permit communication with the device for programming or retrieving diagnostic information. Greatbatch invented the first pacemaker with only eight components (Aquilina, 2006). The surgical process was far more complex than today's transvenous approach, requiring a thoracotomy and an epicardial lead sewn onto the heart's surface. Today's pacemakers are highly programmable, contain hundreds of

components, and can communicate wirelessly, allowing physicians to monitor devices while patients are at home without requiring patient contact to trigger transmission (Haddad et al., 2006, Mond and Freitag, 2014).

Looking ahead, the future of pacemaker technology is poised for significant advancements. Miniaturisation will continue to play a crucial role, with leadless pacemakers offering less invasive options and reducing complications associated with traditional leads. Biocompatible materials and advanced battery technology will further enhance device longevity and patient safety (Bussooa et al., 2018, Hung et al., 2024)

Moreover, adaptive pacing algorithms are expected to evolve, incorporating artificial intelligence and machine learning to tailor pacing strategies to individual patient needs in real-time. This personalisation could improve outcomes by allowing pacemakers to respond dynamically to changes in a patient's physiological state, such as exercise or stress levels.

Additionally, remote monitoring will likely become even more sophisticated, integrating health data analytics to provide proactive care and timely interventions (Ahmad et al., 2024, Crossley et al., 2009, Mabo et al., 2012, Varma et al., 2015). This shift will enable healthcare providers to manage patients more effectively, identifying potential issues before they escalate.

Finally, regenerative medicine and advancements in bioengineering may lead to pacemakers that not only stimulate the heart but also contribute to cardiac tissue repair, potentially reversing HF rather than merely managing symptoms (Chen et al., 2018, Lee and Walsh, 2016, Vunjak-Novakovic et al., 2011).

In summary, the future of pacemaker technology promises to enhance patient care through innovation, personalisation, and improved connectivity, ultimately leading to better health outcomes for patients with cardiac rhythm disorders.

Chapter 2 Literature review of advanced cardiac echocardiography measures in the assessment of dyssynchrony in people receiving pacing therapy

2.1 Introduction

For over 60 years, pacemakers have been the standard treatment for patients with bradycardia, demonstrating a robust safety profile and offering a wide range of advanced features for optimised patient care (Furman and Schwedel, 1959, Lamas et al., 1998). However, despite significant advancements aimed at avoiding right ventricular (RV) pacing (RVP), the potential detrimental effects of RVP-related dyssynchrony on cardiac function remain an area of ongoing concern (Lee et al., 1994, Begg et al., 2011a, Gierula et al., 2014, Paton et al., 2021). Echocardiography, as a first-line cardiac imaging modality, is routinely employed to assess left ventricular (LV) remodelling following pacemaker therapy, yet current clinical guidance to drive pacemaker therapy prescription prior to implant is primarily based on electrophysiological parameters and symptoms classified by the New York Heart Association (NYHA) (NICE, 2005).

In recent years, research has shifted towards exploring advanced echocardiographic parameters as potential tools for early risk stratification, particularly in patients receiving pacing therapy, where artificial myocardial stimulation can result in mechanical dyssynchrony, LV remodelling, and subsequently, heart failure (HF) (Russell et al., 2013, Russell et al., 2012, El Mahdiui et al., 2019, Mao et al., 2023, Duchenne et al., 2019b, Duchenne et al., 2019c). These novel echocardiographic measurements could provide additional insights into the management of patients with cardiac devices, allowing clinicians to implement targeted preventative interventions earlier.

Therefore, this review aims to evaluate the potential of advanced non-invasive echocardiographic techniques in predicting and identifying LV remodelling in patients receiving pacing therapy, through a comprehensive review of the current literature.

2.2 Literature review search methods

A systematic literature review was performed based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (Moher et al., 2009). Databases EMBASE and MEDLINE were searched from 2018 to 2024 to examine echocardiographic parameters related to pacing-associated LV remodelling. Studies published before 2018 were excluded from this review, as the first significant human studies applying both pacing population and MW (Cvijic et al., 2018) published after years following the publication of the initial theories on MW (Boe et al., 2015). A search was performed using keywords "pacing" OR "pacemaker" AND "dyssynchrony" OR "remodelling" AND "echocardiography". The search was limited to human studies and to articles published in English. Additionally, the references of all included articles were hand searched to identify additional studies. Studies that included imaging assessment pre implant, post implant or at both time points were considered for inclusion.

The full text of potentially relevant studies was obtained, and data extraction was performed by two independent reviewers (NHAS and MFP). Key findings from each study and critical appraisal points were summarised **(Table 2-1)** prior to narrative synthesis. The population of interest was adults (>18 years old) with cardiac implantable electronic devices, with reported measures of LV remodelling or dyssynchrony derived from echocardiography.

2.3 Literature review result

2.3.1 Literature search

A total of 4041 potentially relevant studies were identified. Upon screening, 505 duplicated reports were removed. Of those remaining, 3205 articles were excluded as they either did not report data on LV remodelling or were not conducted within a population of people with implantable electronic cardiac devices. Subsequently 83 relevant studies were identified which fulfilled the inclusion criteria. Following a thorough review of titles, abstracts, and subsequently full articles, eleven studies were of an appropriate subject to be included in the review **(Figure 2.1).**

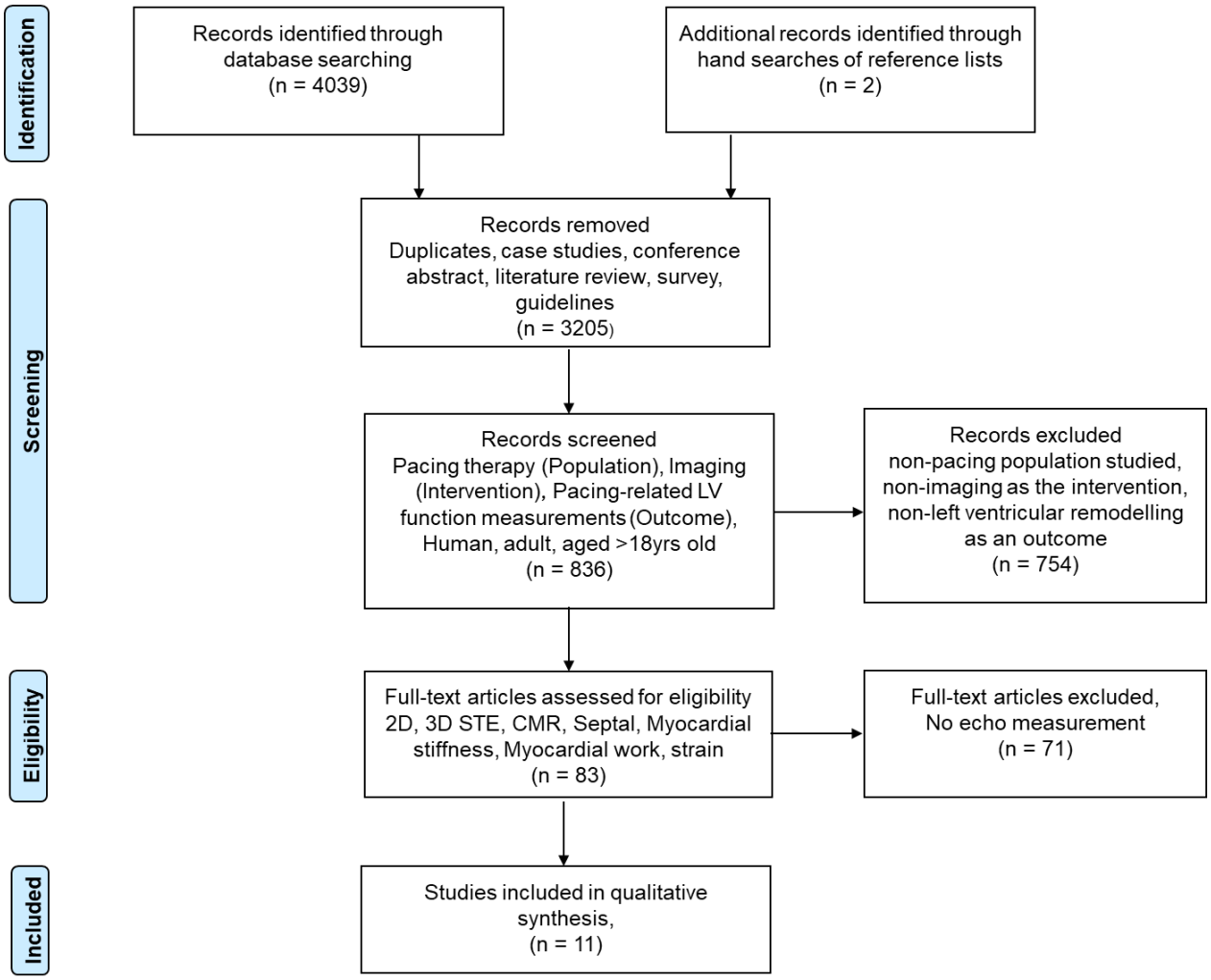


Figure 2.1 Flow diagram of the studies selection

2.3.2 Study characteristics

A description of eleven included studies (Chen et al., 2023b, Cvijic et al., 2018, Galli et al., 2018b, Galli et al., 2022, Højgaard et al., 2023, Kostyukevich et al., 2019, Mao et al., 2023, Mei et al., 2023, Xu et al., 2019, Zweerink et al., 2018, Duchenne et al., 2020) and the patient characteristics are shown in **Table 2-1.** A total of 1846 patients receiving pacing therapy were included from the eleven studies. The number of participants in each study varied from 26 to 903, with mean age was 67 years and an average proportion of investigated males of 54%. Patient follow-up varied for each study but ranged from 5.5 months to 53 months after implant.

Table 2-1 Study description and patient characteristics of the 11 studies included (Chen et al., 2023b, Cvijic et al., 2018, Galli et al., 2018b, Galli et al., 2022, Højgaard et al., 2023, Kostyukevich et al., 2019, Mao et al., 2023, Mei et al., 2023, Xu et al., 2019, Zweerink et al., 2018)

First author, year, (reference), country	Sample size (n)	Participant characteristics	Length of follow-up	Manufacturer	Image acquisition	Device	Measures	Finding
(Xu et al., 2019) China	68	human, mean age: 69±8, sex M: 68%	12 months	Philips	2D, 3D	Dual chamber pacemaker RVP	GLS	GLS showed correlation with LVEF reduction (r=0.68, p>0.001) from baseline at 1 month to 12 months
(Galli et al., 2018b) Norway, France	97	human, mean age: 65±10, sex M: 69%	5.5 - 6.9 months (median 6.1)	GE	2D	CRT	GLS, MW, septal flash	At multivariate analysis, global CW and septal flash (OR 14.69, p= 0.005 and OR 8.05, p= 0.004, respectively) were the only significant predictors of CRT positive response.
(Cvijic et al., 2018) Belgium, Turkey Poland, Norway Germany, Serbia	26	human, mean age: 63±9, sex M: 69%	7-29 months (median 14.5)	GE	2D	CRT	MW	Dyssynchronous myocardial shortening seen related to a reduction of MW prior to CRT implant. Whilst septal and anteroseptal walls were significantly thinner than lateral and posterior segments prior CRT (p<0.001), post CRT reverse remodelling increased thickness in septal and anteroseptal and thinned lateral and posterior segments (p <0.001).
(Zweerink et al., 2018) The Netherlands	27	human, mean age: 65±9, sex M: 58%	12 months	GE, Philips	CMR, 2D	CRT	Septal strain	End-systolic septal strain was the only measure with a consistent good correlation (R2 0.60, p <0.001) to LV remodelling after a CRT implant
(Kostyukevich et al., 2019) The Netherland	175	human, mean age: 64±10, sex M: not reported	6 months	not reported	2D	CRT	MW	A positive CRT response reflected in a greater amount of WW (313.2±144.9 mmHg% vs 215.1±102.5 mmHg% and 229.0±113.5 mmHg%, respectively; p < 0.001) and reduced LV myocardial work efficiency (67.6±9.9 mmHg% vs 72.7±9.7 mmHg% and 75.4±9.6 mmHg%, respectively; p <0.001) at baseline.
(Duchenne et al., 2020)	129	human, mean age: 69±11, sex M: 69%	12 months	GE Healthcare Vivid E95	2D	CRT	GLS, MW	CRT significantly redistributed MW in the LV, increasing septal work and decreasing lateral wall work (p<0.05). The acute changes in work distribution correlated strongly with long-term volumetric reverse remodelling (r=0.62, p<0.0001 and the strongest predictor of reverse remodelling after CRT (R^2=0.414, p< 0.0001).

(Galli et al., 2022) Rennes, Oslo, Leuven, Aalst, and Stockholm	221	human, mean age: 67±11, sex M: 30%	6 months	GE	2D	CRT	LARS, GLS	At multivariate analysis LARS was the only significant predictors of LV systolic and diastolic remodelling (r= -0,14, p =0.049 and r= -0.17, p = 0.002, respectively). GLS were the strongest measure correlated with LARS (r=0.59, p<0.0001) after CRT implant at 6-month follow-up
(Mei et al., 2023) China	90 LBBAP (30) RVSP (30) RVAP (30)	human, LBBAP mean age: 63±13, sex M: 60% RVSP mean age: 66±12, sex M: 50% RVAP mean age: 63±15, sex M:53%	1 month	Philips Medical QLAB V.13.0: 3D adv, Heartmodel	2D,3D	Pacemaker (LBBAP vs. RVSP vs. RVAP)	GLS	GLS improved (−19.4 ± 2.4% vs. −19.3 ± 3.4% vs. −17.3 ± 3.5%, p = 0.026), and reduced dyysynchrony measures (SDI) (2.5 ± 0.3 vs. 5.9 ± 0.9 vs. 7.7 ± 1.2, p = 0.001) in LBBAP group.
(Mao et al., 2023) China, Belgium	60 LBBAP (31) RVP (29)	human, LBBAP mean age: 75±9, sex M: 79% RVP mean age: 71±10, sex M: 58%	12 months (mean15±9)	GE Healthcare Vivid E95	2D	Pacemaker (LBBAP vs RVP)	GLS, MW	LVEF and GLS were more decreased in RVP compared with LBBAP (ΔLVEF: −7.4 ± 7.0% vs. 0.3 ± 4.1%; ΔLVGLS: −4.8 ± 4.0% vs. −1.4 ± 2.5%, both P < 0.01). In addition, ΔLW–SW work difference was independently correlated with LV adverse remodelling (r = 0.42, P < 0.01) and LVSD (ΔLVEF: r = −0.61, P < 0.01 and ΔLVGLS: r = −0.38, P = 0.02).
(Chen et al., 2023b) China	903 RVSP (425) RVAP (612)	human, LBBAP median age: 72, sex M: 60% RVP median age: 73, sex M: 60%	48 months (mean 29)	Philips Medical EPIQ 7	2D,3D	Pacemaker (LBBAP vs. RVP)	GLS	LBBAP had a higher absolute value of GLS (−19.56 ± 7.11 vs. −15.90 ± 6.67%, p < 0.001), GCS (−28.86 ± 6.13 vs. −26.09 ± 5.64%, p = 0.006). However, compared with the RVP group, they did observe a lower SDI (5.68 ± 1.92 vs. 6.50 ± 2.28%, p = 0.012) in the LBBAP group. No significant difference in the LVEDV and LVEF was detected between the groups.
(Højgaard et al., 2023) Denmark	50 BiV-CRT (31) His-CRT (19)	human, BiV-CRT mean age: 67±9, sex M:77% His-CRT mean age: 63±9 sex M:42%	6 months	GE Healthcare Vivid E95	2D	CRT (BiV-CRT vs His-CRT)	GLS	GLS improved in both groups [BiV-CRT group from −9.1% (±2.7) to −10.7% (±2.6), *P* = 0.02, and His-CRT group from −8.6% (±2.1) to −11.1% (±2.0), p<0.001], but no significant differences could be demonstrated in changes from baseline to follow-up [−0.9% (−2.4; −0.6), p=0.25] in both groups

2.3.2.1 Pacing therapy modality

Out of eleven studies, six examined the relationship between echocardiographic measurements and LV remodelling in patients undergoing cardiac resynchronisation therapy (CRT) (Galli et al., 2018b, Cvijic et al., 2018, Zweerink et al., 2018, Kostyukevich et al., 2019, Duchenne et al., 2020, Galli et al., 2022). One study focused on echocardiographic measures and LV function in those with right ventricular pacing (RVP) (Xu et al., 2019). Three studies explored LV remodelling with either RVP or conduction system pacing (His bundle or left bundle branch area pacing) (Mei et al., 2023, Mao et al., 2023, Chen et al., 2023b). Another study observed changes in echocardiographic measures over time in patients with His-CRT or Biventricular-CRT ((Højgaard et al., 2023)).

2.3.2.2 Echocardiographic measures

All studies (Chen et al., 2023b, Cvijic et al., 2018, Galli et al., 2018b, Galli et al., 2022, Højgaard et al., 2023, Kostyukevich et al., 2019, Mao et al., 2023, Mei et al., 2023, Xu et al., 2019, Zweerink et al., 2018, Duchenne et al., 2020) reported two-dimensional (2D) echocardiographic measurements, with three (Chen et al., 2023b, Mei et al., 2023, Xu et al., 2019) studies also reporting three-dimensional (3D) echocardiographic datasets.

All studies (Chen et al., 2023b, Cvijic et al., 2018, Galli et al., 2018b, Galli et al., 2022, Højgaard et al., 2023, Kostyukevich et al., 2019, Mao et al., 2023, Mei et al., 2023, Xu et al., 2019, Zweerink et al., 2018, Duchenne et al., 2020) reported similar traditional echocardiographic measurements that included LVEF, LVESD and LVEDD. In contrast, reported advanced echocardiographic measurements showed some variability. Global longitudinal strain (GLS) was the most commonly reported advanced measure (eight studies), with myocardial work (MW) being the focus of five studies (Cvijic et al., 2018, Galli et al., 2018b, Kostyukevich et al., 2019, Mao et al., 2023, Duchenne et al., 2020). One study reported LV mass (Zweerink et al., 2018) and one study reported LA strain (Galli et al., 2022).

2.3.2.3 Strain measurements in right ventricular pacing (RVP)

Xu et al investigated 68 patients receiving dual chamber pacemakers and found that both LVEF (55.5%±6.0 vs 60.9± 5.1%,p=0.004) and GLS (-14.9%±1.8% vs -16.1±1.7%,p=0.014) were significantly reduced at one month post implant in patients who subsequently developed RVP-related LV dysfunction (LVSD), defined as a reduction of ≥5% LVEF at 12 months, compared to those who did not (Xu et al., 2019) . Further multivariate analysis showed that GLS was the only independent predictor of adverse LV remodelling following pacemaker implantation (p=0.009), with a high predictive accuracy for the development of LVSD at 12-months (area under curve (AUC)=0.88) (Xu et al., 2019).

2.3.2.4 Strain measurements in between conduction system pacing (His bundle or left bundle branch) and RVP

Mao et al investigated whether left bundle branch area pacing (LBBAP, n=31) better preserved LV synchrony and function compared to RVP (n=29) in a retrospective audit of 60 bradycardia patients from two hospitals (China, n=33 and Belgium, n=27). The patients were matched for key clinical characteristics (age and sex), with the LBBAP group (mean age 71±10years, 58% male) and the RVP group (mean age 75±9years, 79% male) undergoing follow-up echocardiography. The study assessed the effects of pacing on LV mechanical synchrony and function before implantation, shortly after, and at a 12-month follow-up in both groups. Both change in LVEF (−7.4±7.0% vs. 0.3±4.1%, p=0.01, respectively) and change in LVGLS (−4.8±4.0% vs. −1.4±2.5%, p<0.01, respectively) showed greater declines in the RVP group compared to the LBBAP group (Mao et al., 2023).

Chen et al aimed to compare the safety and effectiveness of LBBAP (n=425) versus RVP (n=612) in patients with AVB. This observational cohort study included 903 patients who underwent pacemaker implantation that completed their follow up (mean: 20 months). Of these, a 1:1 propensity-score matched cohort was created for LV function analysis, matching

patients based on age, gender, and baseline comorbidities, resulting in 191 patients in each group (LBBAP, n=191 vs RVP, n=191). In this matched cohort, LBBAP demonstrated preservation in several measurements compared to RVP: higher GLS (−19.56±7.11% vs. −15.90±6.67%, p<0.001), higher global circumferential strain (GCS) (−28.86±6.13% vs. −26.09±5.64%, p=0.006, respectively), and reduced systolic dyssynchrony index (SDI) (5.68±1.92% vs. 6.50±2.28%, p=0.012, respectively). There were no significant differences in LVEDV and LVEF between the groups. The study concluded that LBBAP may be a promising pacing method to improves patient outcomes by preserving LV systolic synchrony compared to conventional RVP (Chen et al., 2023b).

Mei et al conducted a prospective cohort study to evaluate the effects of different pacing sites; left bundle branch area pacing (LBBAP, n=30), right ventricular septal pacing (RVSP, n=30), and right ventricular apical pacing (RVAP, n=30) on echocardiographic findings in a total of 97 indicated for elective permanent dual chamber pacemaker implantation with patients with normal left ventricular ejection fraction (LVEF). Patients were divided into three groups based on the pacing site, with seven patients excluded due to unsatisfactory tracking on 2D speckle tracking echocardiography. Key measurements included global longitudinal strain (GLS), systolic dyssynchrony index (SDI), and time to peak strain. The results indicated that LBBAP led to significantly better surrogate outcomes compared to RVSP and RVAP, with lower QRS duration (115±26 ms vs. 134±28 ms vs. 157±29 ms, p=0.012), improved GLS (−19.4±2.4% vs. −19.3±3.4% vs. −17.3±3.5%, p=0.026), and reduced SDI (2.5±0.3 vs. 5.9±0.9 vs. 7.7±1.2, p=0.001). These findings indicate that LBBAP promotes better left ventricular electrical and mechanical synchronisation compared to RVSP or RVAP (Mei et al., 2023).

2.3.2.5 Myocardial work measurements right ventricular pacing (RVP)

Mao et al's retrospective assessment in patients pacemakers implanted for bradycardia, comparing the effects of LBBAP (n=31) and right ventricular pacing (RVP) (n=29) on LV mechanical synchrony and function, found that RVP caused a significantly larger lateral wall-

septal wall (LW–SW) work difference compared to LBBAP (1253 ± 687 mmHg·% vs. 439 ± 408 mmHg%, p<0.01), despite both groups having similar LW–SW work differences at baseline. Interestingly, the LW–SW work difference was positively correlated with LV adverse remodelling (r = 0.42, P < 0.01) and LVSD (ΔLVEF (r = −0.61, p<0.01) and ΔLVGLS (r = −0.38, p=0.02). They also reported a good intra-observer and inter-observer interclass correlation coefficient (ICC) for LW–SW work difference was (0.95, 95% CI: 0.88–0.98) and (0.90, 95% CI: 0.79–0.97), respectively (Mao et al., 2023)

2.3.2.6 Strain measurements in cardiac resynchronisation therapy (CRT)

Galli et al used various echocardiographic measures to investigate the role of LA strain on LV function in 21 patients receiving CRT. This study focussed on LA strain as predictor of LV systolic and diastolic remodelling, defined by a reduction in LVESV and LVEDV at follow up. LA reservoir strain was found as an independent predictor of LV systolic and diastolic remodelling at 6-month follow up (r=−0.14, p=0.049 and r=−0.17, p=0.002, respectively) (Galli et al., 2022).

In contrast, Zweerink et al aimed to compare the predictive performance of various strain measurements obtained from different imaging techniques including cardiovascular magnetic resonance tagging (CMR-TAG), CMR feature tracking (CMR-FT), and speckle tracking echocardiography (STE) in predicting response to CRT. Twenty-seven patients were prospectively enrolled and underwent both CMR and echocardiographic examinations before CRT implantation, with strain analysis performed in circumferential (CMR-TAG, CMR-FT, and STE-circ) and longitudinal (STE-long) orientations. Regional strain values, measures of dyssynchrony, and disco-ordination were calculated. After 12 months, a positive CRT response was assessed by the reduction of 15% or more in LVESV. Of the 26 patients who completed follow-up, the mean LVESV change was −29±27%, with 17 patients (65%) exhibiting ≥15% LVESV reduction. While basic strain values for the septal and lateral walls demonstrated weak correlations with LVESV change, the end-systolic septal strain showed

strong predictive performance across all imaging techniques. Specifically, the end-systolic septal strain had high coefficients of determination (R^2) with LVESV change, with values of R^2=0.60 for CMR-TAG, R^2=0.50 for CMR-FT, and R^2=0.43 for both STE-circ and STE-long. Furthermore, in multivariable linear regression analysis, the end-systolic septal strain remained an independent predictor of CRT response after adjusting for QRS duration and QRS morphology. This suggests that the end-systolic septal strain provides additional predictive value beyond current guidelines. The study concluded that end-systolic septal strain is the only parameter showing a reliable association with reverse remodelling after CRT, regardless of the imaging technique used. This highlights its potential utility in clinical practice as a reliable measure for assessing CRT response (Zweerink et al., 2018).

2.3.2.7 Myocardial work measurements in cardiac resynchronisation therapy (CRT)

Duchene et al aimed to investigate the acute impact of CRT on regional MW distribution in the LV. A total of 130 HF patients scheduled for CRT implantation were enrolled in this prospective multicentre study. Regional MW were measured using non-invasive segmental stress-strain loop area calculations before and immediately after CRT. The findings revealed that CRT caused a significant redistribution of MW, with an increase in septal work and a decrease in lateral wall work (all $p<0.05$). Acute changes in work distribution between the septal and lateral walls correlated strongly with volumetric reverse remodelling assessed 11±2 months post-implantation ($r=0.62$, $p<0.0001$). In multivariate analysis, redistribution of work was the strongest predictor of reverse remodelling after CRT ($R^2=0.414$, $p<0.0001$). The study concluded that addressing the loading imbalance through CRT is crucial for optimising patient outcomes (Duchenne et al., 2020).

In a study investigating 97 patients, Galli et al found global constructive work (GCW) and the presence of septal flash to be predictor of a positive CRT response during multivariate analysis (OR 14.69, p= 0.005 and OR 8.05, p= 0.004, respectively), where CRT response was defined as a >15% reduction in LVESV at 6 months. They also performed inter and intra-observer

variability test and confirmed reproducibility of CW (0.92, 95% CI: 0.76-0.97, p< 0.0001 and 0.89, 95% CI: 0.68-0.96, p<0.0001, respectively) (Galli et al., 2018b).

Cvijic et al. examined the relationship between asynchronous myocardial activation, segmental LV wall thickness, and myocardial work in 26 patients with non-ischemic cardiomyopathy who responded to CRT (≥15% reduction in LVESV). Before CRT, the septal and anteroseptal segments had shorter times of onset of longitudinal shortening and were thinner than the lateral and posterior walls (p<0.001). After 14.5 months of CRT, septal thickness increased, and lateral walls thinned (p<0.001), while the time of onset remained unchanged (p=0.733). Initially, myocardial work was unevenly distributed, with lower work in the septal and anteroseptal regions compared to the lateral and posterior walls (p<0.001). After CRT, the myocardial work distribution became more homogeneous across all LV segments (p=0.215), reflecting improved mechanical synchronisation associated with the positive response to therapy. They also confirmed a good inter and intra-observer variability of segmental LV wall thickness (0.918 (0.881–0.944) and 0.825 (0.730–0.886), respectively) as well as for relative LV stress–strain loop area (0.930 (0.893– 0.954) and 0.874 (0.809-0.918, respectively) (Cvijic et al., 2018)

Kostyukevich et al. investigated the impact of LBBB, defined by Strauss and ESC 2013 criteria, on LV MW and response to CRT. A positive response to CRT was defined as a reduction in LVEDV by ≥15% at a 6-month follow-up. A total of 175 patients were included and divided into three groups: LBBB by Strauss criteria (group 1, n=109), LBBB by ESC 2013 criteria (group 2, n=22), and non-LBBB morphology (group 3, n=44). Patients in group 1, who had a higher probability of a positive CRT response, showed significantly greater wasted work (WW) at baseline (313.2±144.9 vs 215.1±102.5 vs 229.0±113.5 mmHg%, p<0.001) and reduced left ventricular myocardial work (MW) efficiency (67.6±9.9 vs 72.7±9.7 vs 75.4±9.6 mmHg%, p<0.001) compared to patients in group 2 and group 3, respectively (Kostyukevich et al., 2019).

2.3.2.8 Strain measurement in between His-CRT and Biventricular (BiV)-CRT

Højgaard et al compared several echocardiographic measurements to evaluate the effects of His-CRT (n=19) vs. BiV-CRT (n=31). The most important echocardiographic measurements they focused on was the time-to-peak strain in 12 midventricular and basal segments, as a marker of mechanical dyssynchrony, and GLS to assess longitudinal contractile function. Mechanical dyssynchrony (reduced from 120±45 ms to 63±22 ms, p<0.001 vs. 116±54 ms to 49±11 ms, p<0.001) and GLS (improved from −9.1±2.7 % to −10.7±2.6 %, p=0.02 vs. −8.6±2.1 % to −11.1±2.0%, p<0.001) improved significantly in both BiV-CRT and His-CRT groups from baseline to 6-month follow up, although no significant difference was seen between His-CRT and BiV-CRT groups for both mechanical dyssynchrony and GLS changes over time (mean difference −9.0 (95%CI: −36 to 18) ms, p=0.50 vs. −0.9 (95%CI:−2.4; −0.6) %, p=0.25, respectively). The authors summarised that His-CRT was non-inferior to conventional BiV-CRT (Højgaard et al., 2023).

2.4 Literature Review Discussion

This systematic review highlights the potential of advanced non-invasive echocardiographic measures in risk stratifying people receiving *de novo* pacing therapy. Quantifying LV systolic function is vital in predicting adverse outcomes to allow clinicians to initiate medical treatment and consider alternate interventions.

LV systolic function is commonly derived from a 2D echocardiographic measurement of LVEF; however, traditional measurements are frequently affected by poor fidelity due to factors such as image quality, endocardium tracing, and geometric assumptions (Robinson et al., 2020, Steeds et al., 2017). Obtaining these measurements from cardiac magnetic resonance (CMR) imaging is considered the gold standard, but often this is challenging due to accessibility, cost and contraindications (Saunderson et al., 2020). Comparatively, transthoracic

echocardiography is widely available, convenient and inexpensive, allowing a timelier assessment.

My review indicates that strain is the most commonly investigated advanced echocardiographic measure; however, there are considerable reporting discrepancies, regarding the level of assessment, whether global or regional. There are limitations from vendor-specific software differences, which can affect the tracking approach, and the default strain values reported (Voigt and Cvijic, 2019). These variations prevent the interchangeability of strain measurements across different vendors. Strain can also be influenced by loading conditions (Voigt and Cvijic, 2019). Addressing these limitations is crucial for standardising strain assessment in clinical practice. MW demonstrates potential superiority over strain measures with its ability to be adjusted for loading conditions, but the technique has limited evidence to date and has not yet been adopted into widespread use in clinical practice.

2.4.1 Longitudinal speckle tracking strain

All studies reported an association between regional or global longitudinal strain and response to device therapy (Chen et al., 2023b, Cvijic et al., 2018, Galli et al., 2018b, Galli et al., 2022, Højgaard et al., 2023, Kostyukevich et al., 2019, Mao et al., 2023, Mei et al., 2023, Xu et al., 2019, Zweerink et al., 2018, Duchenne et al., 2020). Speckle tracking strain has emerged as a key echocardiographic parameter in recent years as it indicates myocardial deformation rather than volumetric change as shown by the LVEF approach. In fact, GLS is potentially a more sensitive tool than LVEF for the early detection of myocardial functional response, as it has been shown effective in identifying people who are more likely to suffer a deterioration in LV systolic function following right ventricular (RV) pacing, even when they have a normal LVEF (Tracy et al., 2012).

Further prognostic information may be gained from also considering regional assessment rather than global measures. Zweerink et al investigated 27 patients and compared echocardiographic measures with gold standard CMR measurements, showing septal strain was the only parameter with a consistently good correlation to LV remodelling after CRT implantation. Further investigation of these hypotheses is required in larger studies to assess the efficacy of strain, particularly septal strain, in the early prediction of response to device therapy (Zweerink et al., 2018).

Interestingly, regional strain measures are still not commonly reported in clinical practice (D'hooge et al., 2000). One reason for this may be inter-vendor differences, which have been highly publicised. Whilst this has improved considerably with respect to GLS, there remains much greater variation across regional strain data (Shiino et al., 2017, Voigt and Cvijic, 2019), therefore, there continues to be potential for improvement. This is a particularly important consideration in serial assessment, where further standardisation may allow identification of progressive deterioration more readily.

2.4.2 Myocardial work

The potential effectiveness of MW measurements in the assessment of LV remodelling highlighted in this review are similar to those in an early extensive study of MW in animals, which reported measures of MW in comparison to detailed, multi-modality assessment of LV remodelling (Duchenne et al., 2019a). In the animal study, during RV pacing, regional MW was found to increase by +41% in lateral LV wall (from 661 ± 272 to 943 ± 374 mm Hg/%, $p= 0.005$) and decrease by -69% in septum (from 611 ± 146 to 190 ± 139 mm H g/%, $p < 0.0001$). The underlying pathophysiology may vary in humans, and due to the acute length of follow-up, pathophysiological changes over a longer period may differ from those observed, thus supplementary in-human research remains essential to apply MW analysis in a clinical setting.

My review of in-human research shows that MW allows for a regional assessment, highlighting differences in myocardial function between the septal and lateral walls, offering a focused analysis of the septal-to-lateral work difference (Mao et al., 2023, Cvijic et al., 2018, Duchenne et al., 2020). This regional perspective is particularly important in understanding the heterogeneity of LV function, which can be obscured in global measures alone. However, most of the research is focussed on patients with or receiving CRT, with limited studies on pacemaker patients. Of eleven studies reviewed, only one study focussed on pacemaker patients, although this did suggests similar measures, particularly septal and lateral region work differences, were likely important in risk stratification (Mao et al., 2023).

MW has the advantage of being adjusted to loading conditions, making it valuable tool in the evaluation of regional myocardial function (Russell et al., 2012, Russell et al., 2013). While this adjustment enhances the accuracy of MW assessment, it has not been extensively validated in specific populations, such as patients with atrial fibrillation (AF) (Liu et al., 2024) and aortic stenosis (AS) (Chan et al., 2018, Fortuni et al., 2021). Addressing these gaps is important for confirming the potential of MW in measuring LVSD.

2.4.3 Predictive value of advance echocardiographic measurements

The present review found that several studies evaluated whether advanced echocardiographic measures could be a predictor measures. For strain measures, Xu et al demonstrated GLS as the only predictor measures of adverse remodelling and Zweerink et al shows end-systolic septal strain as predictor of CRT response. Whilst Galli et al reported LA reservoir strain as an independent predictor of LV systolic and diastolic remodelling, it's a single study with a small number of participants and interdependence between LA and LV already well known. Therefore, it may not have predictive value in measuring LV remodelling.

On the other hand, MW measures, Duchenne et al demonstrated redistribution of work was the strongest predictor of reverse remodelling and Galli et al shows GCW and the presence of septal flash to be predictor of a positive CRT response. Perhaps, benefit may now be gained from assessing advanced echocardiographic measurements such as strain and MW prior to pacemaker implant to allow for tailored device prescription.

2.4.4 Advanced echocardiographic measurements in various cardiac diseases

While my primary focus is on advanced echocardiographic measurements in pacing populations, there is no dominant in specific population studied. Therefore, it is essential to consider their relevance in various cardiac diseases.

People who undergo cancer therapies, such as chemotherapy and radiation, may experience adverse effects on cardiac function, leading to cardiotoxicity (Plana et al., 2014, Tan et al., 1967). Some of the earliest studies on the clinical application of strain imaging were conducted in oncology populations to monitor changes in cardiac function both during and after the administration of potentially cardiotoxic cancer treatments (Lenzhofer et al., 1983, Ramos et al., 1976, Ewer et al., 1984). A systematic review of eight studies involving 452 cancer patients treated with anthracyclines and/or trastuzumab identified an early decline in GLS as the most reliable predictor of subsequent LVEF reduction or HF (Thavendiranathan et al., 2014). These findings, alongside advancements in speckle-tracking echocardiography (STE), have driven interest in strain imaging for cardio-oncology. The ASE/EACVI consensus now recommends GLS assessment before, during, and after cancer therapy (Plana et al., 2014, Mitchell et al., 2019). Despite its proven predictive value (Oikonomou et al., 2019, Liu et al., 2020), GLS adoption remains limited due to inter-vendor variability and patient-specific influences such as age, gender, and blood pressure (Yingchoncharoen et al., 2013). The use of negative systolic GLS values can also cause confusion, with some advocating for absolute values (Lang et al., 2015). Standardised vendor use is crucial for consistent longitudinal follow-up. Whilst myocardial work (MW) are vendor-specific measurements that offer an alternative, integrating

strain analysis with non-invasive blood pressure to provide a less dependent assessment of LV function. A study evaluating MW measures in 136 women with HER2+ breast cancer undergoing anthracycline and trastuzumab treatment found that while global work index (GWI) and global constructive work (GCW) helped diagnose concurrent myocardial dysfunction, they did not improve prognostic ability over GLS and clinical risk factors (Argulian and Narula, 2022). However, MW measures were particularly useful in a subset of patients with minor GLS reductions, but significant blood pressure drops. Additionally, normal GLS and GWI values during treatment strongly predicted the absence of cancer treatment related cardiac disease. These findings underscore the potential of MW measures in refining cardiac risk stratification, suggesting further research in high-risk populations and those with fluctuating blood pressure.

Left ventricular hypertrophy (LVH) characterised by LV thickening and commonly induced by hypertension, aortic stenosis or prolonged intense physical activity. While LVH can be a physiological response in athletes, in other cases it may indicate underlying cardiovascular issues, including coronary artery disease, arrhythmias, and HF. Identifying LVH early is crucial for managing these potential risks and improving long-term cardiac performance. A study aimed to determine whether strain rate imaging could differentiate between hypertensive LVH and strength-training athletic LVH (Saghir et al., 2007). A total of 108 participants (30 with hypertensive LVH, 30 with athletic LVH, and 48 controls) were compared using echocardiography, assessing strain and strain rate during systole and diastole. Results showed that athletes had no significant differences in strain or strain rate compared to controls, suggesting their LVH was benign. In contrast, individuals with hypertensive LVH had significantly reduced strain and strain rates (systolic and diastolic) compared to controls. The study concluded that strain rate imaging could be clinically useful in distinguishing physiologic LVH from hypertensive LVH. Whilst, hypertrophic cardiomyopathy (HCM) is the most common inherited heart condition, characterised by abnormal LV thickening. Unlike LVH, HCM caused by genetic mutations and can result in arrhythmias, HF, and sudden cardiac death. A study investigated myocardial work in patients with non-obstructive HCM using pressure-strain loops

and assessed its correlation with LV fibrosis by comparing 82 HCM patients with 20 healthy controls (Galli et al., 2019b). The results showed that GCW was significantly reduced in HCM patients (1599 ± 423 vs. 2248 ± 249 mm Hg%, $p<0.0001$), while no differences were found in wasted work (GWW) or LVEF between the groups. GCW was identified as the only predictor of LV fibrosis, with a cutoff value of 1623 mm Hg% showing good sensitivity (82%) and fair specificity (67%) for predicting myocardial fibrosis. The study concludes that reduced GCW in HCM, despite normal LVEF, is associated with LV fibrosis.

A systematic literature search identified 10 studies involving 1,385 patients evaluating the accuracy of GLS in diagnosing coronary artery disease (CAD) (Liou et al., 2016). The pooled sensitivity and specificity of abnormal GLS for detecting moderate to severe CAD were 74.4% and 72.1%, respectively. Mean GLS values for patients with CAD were reduced compared those without CAD (−16.5% vs. −19.7%, respectively). The study concludes that GLS is a valuable tool for detecting obstructive CAD in symptomatic patients and can complement existing diagnostic methods, serving as an early marker of cardiac ischemia. Whilst, a study aimed to evaluate whether global MW at rest, can predict significant CAD in patients with preserved LVEF and no regional wall motion abnormalities (Edwards et al., 2019b). A total of 115 patients referred for coronary angiography were assessed using echocardiography. The results showed that patients with significant CAD had significantly reduced global MW compared to those without CAD ($p<0.001$). GLS was reduced in patients with multivessel CAD but not in those with single-vessel CAD. Receiver operating characteristic analysis demonstrated that global MW was a stronger predictor of significant CAD than GLS compared to GLS (AUC 0.786 vs 0.693, respectively). The optimal cutoff for global MW to predict significant CAD was 1810 mmHg%, with 92% sensitivity and 51% specificity. The study concludes that global MW is a more sensitive index than GLS for detecting significant CAD in patients with normal LVEF and no regional wall motion abnormalities, suggesting it as a promising clinical tool for early CAD diagnosis.

Whilst a study investigated the prognostic value of preoperative GLS in patients with severe aortic stenosis (AS) undergoing aortic valve replacement. Among 125 patients with LVEF>40%, those with lower GLS had significantly higher rates of major adverse cardiac events and cardiovascular mortality over a 4-year follow-up. GLS remained an independent predictor of outcomes, outperforming traditional risk models. The findings highlight that reduced GLS, even with preserved ejection fraction, is a strong prognostic marker in AS and should be considered in preoperative risk assessment.

While strain and MW enhance cardiac risk stratification, their widespread adoption requires standardisation across imaging vendors and further validation in diverse populations. Future research should focus on integrating these advanced echocardiographic techniques into routine clinical workflows to optimise patient outcomes.

2.5 Limitations

Many studies included in this review had relatively small in sample sizes, and different studies utilised different manufacturer's software for echocardiographic analysis, which may introduce heterogeneity between studies (Bansal et al., 2008, Gayat et al., 2011). Whilst it is well documented that this can cause disparity across measurements, emphasis should still be placed on providing transparent reporting within research, hence it is important the authors specify their research practices and protocols. Most of the studies performed 2D echocardiography only. In fact, only three of ten studies used 3D measurement to assess predictors of LV remodelling, introducing an additional source of variation. Also, due to the relatively short length of follow-up ranging between 6 months and 48 months, clinical outcomes was not reported, with outcome variables was restricted to surrogate imaging measures. Further research is warranted to investigate the effectiveness of the novel measures on clinical outcomes.

2.6 Conclusion

Strain and MW clearly dominate the evidence base as novel echocardiographic measures for predicting response to cardiac device therapy, but also in multiple cardiac disease conditions, with the benefit of being able to provide regional and likely subclinical data on cardiac function. Whilst their full clinical adoption requires additional evidence, this review supports the hypothesis that there is a potential utilisation of advanced non-invasive echocardiography measures as an early LV remodelling risk stratification tool, prior to cardiac device implantation.

2.7 Dissemination of findings

This review is being prepared for publication in the *Echo Research Practice* journal.

2.8 Aims and Hypotheses

The current thesis expands on this literature review to answer to evaluate the potential of advanced echocardiography parameters in identifying patients at risk following RV pacing.

2.8.1 The relationship of cardiovascular comorbidities and right ventricular pacing requirement: a cohort study

Question: Who is at risk of left ventricular dyssynchrony, heart failure hospitalisation, and mortality in a population of patients receiving standard right ventricular pacing?

Aim: To identify patients who have a standard bradycardia pacemaker implanted and are at risk off adverse outcomes

Hypothesis: RV pacing is not the only significant factor in determining who is more likely to develop LV dyssynchrony and adverse clinical outcomes following the introduction of RV pacing.

2.8.2 Left ventricular mechanics in patients receiving right ventricular pacing: a retrospective analysis

Question: What are the key echocardiographic measures that can be used to assess left ventricular dyssynchrony in a standard bradycardia pacing population?

Aim: To retrospectively assess which echocardiographic measures are associated with left ventricular dyssynchrony in patients receiving new bradycardia pacemakers

Hypothesis: Key echocardiographic measures of LV mechanics are significantly associated with the development of left ventricular dyssynchrony in patients receiving RVP.

2.8.3 Predicting left ventricular systolic dyssynchrony and adverse remodelling using measures of left ventricular mechanics

Question: Can we predict pacemaker related left ventricular dyssynchrony?

Aim: To prospectively explore changes in advanced echocardiographic measurement following pacemaker implantation and to evaluate echocardiographic predicters of left ventricular dyssynchrony prior to pacemaker implant.

Hypothesis: Echocardiographic measures of LV mechanics pre-implantation predict the development of pacemaker-related LV dyssynchrony and adverse remodelling after 6-month post device in patient who received device for AVB.

2.8.4 The effects of novel conduction system pacing compared to traditional right ventricular pacing on left ventricular mechanics

Question: Can conduction system pacing protect patients at risk of LV dyssynchrony?

Aim: To compare changes in advanced echocardiographic measurements over time in patients receiving CSP compared to an age and sex-matched cohort of patients receiving RVP.

Hypothesis: CSP results in less LV dyssynchrony and improved LV mechanics at 6-month post device implantation compared to traditional RVP in patient who received device for AVB.

Chapter 3 Methodology

My investigation was designed to assess endpoints of patient-orientated clinical outcomes, and surrogate clinical endpoints including echocardiographic measurements and pacing measurements. In this chapter, the methodology for each investigation performed, and a discussion of each chosen endpoint, is outlined.

3.1 Transthoracic echocardiography

Transthoracic echocardiography (TTE) is a widely utilised imaging modality in cardiovascular medicine, known for its versatility and broad application (Steeds et al., 2017, Matulevicius et al., 2013). Unlike cardiovascular magnetic resonance imaging (MRI), which is the gold standard for evaluating cardiac structure and function but is not universally approved for all legacy pacemaker devices and may not be well-tolerated by all patients (Artis et al., 2008, Ferreira et al., 2014, Wilkoff et al., 2011), TTE offers a valuable alternative.

TTE is widely available in hospitals across the UK and is characterised by its lack of contraindications, real-time imaging capability, and relatively low cost (Artis et al., 2008). This technique employs ultrasound imaging methods, including two-dimensional and three-dimensional imaging, colour flow Doppler, continuous and pulsed wave Doppler, tissue Doppler imaging (TDI), and myocardial deformation imaging (strain and strain rate), as well as contrast imaging. It is particularly effective for assessing cardiac functional and structural aspects, especially in patients with heart failure (HF), where it commonly focuses on LV size and systolic function (Ponikowski et al., 2016, Lang et al., 2015).

Overall, TTE's comprehensive imaging capabilities and accessibility make it a crucial tool in the evaluation and management of cardiovascular conditions.

3.1.1 Test overview

During a resting TTE, the patient lies in the left lateral decubitus position (Ottenhoff et al., 2022) while a transducer is positioned on numerous relatively standardised areas of their chest. This transducer emits ultrasound waves that travel through the chest. When these waves encounter different structures, they are reflected as "echoes." The transducer then detects these echoes and converts the reflected mechanical energy into electrical signals. These signals are processed by software to create either still or moving images of the heart (Abbas and Bassam, 2009, Hunt et al., 1983, Szabo, 2013).

3.1.2 Standardised TTE assessment

All participants underwent a two-dimensional transthoracic echocardiographic assessment including grey-scale and tissue Doppler images. Images were obtained using a GE Vivid E95 ultrasound machine (GE Vingmed Ultrasound AS, Horten, Norway) and stored anonymously offline on the EchoPAC version 206 (GE Vingmed) for analysis.

3.1.3 Measuring left ventricular volumes

LV volumes can be measured using two- or three-dimensional echocardiography. Traditional techniques involve tracing the internal border between the LV cavity and the myocardium. LV length is defined as the distance from the LV apex to the midpoint of a line across the mitral annulus. For accurate LV volume measurements, the apical four- and two-chamber views are recommended (Wharton et al., 2015b).

Whilst two-dimensional echocardiography uses the modified biplane Simpson method to assess LV volumes from these views, it may still miss geometric variations in the LV walls (Schiller et al., 1979, Otterstad, 2002). Three-dimensional echocardiography addresses these limitations by providing a more comprehensive and reproducible assessment (Lang et al.,

2006). When feasible, three-dimensional volumes are acquired over a single cardiac cycle, improving accuracy.

These volumetric measures are crucial for calculating the left ventricular end-systolic volume indexed to body surface area (LVESVi), which serves as a robust marker of LV remodelling and a predictor of HFH (Curtis et al., 2013). A change in LVESVi greater than 15% is often considered clinically significant as it has been repeatedly related to clinical outcomes in trials (Isomura et al., 2011, Curtis et al., 2013). Therefore, this study uses an increase of 15% or more in LVESVi as a key outcome to assess significant decline in LV systolic size.

3.1.4 Measuring left ventricular function

3.1.4.1 Ejection fraction

Ejection fraction (EF) is a crucial measure of LV function. It is calculated using modified Simpson's rule, which involves tracing the endocardial border while excluding the papillary muscles (Lang et al., 2015). This measurement is typically obtained from apical four-chamber and two-chamber views.

The reference ranges for normal EF can vary, with some sources suggesting a range of 55.5-73.9% (Kou et al., 2014). However, an LVEF below 50% is commonly used to distinguish between HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) (Hogg et al., 2004, Owan et al., 2006).

A reduction in LVEF of 10% or more has been associated with a 39% increase in all-cause mortality, with a hazard ratio of 1.39 (95% CI 1.32-1.46) for every 10% reduction below 45% (Solomon et al., 2005). In my studies, a decrease in LVEF of 10% or more is used as a key outcome measure, reflecting a significant decline in LV function.

Although EF remains a standard of LV function assessment, it has several limitations that make it an incomplete marker of myocardial performance. EF is load-dependent, meaning it can remain within normal ranges even when intrinsic myocardial contractility is impaired, as seen in conditions like HFpEF, early-stage cardiomyopathy, and IHD. Additionally, EF reflects global volumetric changes rather than intrinsic myocardial deformation, making it less sensitive to subclinical dysfunction.

3.1.4.2 Strain

Strain imaging provides a sensitive assessment of LV function by quantifying myocardial deformation, reflecting intrinsic myocardial contractility beyond conventional volumetric measures. It is most commonly assessed using speckle-tracking echocardiography, which tracks natural acoustic markers (speckles) within the myocardium throughout the cardiac cycle to compute strain values in multiple dimensions: longitudinal, circumferential, and radial (Mada et al., 2014). Strain refers to the percentage change in myocardial length such as longitudinal shortening from base to apex, circumferential narrowing, and radial thickening reflecting how much the heart muscle deforms. Strain rate, on the other hand, measures how quickly this deformation occurs over time, offering insight into the speed of myocardial contraction and relaxation. (Johnson et al., 2019). A comprehensive understanding of myocardial contraction mechanics is crucial for interpreting strain measurements accurately. (Johnson et al., 2019).

During each cardiac cycle, these strain components exhibit distinct temporal patterns that reflect the underlying fibre orientation and mechanical demands of each phase that optimise blood ejection and ventricular filling. This process is governed by myocardial fibre orientation and deformation patterns, including longitudinal, circumferential, and radial strain, as well as LV twist mechanics.

At the onset of systole, the LV enters the isovolumetric contraction phase, where pressure rises rapidly while both the mitral and aortic valves remain closed. During this phase,

longitudinal shortening (global longitudinal strain, GLS) begins as the subendocardial fibres contract, pulling the base of the heart toward the apex. Simultaneously, the apex rotates counterclockwise, and the base rotates clockwise, generating LV twist, which enhances the efficiency of ejection. Once LV pressure exceeds aortic pressure, the aortic valve opens, initiating the ejection phase. Peak circumferential strain occurs as the mid-wall myocardial fibres contract, reducing the LV's short-axis diameter, while radial strain reaches its maximum as the myocardium thickens. The LV twist also peaks at end-systole, maximising contractile force and ensuring optimal stroke volume output.

Following ejection, the LV transitions into diastole, beginning with isovolumetric relaxation, where pressure drops while volume remains unchanged. During this phase, the stored energy from systolic twist is rapidly released, leading to untwisting, which reduces ventricular pressure and facilitates diastolic suction. This contributes to early rapid filling, where blood enters the LV as the mitral valve opens. The majority of LV filling occurs during this phase, aided by continued longitudinal strain recovery and myocardial relaxation. As ventricular pressure equalises with the left atrium, filling slows during diastasis, before a final contribution occurs from atrial contraction, completing the cycle and preparing the LV for the next cardiac cycle.

Among these deformation patterns, global longitudinal strain (GLS) is the most clinically relevant because it primarily reflects subendocardial function, which is the first to be affected in conditions such as ischemia, hypertrophy, and HF. Additionally, many studies showed that GLS were important compared to radial and circumferential strain (Zhang et al., 2019a, Diao et al., 2017, Abou et al., 2020)

GLS measuring the percentage change in LV length from its relaxed to contracted state, thereby providing insights into LV function and myocardial contractility (Voigt et al., 2000). GLS measurements are highly reproducible and offer valuable prognostic information (Klaeboe and Edvardsen, 2019, Potter and Marwick, 2018). They are determined by averaging

the strain measurements from eighteen LV segments, derived from standard apical views; four-chamber, two-chamber, and long-axis views at a frame rate of at least 60 frames per second. In this study, GLS measurements were standardised using EchoPAC version 206 (GE Vingmed).

GLS is not yet as widely used clinically as LVEF, yet it is emerging as a robust indicator of LV function with potentially superior predictive value, especially in acute HF scenarios (Kalam et al., 2014, Park et al., 2018, Yingchoncharoen et al., 2013). Regional function can also be assessed using speckle-tracking analysis, which measures parameters such as strain and strain rate. These measures are less affected by the orientation of cardiac motion relative to the transducer (Heimdal et al., 1998, Leitman et al., 2004). However, regional strain measurements can vary based on the myocardial region, methodology, and equipment used (Heimdal et al., 1998, D'hooge et al., 2000, Smiseth et al., 2015, Amzulescu et al., 2019). Evaluating both the magnitude of strain and changes in deformation over time provides crucial insights into regional LV function and can help identify issues such as ischemia or scarring (Voigt et al., 2003, Smiseth et al., 2015). The value of these measures continues to be explored, but they offer significant information about the heart's regional function.

The accuracy of GLS measurements can be influenced by several factors, including image quality, frame rate, the software algorithm used for analysis. To mitigate these limitations, several strategies can be employed. Firstly, ensuring high-quality, artifact-free images with appropriate resolution and contrast enhances the precision of strain measurements (Johnson et al., 2019, Voigt et al., 2014, Popescu et al., 2009). Secondly, utilising imaging modalities with higher frame rates is essential for capturing rapid myocardial movements, thereby improving the reliability of strain analysis (Johnson et al., 2019, Popescu et al., 2009). Thirdly, implementing consistent imaging protocols, including standardised views and patient positioning, reduces variability and enhances the reproducibility of strain measurements (Johnson et al., 2019, Popescu et al., 2009). Fourthly, employing validated software algorithms

for strain assessment ensures reliable and accurate measurements, minimising potential errors associated with unverified tools (Johnson et al., 2019, Tseng et al., 2022). Fifthly, establishing rigorous quality control protocols, such as regular calibration of imaging equipment and comprehensive training for personnel, helps identify and correct potential sources of error in strain measurements (Johnson et al., 2019, Popescu et al., 2009). Lastly, incorporating artificial intelligence and machine learning techniques can enhance the precision of strain measurements by automating detection and reducing human error, leading to more accurate and efficient assessments (Alsharqi et al., 2018, Tseng et al., 2022). By integrating these strategies, the reliability and accuracy of myocardial strain measurements can be significantly improved, leading to more precise assessments of cardiac function.

However, the key limitation of GLS is its dependency on loading conditions of patients' haemodynamic, meaning that variations in preload and afterload can influence GLS measurements, potentially masking underlying myocardial dysfunction.

3.1.4.3 Advanced echocardiography measurement: myocardial work

In recent years, myocardial work (MW) has emerged as a valuable tool for assessing myocardial function, offering a comprehensive evaluation of cardiac performance beyond traditional measures (Duchenne et al., 2019c, Duchenne et al., 2019a). Unlike conventional parameters such as LVEF and GLS, MW incorporates both the mechanical energy generated by the heart and the loading conditions during contraction, providing a nuanced view of cardiac efficiency (A'roch et al., 2012, Donal et al., 2009, Burns et al., 2010).

The methodology for calculating myocardial work involves creating a pressure-strain loop (PSL), which is constructed by combining estimated LV pressure curves with strain data obtained through speckle-tracking echocardiography (Russell et al., 2012, Moya et al., 2023) (Moya et al., 2023). This loop provides detailed insight into the heart's contraction and relaxation phases, with the pressure data being non-invasively estimated from brachial artery

cuff measurements and the strain data derived from GLS measurements. This methods has shown promising results in experimental studies (Duchenne et al., 2019a, Cvijic et al., 2018, Boe et al., 2015, Russell et al., 2013, Russell et al., 2012), to which non-invasive measurements correlating well with invasive measurements, thus supporting its use as an index of myocardial function.

Recent advancements have enabled the non-invasive calculation of MW through commercially available echocardiographic software, which estimates LV pressure from brachial artery cuff measurements and adjusts for the isovolumic and ejection phases, defined by valve timings such as the opening and closure of the aortic and mitral valves (Moya et al., 2023). The software utilised the input data to calculate the MW components which it generates the bull's eye of the global work index (GWI) and global work efficiency (GWE), offering a detailed assessment of LV mechanics **(Figure 3.1)**.

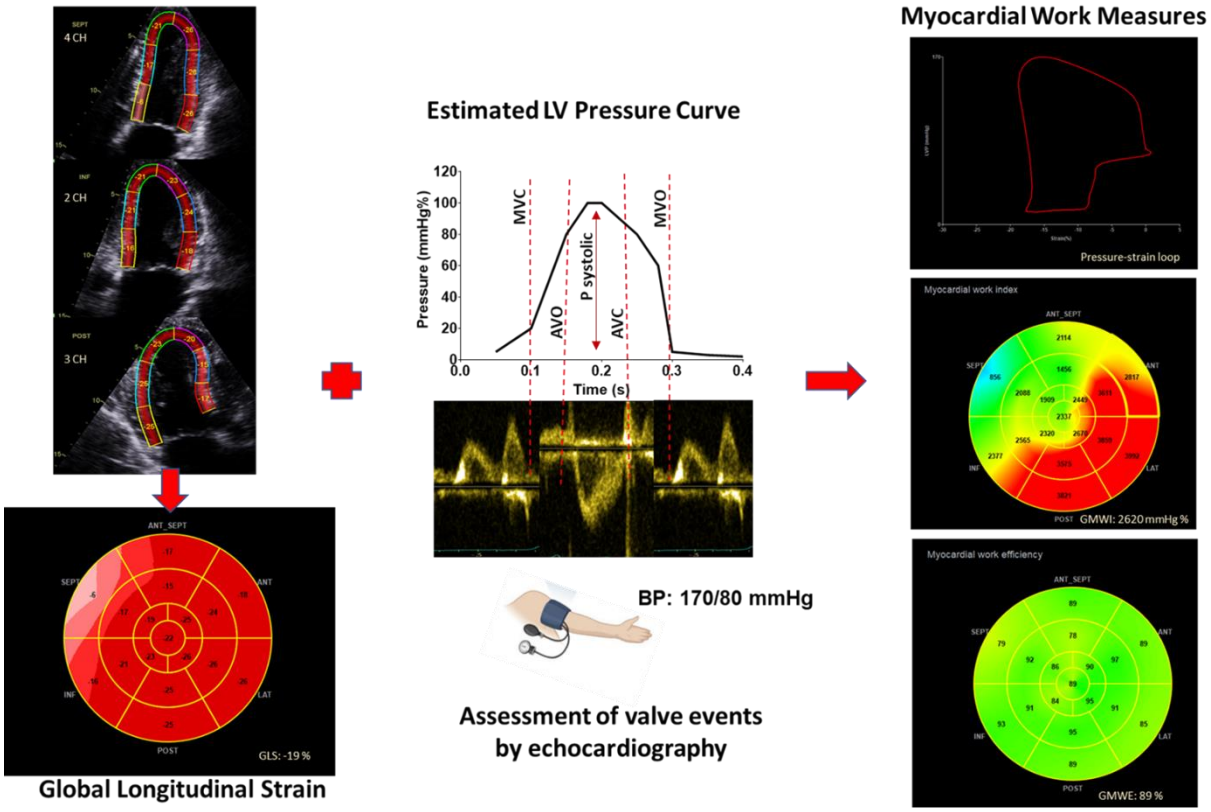


Figure 3.1 Advanced echocardiography - myocardial work measurements

GWI represents the area of the PSL from the time of mitral valve closure (MVC) to mitral valve opening (MVO), which corresponds to mechanical systole, including isovolumic contraction. Whilst GWE is calculated as the ratio of global constructive work (GCW) to the sum of GCW and global wasted work (GWW), expressed as a percentage (Papadopoulos et al., 2021). This provides a measure of how efficiently the LV is functioning in relation to the energy expended during the cardiac cycle (Papadopoulos et al., 2021). GCW is defined as the work performed during systolic shortening, plus the negative work that occurs during lengthening in isovolumic relaxation (Papadopoulos et al., 2021). This work contributes to the effective ejection of blood from the LV. In contrast, GWW is the negative work performed during myocardial lengthening in systole, plus the work performed during shortening in isovolumic relaxation. This work does not contribute to the ejection of blood (Table 3-1).

Table 3-1 Myocardial work components descriptions (Papadopoulos et al., 2021)

Measures	Descriptions
Global work index (GWI)	Total work; the PSL area calculated from mitral valve closure to mitral valve opening
Global constructive work (GCW)	Total work contributing to pump function; shortening of the myocytes during systole and lengthening during isovolumic relaxation
Global wasted work (GWW)	Work that does not contribute to ejection; elongation of myocytes during systole and shortening against a closed AV
Global work efficiency (GWE)	Fraction of GCW to GCW + GWW

GWI; Global myocardial index, GCW; Global constructive work, GWW; Global wasted work, GWE; Global work efficiency, PSL; pressure strain loop, AV; atrioventricular

As MW is a relatively recent innovation, the establishment of normal reference values is essential for interpreting the results. The NORRE study was one of the first large-scale studies to determine the normal reference values for MW components based on age and sex (Manganaro et al., 2019). This study included 226 healthy middle-aged subjects and

established normative ranges for the various MW indices. Other studies, such as the STAAB cohort and Galli et al., have further refined the understanding of MW components across different age groups and genders (Galli et al., 2019a, Morbach et al., 2020). These studies demonstrated that MW indices are generally stable until the age of 45, with differences in GWI between men and women, and a slight increase in GWI, GCW, and GWW with age. These normal reference values are widely used in clinical practice to assess LV function in healthy individuals and those with heart disease.

	Total Mean ± SD or Median (IQR)	**Total Mean ± SD or Median (IQR)**	**Total Mean ± SD or Median (IQR)**	**Total Mean ± SD or Median (IQR)**
Measures	GWI (mmHg%)	GCW (mmHg%)	GWW (mmHg%)	GWE (mmHg%)
NORRE study (Manganaro et al., 2019)	1896 ± 308	2232 ± 331	78.5 (53–122.2)	96 (94–97)
STAAB cohort (Morbach et al., 2020)	2209 ± 307	2430 ± 351	74 (54–101)	96 (95–97)
Galli et al.(Galli et al., 2019a)	1926 ± 247	2224 ± 229	90 (61–123)	96 (94–97)

GWI; Global myocardial index, GCW; Global constructive work, GWW; Global wasted work, GWE; Global work efficiency, SD; standard deviation, IQR; Interquartile range

Despite some limitations in pressure estimation accuracy under certain conditions whereby afterload cannot be effectively accounted for, such as severe aortic stenosis, (Chan et al., 2018, Fortuni et al., 2021), the method provides valuable insights into cardiac function by helping to detect subtle changes in myocardial function that may not be evident with conventional methods like LVEF or GLS alone. Additionally, a key advantage of MW technique is its integration of blood pressure data using a non-invasive method (brachial cuff), which makes it practical and easy to use in daily echocardiographic practice.

3.2 Pacemaker interrogation

3.2.1 Introduction

Following discharge from the hospital, patients with pacemakers should undergo their first face to face follow-up within four to six weeks, with subsequent check-ups scheduled every six or 12 months (BHRS, 2022). The follow-up process involves a comprehensive protocol for communication and support between the cardiac physiologist and the consulting cardiologist. For device interrogation, standard follow-up appointments for pacemakers typically last 20–30 minutes. During a pacemaker check, a trained physiologist performs a thorough assessment of the device and lead functionality. This process may include remote follow-up options to enhance convenience and monitoring efficiency. During each visit, routine device assessments should be conducted alongside an evaluation of the diagnostic data provided by the device and the patient's symptoms (Whellan et al., 2010, van Eck et al., 2008). A visual evaluation of the pacemaker site is advised to identify indications of infection or erosion (Ellenbogen et al., 2011).

3.2.2 Test overview

A pacemaker check is an essential procedure to verify the device's functionality and optimise its settings according to the patient's needs (Burri et al., 2023, Foley et al., 2024). During the check, the patient typically sits or reclines comfortably on an examination table in a quiet environment, which helps ensure accurate readings and effective communication with the healthcare provider. A specialised programmer or analyser device is used to interface with the pacemaker, either wirelessly or through a direct connection, to retrieve detailed data and make necessary adjustments. Additionally, an electrocardiogram (ECG) is often employed to provide real-time information on the heart's electrical activity, which aids in assessing the pacemaker's performance and identifying any abnormalities. The programmer, equipped with advanced diagnostic tools and software tailored to the specific pacemaker model, facilitates a comprehensive evaluation and optimisation of the device's settings.

3.2.3 Functional pacemaker measures

All participants underwent a comprehensive pacemaker check, whereby a competent clinical cardiac physiologist assessed the pacing percentage to determine how often the device was actively pacing compared to sensing. This provided insight into the overall function and any potential issues with the heart's natural rhythm. Lead impedances were evaluated, with standard values typically ranging from 400 to 1,200 ohms (Mulpuru et al., 2017). Sensing thresholds were checked to ensure that the device was accurately sensing the heart's intrinsic signals, with normal values greater than 1.5mV for atrial leads and greater than 5.0mV for ventricular leads (Mulpuru et al., 2017). Pacing thresholds were measured to ensure that the device uses minimal energy for stimulation, with a typical acceptable threshold is under 1.5V with a pulse width of 0.5ms at implant for both atrial and ventricular pacing (Mulpuru et al., 2017). Battery longevity was assessed to predict when replacement may be needed, usually between 5 and 10 years. Output settings, including pulse amplitude and width, were reviewed and adjusted as necessary to optimise performance. The base rate, typically set at 50 beats per minute, is fine-tuned along with sleep, rest, and hysteresis rates, which may be adjusted down to 40bpm, based on previous research (Paton et al., 2021). The upper tracking rate (UTR) was calibrated based on the patient's age, activity levels, and comorbid conditions to ensure effective pacing. Abnormal rhythms or device-related issues, including non-sustained ventricular tachycardia (NSVT), atrial fibrillation (AF), atrial tachycardia, and premature ventricular contractions (PVCs), were carefully observed and evaluated. This assessment ensures that the pacemaker's settings were precisely adjusted to address the patient's clinical needs, thereby enhancing the device's reliability and effectiveness.

3.2.4 Measuring right ventricular pacing requirement

Assessing the right ventricular (RV) pacing requirement is a critical component of pacemaker management, aimed at optimising cardiac function and enhancing device performance. To minimise unnecessary RV pacing, it is essential to evaluate and adjust the device's

programming settings based on individual patient needs. This involves selecting the most appropriate pacing mode and utilising algorithms designed to reduce RV pacing, such as AV search or extended AV delays. Regular monitoring of the ventricular pacing burden, intrinsic rhythm, and the impact of programming adjustments on left ventricular (LV) systolic function, provides valuable insights (Paton et al., 2019).

3.3 Medical History

A detailed assessment of comorbidities was undertaken for all participants. Ischemic Heart Disease (IHD) was clinically documented as a critical factor, often resulting from reduced blood flow to the heart muscle due to coronary artery disease, which can lead to structural and functional changes in the LV (Bonow et al., 2011). Participants with a history of myocardial infarction (MI), had undergone percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) were evaluated for their impact on cardiac function, given that these interventions can also imply a potential degree of LVSD (Massoudy et al., 2009). Additionally, the presence of cerebrovascular accident (CVA), commonly known as a stroke, was considered due to its association with systemic vascular issues that might impact HF and LV function (Members et al., 2012). Diabetes mellitus (DM) was another important comorbidity, as this metabolic disorder can exacerbate cardiovascular complications and contribute to changes in LV structure and function (Poulsen et al., 2010). Hypertension, or high blood pressure, was documented as it can lead to increased cardiac workload and alterations in LV geometry (Schillaci et al., 2002). Lastly, atrial fibrillation (AF) was assessed for its role in irregular heart rhythms, which can affect cardiac output and contribute to the progression of HF and LV remodelling (McMurray et al., 2013). Each of these conditions was carefully recorded, given their potential to influence LV remodelling and the overall progression of HF, thus providing valuable context for the study outcomes.

3.4 Blood pressure – estimated LV pressure

Non-invasive blood pressure was measured using an automatic sphygmomanometer, with patient lying on left side according to oscillometry technique which records blood pressure electronically and provides both systolic and diastolic readings (Ogedegbe and Pickering, 2010). Systolic pressure is indicated at the point of the first detection of blood flow, while diastolic pressure is recorded when the blood flow returns to normal. This non-invasive method of measuring blood pressure has been shown to accurately estimate LV pressure, as supported by recent studies in animal models and novel research (Russell et al., 2012, Duchenne et al., 2019a).

3.5 Blood sampling

A competent healthcare professional conducted venepuncture on a peripheral vein. These samples were subsequently analysed at the clinical pathology laboratories of Leeds Teaching Hospitals Trust, following departmental protocols. Where specified,, a N-terminal pro–B-type natriuretic peptide (NT-proBNP) test was conducted to assess HF biomarkers (Zile et al., 2016). NT-proBNP is an active peptide (protein) that's released by the heart in response to increased pressure and volume overload. Elevated levels of NT-proBNP in the blood are indicative of HF, as the peptide helps in diagnosing and monitoring the severity of the condition, NT-proBNP levels below 400 pg/ml are less likely to indicate HF, while levels above 400 pg/ml are elevated and indicate a possibility of HF (NICE, 2024). Full blood count, urea and electrolytes test were part of the standard care assessment and were recorded.

3.6 Data analysis

The IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp, Armonk, NY, USA, 2020) was used to conduct all statistical analysis. The Shapiro-Wilk test was performed to determine whether parameters were normally distributed. Continuous variables that were normally

`distributed were reported as the mean and standard deviation (SD) within and between groups, whilst non-normally distributed were reported as median and interquartile range (IQR). Frequencies and percentages were used to describe categorical data.

Univariable Cox regression analysis was performed to determine associations between independent variables and time to clinical outcomes. Clinically relevant variables and significant variables were included in a subsequent multivariable Cox regression model. Where statistical modelling was appropriate, linear regression was performed if the outcome variable is continuous, or logistic regression if the outcome is dichotomous.

Sample size was calculated to power according to the precision and variance of measurements from known pilot data or following rule of thumb for sample sizes where appropriate and was described within each chapter methods and subsequently. Changes over time in continuous variables were analysed using repeated measures ANOVA and adjusted for repeated analysis using Bonferroni correction. A p-value of less than 0.05 was considered statistically significant.

The Interclass Correlation Coefficient (ICC) and Bland-Altman plots were used to characterise and illustrate the inter- and intra-observer reproducibility of echocardiographic parameters between two blinded echocardiographic readers. Based on the 95% confident interval of the ICC estimate, values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively. (Koo and Li, 2016). Consistent with previous research (Oxborough et al., 2012, Vassallo et al., 1986) an ICC larger than 0.60 was deemed to be acceptable.

Chapter 4 The relationship of cardiovascular comorbidities and right ventricular pacing requirement: a cohort study

4.1 Abstract

Introduction

Despite the reported risk of left ventricular (LV) systolic dysfunction (LVSD) and subsequent heart failure (HF), right ventricular apical (RVA) pacing remains the most common method of treating bradycardia. Whilst alternative ventricular pacing sites have been proposed, whether they provide reliable and safe long-term rate support, reduce HF events, and in which patients they should be applied, remains unproven.

Aim

The aim of this investigation was to evaluate the prevalence of LVSD, and to assess the patient-oriented clinical composite outcome of HF requiring hospitalisation (HFH) and death in patients undergoing pacemaker therapy for bradycardia, specifically in those receiving RVA pacing. A key focus was identifying the group at risk in those receiving a de novo pacemaker (new implant - NI), and those undergoing a pacemaker generator replacement (PGR), two important opportunities for intervention.

Method

Prospective data were obtained from 514 consecutive patients who underwent NI between 2014 and 2017, and 510 patients requiring PGR between 2008 and 2011 at Leeds Teaching Hospitals – Leeds General Infirmary, a single tertiary centre in the United Kingdom. All patients were indicated for device therapy according to international guidelines. Logistic regression analysis was used to investigate risk factors associated with prevalent LVSD, defined as an LV ejection fraction (LVEF) of <50%. Patients were followed with a view to determining

predictors of time free from composite outcome of HFH and all-cause of death which were assessed in Cox proportional hazards models.

Results

Of the 1024 patients in the cohort, 344 (37%) patients had prevalent LVSD (LVEF <50%). The rate of LVSD in those receiving a NI was higher than in those receiving a PGR (20% vs 17% respectively, p<0.01). A history of ischaemic heart disease (IHD) (OR=2.56, CI:1.58, 4.13, p<0.01) and a ventricular pacing burden (VPB) greater than 80% (OR=2.13, CI:1.29, 3.52, p<0.01) were identified as important clinical features associated with the presence of LVSD in adjusted regression model. After a median follow-up of 30 months (Interquartile Range (IQR):16-42), 341 (33%) patients had been hospitalised for HF or died, of whom 79 (8%) were NI patients, and 262 (25%) were PGR patients (p<0.01). Being in the PGR group (Hazard Ratio (HR)=0.09, CI:0.01, 0.62, p=0.02), age (HR=2.19, CI:1.19, 4.05, p=0.01), the presence of atrial fibrillation (AF) (HR=2.26, CI:1.37, 3.72, p= 0.01) and having an LVEF less than 50% (HR=1.77, CI:1.30,3.03, p=0.04) were independently associated with clinical outcomes in a multivariate survival model.

Conclusion

This study shows that managing pacemaker patients is complex due to the high prevalence of LVSD and multiple comorbidities. A target population in which to screen for prevalent LVSD and subsequently deliver therapeutic strategies for prevention of heart failure events could be those with a high pacing requirement, IHD, and multiple additional cardiovascular comorbidities.

Keywords

Heart Failure, Pacemaker, Mortality, Left ventricular systolic dysfunction

4.2 Introduction

Pacemaker therapy is the only long-term treatment for bradycardia and is proven to extend longevity and improve quality of life (Lamas et al., 1998). Right ventricle (RV) pacing (RVP) support is a common intervention with approximately 400,000 people in European Society of Cardiology (ESC) countries undergoing pacemaker implantation each year (Timmis et al., 2020). The RV apical (RVA) position for the ventricular lead has been standard of care for half a century and has proven itself to be safe and reliable (Furman and Schwedel, 1959, Members et al., 2008). However, standard RVP can cause a dyssnchronous LV contraction pattern and has been associated with adverse left ventricular (LV) remodelling (Lee et al., 1994, Begg et al., 2011a).

Recent catheter and lead developments offering stimulation of the conduction system in an attempt to reduce pacemaker-related electrical and mechanical dyssynchrony, have provided the opportunity for alternate lead positions in the hope of reducing the incidence of LV systolic dysfunction (LVSD) and heart failure (HF) events in this population. However, conduction system pacing (CSP) comes with new challenges. His bundle pacing (HBP) for example is associated with longer implant times, higher complication rates, has lower long-term pacing stability, poorer sensing and higher thresholds such that a back-up apical lead is recommended potentially compromising device longevity (Vijayaraman et al., 2018b, Bhatt et al., 2018, Burri et al., 2023). On the other hand, whilst left bundle branch area pacing (LBBAP) does not suffer the lead displacement rates of HBP, there remain challenges with position and risk of septal perforation (Burri et al., 2023). Short-term follow-up data suggest that HBP and LBBAP may result in fewer HF clinical outcomes than RVA pacing, although there is limited long-term evidence (Keene et al., 2023, Padala and Ellenbogen, 2020, Lin et al., 2020, Vijayaraman et al., 2018a).

Given the extra time and risks required to implant either CSP approach, further definition of patient subgroups at risk of RVP-associated LVSD and HF events is crucial to allow a degree of personalisation of the pacing strategy, but also to identify potential trial cohorts for assessing the clinical efficacy of these approaches.

Therefore, this study aimed to evaluate the prevalence of LVSD, and to assess the value of patient-oriented clinical characteristics as predictors of LVSD, and a composite clinical outcome of HF requiring hospitalisation (HFH) and all-cause of death, in patients undergoing pacemaker therapy for bradycardia. Patients were investigated if receiving RVA at the time of their new pacemaker implant (NI) and those who required pacemaker generator replacement (PGR).

4.3 Methods

4.3.1 Study population

The present analysis utilises two pre-existing prospectively collected research dataset in patients who underwent either a NI between 2014 and 2017 or a PGR between 2008 and 2011 in Leeds Teaching Hospitals – Leeds General Infirmary, a single tertiary centre in the United Kingdom. In both groups, patients were eligible for inclusion if they were aged ≥18 years, capable of providing informed written consent, and had, or were receiving an implantable pacemaker for bradycardia for any guideline indication (NICE, 2005). Exclusion criteria were only cognitive impairment limiting consent and the plan to receive an implantable cardioverter defibrillator (ICD), or cardiac resynchronisation therapy (CRT) device. Ethical approval was obtained for both cohorts prior to any patient-related activities (12/YH/0487 and 08/H1307/12, respectively), and all participants provided informed written consent. All research activities adhered to the principles outlined in the Declaration of Helsinki. Due to the observational nature of the study, we employed a convenience sampling strategy, selecting participants from these available cohorts, all of which had previously obtained ethical approval.

Ethical approval was obtained for both cohorts in advance of any patient-related activity (12/YH/0487 and 08/H1307/12 respectively), and all patients provided informed written consent. All research activity complied with the principles of the Declaration of Helsinki.

4.3.2 Data collection

As described in **Figure 4.1**, at the 6-week baseline assessment post NI or PGR, patients provided informed written consent. Demographic and clinical data including age, sex, vital signs, height, weight, comorbidities, medical history, current medical therapy, and blood chemistry were collected. Echocardiography was conducted according to the European Association and British Society of Echocardiography's minimum dataset guidelines which included assessments of left ventricular (LV) function, LV diameter, and left atrial (LA) diameter (Evangelista et al., 2008, Wharton et al., 2015a).

At the follow-up assessment, conducted at least 12 months post NI or PGR, the same echocardiographic protocol was followed, along with a device interrogation. Data from the echocardiography and pacing measurements including programmed pacemaker mode, base rate, and cumulative pacing percentages were recorded**.**

To account for the impact of varying pacing status on LVEF measurements, patients were stratified based on their ventricular pacing burden (VPB) at the time of assessment. VPB was categorised into three groups: <20%, 40-80%, and >80% VPB. This stratification allowed for an analysis of the effect of different pacing burdens on LVEF changes while minimising the confounding influence of intrinsic conduction.

Figure 4.1 Study flowchart of methodology

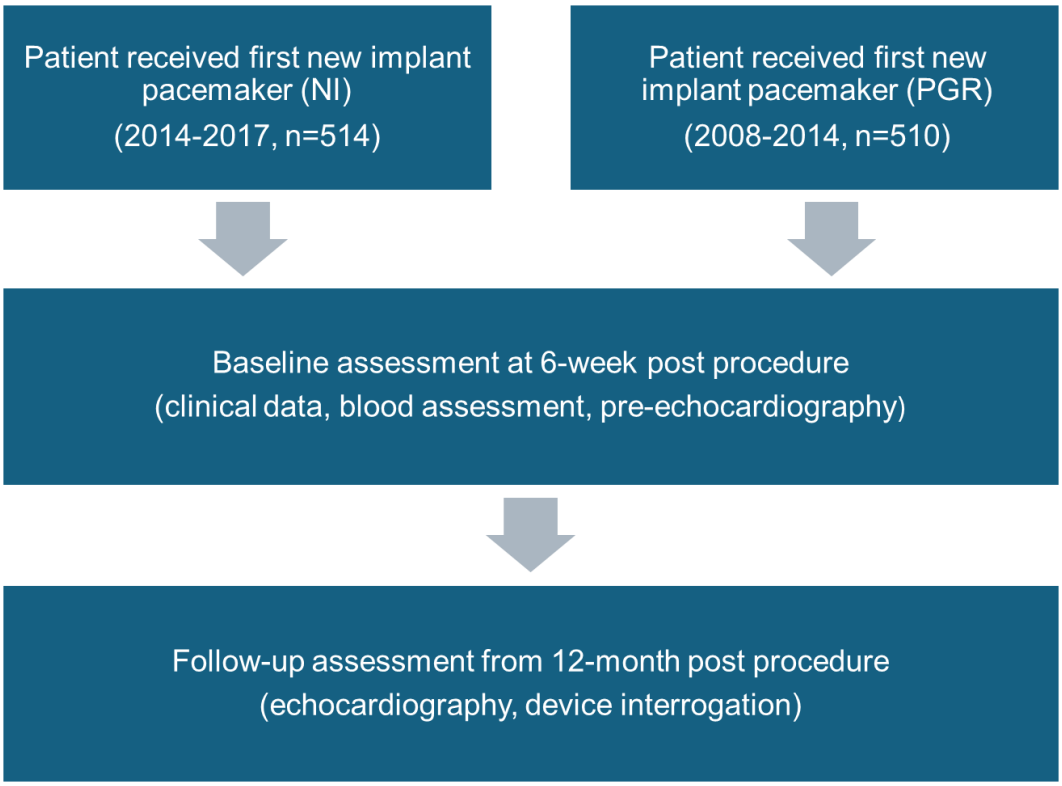


Figure 4.1 Study flowchart of methodology

4.3.3 Outcome measure

The primary outcome was to investigate the prevalence and patient-oriented clinical features associated with LVSD, defined as an LV ejection fraction (LVEF) <50% in line with ESC guidelines at the time of study initiation (McDonagh et al., 2021).

Secondary outcomes included an investigation of patient-oriented clinical predictors of time free from composite outcome of HFH and all-cause of death, and exploratory analyses of risk according to baseline VPB.

4.3.4 Data analysis

4.3.4.1 Descriptive analysis

Baseline continuous data were firstly assessed for normality using Shapiro-Wilk test. Normally distributed data are presented as mean (standard deviation), and continuous non-normally distributed data as median (interquartile range). Categorical data are presented as number (percentage). Student t-tests or ANOVA were used to analyse normally distributed continuous data, Mann-Whitney U-tests or Kruskal-Wallis H-tests for non-normally distributed continuous data, and Pearson $\chi 2$ tests for categorical data.

4.3.4.2 Statistical analysis

Logistic regression analysis was undertaken to investigate risk factors for prevalent LVSD. I estimated that I would require approximately 7 events per covariate to prevent overfitting, and that I would require at least 70 observed events to provide adequate power in the regression models based on the rules of thumb (Babyak, 2004, Tabachnick and Fidell, Green, 1991). I prespecified the inclusion of seven key clinical characteristics of LVSD determined by previous work (Paton et al., 2019, Gierula et al., 2014, Gierula et al., 2015, Paton et al., 2021, Begg et al., 2011a): patient group (NI or PGR), sex (male/female), age (<75, 75-80 and >80), history of IHD (yes/no), diabetes mellitus (Type II) (yes/no), the presence of atrial fibrillation (AF) (yes/no) and the ventricular pacing burden (VPB) (<40%, 40%-80%, and >80%). The clinically important variables (age, sex, history of IHD, diabetes mellitus and AF) and statistically significant variables were included in univariate and multivariate regression analysis and bootstrap analysis was applied to assess model robustness. Additionally, the sensitivity and specificity of the important clinical characteristics of LVSD were analysed.

Predictors of time free from composite outcome of HFH and all-cause death were assessed in Cox proportional hazards models and described using Kaplan-Meier curves after a minimum of 12 months follow-up with a censor date set on 28th July 2018 for NI patients and 31st

December 2012 for PGR patients. Clinical variables assessed as predictors are those described above with the addition of LVEF, LV end-systolic diameter (LVESD) and LV end-diastolic diameter (LVEDD).

Subsequent exploratory analyses included stratification into groups according to baseline VPB (<40%, 40%-80%, and >80%). Given recent data describing the utility of upgrade to CRT in people with less VPB than previously tested, a secondary exploratory analysis was conducted to specifically examine a subgroup with VPB >20% (Merkely et al., 2022).

Data analysis was performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp, Armonk, NY, USA, 2020). A statistical significance was pre-specified as $p < 0.05$, accompanied by a 95% confidence interval (CI).

4.4 Results

4.4.1 Population characteristics

A total of 1024 patients were prospectively enrolled, of whom 514 patients were enrolled shortly after a NI and 510 after PGR. Baseline characteristics of the entire cohort, and by group are shown in **Table 4-1**. The mean age of patients undergoing NI and PGR were similar (76 ±10 years vs. 76 ±12 years, p=0.33). Compared with those receiving a PGR, NI patients were more likely to be male (66% vs.56%, p<0.01), have a history of IHD (31% vs. 14%, p<0.01), and more likely to have type II diabetes mellitus (24% vs. 6%, p<0.01), but less likely to have atrial fibrillation (AF) (25% vs. 33%, p<0.01).

Table 4-1 Baseline characteristics of study population

	Total Cohort *n=1024*	**NI Group** *n=514*	**PGR Group** *n=510*	**p-value**
Age (years)	76 (±11)	76 (±10)	76 (±12)	0.33
Sex (male)	628 [61%]	341 [66%]	287 [56%]	<0.01*
Height (cm)	167 (±12)	167 (±10)	166 (±16)	0.66
Weight (kg)	78 (±18)	79 (±18)	76 (±18)	0.01*
Atrial fibrillation	296 [29%]	128 [25%]	168 [33%]	<0.01*
Type II Diabetes Mellitus	153 [15%]	121 [24%]	32 [6%]	<0.01*
Ischaemic heart diseases	232 [23%]	160 [31%]	72 [14%]	<0.01*
MI	154 [15%]	119 [23%]	35 [7%]	<0.01*
PCI	63 [6%]	46 [9%]	17 [3%]	<0.01*
CABG	113 [11%]	58 [11%]	55 [11%]	<0.01*
Baseline pacing indication				
Sinus node disease	385 [40%]	159 [31%]	227[45%]	<0.01*
Atrioventricular block	367 [38%]	218 [42%]	179 [35%]	<0.01*
Other	222 [23%]	137 [27%]	104 [20%]	<0.01*
Medical therapy				
β-blockers	320 [31%]	214 [42%]	106 [21%]	<0.01*
ACE-inhibitors	347 [34%]	236 [46%]	111 [22%]	<0.01*
Spironolactone	126 [15%]	110 [21%]	16 [3%]	0.01*
Furosemide	178 [17%]	110 [21%]	68 [13%]	<0.01*
Pacing system				
Dual chamber pacing	810 [79%]	400 [78%]	410 [80%]	0.31
Pacing programming				
DDD (R)	490 [48%]	172 [34%]	217 [44%]	<0.01*
RV pacing avoidance algorithm	193 [19%]	193 [38%]	79 [16%]	<0.01*
VVI (R)	249 [24%]	116 [23%]	143 [29%]	<0.01*
AAI (R)	27 [3%]	25 [5%]	3 [1%]	<0.01*
DDI (R)	46 [4%]	5 [1%]	34 [7%]	<0.01*
VDD	26 [2%]	3 [1%]	23 [5%]	<0.01*
Pacing requirement				
Rate response	321 [31%]	78[15%]	215 [42%]	<0.01*
Base rate (bpm)	54 (±8)	50 (±4)	58 (±9)	<0.01*
Max track rate (bpm)	126 (±12)	130 (±11)	123 (±12)	<0.01*
APB (%)	9 (1-52)	2 (1-25)	39 (3-85)	<0.01*
VPB (%)	14 (1-96)	10 (1-83)	24 (1-99)	<0.01*
Echocardiographic measurement				
LVEF (%)	50 (±10)	50 (±8)	50 (±12)	0.61
LVEDD (mm)	47 (±7)	47 (±6)	47 (±7)	0.83
LVESD (mm)	35 (±7)	35 (±7)	35 (±8)	0.31
LA diameter (mm)	41 (±8)	41 (±7)	41 (±9)	0.82

Continuous data are presented as mean (± standard deviation) or median (interquartile range) and categorical data are presented as n (%). A p-value ≤0.05 denotes * was considered significant.

MI; myocardial infarction, PCI; percutaneous coronary intervention, CABG; coronary artery bypass graft, ACE inhibitors; angiotensin-converting enzyme inhibitor, β-blockers; beta-blockers, RV; right ventricular, APB; atrial pacing burden, VPB; ventricular pacing burden, LVEF; left ventricular ejection fraction, LVESD; left ventricular end-systolic dysfunction, LVEDD; left ventricular end-diastolic diameter, LA; left atrial.

4.4.1.1 Pacing indication, device prescription and requirement

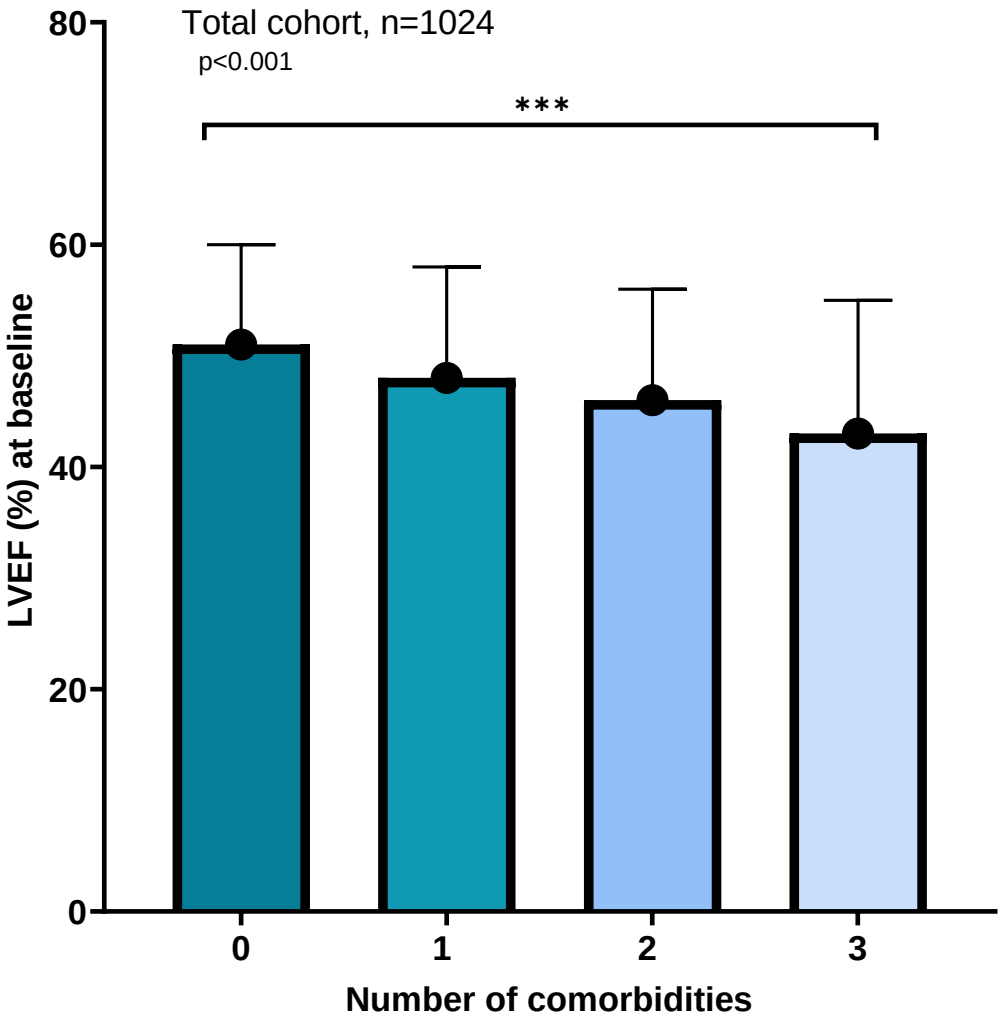
Patients receiving a NI were more likely to have a bradycardia pacing indication of atrioventricular block (AVB) compared to those at PGR (42% vs. 35%, p<0.01). Device prescription was overwhelmingly dual chamber in both groups with no difference between those at NI or PGR (78% vs. 80%, p=0.31, respectively). Patients receiving NI were more likely than those following PGR to have RV pacing avoidance algorithms activated (38% vs. 16%, p<0.01), less likely to receive rate-adaptive pacing (15% vs. 42%, p<0.01), and demonstrated a lower requirement for pacing than those receiving PGR for both atrial pacing burden (2% (IQR:1-25) vs. 39% (3-85), p<0.01) and ventricular pacing burden (VPB) (10% (IQR:1-83) vs. 24% (1-99), p<0.01).

4.4.1.2 Medication prescription

Cardiovascular medical therapy was more commonly prescribed in those receiving a NI compared to those at PGR, including β-blockers (42% vs. 21%, p<0.01), ACE-inhibitors (46% vs. 22%, p<0.01), spironolactone (21% vs. 3%, p<0.01), and furosemide (21% vs. 13%, p<0.01).

4.4.1.3 Baseline echocardiographic measures

Mean baseline LVEF was the same in both groups (50±8% vs. 50±12%, p=0.61), however was significantly lower in the whole cohort in those with increasing numbers of comorbidities (IHD, DM and AF) (51±9% for 0 comorbidities; 48±10% for 1 comorbidity; 46±10% for 2 comorbidities; 43±12% for 3 comorbidities, p<0.01) **(Figure 4.2).** Mean LV dimensions at baseline were not significantly different between patient groups (LVEDD 47±6mm vs. 47±7mm, p=0.83; LVESD 35±7mm vs. 35±8mm, p=0.31).



Comorbidities include ischaemic heart disease (IHD), diabetis mellitus (DM), and atrial fibrillation (AF). Color coded bar represent number of comorbidities either patient has 0 comorbidities, 1 comorbidities, 2 comorbidities or 3 comorbidities. LVEF; left ventricular ejection fraction. p <0.001*.

Figure 4.2 Left ventricular ejection fraction (LVEF) percentages according to number of comorbidities at baseline in total cohort (n=1024). A p value <0.05 is statistical significance and denote as *

4.4.2 Factors associated with prevalent LVSD

344 (37%) patients had LVSD, of whom 182 (20%) underwent a NI, and 162 (17%), a PGR. Univariate analysis revealed that male sex (Odds Ratio (OR)=2.19, 95%CI:1.66,2.91, p<0.01), age>80 years (OR=1.64, 95%CI:1.04, 2.57, p=0.03), a history of IHD (OR=2.49, 95%CI:1.80,3.44, p<0.01), the presence of AF at baseline (OR=1.36, 95%CI:1.03,1.81, p=0.03) and VPB >80% (OR=2.34, 95%CI:1.55,3.52, p<0.01) were independently associated with LVSD **(Table 4-2)**. After including clinically relevant variables **(Table 4-2)**, in a multivariable analysis, having a history of IHD (OR=2.36, CI: 1.67, 3.33, p<0.01), and VPB >80% (OR=1.87, CI: 1.31, 2.68, p=0.01) remained significant independent characteristics of those with LVSD **(Figure 4.3).** Sensitivity and specificity for prevalent LVSD in those with IHD and VPB >80 was 77% and 53% respectively.

Table 4-2 Factors associated with prevalent LVSD in regression analysis (A) Unadjusted odds ratios for each covariate, (B) Adjusted odds ratio for all covariates

Variables	Parameter estimate	Standard error	Wald χ^2 p-value	Odds Ratio (95% CI)
(A) Unadjusted odds ratios				
Patient Group (PGR)	0.10	0.14	0.15	1.21 (0.93 – 1.57)
Sex (male)	0.65	0.15	<0.01*	2.19 (1.66 – 2.91)
Age < 75 (years)				1.00 (ref)
75 – 80	0.28	0.27	0.29	1.33 (0.78 – 2.24)
≥80	0.49	0.23	0.03*	1.64 (1.04 – 2.57)
IHD	0.70	0.16	<0.01*	2.49 (1.80 – 3.44)
Type II Diabetes Mellitus	0.01	0.19	0.54	1.12 (0.76 – 1.62)
AF	0.40	0.15	0.03*	1.36 (1.03 – 1.81)
VPB <40 (%)				1.00 (ref)
40 – 80	0.85	0.21	0.11	1.72 (0.89 – 3.34)
≥80	0.54	0.34	<0.01*	2.34 (1.55 – 3.52)
(B) Adjusted odds ratios				
Patient Group (PGR)	-0.11	0.27	0.83	0.94 (0.56 – 1.59)
Sex (Male)	0.40	0.29	0.07	1.67 (0.95 – 2.93)
Age < 75 (years)				1.00 (ref)
75 – 80	0.06	0.33	0.78	1.09 (0.58 – 2.05)
≥80	0.27	0.28	0.26	1.37 (0.79 – 2.35)
IHD	0.933	0.25	<0.01*	2.56 (1.58 – 4.13)
Type II Diabetes Mellitus	0.02	0.29	0.47	1.22 (0.71 – 2.09)
AF	0.24	0.26	0.09	1.52 (0.93 – 2.51)
VPB <40 (%)				1.00 (ref)
40 – 80	0.06	0.44	0.88	1.06 (0.45 – 2.49)
≥80	0.76	0.26	0.01*	2.13 (1.29 – 3.52)

Values are expressed as odds ratio (95% Confidence Interval. A p-value <0.05 denotes * was considered significant. Ref denotes reference group. IHD; Ischaemic Heart Disease, AF; atrial fibrillation, APB; atrial pacing burden, VPB; ventricular pacing burden.

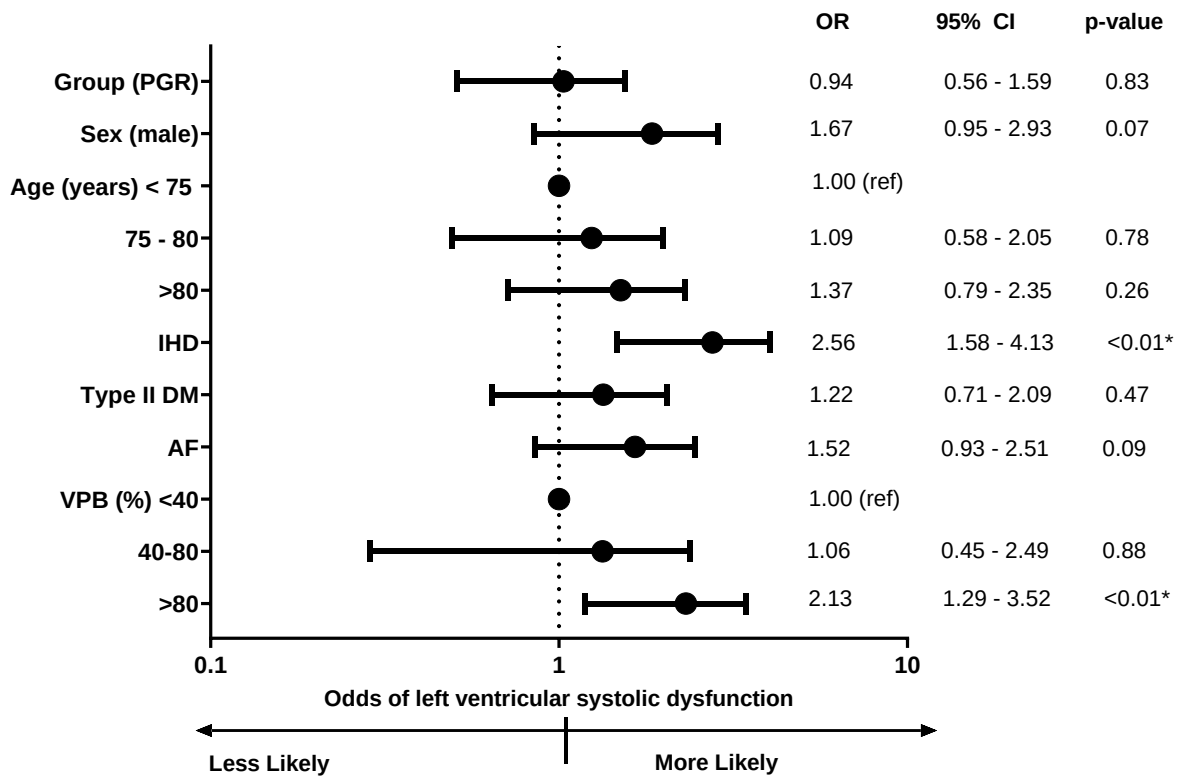


Figure 4.3 Factors associated with left ventricular dysfunction amongst pacemaker's patients. A p value <0.05 is statistical significance and denote as *

4.4.3 Factors associated with incident reduction in LVEF following new pacemaker implantation

In the first 12 months following NI, mean change in LVEF was -1.23 (SD±8.45) **(Figure 4.4)**. 31 (8%) patients experienced a clinically significant reduction in LVEF, defined as a reduction of equal to or more than 10% (Solomon et al., 2005).

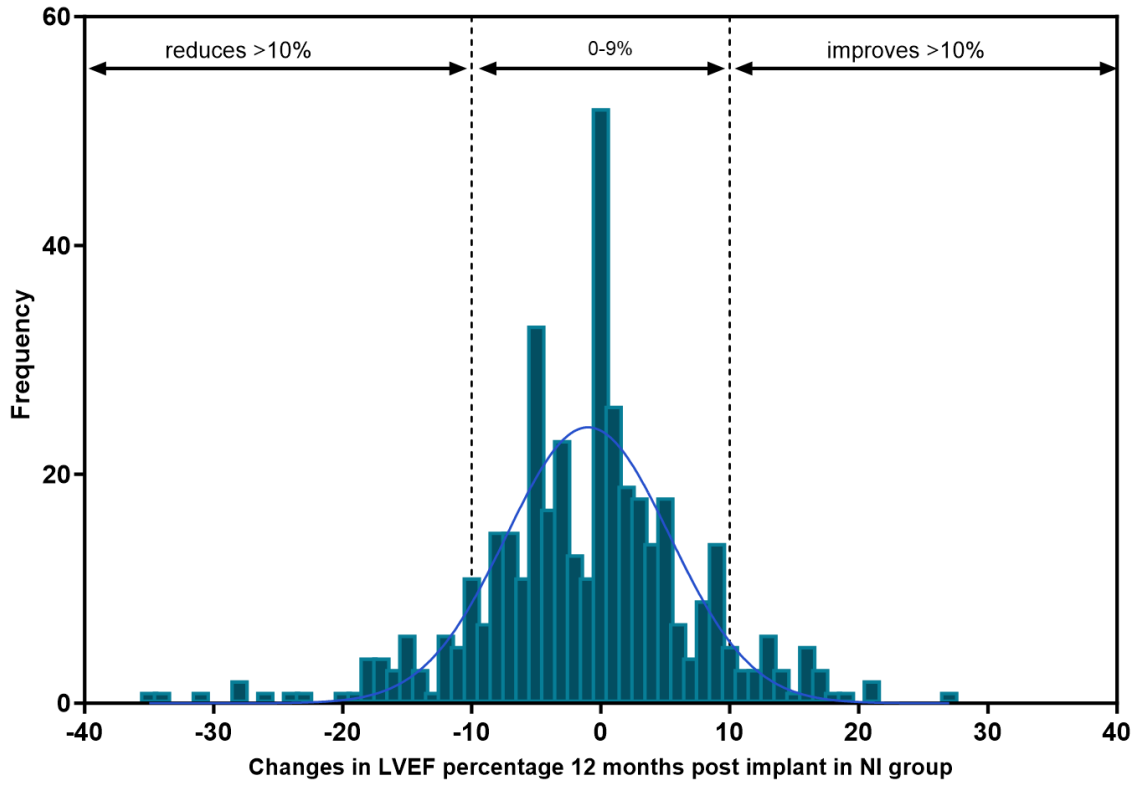
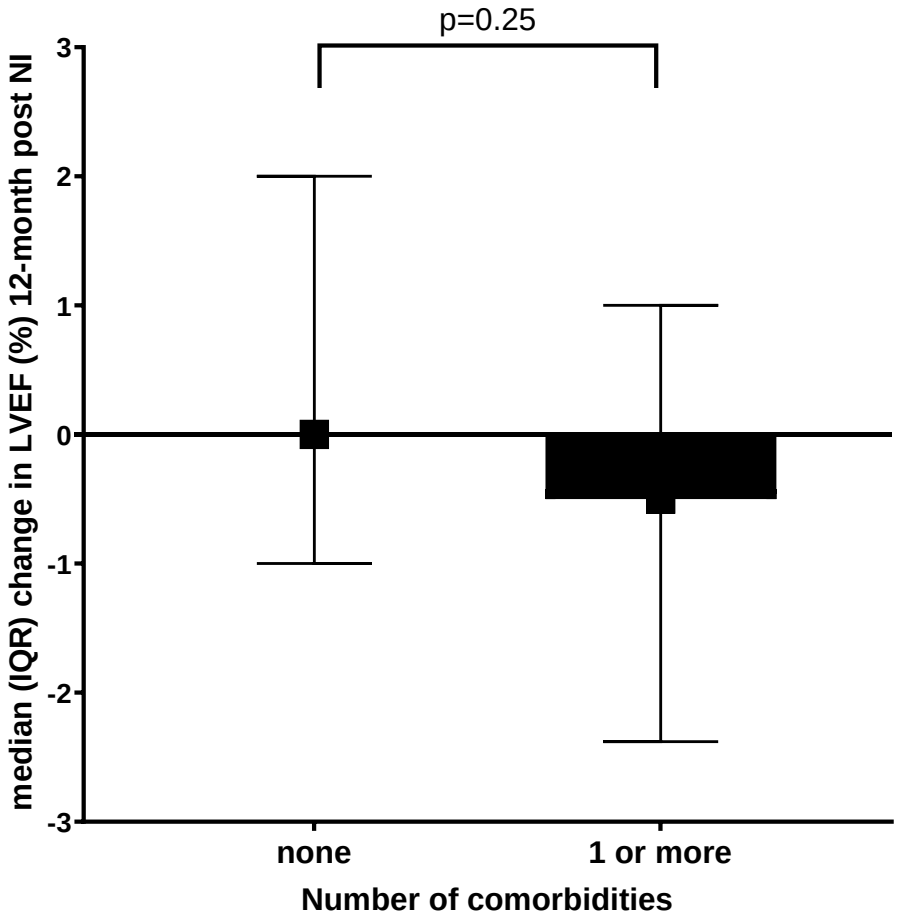


Figure 4.4 Changes in left ventricular ejection fraction (LVEF) percentage at 12- month post procedure in new implant (NI) group (n=514)

The data suggests that mean LVEF difference was not significantly (p=0.76) associated with the number of comorbidities in the first 12 months following NI **(Figure 4.5).**



Comorbidities include ischaemic heart disease (IHD), diabetes mellitus (DM), and atrial fibrillation (AF). Colour coded bar represents number of comorbidities either patient has 0 comorbidities, 1 comorbidity, 2 comorbidities or 3 comorbidities. LVEF; left ventricular ejection fraction. p=0.25

Figure 4.5 Median (IQR) change in LVEF percentage according to number of comorbidities in new implant (NI) group (n=514). A p value <0.05 is statistical significance and denote as *

4.4.4 Factors associated with event-free to first composite outcome of HFH and all-cause of death

After a median follow-up period of 30 months (IQR: 16-42), a total of 341 patients (33%) had been hospitalised for HF (20%) or died (13%). In univariable analyses, receiving a PGR (Hazard Ratio (HR)=3.03, 95%CI: 2.35,3.96; p=0.02), having an age ≥80 years (HR=2.41, 95%CI:1.51,3.84; p<0.01), the presence of AF (HR=2.25, 95%CI:1.73,2.94; p<0.01), a requirement of VPB ≥80% (HR=2.14, 95%CI:1.21,3.76; p=0.01), and LVEF <40% (HR=0.50, 95%CI:0.28,0.87; p=0.02) were independently associated with event-free to first composite outcome of HFH and all-cause of death **Table 4-3(A)**.

Table 4-3 (A) Unadjusted hazard ratios for time to first composite outcome of HFH or all-cause of death, for each covariate, (B) Adjusted hazard ratio for time to first composite outcome of HFH or all-cause of death for all covariate in combined

Variable	Parameter Estimate	Standard Error	Wald χ^2 P-Value	Hazard Ratio (95% CI)
(A) Unadjusted hazard ratios				
Patient Group (PGR)	1.11	0.13	0.02*	3.03 (2.35 – 3.96)
Sex (Male)	0.16	0.11	0.91	1.18 (0.90 – 1.55)
Age <75 (years)				1.00 (ref)
75 - 80	0.21	0.31	0.48	1.24 (0.68 – 2.26)
>80	0.88	0.24	<0.01*	2.41 (1.51 – 3.84)
IHD	0.01	0.16	0.98	1.00 (0.73 – 1.37)
Type II Diabetes Mellitus	0.10	0.19	0.60	1.11 (0.76 – 1.61)
AF	0.81	0.14	<0.01*	2.25 (1.73 – 2.94)
VPB <40 (%)				1.00 (ref)
40 – 80	0.27	0.22	0.21	1.32 (0.85 – 2.04)
>80	0.76	0.29	0.01*	2.14 (1.21 – 3.76)
LVEF >50 (%)				1.00 (ref)
40 – 50	-0.13	0.28	0.65	0.88 (0.51 – 1.53)
<40	-0.70	0.29	0.02*	0.50 (0.28 – 0.87)
LVESD (mm)	0.01	0.01	0.54	1.01 (0.99 – 1.03)
LVEDD (mm)	0.01	0.01	0.57	1.01 (0.99 – 1.03)
(B) Adjusted hazard ratios				
Patient group (PGR)	-2.49	1.01	0.02*	2.27 (1.78 – 4.16)
Sex (male)	-0.29	0.29	0.35	0.76 (0.43 – 1.35)
Age <75 (years)				1.00 (ref)
75 - 80	0.28	0.37	0.45	1.32 (0.64 – 2.72)
>80	0.78	0.31	0.01*	2.19 (1.19 – 4.05)
IHD	0.03	0.27	0.68	1.11 (0.68 – 1.82)
Type II Diabetes Mellitus	-0.02	0.30	0.94	1.03 (0.60 – 1.75)
AF	0.88	0.26	0.01*	2.26 (1.37 – 3.72)
VPB <40 (%)				1.00 (ref)
40 – 80	0.25	0.35	0.79	1.08 (0.61 – 1.89)
>80	0.07	0.28	0.47	1.29 (0.65 – 2.54)
LVEF >50 (%)				1.00 (ref)
40 – 50	0.49	0.41	0.23	1.64 (0.73 – 3.68)
<40	0.57	0.26	0.04*	1.77 (1.30 – 3.03)
LVESD (mm)	0.02	0.03	0.54	1.02 (0.96 – 1.08)
LVEDD (mm)	-0.02	0.03	0.47	0.98 (0.93 – 1.04)

Values are expressed as hazard ratio (95% Confidence Interval). * Denotes as statistical significance $p < 0.05$. Ref denotes as reference group. IHD; Ischaemic Heart Disease, AF; atrial fibrillation, VPB; ventricular pacing burden, LVEF; left ventricular ejection fraction, LVESD; left ventricular end-systolic diameter, LVEDD; left ventricular end-diastolic diameter.

After accounting for clinically relevant variables, **Table 4-3 (B)**, VPB >80% was no longer a significant independent predictor of event-free to first composite outcome of HFH and all-cause of death (HR:1.29, 95%CI:0.65-2.54, p=0.47). Being at PGR (HR=2.27, 95%CI:1.78,4.16, p=0.02), an age >80years (HR=2.19, 95%CI:1.19,4.05, p<0.01), the presence of AF (HR=2.26, 95%CI:1.37,3.72, p<0.01) and having an LVEF <40% (HR=1.77, 95%CI:1.30,3.03, p=0.04) **(Figure 4.6)** were associated with time to first composite outcome of HFH or all-cause of death.

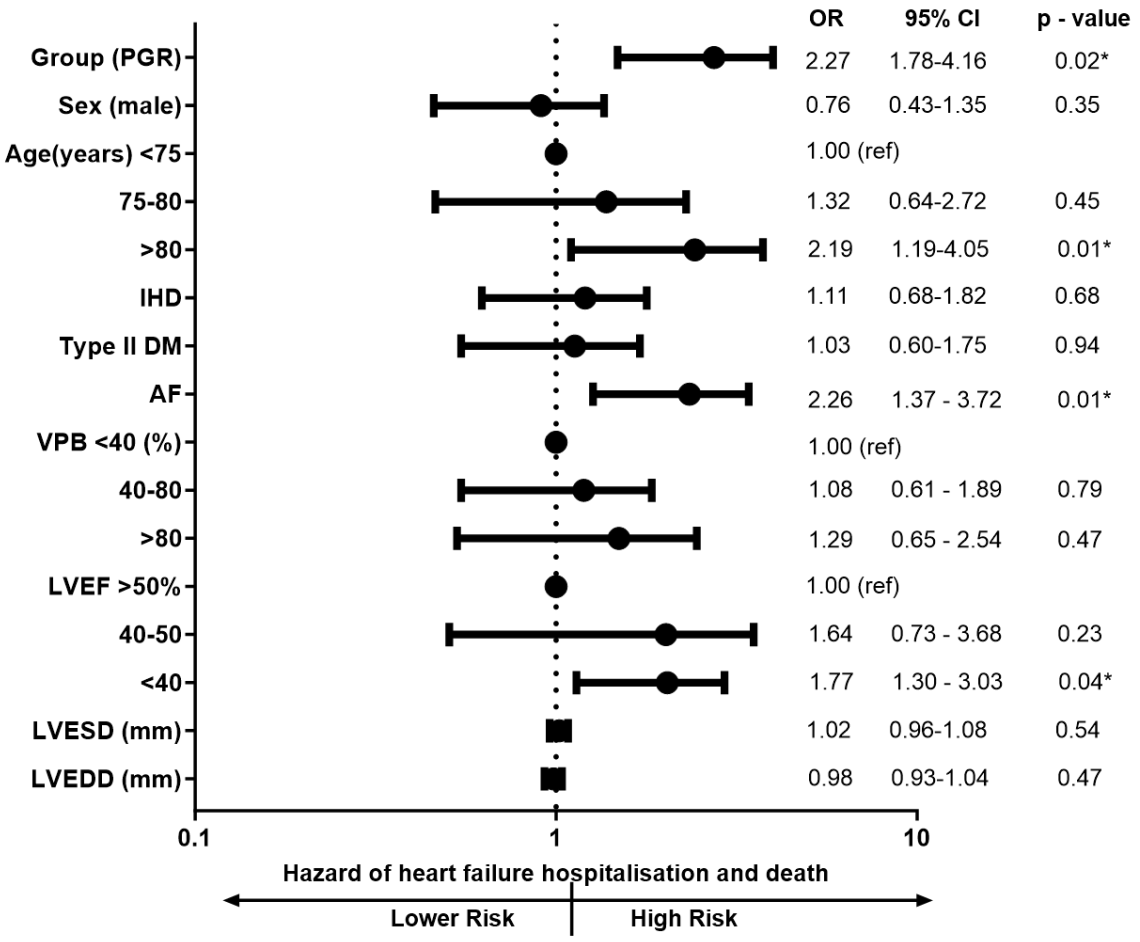
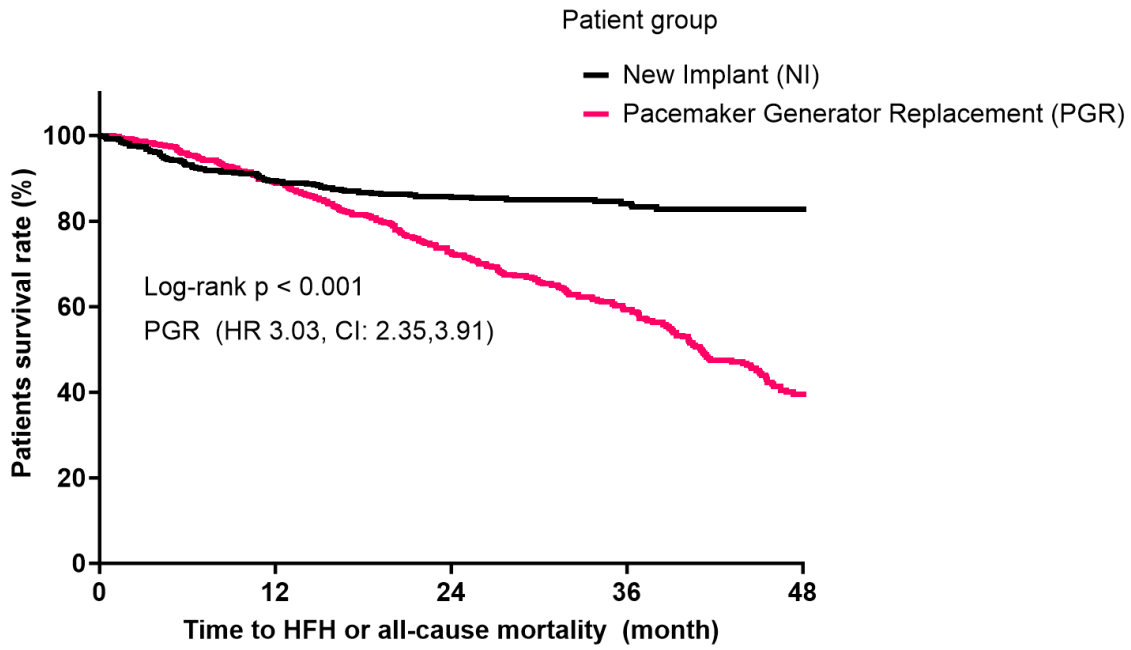


Figure 4.6 Predictors of time to composite outcome of heart failure hospitalisation (HFH) and all-cause of death amongst pacemaker patients after a minimum of 12 months follow up with a censor date on 28th July 2018 for new implant (NI) group vs. 31st Dec 2012 for PGR group. A p value <0.05 is statistical significance and denote as *

Kaplan Meier **(**

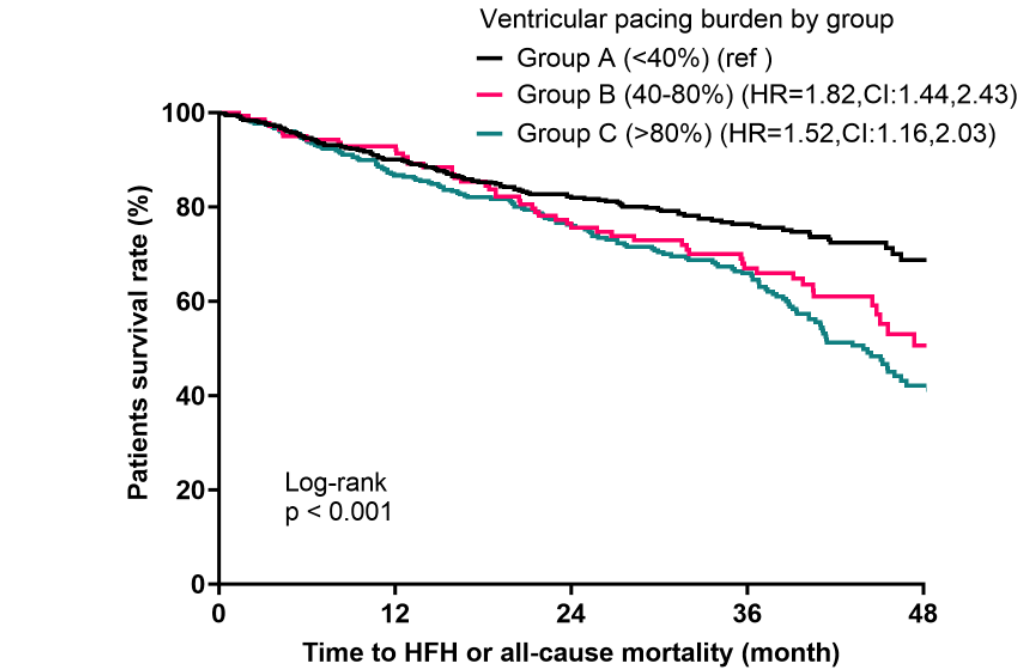
Figure 4.7**)** analysis shows time free from HFH or death in those who received NI was higher (85%) compared to those who required PGR (66%) at median follow-up of 30 months (IQR: 16-42).



No at risk					
NI	514	458	331	192	20
PGR	510	425	298	202	78

Figure 4.7 Kaplan Meier showing estimates composite outcome of heart failure hospitalisation (HFH) and all-cause of death event-free survival rate according to patient group (NI: new implant, PGR; pacemaker generator replacement) (log rank p <0.001)

In exploratory analyses, those with a VPB of ≥80% had increased risk of HFH or mortality (79%) compared to those with a VPB 40-80% (72%) and to those with a VPB <40 (70%) at median follow-up of 30 months (IQR: 16-42) in univariate analysis **(Figure 4.8).** In further exploratory univariate analysis, VPB with a cut-off of >20% was associated with time to the composite endpoint (HR = 1.64, CI: 1.09, 2.45; p = 0.02), although this was not significant in multivariable analysis.



No at risk					
<40%	534	466	321	184	37
40-80%	139	127	91	66	20
>80%	351	291	217	133	28

Figure 4.8 Kaplan Meier showing estimates patients survival rate (group: from composite outcome of heart failure hospitalisation (HFH) or all-cause of death by ventricular pacing burden (VPB) group : Group A <40% as reference, Group B >40% and Group C >80%, log rank p<0.001.

4.5 Discussion

This present study highlights clinical characteristics associated with LVSD in pacemaker patients from those who received first implant to those required PGR, in the era of RV pacing avoidance. The analysis demonstrates that VPB is not an isolated driver of adverse clinical events, and that clinical characteristics including having a history of IHD and AF, and the number of co-morbidities present, are associated with risk of clinical events. These findings may be useful to identify a population in whom targeted screening may be an appropriate use of resource, to subsequently direct therapeutic strategies including device and medical therapy optimisation.

4.5.1 The adverse effect of RVA pacing

LVSD is a critical factor in the progression of HF and is associated with increased hospitalisation and mortality, with higher rates observed in people with pacemakers for bradycardia compared to the general population (Tayal et al., 2019). This association between long-term ventricular pacing and the development of LVSD and HF-related events, has led to the development of algorithms encouraging intrinsic rhythm whenever possible (Sharma et al., 2005, Sweeney et al., 2003). The MOST study (Lamas et al., 2002b), investigating patients with SND and normal QRS duration, described that a high VPB was associated with an increased risk of HFH and AF. However, participants in this study did not undergo systematic echocardiography prior to implantation, limiting the ability to define causation. Consequently, it remains unclear if the conclusions drawn from this study are applicable to all pacemaker recipients, especially those who fall outside the trial's inclusion criteria, and those receiving treatments that potentially prevent the progression of LVSD (Sweeney et al., 2003).

Whilst MOST (Lamas et al., 2002b) and DAVID (Wilkoff et al., 2002) highlighted that those with a VPB beyond 40% were more likely to experience LVSD and HF-related events, and subsequently, even more likely above 80% (Gierula et al., 2015),, the results of the

BUDAPEST (Merkely et al., 2022) randomised study (n=360) highlighted the benefit of CRT in people with a VPB >20% on clinical outcomes, which prompted me to expand my exploration into whether a lower threshold of VPB might also have clinical relevance in the population. In this study, most patients either preserved or slightly improved their LVEF, while a minority experienced significant reductions, highlighting the variability in patient outcomes within the NI group 12 months post implant. I found that VPB alone, especially at lower rates of pacing, is often not an isolated driver of LVSD, and investigators could in fact be misled if this were assessed alone. Patients requiring higher VPB often present with several cardiac co-morbidities prompting me to propose that LVSD and clinical events, rather than being simply a consequence of ventricular pacing, are the consequences of the underlying cardiac disease that drive the need for pacing support in the first place, complicating the clinical scenario beyond simply the measurement of VPB.

4.5.2 Contribution of co-morbidities

The present study demonstrates very little overall change in LVEF after 12 months of RVA in most patients, consistent with findings from previous studies indicating that RVA pacing is a safe and reliable low risk option for most patients requiring treatment of bradyarrhythmia (Gierula et al., 2014, Paton et al., 2019). Nevertheless, some patients do experience a large and clinically relevant drop in LVEF, which is more likely in people with comorbidities such as IHD and AF, especially if concomitantly, high percentage of VPB is required, reinforcing the proposition that co-morbidities are also an important contributor.

The association of LVEF <40% with a lower risk of HFH and all-cause mortality (HR: 0.50, 95%CI: 0.28-0.87, p=0.02) initially appears counterintuitive, given that a lower LVEF is generally associated with worse outcomes. This paradoxical finding can be attributed to several possible explanations. Firstly, patients with severely reduced LVEF may have been treated with more aggressive therapeutic strategies, including optimised HF medication management and device therapy, which could have reduced their risk of HFH and death

despite their low baseline LVEF. This is supported by the observed treatment intensification often seen in patients with severe heart failure (Sam et al., 2021, Rastogi et al., 2023)

Moreover, the multivariable analysis adjusted for clinically relevant variables, showing that LVEF <40% is associated with an increased risk of HFH and death (HR: 1.77, 95%CI: 1.30-3.03, p=0.04), further strengthens the hypothesis that low LVEF is indeed a risk factor when considering other confounding factors. Interestingly, VPB >80% was no longer a significant predictor in the adjusted model, indicating that the effect of high VPB might be confounded by other factors, such as comorbidities and treatment strategies, which are not captured by the univariable analysis alone.

Thus, while LVEF <40% was initially associated with a reduced risk of HFH and death, the multivariable analysis suggests that this effect is likely due to more aggressive treatment and patient selection factors, which highlight the complexity of the relationship between LVEF, pacing burden, and clinical outcomes. Further studies, including sensitivity analyses and more granular data on treatment modalities, are needed to better understand this complex interaction.

In particular, I show that IHD increases the risk of LVSD, the mechanism of which has been hypothesised to be increased myocardial fibrosis and mechanical dyssynchrony (Lye and Donnellan, 2000, Finegold et al., 2013). In patients with evidence of focal fibrosis detected by cardiovascular magnetic resonance before pacemaker implant, a greater rate of deterioration in LV function following RV pacing can be observed, compared to those without fibrosis (Saunderson et al., 2021). Whilst advanced cardiac imaging might be useful in risk stratification, I observed that adverse clinical outcomes occurred in about half of the population, therefore, it remains unclear if broad population diagnostic screening prior to treatment of bradyarrhythmia would be useful, rather a more focussed assessment based

upon simple clinical variables might be a practical way to select those that might benefit from further investigation.

4.5.3 Mitigating the Risk of RV Pacing: Optimised programming

The data suggest that while VPB might not be the only driver for progressive LVSD and clinical events, reducing VPB is likely to remain important, not least for battery longevity. Preventative strategies, including RV pacing avoidance algorithms recommended by (Chung et al., 2023), should be widely adopted to improve clinical outcomes (Gillis et al., 2006, Quesada et al., 2008). Approximately 30% of patients implanted with a pacemaker for AVB have intact conduction at their first outpatient assessment (Sweeney et al., 2005). Hence, intrinsic conduction should always be sought and documented. Personalised programming to reduce unnecessary RV pacing can improve LV systolic function and indexed LV end systolic volume at 6 months (Paton et al., 2021). However, managing patients with unavoidable RV pacing due to complete AVB indication remains challenging. Programming pacing requirements should be carefully tailored to the clinical needs, especially in cases of IHD and AF, where reprogramming to avoid unnecessary RV pacing shows no detrimental effect on quality of life (Paton et al., 2021, Gierula et al., 2014). Comprehensive management strategies, including medication therapy and device prescription, should be implemented to improve clinical outcomes in these patients.

4.5.4 Primary prevention of HF

The traditional approach of RVA pacing has been applied for more than half a century due to its proven safety and reliability (Lamas et al., 1998, Timmis et al., 2020, Furman and Schwedel, 1959). RVA pacing can exacerbate the progression of LVSD in at-risk populations (Nielsen et al., 2012). Alternative pacing sites have not been universally successful at mitigating this risk yet (Holmqvist and Daubert, 2013, Kaye et al., 2015). CSP attempts to

achieve more physiological ventricular activation, preserving ventricular synchrony, haemodynamic function (Zanon et al., 2018) and possibly myocardial work.

The HOPE-HF trial (n=167) was a cross-over study with 6 month phases, comparing HBP or back-up pacing only (using non-HIS lead) demonstrated improved quality of life during the HBP phase (Keene et al., 2018). Whilst observational studies hint at benefits on clinical outcomes, issues of non-randomised approaches and heterogeneity across patient groups limit their relevance (Abdelrahman et al., 2018). HBP has an 80% success rate even in experienced hands, and routinely requires higher pacing outputs, possibly underlying its lack of wide adoption (Zanon et al., 2011, Sharma et al., 2015, Vijayaraman et al., 2015, Vijayaraman et al., 2018b). Hence, careful selection is required to establish in whom physiological pacing might be of benefit.

In contrast, studies comparing LBBAP (n=125) and HBP (n=126) demonstrated higher success rates, shorter procedure and fluoroscopy time, lower pacing threshold and higher R-wave amplitude with LBBAP suggesting this might be a more generalisable method of delivering pacing, thereby justifying further randomised trials (Hua et al., 2020). The results of the ongoing double-blind PROTECT-HF trial (n = 2600), comparing traditional RV pacing and CSP (LBBAP and HBP) on patient-orientated endpoints will help determine whether CSP should be routine, or reserved for those at greatest risk (Whinnett, 2023).

The findings highlight the potential group of patients with similar key clinical features where these alternative pacing strategies could be targeted to achieve the greatest benefit; those with higher VPB requirements and a history of IHD and AF. A clinical event rate of around 11% also help calculate the sample size required to show clinical benefit compared with a real-world cohort of patients with contemporary pacemaker programming (Tayal et al., 2019, Mazza et al., 2013).

4.6 Limitations

The present study comes with some limitations. Firstly, this was an exploratory analysis of previously collected prospective data and reports a single centre experience. The differences in recruitment intervals between the NI and PGR groups pose a significant limitation in the interpretation of the findings. As patients were recruited from different years, variations in the treatment guidelines, and pacing programming techniques could have influenced the outcomes. For instance, PGR group were already being pace for 8 to years prior and seems to have less medical therapy. The pacing programming itself may have evolved with newer technologies and clinician practices, which might not be comparable between groups. Similarly, pharmacological advancements or changes in the standard of care over the years could have impacted the management of patients in the study. Additionally, there was an insufficient echocardiographic dataset available for the PGR group at follow-up. As a result, changes in EF from baseline could only be assessed in the NI group, limiting the comparative analysis. These temporal variations in clinical management represent an inherent confounding factor that may affect the comparability of the two groups. As such, caution must be exercised when drawing conclusions based on these two groups, as the differences in treatment approaches may not be fully accounted for in the analysis. Further research, ideally with more uniform recruitment periods and standardised clinical protocols, would be needed to validate and strengthen the findings from this study.

Secondly, clinical and biomarker data were restricted by pre-specified study protocols, limiting the ability to describe the value of NT-pro BNP, for example, in predicting adverse outcomes in people with or receiving pacemakers.

Thirdly, survival bias is likely present in the PGR group, which may lead to an underrepresentation of certain high-risk individuals. To address this, stratified analyses could be beneficial in longer-term studies. Additionally, although patients were stratified based on their VBP (<20%, 40-80%, and >80%), the pacing status within the study introduces potential

bias. Variations in patients being assessed in either an intrinsic or paced rhythm may influence cardiac function and haemodynamic, thereby reducing the validity of comparing groups within the cohort. Future studies should focus on patients requiring a high degree of right ventricular pacing, which would allow for better standardisation of the cohort and reduce this inherent bias

Finally, as with many of the available published evidence, my work is observational, and thereby causation cannot be established. Hence, whilst I can describe risk features associated with prevalent and incident LVSD, incident of HFH and mortality, I cannot determine whether these are driven by the RVA pacing, or the constellation of clinical features that also contribute to a higher VPB.

4.7 Conclusion

This study emphasises the complexity of managing pacemaker patients and the multifactorial nature of LVSD risk. Attention should be directed towards investigating patients with a high pacing requirement who also have concomitant cardiovascular comorbidities, to allocate resources and develop more efficient and precise screening tools to prevent a deterioration in LV function, and subsequent adverse clinical outcomes. Furthermore, these findings could inform clinical trial cohorts, facilitating focussed exploration of novel pacing strategies, pharmacological and device.

4.8 Dissemination of findings

The study preliminary findings have been presented as an oral presentation at European Society of Cardiologist (ESC) conference in Barcelona Spain, in 2022 and subsequently

published in the conference supplement of the European Heart journal. The full-text manuscript is currently submitted for review in *Europace*.

Chapter 5 Left ventricular mechanics in patients receiving right ventricular pacing: a retrospective analysis

5.1 Abstract

Introduction

Right ventricular (RV) pacing (RVP) is the most common method of delivering bradycardia pacing, but it is associated with left ventricular systolic dysfunction (LVSD) in 40% of patients. Animal models have shown that RVP-related electrical conduction delay leads to dyssynchronous LV activation, resulting in uneven myocardial work (MW) distribution. This work redistribution is believed to trigger adaptive structural remodelling, aiming to achieve a more uniform LV load distribution. Cardiac resynchronisation therapy (CRT) responders demonstrate normalised MW distribution however, there is limited evidence on MW in patients with pacemakers.

Aim

To evaluate the influence of long-term RVP on MW echocardiographic measurements in atrioventricular block (AVB) patients.

Methods

Data were collected from consecutive patients with AVB who received pacemaker therapy at two tertiary hospitals, one in Belgium (University Hospitals Leuven: Site 1) and another in England (Leeds Teaching Hospitals – Leeds General Infirmary: Site 2). Clinical data, medical history, echocardiographic and pacing measurements were obtained at baseline (pre-implant),

6 weeks, and a minimum of 12 months post-implant. Patients aged ≥18 years, capable of providing informed consent, and receiving pacemaker therapy for bradycardia were included. Those receiving an implantable cardioverter defibrillator (ICD), or cardiac resynchronisation therapy (CRT) were excluded.

Results

A total of 118 patients (mean age 75±10 years; 69% male) with high grade AVB receiving pacemaker therapy were included. At long-term follow-up (median 454 days post implant, IQR:64-857), 33 patients (28%) had LVSD (LVEF <50%). Repeated measure (ANOVA) with Bonferroni correction demonstrated LVEF statistically significant reduced from baseline (median -20 (IQR:4-132) days pre implant) to mid-term follow up (median 10 (IQR:2-156) days post implant) to long-term follow up (median 454 (IQR:54-857) days post implant) (56±8% to 53±8% to 48±10%, respectively<0.001). Global work index (GWI), global constructive work (GCW) and global wasted work (GWW) measurements were significantly different between those who preserved LVEF ≥50% and those whose LV systolic function declined over time (LVEF <50%) (all p<0.01).

Conclusion

Early deterioration in septal constructive MW is associated with the subsequent development of LVSD in pacemaker patients with high grade AVB. Myocardial work measurements may be useful in identifying patients at risk of RVP-associated LVSD, who may benefit from alternative pacing therapies, such as CSP or CRT.

Keywords

Right ventricular pacing, left ventricular dyssynchrony, left ventricular mechanics, myocardial work

5.2 Introduction

Pacemakers are a common and often life-saving treatment for individuals suffering from bradycardia (Lamas et al., 1998, Tracy et al., 2012). Despite advancements in cardiac pacing strategies, right ventricular pacing (RVP) remains the most used method for delivering bradycardia pacing worldwide (Members et al., 2008, Members et al., 2013). However, RVP has been associated with left ventricular (LV) systolic dysfunction (LVSD) in approximately 40% of the pacing population (Thackray et al., 2003, Gierula et al., 2015, Paton et al., 2021).

Studies conducted on animal models have demonstrated that electrical conduction delays resulting from RVP can induce dyssynchronous activation of the LV, causing a redistribution of myocardial work (MW) between early and late electrically activated regions (Duchenne et al., 2019b). This altered distribution of work has been proposed as a precursor to adaptive structural remodelling, aimed at homogenising the workload distribution between LV regions (Bernard et al., 2015, Lumens et al., 2012, Leenders et al., 2012, Lim et al., 2008).

The concept of MW includes both constructive work, which contributes to effective myocardial contraction, and wasted work, which indicates inefficiencies in cardiac mechanics (Smiseth et al., 2021). Previous clinical studies have demonstrated that individuals who respond positively to cardiac resynchronisation therapy (CRT) often show a normalisation of myocardial work (MW) distribution (Duchenne et al., 2019b, Bernard et al., 2015, Lim et al., 2011, Russell et al., 2013). Additionally, observational studies suggest that constructive work (CW) and wasted work (WW) measurements may have predictive value in identifying patients likely to respond to CRT prior to CRT (Galli et al., 2018a). However, there is little evidence investigating MW in patients receiving a standard bradycardia pacemaker.

As discussed in my previous work in chapter 4, managing pacemaker patients is complex, particularly due to the multifactorial risks associated with LVSD. There is a need to focus on identifying pacemaker patients at higher risk. Therefore, this study aims to investigate the

effects of RVP on MW measures in patients who may requiring a high ventricular pacing burden (VPB) due atrioventricular block (AVB) over time that includes second degree and third degree AVB. Although not all second degree AVB will have a high burden of pacing because it depends on the specific type (Mobitz I or Mobitz II) in which Mobitz II typically tend to have severe damage to the conduction system and generally often requires higher pacing burden (Barold and Hayes, 2001, Kashou et al., 2024)

5.3 Method

5.3.1 Study population

This study collected data from consecutive patients diagnosed with AVB who received pacemaker therapy in two tertiary hospitals in Europe (University Hospitals Leuven: Site 1 and (Leeds Teaching Hospitals – Leeds General Infirmary: Site 2), at baseline (pre implant), mid-term (6-week) and long-term (a minimum of 12-month) follow up post implant.

In the Belgium group, patients (Site 1, n=115) who received pacemaker for bradycardia following ESC guidelines were retrospectively included as part of a clinical audit, whilst in the UK group, patients (Site 2, n=3) who received pacemaker for bradycardia according to NICE guidelines were prospectively recruited for an observational study. Patients who received an implantable cardioverter defibrillator (ICD), or CRT device were excluded.

Ethical approval was obtained for the UK hospital prior to patient enrolment (12/4H/0487), and all patients provided informed written consent. The institutional medical ethical committees of the Belgium hospital had approved the protocol as a service evaluation. All research activity complied with the principles of the Declaration of Helsinki.

5.3.2 Data collection

This study employed a structured methodology to explore cardiac performance in patients with second and third degree AVB receiving pacemaker therapy. Baseline data including clinical history, medication, pacing indication and echocardiography measurements were collected at pre implant. Device interrogations were conducted as part of standard post-implant care, focusing on the percentage of RVP, alongside a transthoracic echocardiography assessment. The study design and workflow are shown in **Figure 5.1**. This combined approach allowed for a comprehensive evaluation of both device performance and myocardial function, providing insights into the effects of RVP on LV performance overtime.

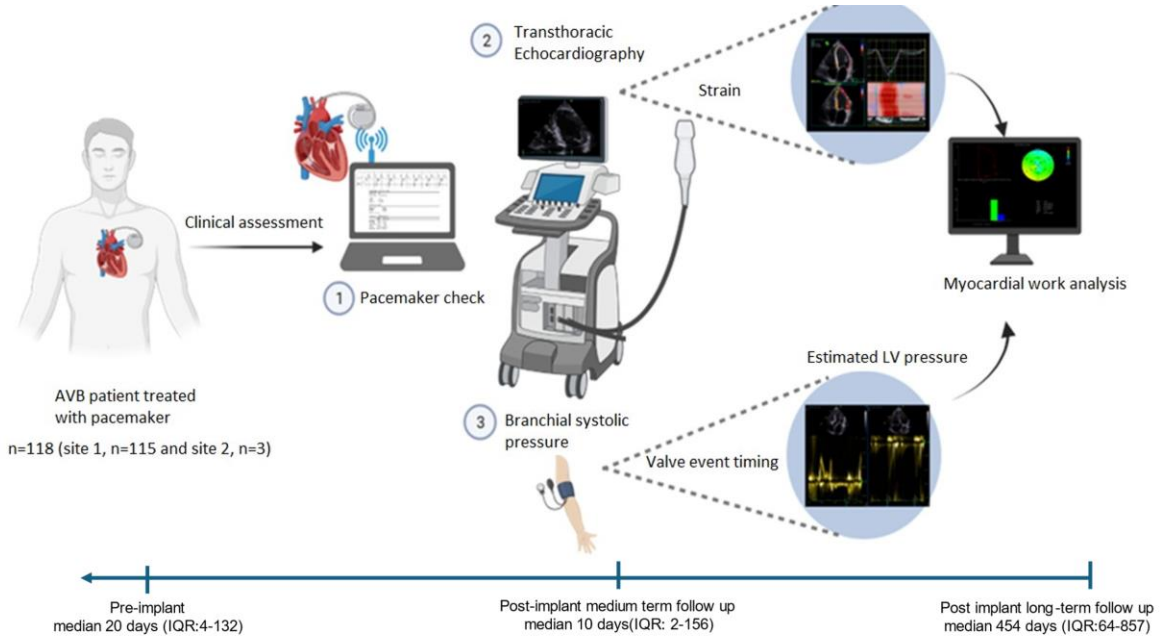


Figure 5.1 Study Flowchart – Follow-up Timeline for Atrioventricular-Block (AVB) Patients Undergoing Pacemaker Implantation and Clinical Assessment: Echocardiographic Measures, and Myocardial Work Analysis

5.3.2.1 Pacemaker assessment

During device interrogation at 6 week and a minimum of 12-month post implantation, the primary data collected for analysis was the percentage of RVP. Other device measurements, such as lead thresholds, sensing values, impedance, and battery status, were recorded as part of standard care but were not included in the primary analysis.

5.3.2.2 Echocardiography assessment

Transthoracic echocardiography was conducted using a Vivid E95 ultrasound machine (GE Vingmed Ultrasound AS, Horten, Norway) with an 4Vc-D probe at three time points: baseline (pre-implant), mid-term (6 weeks), and long-term (a minimum of 12 months) post-implant. Apical four-chamber, two-chamber, and three-chamber images were captured over at least three cardiac cycles at a frame rate of 45 or more per second and stored digitally for subsequent offline analysis. Peak systolic LV pressure was assumed to equal branchial cuff of the LV pressure (Russell et al., 2012), therefore blood pressure was measured via a brachial cuff at the start of each examination with the patient laying on their left side.

The modified Simpson's approach was used to calculate the LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV ejection fraction (LVEF) (Lang et al., 2015).

Global longitudinal strain (GLS) and segmental strain in the LV were analysed using the speckle tracking echocardiography (Mor-Avi et al., 2011, D'hooge et al., 2015). The reference for zero strain being the electrocardiogram (ECG) R-trigger. Spectral Doppler recordings were used to determine the timing of valvular events (Mada et al., 2015).

A specialised workstation (EchoPAC version 206, GE Vingmed) was set up to analyse the echo data. An observer performed MW analysis using the GE automated algorithm of the workstation where strain and pressure data were synchronised, and the area within the pressure-strain loops (PSL) provided measurements for each myocardial segment (Smiseth et al., 2021). CW and WW were defined based on segmental shortening and lengthening during systole and isovolumic relaxation. Global MW was defined based on the overall work performed by the entire LV and was measures by averaging segmental work data from each LV segments, whilst regional MW focuses on the performance of individual segments within the LV. MW measures includes work index (WI), CW, WW and MWE. An example of work efficiency (WE) in a patient with LV dyssynchrony (Panel A) and without LV dyssynchrony (Panel B) is illustrated in **Figure 5.2**. In Panel A (with LV dyssynchrony), the septal segment shows very low efficiency (19%), while the lateral segment is better (71%). The irregular and smaller S-shape pressure-strain loop reflects inefficient contraction, while the lateral loop is larger but still impaired. In contrast, Panel B (without LV dyssynchrony) shows much higher, uniform efficiency across all segments (91% septal, 96% lateral), with well-formed pressure-strain loops indicating synchronous and efficient contraction throughout the heart. This comparison highlights how LV dyssynchrony leads to inefficient and unco-ordinated heart function.

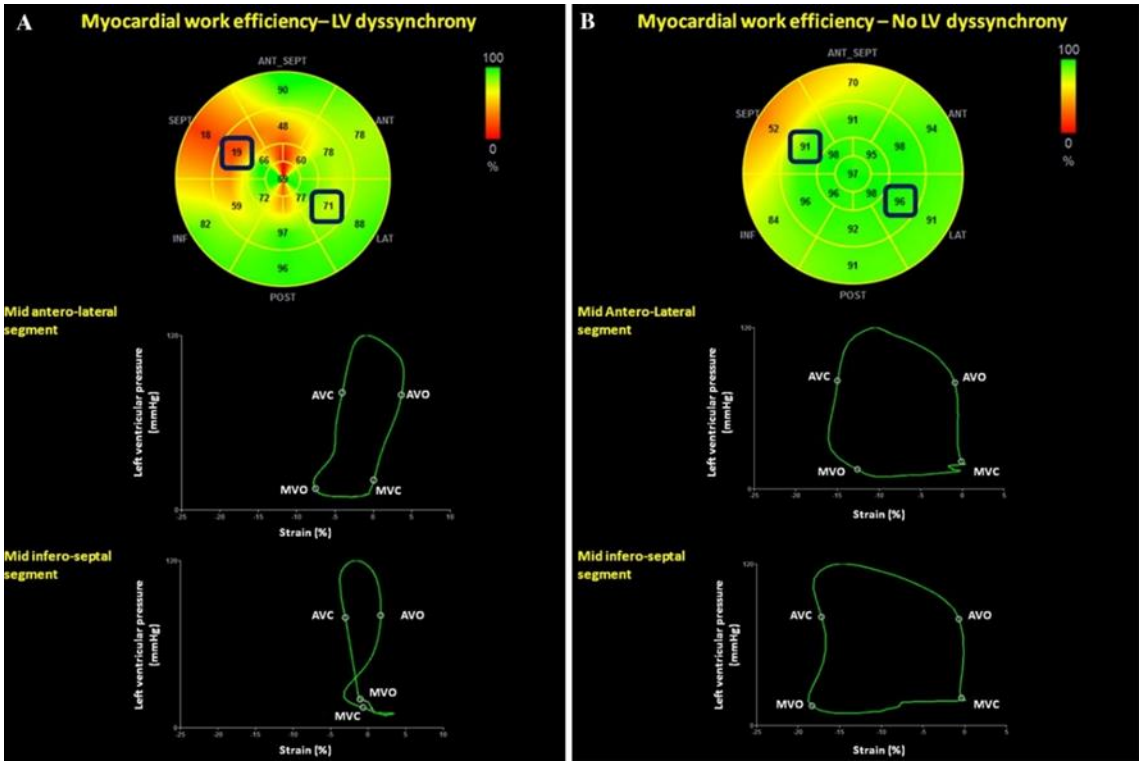


Figure 5.2 Comparison of Myocardial Work Efficiency in Patients With and Without Left Ventricular Dyssynchrony. Bull's-eye representing myocardial work efficiency demonstrates myocardial work in a patient with left ventricular dyssynchrony (Panel A) and in a patient without left ventricular dyssynchrony (Panel B). The pressure-strain loops, illustrating septal and lateral work, are provided under each corresponding bull's-eye.

This figure is in the public domain and was sourced from [Schrub, F., Schnell, F., Donal, E. et al. Myocardial work is a predictor of exercise tolerance in patients with dilated cardiomyopathy and left ventricular dyssynchrony. Int J Cardiovasc Imaging 36, 45–53 (2020). https://doi.org/10.1007/s10554-019-01689-4

5.3.3 Outcome measures

The primary outcome was to assess both global MW index between those who preserved LVEF (LVEF≥50%) and those who did not (LVEF<50%) over time, post pacemaker implantation.

5.3.4 Data analysis

5.3.4.1 Descriptive analysis

Baseline continuous data were firstly assessed for normality using Shapiro-Wilk test. Normally distributed data are presented as mean (standard deviation), and continuous non-normally distributed data as median (interquartile range). Categorical data are presented as number (percentage). Student t-tests or ANOVA were used to analyse normally distributed continuous data, Mann-Whitney U-tests or Kruskal-Wallis H-tests for non-normally distributed continuous data, and Pearson $\chi 2$ tests for categorical data.

5.3.4.2 Statistical analysis

Repeated measures analysis of variance (ANOVA) with Bonferronni correction was performed to investigate the effect of RVA pacing on LV ejection fraction (LVEF) and MW measures from baseline (pre-implant) to mid-term (6-week) to long-term (a minimum of 12-month) post pacemaker implantation. Additionally, changes in MW measures observed between those that developed LVSD (defined as an LVEF of <50%) were compared to those with a preserved LVEF ≥50%. Data analysis was performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp, Armonk, NY, USA, 2020). A statistical significance was pre-specified as $p < 0.05$.

5.4 Result

5.4.1 Population characteristics

A total of 118 patients who received pacemaker therapy for second and third degree AVB were included for analysis with mean age of 75±10 years with 81 (69%) patients being male **(Table 5-1).** Thirty-three (28%) patients classified as NYHA Class II, 10 (8%) patients as NYHA Class III, and 5 (4%) patients as NYHA Class IV. Forty-two (36%) patients had a history of ischaemic heart disease (IHD), 38 (33%) patients had Type II diabetes mellitus, and 72 (61%) patients had diagnosed hypertension with a mean systolic pressure of 148±24 mmHg and mean diastolic pressure of 72±16 mmHg at baseline.

Table 5-1 Baseline demographics of study population

	***n* = 118**
Age (years)	75 (±10)
Male (%)	81 [69%]
NYHA Classification	
Class II	33 [28%]
Class III	10 [8%]
Class IV	5 [4%]
Diabetes (%)	38 [33%]
Hypertension (%)	72 [61%]
Systolic blood pressure (mmHg)	148(±24)
Diastolic blood pressure (mmHg)	72 (±16)
Medication prescriptions	
B-blocker (%)	52 [44%]
ACEi (%)	45 [38%]
Pacing measures	
Second and third degree AVB indication (%)	118 [100%]
QRS duration (ms)	124 (±29)
RVP burden (%)	99 (77-100)
Traditional echocardiographic measures	
LVEDV (ml)	114 (35-222)
LVESV (ml)	52 (17 -119)
LVEF (%)	56 (±8)
Advanced echocardiographic measures	
GWI (mmHg%)	1893 (±624)
MWI_S (mmHg%)	1766 (±895)
MWI_L (mmHg%)	1940 (±773)

Values are presented as mean (± standard deviation) or median (interquartile range) and *n* (%).
NYHA; New York Heart Association, β-blocker; beta-blocker, ACEi; angiotensin-converting-enzyme inhibitor; AVB; atrioventricular block, RVP; right ventricular pacing, LVEDV; left ventricular end-diastolic volumes, LVESV; left ventricular end-systolic volumes, LVEF; left ventricular ejection fraction, MWI_S; myocardial work index at septal, MWI_L; myocardial work index at lateral, GWI; global work index A p-value <0.05 were considered significant.

5.4.1.1 Medication

Fifty-two (44%) patients were prescribed beta-blockers, and 45 (38%) patients were prescribed angiotensin-converting-enzyme (ACE) inhibitor at baseline.

5.4.1.2 Pacing measures

These patients with second and third degree AVB required a median of 99 (IQR 77-100) % RVP and had a mean QRS duration of 124±29 ms post pacemaker implantation.

5.4.1.3 Baseline echocardiographic measures

Traditional echocardiographic measures showed a median LVEDV of 114 (IQR: 35-222) ml, LVESV of 52 (IQR: 17-119) ml and mean LVEF of 56±8 % at baseline. Advanced echocardiographic measures for global measurements revealed a mean global work index (GWI) of 1893±624 mmHg%, whilst for regional measurements revealed a mean septal myocardial work index (MWI_S) of 1766±895 mmHg% and a mean lateral index ($MWI_{L)}$ of 1940±773 mmHg% at baseline.

5.4.2 The impact of RV pacing on LVEF

Mean LVEF significantly reduced from baseline to mid-term to long-term follow up (mean 56±8% to 53±8% to 48±10%, p=0.001, respectively) after pacemaker implantation **(Figure 5.3)**. After a median long-term follow up of 454 (IQR:54-857) days, 33 (28%) patients had LVSD, defined as an LVEF <50%.

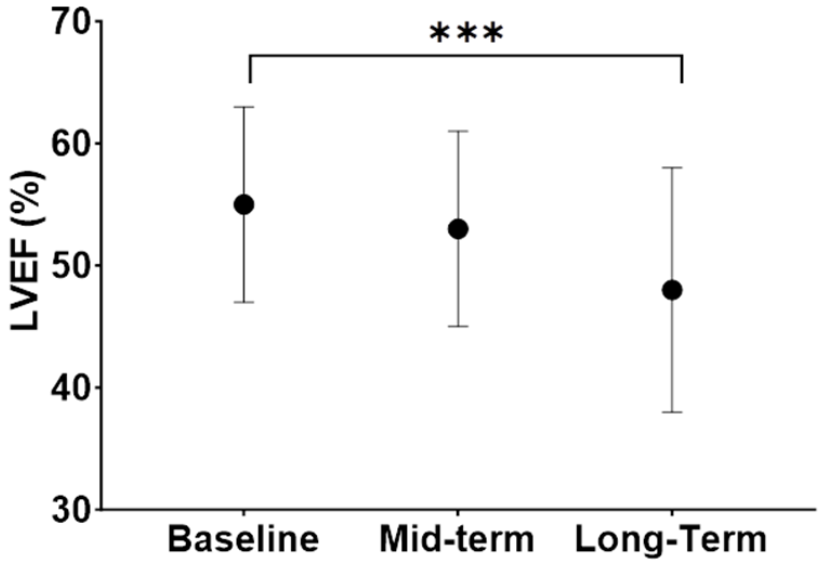


Figure 5.3 Mean ± standard deviation of left ventricular ejection fraction (LVEF) percentage from baseline (median of 20 (IQR:4-132) days pre implant) to mid-term (median of 10 (IQR:2-156) days post implant) to long-term (median of 454 (IQR:54-857) days post implant. A p value <0.05 is statistical significance and denote as * The impact of RV pacing on LV mechanics

Global myocardial work parameters showed significant differences between groups from baseline (median 20 (IQR: 4-132) days, pre implant) to mid-term (median 10 (IQR: 2-156) days, post implant) to long-term (median 454 (IQR: 54-857) days, post implant, with patients who preserved LVEF ≥50% exhibiting consistently higher values for global work index (GWI) compared to those with a reduced LVEF at follow-up (2092±714 mmHg% to 1473±430 mmHg% to 1593±511 mmHg% vs 1760±393 mmHg% to 968±463 mmHg% to 996±522 mmHg% respectively) **(Table 5-2)**

Table 5-2 Repeated measures analysis of variance (ANOVA) from baseline (median of 20 (IQR:4-132) days pre implant) to mid-term (median of 10 (IQR:2-156) days post implant) to long-term (median of 454 (IQR:54-857) days post implant between those that developed LVSD (defined as an LVEF of <50%), compared to those with a preserved EF

	LVEF preserved (>50%) (n=24)			LVEF reduced (<50%) (n=28)			
Global measures	**Baseline** Median -20 days (IQR: 4-132)	**Mid-term** Median 19 days (IQR: 2-156)	**Long-term** Median 454 days (IQR: 64-857)	**Baseline** Median 20 days (IQR: 4-132)	**Mid-term** Median 19 days (IQR: 2-156)	**Long-term** Median 454 days (IQR: 64-857)	**p=value**
GWI (mmHg%)	2092±714	1473±430	1593±511	1760±393	968±463	996±522	<0.01*
GCW (mmHg%)	2477±694	1988±546	2073±471	2033±412	1503±498	1496±521	<0.01*
GWW (mmHg%)	228±190	383±189	394±279	176±120	404±221	292±185	<0.01*
GWE (%)	90±5	83±8	84±7	91±4	79±7	80±9	0.09
	LVEF preserved (>50%) (n=24)			**LVEF reduced (<50%) (n=28)**			
Regional measures	**Baseline** Median 20 days (IQR: 4-132)	**Mid-term** Median 19 days (IQR: 2-156)	**Long-term** Median 454 days (IQR: 64-857)	**Baseline** Median 20 days (IQR: 4-132)	**Mid-term** Median 19 days (IQR: 2-156)	**Long-term** Median 454 days (IQR: 64-857)	**p=value**
MWI_S (mmHg%)	1752±875	1099±474	1223±549	1852±982	710±626	630±605	0.09
MWI_L (mmHg%)	1910±654	1548±572	1789±528	1708±405	972±508	1093±584	0.21

Continuous data are presented as mean (± standard deviation). A p-value ≤0.05 denotes * was considered significant
GWI: global work index; GCW: global constructive work; GWW: global wasted work; GWE: Global work efficiency; MWI_S: myocardial work index at septal; MWI_L: myocardial work index at lateral

Global constructive work (GCW) reduced over time in both those that demonstrated LVEF maintenance, and in those who did not at follow-up, although it was significantly lower over time in patients with a reduction in LVEF (GCW: 2477± 694 mmHg% to 1988±546 mmHg% to 2073±471 mmHg% vs 2033±412 mmHg% to 1503±498 mmHg% to 1496±521 mmHg% respectively). In contrast, global wasted work (GWW) increased in both groups with significantly different measures over time: (LVEF preserved: 228±190 mmHg% to 383±189 mmHg% to 394±279 mmHg% vs LVEF reduced: 76±120 mmHg% to 404±221 mmHg% to 292±185 mmHg%). ($p<0.01$ for all comparisons) **(Figure 5.4).**

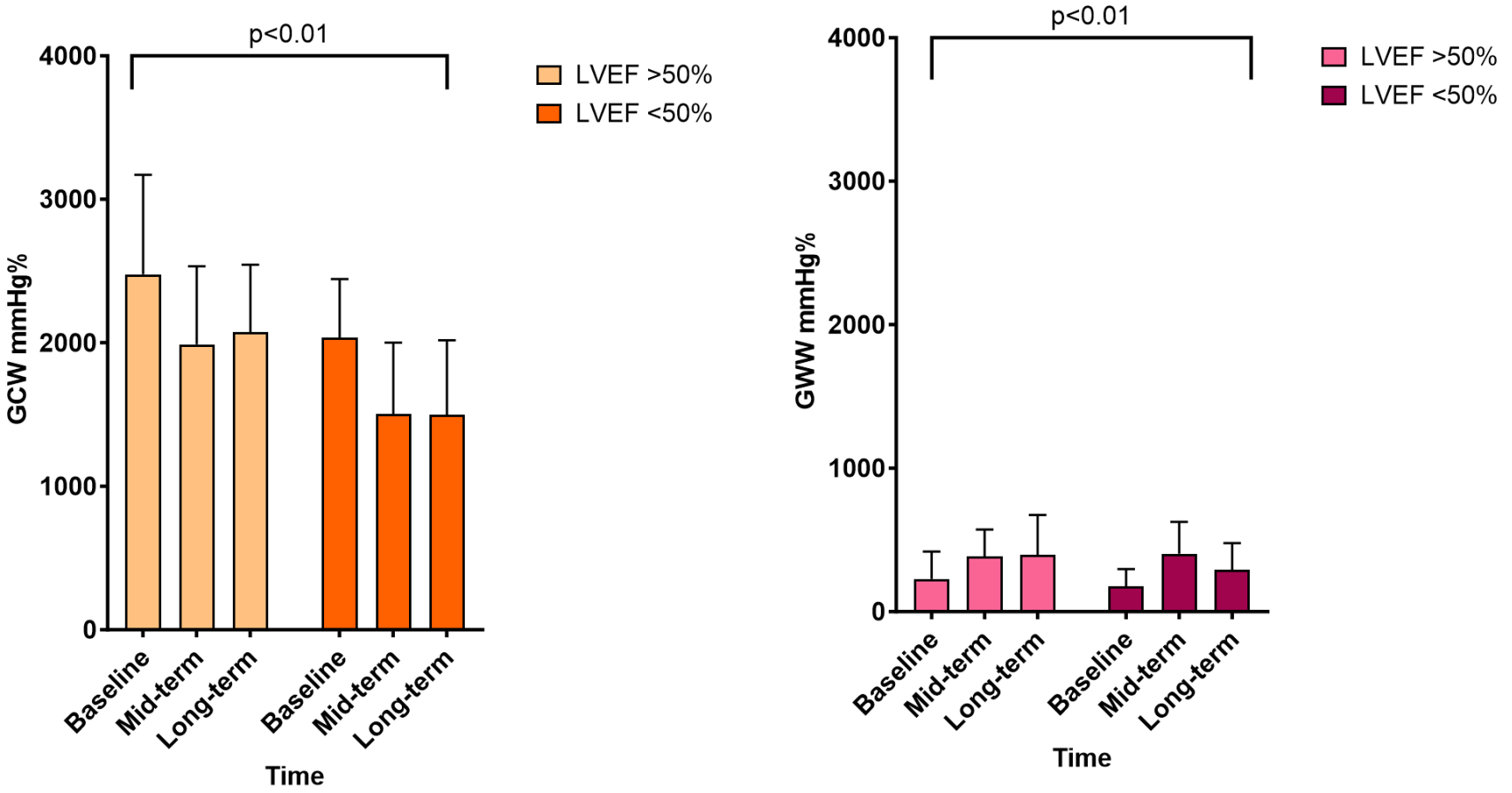


Figure 5.4 Distribution of global myocardial work (GCW) and global wasted work (GWW) by left ventricular ejection fraction (LVEF) from baseline (median of 20 (IQR:4-132) days pre implant) to mid-term (median of 10 (IQR:2-156) days post implant) to long-term (median of 454 (IQR:54-857) days post implant. A p value <0.05 is statistical significance and denote as *

Regional LV MWI measurements did show any significant difference between the groups (preserved LVEF ≥50% vs reduced LVEF <50%) over time, both at the septal (MWIs) ((1752±875 mmHg% to 1099±474 mmHg% to 1223±549 mmHg%) vs. (1852±982 mmHg% to 710±626 mmHg% to 630±605 mmHg%), p=0.09, respectively) and lateral regions specifically (MWI_L) ((1910±654 mmHg% to 1548±572 mmHg% to 1789±528 mmHg%) vs. (1708±405 mmHg% to 972±508 mmHg% to 1039±584 mmHg%), p=0.21, respectively) **(Table 5-2)**. Although MWI_S shows sharp decline in patients who develop LVSD (LVEF<50%) and a trend towards statistical significance for the difference between groups during follow-up **(Figure 5.5).**

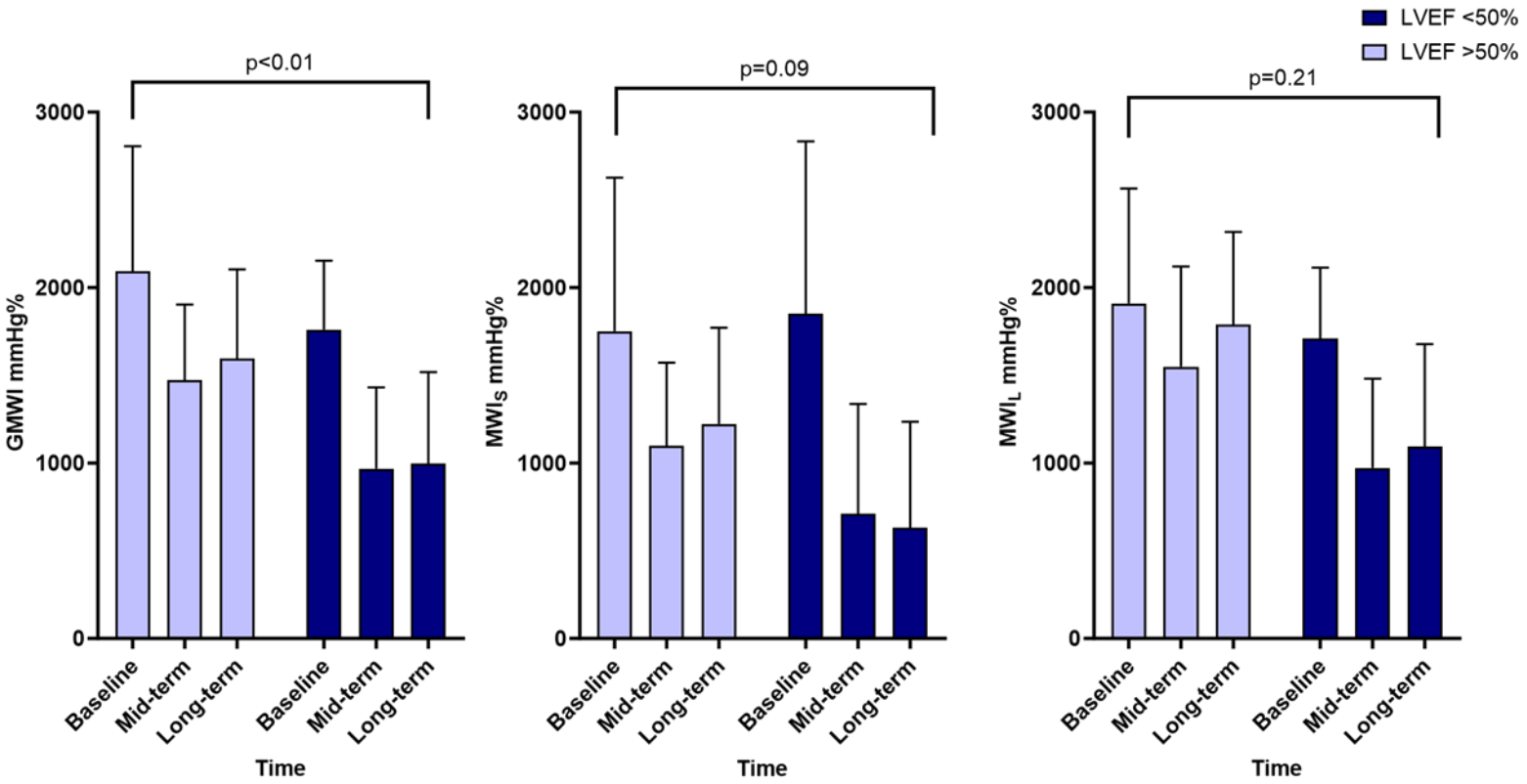


Figure 5.5 Distribution of myocardial work index at global (GWI), septal (MWIS) and lateral (MWIL) by left ventricular ejection fraction (LVEF) group from baseline (median of 20 (IQR:4-132) days pre implant) to mid-term (median of 10 (IQR:2-156) days post implant) to long-term (median of 454 (IQR:54-857) days post implant). A p value <0.05 is statistical significance and denote as *

5.5 Discussion

I confirmed that LVEF progressively declines over long-term follow-up in patients receiving a pacemaker implants, but that limited changes in LVEF could be observed in the medium term.

In contrast, significant reductions in MW measures were observed more acutely following implantation. Specifically, significant differences were found in GWI, GCW, and GWW between patients who preserved (LVEF ≥50%) and those who did not (LVEF <50%). Patients with a preserved LVEF despite RVP demonstrated higher GWI and GCW, whilst those who did not, exhibited a marked decline in GWI and GCW. These findings indicate MW may have clinical utility in identifying patients at risk of developing LVSD earlier than traditional echocardiographic measures.

5.5.1 Detrimental effect of RVP on LV function

After a median follow-up of 454 (IQR:54-857) days, 28% of the cohort developed reduced systolic function, as evidenced by an LVEF of less than 50%. These findings align with previous studies (Kaye et al., 2015, Gierula et al., 2015, Gierula et al., 2014, Paton et al., 2021) that have identified RVP as a potential contributor to dyssynchronous LV contraction, which may progress to adverse LV remodelling and deteriorating systolic function (Nahlawi et al., 2004).

Moreover, although the clinical significance of an LVEF below 50% can lead to a a diagnosis of HF with reduced ejection fraction and heightened morbidity and HF risk (Davies et al., 2001, van Riet et al., 2016, Thackray et al., 2003, Gierula et al., 2015), the LVEF cut-off is necessarily arbitrary. Whether a reduction in LVEF of 10% has the same adverse effect even if the overall LVEF remains above 50%, is unknown. Nevertheless, the 28% of patients who developed reduced LVEF after pacemaker implantation would generally be considered to be at higher risk for adverse cardiovascular outcomes.

The cumulative decrease in LVEF over time highlight the need for careful patient selection and close monitoring when considering RVP in individuals who have normal baseline LV systolic function (Gierula et al., 2014, Paton et al., 2019, Paton et al., 2021). These results may also advocate for alternative pacing strategies, such as CSP or CRT, to preserve LV function in the long-term (Gierula et al., 2013, Mao et al., 2023). However, while LVEF can indicate the presence of LVSD, it potentially requires cardiac remodelling and functional impairment to have developed to a higher degree before a clinically relevant changes is detected, suggesting a more advanced stage of disease. Whereas utilising measures such as MW may allow for detection of subclinical disease and could enable patients to receive therapy initiation more promptly.

In future research, incorporating exercise data and biomarkers such as NT-proBNP could further enhance the early identification of patients at risk of developing LVSD. Exercise testing, through its ability to assess functional capacity and detect early signs of cardiovascular stress, could complement traditional measures of systolic function by identifying subtle changes in cardiovascular performance that precede overt dysfunction (Ezzatvar et al., 2021, Begg et al., 2011b, Lepretre et al., 2004). Similarly, NT-proBNP, a biomarker associated with HF and increased myocardial stress, could be utilised to detect early elevations that may indicate subclinical HF or impending LVSD (Panagopoulou et al., 2013, Oremus et al., 2014, Doust et al., 2006, Cowie and Mendez, 2002). Together, these tools could aid in identifying patients at risk for deterioration, allowing for more personalised and timely interventions.

5.5.2 Traditional approaches to prevent pacemaker-related LVSD

Pacemaker patients with impaired LV characterised by an LVEF < 35%, HF symptoms, and an extended QRS duration on ECG (Members et al., 2013), are recommended for an 'upgrade' procedure to insert an extra pacemaker lead in order to normalise the heart's contraction. However, this requires the patient to first develop HF, and then undergo a secondary procedure with additional risks associated with complications (Poole et al., 2010b). Although

the evidence is very limited, upgrade procedures account for 25% of all cardiac resynchronisation therapy (CRT) implants in Europe (Poole et al., 2010a).

A retrospective review of patients who underwent CRT according to clinical guidelines revealed that those who were 'upgraded' from RVP, as opposed to patients who received CRT therapy for the first time, had worse outcomes despite comparable improvements in LV systolic function (Rickard et al., 2019). Although this study was conducted at a single location and may not be applicable to all patients, the results suggest that patients with RVP may have a more severe disease condition by the time they are permitted to undergo device upgrade, compared to those who are clinically recommended for de novo CRT. The efficacy of CRT in patients without pre-existing HF diagnoses remains uncertain. Only one trial, conducted in Leeds, prospectively investigated the effectiveness of implanting CRT in individuals with a significant level of unavoidable RVP and LVSD, but with low symptoms (Gierula et al., 2013). 'Upgrading' from RVP to CRT implantation in patients who do not yet meet all the requirements for CRT implantation was both safe and resulted in improved LV function, exercise capacity, and quality of life. However, the study utilised surrogate outcomes of LVEF, NT-proBNP levels, peak oxygen consumption and quality of life and would benefit from further investigation assessing clinical outcomes.

The BLOCK-HF trial investigated the comparative effectiveness of CRT and RVP in individuals receiving their de novo implantation with high grade AVB, LVSD with LVEF <50%, and mild HF symptoms (Curtis et al., 2007). The use of CRT was linked to a reduced incidence of a composite outcome of all-cause death, HFH, and worsening LV function compared to RVP (Curtis et al., 2007). Nevertheless, the study's design was limited by the absence of a true control group, making it difficult to assess the benefits of CRT over RV pacing. Implanting CRT in all patients with half programmed to RVP only restricted comparisons as CRT procedures have 14% higher complication rates with 10% related to the LV lead compared to standard RVP, especially outside a trial setting (Witte, 2014). Additionally, CRT implantation takes

longer, and battery life is shorter, increasing costs. Accurate cost-benefit analyses require data from both standard care and intervention groups to weigh reduced HFH against the higher risks and costs associated with CRT (Funck et al., 2006, Vijayaraman, 2019). Therefore, CRT has not yet been universally accepted as the primary treatment for these patients, requiring additional research with improved study design.

In 2005, the second ‘prevention’ trial BIOPACE randomised 1200 patients to CRT or a standard RVP for 5 years (Funck et al., 2006).Despite study extensions, recruiting 1810 individuals and following up for 5.6 years, the 2014 conference report found no change in all-cause mortality and HF hospitalisation (Barold and Israel, 2015). It is widely believed that improved patient selection may have provided different results.

5.5.3 Advanced echocardiography as a novel measure

When considering global MW measurements, the differences between patients with preserved and reduced LVEF were more pronounced. Those who preserved LVEF consistently exhibited higher GWI and GCW values throughout the follow-up period, while GWW remained relatively stable. In contrast, those who did not (LVEF <50%) experienced significant declines in both GWI and GCW, alongside a significant increase in GWW ($p<0.01$). These findings suggest that, globally, the heart's ability to perform effective constructive work diminishes in patients with pacing-related LVSD, with a concurrent increase in wasted energy, further contributing to overall LV inefficiency (Russell et al., 2013). The progressive decline in GWI and GCW in the reduced LVEF group aligns with the observed reduction in LVEF, suggesting a strong association between impaired early MW and longer-term systolic function. Global measures may provide a more comprehensive understanding of the heart’s response to chronic pacing, demonstrating the cumulative impact on myocardial performance and LV remodelling over time.

On a regional level, Selective deterioration in septal LV mechanics likely arises due to the abnormal electrical activation associated with RVP, which disrupts normal contraction mechanics, primarily in the septum, a key region for maintaining co-ordinated ventricular contraction (Bank et al., 2012, Duchenne et al., 2019c, Russell et al., 2013).Interestingly, regional MWI in both the septal (p=0.09) and lateral (p=0.21) LV walls did not show significant changes over time despite the observed decline in MWI_S. It is possible that regional adaptations within the LV may occur in response to pacing in order to compensate in an attempt to maintain homogeneity in work distribution, but that these compensatory mechanisms are insufficient to prevent global LVSD in some patients (Russell et al., 2013, Duchenne et al., 2019c).

5.5.4 Predictive value of baseline MW measurements

In summary, both global and regional MW measurements may have their merits in assessing LVSD. Global MW measurements provide a comprehensive view of overall cardiac performance. They account for the cumulative effects of all myocardial regions, making them useful for identifying systemic changes in cardiac function. Global measurements may be more sensitive to overall cardiac efficiency and the overall workload of the heart. My finding emphasise they may have value in can detecting declines in performance that might indicate early stages of LVSD before regional changes become pronounced.

Regional measurements, particularly those focused on the septal wall, can provide insights into localised dysfunction that may arise from RVP-related dyssynchrony or other conditions. They help identify specific areas of the heart that may be at risk and may offer an early warning for LVSD, especially in patients experiencing electrical conduction abnormalities.

In clinical practice, a combination of both approaches may provide the most accurate and timely predictions of LVSD. Monitoring global measurements can alert clinicians to impending

dysfunction allowing the initiation of protective medical therapy while regional assessments can pinpoint areas needing intervention or further evaluation.

5.5.5 Clinical implications of findings

The findings of this study emphasize the impact of RVP on LV function, as evidenced by the observed reductions in LVEF and MW measurements over time. These results suggest that conventional RVP may contribute to progressive LVSD, reinforcing the importance of assessing alternative pacing strategies for patients at risk of LV dysfunction. Importantly, the association between declines in MW and LVEF over time highlights MW as a potential tool for linking RVP with long-term reductions in LV function.

Given these findings, there is an urgent need to study if MW measures can predict the likelihood of LVSD prior to the initial pacing implant. Early identification of patients with a high risk of LV dysfunction would allow for pre-emptive intervention with alternative pacing modalities such as CRT or CSP, which have shown promise in preserving LV function by co-ordinating or restoring more physiological ventricular activation patterns. Focussing on predictive MW measures at this stage may improve patient outcomes by guiding pacing strategy decisions prior to permanent LV failure, minimising the need for subsequent treatments and, eventually, improving patient care.

5.6 Limitations

This study has several limitations that should be considered when interpreting the results. First, the study's observational design limits the ability to establish causal relationships. While the findings indicate significant changes in MW distributions over time according to following pacemaker implantation, they do not definitively prove that RVP is the only predictor of LVSD. Other confounding factors, such as underlying comorbidities and patient characteristics, could influence the outcomes.

Second, the sample size of 118 patients, while adequate for preliminary analysis, may limit the generalisability of the findings to broader populations. The specific demographic characteristics of the patient population, including a high mean age (75±10 years) and a predominance of male patients (69%), may not represent younger or female populations who may also be candidates for pacemaker therapy. Moreover, there were only 3 patients of total cohort who included from the UK centre. This was due to a lack of pre-implant echocardiography assessment. Importantly, the retrospective nature of the study also led to considerable variation in the follow-up intervals and length between patients, indicated by a wide interquartile range of 64 to 857 days. In order to fully understand the development of LVSD in this patient population, the LV mechanical work distribution, and its predictive value, patient data from patient's pre-implant, and structured follow-up data is required. Consequently, in order to perform.an assessment of predictors, prospective investigations are required.

Finally, while advanced echocardiographic measures of MW provide valuable insights, their interpretation may be limited by the variability in imaging techniques and the potential for operator-dependent biases. Standardisation of measurement protocols and techniques, and assessment of reliability and reproducibility, is crucial when highlighting the usability diagnostic measures.

5.7 Conclusion

This study demonstrates that RVP significantly impacts LV function in patients with AVB, leading to a decline in LVEF and altered MW distribution, particularly at the septal wall. Patients who maintain LVEF above 50% show more favourable MW measurements throughout follow-up, and those who experience a longer-term reduction in LVEF, demonstrate a more acute change in LV mechanics

Given the association of RVP with LVSD, this research highlights the need for therapeutic optimisation.MW distribution patterns change according to outcome, and therefore further investigation of their predictive value in to aid early identification of those who could benefit from these interventions, ultimately enhancing patient care should be assessed in clinical practice.

In conclusion, this study advocates for a paradigm shift in the management of patients with AVB, emphasising the importance of individualised pacing strategies to mitigate the risk of RVP-related LVSD and that advanced echocardiography measurements such as MW could potentially be valuable to give insight into determining patients at risk earlier. Further prospective and standardised assessments on MW measurements, is required to further explore the development of mechanical dysynchrony in pacing patients.

5.8 Dissemination of findings

The study preliminary findings have been presented as a poster presentation at the American Heart Association Conference (AHA) in Philadelphia, United States, in 2023. The conference abstract has been published on the AHA journal. The full-text manuscript is currently in preparation for submission to *Echo Research and Practice*.

Chapter 6 Predicting left ventricular systolic dyssynchrony and adverse remodelling using measures of left ventricular mechanics

6.1 Abstract

Introduction

Right ventricular (RV) pacing (RVP) can lead to left ventricular (LV) dyssynchrony, resulting in LV remodelling and dysfunction in up to 40% of pacemaker patients, increasing the risk of heart failure (HF) and the need for device upgrades to cardiac resynchronisation therapy (CRT). However, it is unclear which patients are most vulnerable to RVP-related LV remodelling before pacemaker implantation. Novel myocardial work (MW) measurements change in patients who experience a reduction in LV function following pacemaker implantation and thus may offer valuable insights to better identify patients at risk for LV remodelling prior to implantation.

Aim

To evaluate changes in LV function and mechanics over time in patients with atrioventricular block (AVB) using MW measurements and to assess if measures prior to implant can identify patients at risk of developing RVP-related LV systolic dysfunction.

Methods

Patients aged 18 and older, referred for pacemaker implantation due to high-degree AVB between July 2022 and August 2024 from a single tertiary hospital (Leeds Teaching Hospitals – Leeds General Infirmary) were recruited. Baseline data included demographics, medical history, physical measurements, blood pressure, and blood tests. Echocardiography was performed pre-implant, shortly after implant, at 6 weeks, and at 6 months. Device interrogations were conducted at 6 weeks and 6 months as standard care. Changes in LV

function and mechanics were analysed using repeated measures ANOVA with Bonferroni correction from baseline (pre implant) to acute (0-6 weeks) and mid-term (6 months) post implant. Multivariable linear regression assessed the relationship between pre-implant myocardial work (MW) patterns and post-implant LV remodelling, defined as a ≥15% increase in LV end systolic volume index (LVESVi) or a ≥10% decrease in LV ejection fraction (LVEF).

Result

A total of 90 patients (mean age 75±11 years, 23% female) were included. Over time, significant differences were found between groups of patients who preserved LVEF (≥50%) and those who did not (LVEF<50%), in global MW index (GWI) ((2047±730 mmHg% to 1714±402 mmHg% to 1696±561 mmHg%) vs. (1764±614 mmHg% to 1515±712 mmHg% to 1410±590 mmHg%,) respectively, p=0.01) and global constructive work (GCW) ((2583±735 mmHg% to 2175±471 mmHg% to 2168±668 mmHg%) vs. (2263±764 mmHg% to 1954±650 mmHg% to 1873±611 mmHg%), respectively, p=0.01). Regional MW at the septal wall (MWI_S) differed significantly according to long-term LV systolic function (Preserved LVEF:1762±798 mmHg% to 1572±576 mmHg% to 1419±604 mmHg% vs. Reduced LVEF:1623±802 mmHg% to 1150±756 mmHg% to 1256±649 mmHg%, p=0.02), but not at the lateral wall (MWI_L) (p=0.47). Septal-lateral difference (MWI_{S-L}) was also not significantly different between groups over time (p=0.24). Age and VPB significantly predicted LV remodelling (LVESVi >15% or LVEF <10%) in both unadjusted (HR 1.04, 95% CI: 1.04-1.32; HR 1.05, 95% CI: 1.00-1.10) and adjusted models (HR 1.04, 95% CI: 1.04-1.32; HR 1.05, 95% CI: 1.00-1.10).

Conclusion

LVEF and LV volumes predominantly remained stable post pacemaker implantation, but significant declines in MW measures suggest early changes in LV remodelling. These advanced echocardiographic measures change acutely in patients who develop RVP-related LV remodelling. This may enable directed tailoring of alternative protective pacing strategies

or protective medical therapy. However, the utility of MW measures in predicting LV remodelling before pacemaker implant remains unclear.

Keywords

Right ventricular pacing, left ventricular remodelling, left ventricular mechanics, myocardial work.

6.2 Introduction

Left ventricular systolic dysfunction (LVSD) is seen in up to 40% of patients with a pacemaker (Thackray et al., 2003, Gierula et al., 2015, Paton et al., 2021). Unfavourable left ventricular (LV) remodelling in the presence of a pacemaker is progressive, and reprogramming to minimise right ventricular (RV) pacing (RVP) requirement can lead to an improvement in cardiac function in patients who are not pacemaker dependent (Gierula et al., 2014, Paton et al., 2019). Those who develop LVSD but cannot be reprogrammed (pacing dependent) can undergo a second procedure to upgrade to a cardiac resynchronisation therapy (CRT) device (Gierula et al., 2013), yet this comes with a higher risk of complications. Prior to the first implant, there is currently no adequate way to predict whether a patient is at risk of LVSD. Such information would allow personalisation and optimisation of the prescription for the first device. Conversely, a conventional pacemaker could be safely implanted in patients who have a lower likelihood of developing LVSD in response to RVP.

A maladaptive response to heterogeneous myocardial loading conditions as a consequence of the dyssynchrony related to pacing may encourage adverse remodelling in response to RVP (Cheng et al., 2009). While left ventricular ejection fraction (LVEF) is commonly used to assess global ventricular function, it does not sufficiently capture the regional disparities in myocardial strain and work that arise from RVP-related dyssynchrony. Echocardiographic measurements of regional myocardial work (MW) have previously shown that MW becomes

more heterogeneous in sheep following RVP (Duchenne et al., 2019a), particularly in those that go on to experience LVSD. This is especially true for the septal and lateral regions, which are most affected by the asynchronous contraction patterns that develop during RVP (Prinzen and Peschar, 2002, Bank et al., 2012). The septal region tends to activate prematurely, while the lateral wall is delayed, exacerbating the disco-ordinated distribution of MW and leading to impaired global LV function.

According to my previous work in chapter 5, patients who develop LVSD following pacemaker implantation may also display distinct differences in MW patterns compared to those who preserved LVEF. Interestingly, early deterioration of MW measurements was also observed in those patients that subsequently preserved an LVEF of greater than 50%. Additionally, in patients with HF who demonstrate successful LV remodelling following CRT pacing, the MW pattern within the LV has been observed to become more homogenous between regions (Cvijic et al., 2018, Duchenne et al., 2019b). These findings highlight the potential of MW to serve as an early indicator of patients at risk of RVP-related LVSD and HF.

Echocardiography, being non-invasive and widely accessible, provides an excellent tool for risk stratification in this regard. By leveraging MW measurements through strain imaging, clinicians may be able to identify early signs of regional LV mechanical dysfunction and stratify patients who are at greater risk of adverse LV remodelling prior to pacemaker implantation. This allows for proactive management to prevent the development of HF including a personalisation of the implanted hardware, perhaps choosing a CRT device or conduction system location for the RV lead.

The proposed prospective research project, therefore, aims to address a key challenge that has hounded pacemaker therapy for the past 20 years: Can clinicians identify patients who are more likely to develop RVP-related LVSD before a pacemaker is implanted? By focusing on regional MW patterns in patients who require high ventricular pacing burden (VPB) due to

atrioventricular block (AVB), this project seeks to develop predictive models that could guide clinical decision-making, potentially improving long-term outcomes for patients receiving pacemakers.

6.3 Method

6.3.1 Study population

This was a prospective observational study. Patients over 18 years of age, indicated for pacemaker implantation due to AVB (ESC guidelines), and capable of providing informed consent were eligible for participation. Patients with life-threatening co-morbidities, significant cognitive impairment affecting their ability to consent, or those for whom diagnostic ultrasound images cannot be obtained, were excluded. All eligible patients referred for pacemaker implantation during the study period (July 2022- August 2024) at a single tertiary hospital (Leeds Teaching Hospitals – Leeds General Infirmary) were invited to participate. Ethical approval was obtained (22/EE/0080) and all participants provided written informed consent prior to inclusion in the study. All research efforts adhered to the principles outlined in the Helsinki Declaration.

6.3.2 Data collection

6.3.2.1 Baseline assessment

Baseline data collection occurred prior to pacemaker implantation, and included patient demographics, medical history, physical measurements (height and weight) and non-invasive blood pressure. Blood samples were drawn to assess full blood count, urea and electrolytes, and N-terminal pro–B-type natriuretic peptide (NTpro-BNP). Participants received a focused echocardiogram to assess LV function pre implant.

6.3.2.2 Follow-up assessment

Participants underwent follow-up assessments at 6 weeks, and 6 months post pacemaker implantation for routine standard of care device interrogations. During this appointment an additional focused echocardiogram was conducted for research **(Figure 6.1)**. The research team had access to the participants' medical records to collect clinical outcome data throughout the 6-month follow-up period.

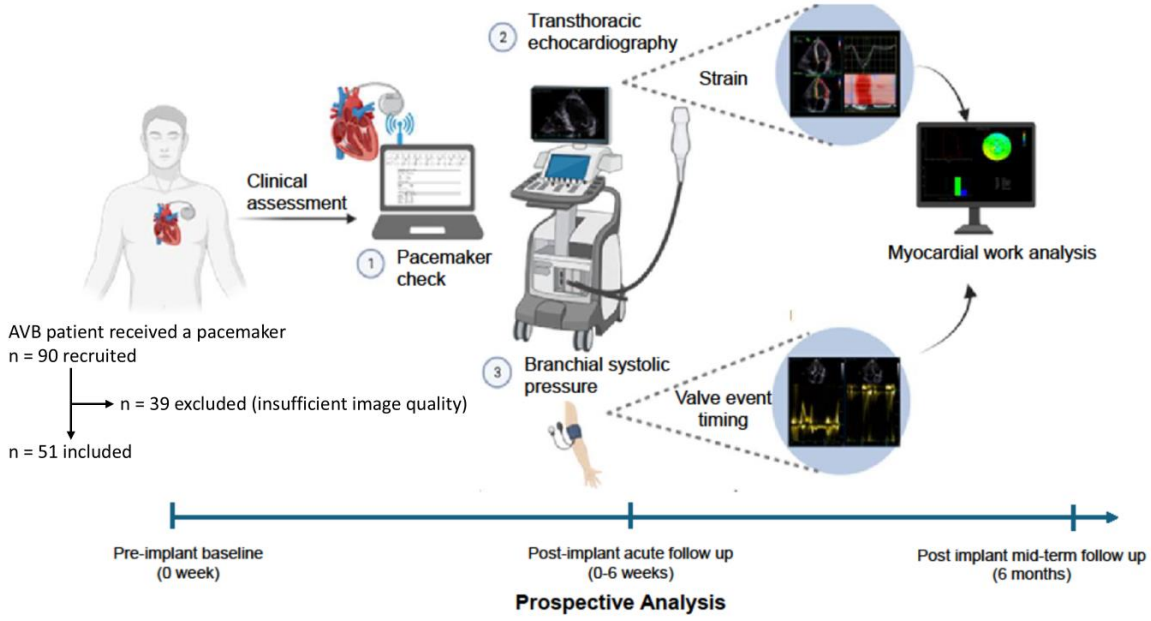


Figure 6.1Study Flowchart – Prospective Follow-up Timeline for Atrioventricular-Block (AVB) Patients Undergoing Pacemaker Implantation and Clinical Assessment: Echocardiographic Measures, and Myocardial Work Analysis

6.3.3 Outcome measures

The primary outcome measured was change in MW patterns according to follow-up LV systolic function from baseline (pre implant) to acute follow up (0-6 week) and to mid-term (6-month), post implantation. MW change may provide a more comprehensive and afterload-sensitive assessment of LV systolic function by integrating pressure and strain, and potentially reproducible.

The secondary outcome was determining predictors of adverse LV remodelling, defined as a composite outcome of increase in LV end systolic index (LVESVi) ≥15% or a reduction in LVEF >10%.

6.3.4 Data analysis

6.3.4.1 Descriptive analysis

Baseline continuous data were firstly assessed for normality using Shapiro-Wilk test. Normally distributed data are presented as mean (standard deviation), and continuous non-normally distributed data as median (interquartile range). Categorical data are presented as number (percentage). Student t-tests or ANOVA were used to analyse normally distributed continuous data, Mann-Whitney U-tests or Kruskal-Wallis H-tests for non-normally distributed continuous data, and Pearson $\chi 2$ tests for categorical data.

6.3.4.2 Statistical analysis

Changes in LVEF, GLS, and MW were analysed using repeated measure analysis (ANOVA) using Bonferroni correction from baseline (pre implant) to acute (0-6week) and mid-term (6-month) post implantation. Multivariable linear regression was used to assess the association between pre-implantation MW patterns and post-implantation LV remodelling defined by a composite outcome of an increase in LVESVi ≥15% or a decrease in LVEF >10%. Adjustments were made for confounding variables (age, history of ischaemic heart disease (IHD) and

ventricular pacing burden (VPB)), and model performance was evaluated using logistic regression analysis. Data analysis was performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp, Armonk, NY, USA, 2020). A statistical significance was pre-specified as $p < 0.05$, accompanied by a 95% confidence interval (CI).

6.4 Result

6.4.1 Population characteristics

The study cohort consisted of 90 patients with an average age of 75±11 years, of whom 23% were female, with an average height of171±10 cm and weight of 8±23 kg. Mean resting heart rate was 57±17 bpm with a systolic blood pressure of 148±26 mmHg and a diastolic blood pressure of 72±12 mmHg **(Table 6-1).**

Table 6-1 Baseline demographics of study population

	Total Cohort, n=90
Age (years)	75 (±11)
Sex (female)	21 [23%]
Height (cm)	171 (±10)
Weight (kg)	84 (±23)
Resting Heart rate (bpm)	57 (±17)
Systolic blood pressure	148 (±26)
Diastolic blood pressure	72 (±12)
Co-morbidities	
Hypertension	37 [41%]
Type II Diabetes Mellitus	24 [27%]
Cerebrovascular accident	5 [6%]
Overt ischaemic heart disease	17 [19%]
MI	7 [9%]
PCI	7 [8%)
CABG	3 [3%]
Blood investigation	
NT-proBNP (pg/ml)	521 (273-1871)
Baseline medication prescriptions	
Beta-blocker	33 [38%]
ACE-inhibitor	36 [40%]
MRAs	13 [15%]
Diuretic	25 [32%]
SGLT2	10 [11%]
Baseline atrial rhythm	
Sinus rhythm	76[84%]
Atrial fibrillation	14 [16%]
Pacing system	
Dual chamber pacing	79 [88%]
Single chamber pacing	11 [12%]
Pacing programming	
DDD (R)	62 [70%]
RV pacing avoidance algorithm (R)	17 [18%]
VVI (R)	11 [12%]
Rate response	11 [12%]
Base rate (bpm)	50 (±4)
Max track rate (bpm)	130 (±10)
Pacing requirement	
Atrial pacing burden (%)	3 (0-81)
Ventricular pacing burden (%)	89 (0-100)
Baseline echocardiographic measures	
LVEF (%)	53 (±8)
LVEDV (ml)	114 (93-150)
LVESV (ml)	56 (41-75)

Continuous data are presented as mean (± standard deviation) or median (interquartile range) and categorical data are presented as n (%). MI; myocardial infarction, PCI; percutaneous coronary intervention, CABG; coronary artery bypass grafting, NT-proBNP; N-terminal pro-B-type natriuretic peptide, ACE inhibitor; Angiotensin-converting enzyme, MRA; Mineralocorticoid receptor antagonists, SGLT2; Sodium-glucose cotransporter-2. RV; right ventricular, LVEF; left ventricular ejection fraction, LVEDV; left ventricular end diastolic volume, LVESV; left ventricular end systolic volume. Pacing data were collected at 6-week follow up

6.4.1.1 Co-morbidities

One or more co-morbidities were present in 60 (67%) patients. Hypertension was present in 37 (41%) patients, and 24 (27%) patients had type II diabetes mellitus. Five (6%) patients had a history of cerebrovascular accident (CVA). Overt ischemic heart disease was reported in 17 (19%) patients, with 7 (9%) patients having had a myocardial infarction (MI), 7 (8%) patients having undergone percutaneous coronary intervention (PCI), and 3 (3%) patients having received coronary artery bypass grafting (CABG).

6.4.1.2 Blood investigations

N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were recorded with a median of 521 pg/ml (interquartile range (IQR): 273-1871).

6.4.1.3 Medication prescriptions

Beta-blockers were used by 33 (38%) patients, angiotensin-converting enzyme (ACE) inhibitors by 36 (40%) patients, mineralocorticoid receptor antagonists (MRAs) by 13 (15%) patients, diuretics by 25 (32%) patients, and sodium-glucose cotransporter-2 (SGLT2) inhibitors by 10 (11%) patients.

6.4.1.4 Pacing system, programming and requirement

The majority were in sinus rhythm (84%) and 14 (16%) patients had atrial fibrillation. The majority of implants were dual chamber devices in 79 (88%) patients and 11 (12%) patients received single chamber pacemakers. DDD(R) was programmed in 62 (70%) patients, 17 (18%) patients were optimised with RV pacing avoidance algorithms, VVI(R) was programmed in 11 (12%) patients, and rate response algorithms were utilised in 11 (12%) patients. The average base rate was 50±4 bpm and the average maximum tracking rate was 130±10 bpm. Median atrial pacing burden (APB) was 3(IQR:0-81) % and the median ventricular pacing burden (VPB) was 89(IQR: 0-100)%.

6.4.1.5 Baseline echocardiographic measures

The average LVEF was 53±8% and median LV end-diastolic volume (LVEDV) and median left ventricular end-systolic volume (LVESV) were 114(IQR: 93-150) mls and 56(IQR:41-75) mls, respectively.

6.4.2 Assessment of LV mechanics using traditional and advanced echocardiographic measurements

The total cohort consisted of 90 patients; however, only 51 patients had imaging data available at three time point (baseline, acute and mid-term) of sufficient quality for analysis. **Table 6-2** presents the comparison of echocardiographic measurements between the patients who preserved LVEF (LVEF ≥50%, n=37) and those who experienced a reduction in systolic function (LVEF <50%, n-14) across each time point. Patients who preserved LVEF ≥50% exhibited stable LVEF values from 53±9% to 52±10% to 57±8%, whilst those who did not (LVEF <50%) experienced decline in LVEF from 51±9% to 50±7% to 43±5%. GLS was better in patients who preserved systolic function (-16±7% to -13±8% to -14±7%), while those who demonstrated a reduction in systolic function showed a progressive deterioration (-15±4% to -13±4% to -12±3%). However, despite these observed trends in LVEF and GLS, the differences were not statistically significant between groups (p=0.49 and p=0.09, respectively).

Table 6-2 Echocardiographic measurements at baseline and follow-up in total cohort

	LVEF preserved (≥50%)			LVEF reduced (<50%)			
	Baseline	**Acute**	**Mid-term**	**Baseline**	**Acute**	**Mid-term**	**p-value**
Haemodynamic measurement							
Systolic blood pressure	149±43	141±18	144±21	154±31	142±23	143±19	0.38
Diastolic blood pressure	74±12	75±12	76±12	74±9	75±9	76±9	0.93
Traditional echo measurement							
LVEF (%)	53±9	52±10	57±8	51±9	50±7	43±5	0.49
LVEDV (ml)	130(103-158)	130(112-148)	114(102-126)	129(110-148)	135(108-163)	131(106-156)	0.54
LVESV (ml)	55(49-61)	66(46-87)	54(47-60)	66(53-80)	64(52-76)	74(58-90)	0.88
GLS (%)	-16±7	-13±8	-14±7	-15±4	-13±4	-12±3	0.09
Global MW							
GWI (mmHG%)	2047±730	1714±402	1696 ±561	1764±614	1515±712	1410 ±590	0.01*
GCW (mmHG%)	2583±735	2175±471	2168±668	2263±764	1954±650	1873±611	0.01*
GWW (mmHG%)	361 (±193)	351 (±196)	372 (±234)	330 (±284)	339 (±158)	330 (±194)	0.98
GWE (%)	86±10	86±6	86±8	86±11	84±6	84±7	0.53
Regional MW							
MWI_S (mmHG%)	1762±798	1572±576	1419±604	1623±802	1150±756	1256±649	0.02*
MWI_L (mmHG%)	2079±939	1879±657	1949±659	1683±822	1646±877	1509±673	0.47
MWI_{S-L} (mmHG%)	-316±788	-306±901	-530±744	-61±743	-496±512	-253±569	0.24
CW_S (mmHg%)	2386±763	2047±550	2018±598	2149±931	1711±786	1719±608	0.02*
CW_L (mmHg%)	2533±937	2278±597	2359±687	2313±1029	1998±734	1934±777	0.09
WW_S (mmHg%)	422 388	325 206	439 321	391 398	432 358	312 209	0.70
WW_L (mmHg%)	309±261	306±311	297±182	316±357	296±154	323±248	0.99

Continuous normally data are presented as mean (± standard deviation), non-normally distributed data as median (interquartile range). A p-value ≤0.05 denotes * was considered significant.

LVEF; left ventricular ejection fraction, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, GLS; global longitudinal strain, GWI; global work index, GCW; global constructive work, GWW; global wasted work, GWE; Global work efficiency, MWIS; myocardial work index at septal, MWIL; myocardial work index at lateral, $MWI_{S-L;}$ myocardial work index difference (septal-lateral)

There is significant difference observed in global MW index (GWI) measurements between patients in the preserved LVEF group (LVEF ≥50%) (2047±730 mmHg% to 1714±402 mmHg% to 1696±561 mmHg%) and those in the reduced LVEF group (LVEF <50%) (1764±614 mmHg% to 1515±712 mmHg% to 1410±590 mmHg%) (p=0.01) over time. Regional MWI measurements of LV wall shows significant differences between the groups, (preserved LVEF ≥50% and reduced LVEF<50%) over time. Septal MWI (MWI_S) remained more stable in those that preserved LVEF compared to those that didn't((1762±798 mmHg% to 1572±576 mmHg% to 1419±604 mmHg%) vs. (1623±802 mmHg% to 1150±756 mmHg% to 1256±649 mmHg%), p=0.02, respectively), however, the lateral MWI (MWI_L)showed no significant difference during follow-up between the groups ((2079±939 mmHg% to 1879±657 mmHg% to 1949±659 mmHg%) vs. (1683±822 mmHg% to 1646±877 mmHg% to 1509±673 mmHg%), p=0.47, respectively) **(Figure 6.2)**

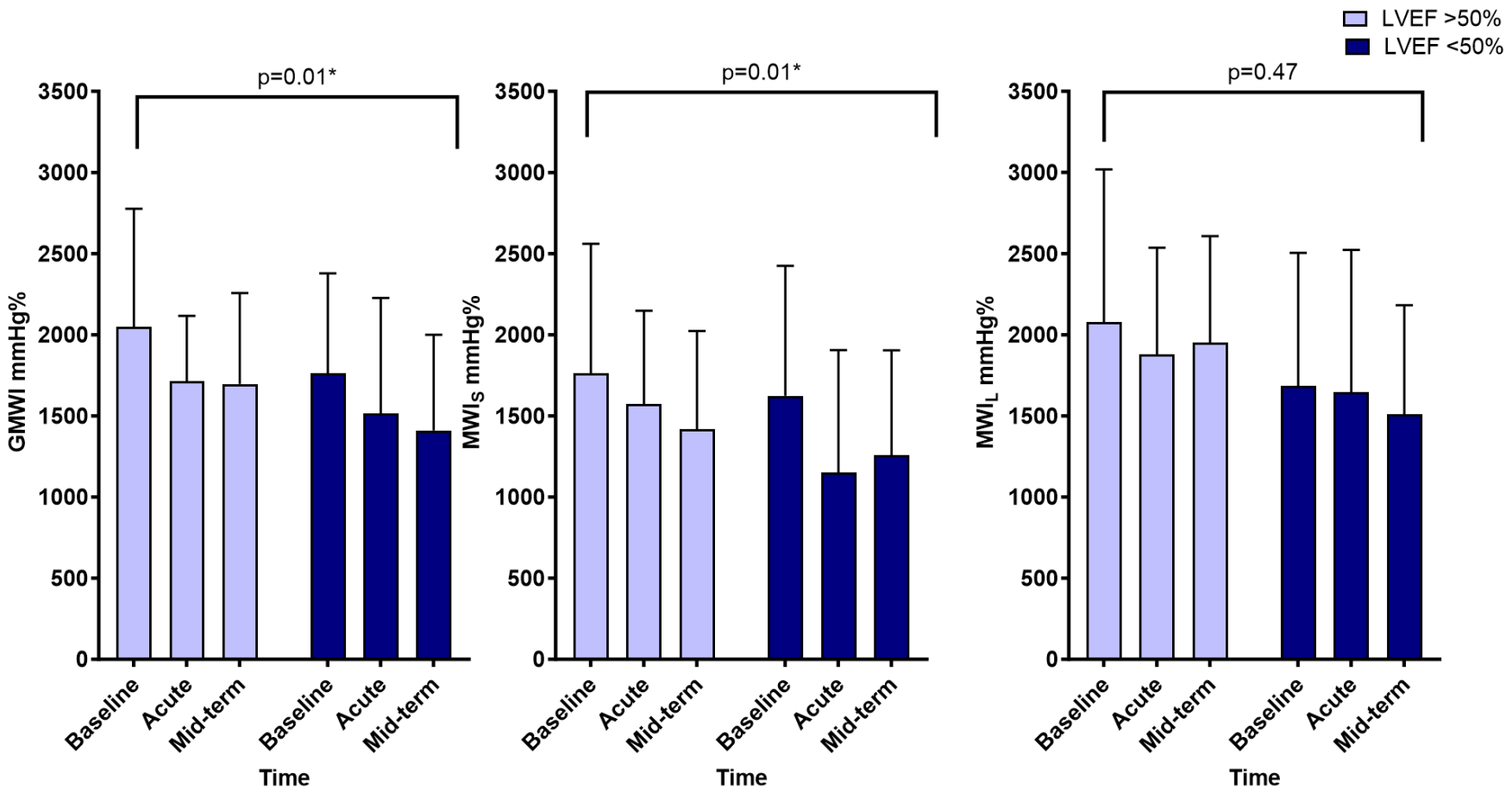


Figure 6.2 Distribution of myocardial work index at global (GWI), septal (MWIS) and lateral (MWIL) by left ventricular ejection fraction (LVEF) group from baseline (0 week) to acute (6-week) to mid-term (6-month). A p value <0.05 is statistical significance and denote as*

GCW in both groups decreased over time (2583±735 mmHg% to 2175±471 mmHg% and 2168±668 mmHg%, vs 2263±764 mmHg% to 1954±650 mmHg% to 1873±611 mmHg%, respectively) with statistically difference observed between groups (p=0.01)**.** In patients who preserved LVEF ≥50%, GWW increased slightly (361±193 mmHg% to 351±196 mmHg% to 372±234 mmHg%, respectively, respectively), while those who showed a reduced LVEF (LVEF <50%) showed a fluctuation in GWW (330±284 mmHg% to 339±158 mmHg% to 330±194 mmHg%, respectively, p=0.98). Similarly, there was no significant difference observed over time between groups in global mechanical work efficiency (GWE) (86±10 % to 86±6 % to 86±8 % vs. 86±11 % to 84±6 % to 84±7 %, respectively, p=0.53). Interestingly, constructive work in the septum (CWI_S) significantly different between groups during the follow-up period (2386±763 mmHg% to 2047±550 mmHg% to 2018±598 mmHg% vs. (149±931mmHg% to 1711±786 mmHg% to 1719±608 mmHg%, respectively, p=0.02) but not in the lateral region, (2533±937 mmHg% to 2278±597 mmHg% to 2359±687 mmHg% vs. 2313±1029 mmHg% to 1998±734 mmHg% to 1934±777 mmHg%, respectively, p=0.09) **(Figure 6.3)**.

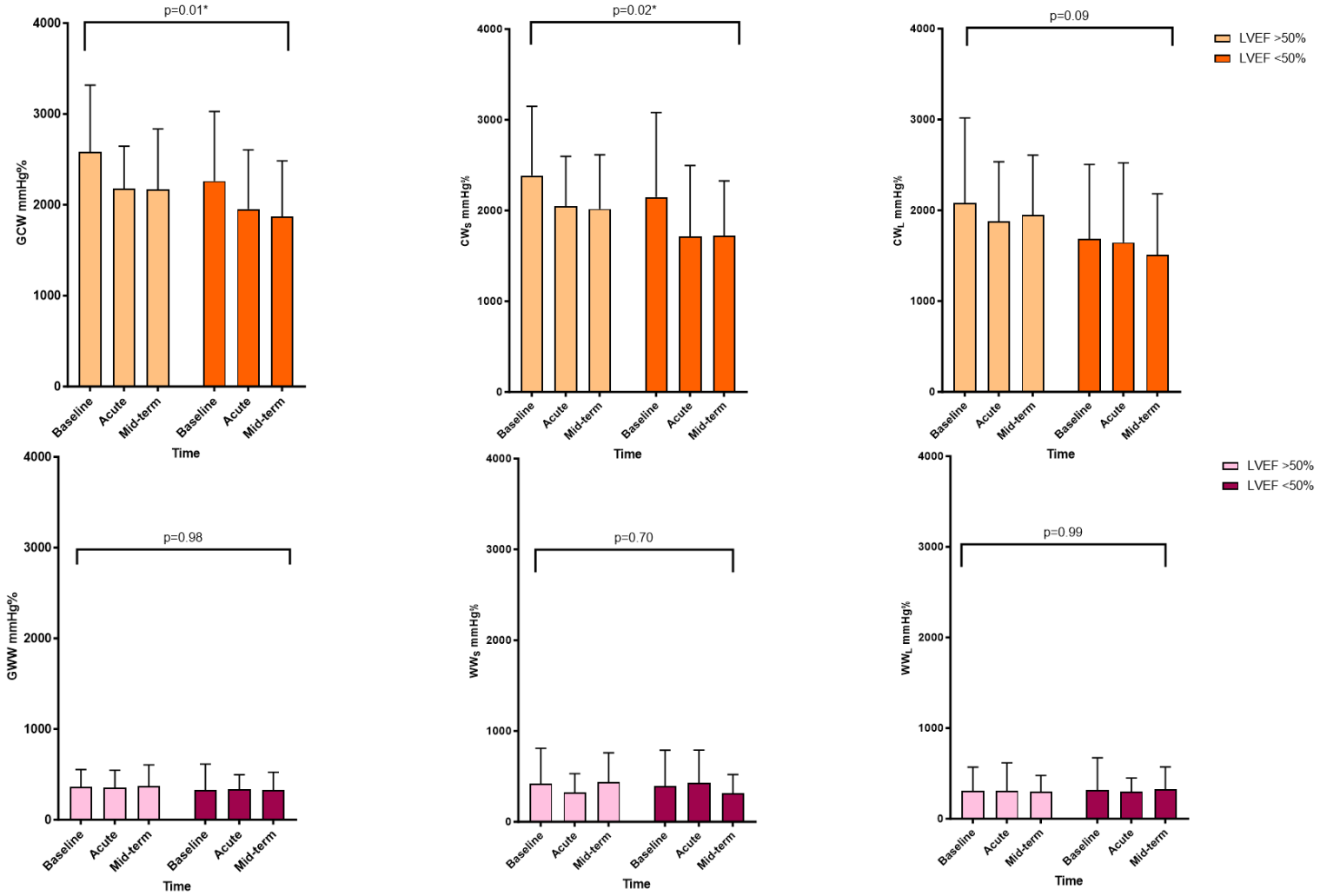


Figure 6.3 Distribution of myocardial global constructive work (GCW) and global wasted work (GWW) by left ventricular ejection fraction (LVEF) group from baseline (0 week) to acute (6-week) to mid-term (6-month). A p value <0.05 is statistical significance and denote as*

Septal to lateral difference (MWI_{S-L}) was inconsistent and showed high variability within groups with no statistical significance between groups over time (preserved LVEF: -316±788 mmHg% to -306±901 mmHg% to -530±744 mmHg% vs. reduced LVEF:-61±743 mmHg% to -496±512 mmHg% to -253 ±569 mmHg%, p=0.24).**(**Table 6-2).

Regional wasted work at both the septal (422±388mmHg% to 325±206mmHg% to 439±321mmHg% vs. 391±398mmHg% to 432±358mmHg% to 312±209mmHg%), respectively, p=0.70) and lateral regions (309±261mmHg% to 306±311mmHg% to 297±182mmHg% vs. 316±357mmHg% to 296±154mmHg% to 323±248mmHg%, respectively, p=0.99) showed no statistical difference over time between the groups.

6.4.3 Predicting pacemaker-related LV remodelling

Table 6-3 presents unadjusted **(panel A)** and adjusted **(panel B)** odds ratios for LV remodelling, defined as an increase in LVESVi ≥15% or a reduction in LVEF >10%. Of the 51 patients included, 12 (24%) had adverse LV remodelling during follow-up. The unadjusted analysis indicates that age and VPB are significant predictors, with hazard ratios of 1.14 (95%CI: 1.03-1.25) and 1.03 (95%CI: 1.00-1.06), respectively. In the adjusted model, age and VPB were included as they were statistically significant in the univariate analysis, while IHD and septal MWI were included due to their clinical relevance and hypothesised mechanistic role in pacing-related LV remodelling. Age remains significant with a hazard ratio of 1.04 (95% CI: 1.04-1.32), as does VPB with a hazard ratio of 1.05 (95% CI: 1.00-1.10). Other variables, including IHD, and septal MWI measures, do not show significant associations with LV remodelling within a multivariable model **(Figure 6.4).**

Table 6-3 (A) Unadjusted odds ratios for LV remodelling (defined as an increase in LVESVi ≥15% or a reduction in LVEF >10%) and (B) Adjusted odds ratio for covariates in combined.

Variable	Parameter Estimate	Standard Error	Wald χ^2 P-Value	Hazard Ratio (95% CI)
(A) Unadjusted hazard ratios				
Characteristic				
Age	0.13	0.05	0.01*	1.14 (1.03-1.25)
IHD	0.38	0.76	0.62	1.46 (0.33-6.54)
VPB	0.03	0.01	0.03*	1.03 (1.00-1.06)
Baseline echocardiographic				
LVEF	0.09	0.05	0.09	1.09 (0.99-1.21)
GLS	-0.04	0.04	0.30	0.97 (0.90-1.03)
Baseline regional myocardial work				
MWI_S	0.00	0.00	0.40	1.00 (1.00-1.01)
MWI_L	0.00	0.00	0.71	1.00 (0.99-1.01)
MWI_{S-L}	0.01	0.00	0.13	1.01 (1.00-1.02)
CW_S	0.01	0.00	0.14	1.01 (1.00-1.01)
CW_L	0.00	0.00	0.86	1.00 (0.99-1.01)
WW_S	0.01	0.01	0.57	1.01 (0.99-1.02)
WW_L	0.00	0.01	0.88	1.00 (0.99-1.02)
Baseline global myocardial work				
Baseline GWI	0.00	0.00	0.67	1.00 (0.99-1.01)
Baseline GCW	0.00	0.00	0.44	1.00 (0.99-1.01)
Baseline GWW	0.00	0.02	0.99	1.00 (0.99-1.03)
(B) Adjusted hazard ratios				
Characteristic				
Age	0.16	0.06	0.01*	1.04 (1.04-1.32)
IHD	0.77	1.07	0.47	2.17 (0.30-17.68)
VPB	0.05	0.02	0.04*	1.05 (1.00-1.10)
Baseline MWI_S	0.00	0.01	0.51	1.00 (0.99-1.01)

Values are expressed as hazard ratio (95% Confidence Interval). A p-value ≤0.05 was considered significant.
IHD; Ischaemic Heart Disease, VPB; ventricular pacing burden, LVEF; left ventricular ejection fraction, GLS; global longitudinal strain, MWIL; myocardial work index at lateral, $MWI_{S-L;}$ myocardial work index difference (septal-lateral), CW_S: Constructive work at septal; CW_L: Constructive work at lateral; WW_S: wasted work at septal; WW_L: wasted work at lateral; GWI; global work index, GCW; global constructive work, GWW; global wasted work

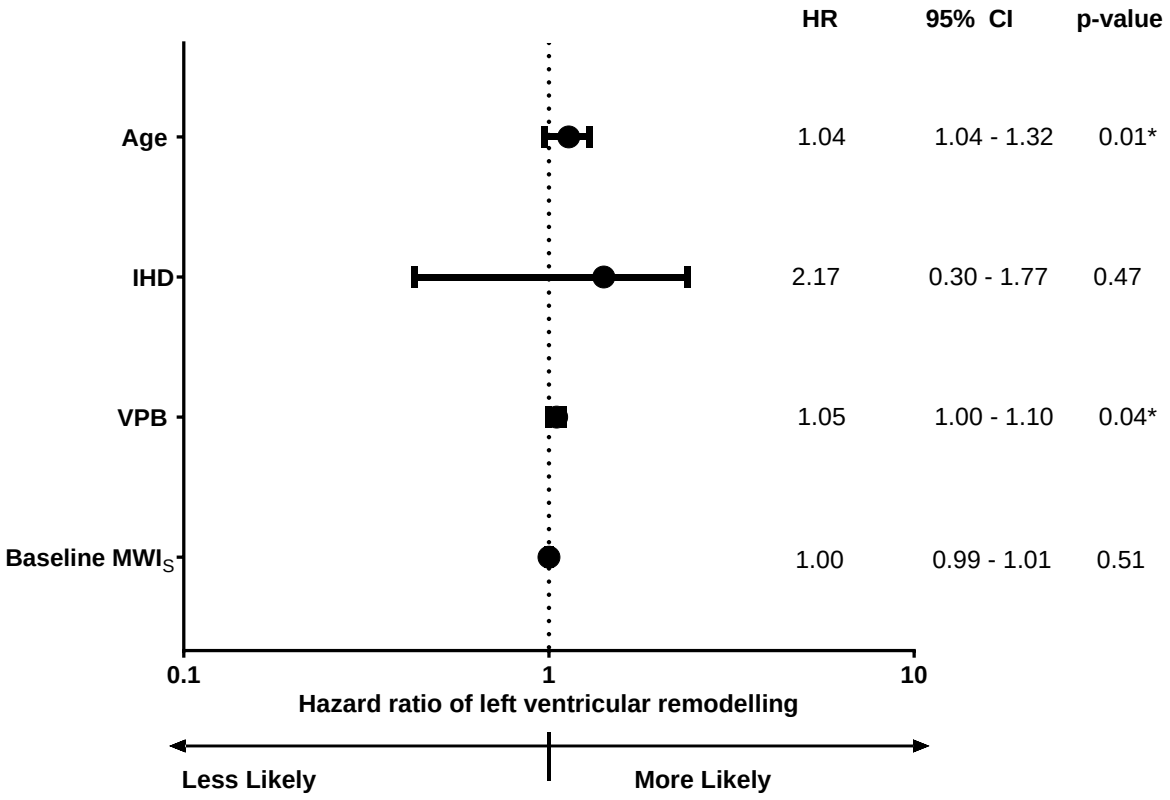


Figure 6.4 Factors associated with left ventricular remodelling (defined as a composite outcome of an increase in left ventricular end systolic index (LVESVi) ≥15% or a decrease in left ventricular ejection fraction (LVEF) >10% in adjusted regression model

6.5 Discussion

My data shows that there were no significant changes in LVEF, LV volumes and GLS over time between those who preserved LVEF ≥50% and those who did not (LVEF <50%). Yet, global MW measurements (GWI and GCW) and regional measurements derived from the septum (MWI_S and CW_S), showed statistically significant changes throughout follow-up between LV function groups. These findings suggest important alterations in LV mechanics detected by myocardial work measures that warrant further investigation. Nevertheless, no pre-implant echocardiographic measure was found to be predictive of clinically relevant adverse LV remodelling after pacemaker implantation in this study. At present, there is no established cut-off value for myocardial work measurements to define remodelling risk in clinical practice. While Boe et al. (Boe et al., 2015) have provided some preliminary reference

data, it remains too early to adopt a fixed threshold. This is partly due to limited longitudinal data, heterogeneity in patient populations, and the need to validate these measures across broader clinical contexts. Defining such a threshold prematurely may lead to over- or underestimation of risk. Future studies should focus on refining the prognostic value of baseline myocardial work measurements through larger, prospective datasets. This approach may ultimately enable the development of evidence-based thresholds that can reliably stratify patients at risk of pacing associated LV remodelling.

The impact of RV pacing on LV function

Right ventricular (RV) pacing can significantly impact left ventricular (LV) function, leading to adverse cardiac effects including HF hospitalisation and mortality. During pacing, the synchronous contraction of the ventricle is disrupted, which can result in altered ventricular mechanics and increased dyssynchrony (Duchenne et al., 2019c). This disruption often leads to a decline in LVEF over time, as the heart struggles to maintain effective contractility and pumping efficiency (Bank et al., 2012, Fang et al., 2011, Kaye et al., 2015). The altered timing of contractions can cause an increase in LV volume, ultimately leading to remodelling and potential HF (Duchenne et al., 2020). Studies have shown that up to 60% of patients with RV pacing experience progressive LVSD, especially in those who require high degrees of RV pacing (Curtis et al., 2013, Gierula et al., 2015, Paton et al., 2019). Furthermore, the long-term consequences of RV pacing may necessitate upgrades to cardiac resynchronization therapy (CRT) to mitigate these effects (Höijer et al., 2006, Witte et al., 2006, Vatankulu et al., 2009, Wokhlu et al., 2009, Merkely et al., 2022).

The current study focused on patients with atrioventricular block (AVB), a group that often requires extensive RV pacing and is at risk of LV remodelling. As expected, the findings revealed a significant relationship between the ventricular pacing burden (VPB) and adverse LV remodelling in both unadjusted and adjusted regression model. Nevertheless, the exact

mechanism of RVP-related LV remodelling in humans is not clearly understood, and thus identifying patients at risk prior to pacemaker implantation is still a key focus of research.

6.5.1 Echocardiographic advancements in assessing LV mechanics

LVEF has traditionally been utilised for assessing LV performance, as it has been demonstrated to be a predictor of adverse outcomes in several clinical trial (Marwick, 2006, Solomon et al., 2005, Stanton et al., 2009). However, LVEF is extremely subjective and has several limitations (Dorosz Jennifer et al., 2012, Konstam and Abboud, 2017), particularly, it is influences by both preload and afterload (Eaton et al., 1979, Duchenne et al., 2020). Structural changes due to scarring and thinning of the myocardium (Konstam et al., 2011, Saunderson et al., 2021) leading to increases or decreases in LVEDV will also strongly influence the LVEF. Finally, there is significant inter- and intra-observer variability to mitigate for (Vignola et al., 1977).

Echocardiography has advanced over time with the introduction of updated software and hardware solutions. Speckle tracking imaging with GLS is becoming more common to detect even subtle myocardial dysfunction as the technique is less angle- and operator-dependent (Potter and Marwick, 2018, Marwick, 2006). Although it has developed into a well-validated tool for clinical use in the assessment of myocardial function, it is still limited by load dependency (Lumens et al., 2015, Kalam et al., 2014). Increasing afterload may reduce GLS, leading to incorrect assumptions about LV contractility, in fact, one study showed a 4% reduction in GLS with an increase in LV pressure of 30% (Boe et al., 2015). Additionally, moderate elevations in arterial pressure have been shown to significantly reduce LVEF and GLS in patients with LBBB (Aalen et al., 2019).

Conversely, MW has been developed to measure the LV pressure–strain relationship noninvasively, thereby providing a measure of function which is adjusted for loading conditions (Chan et al., 2018, Papadopoulos et al., 2021). While it does not calculate actual LV work, it

provides a valid approximation by combining LV pressure with strain. Russel et al. first introduced this method, showing that the pressure–strain loop (PSL) closely correlates with the LV pressure–volume loop in patients with left bundle branch block (LBBB), dyssynchrony, and ischemic heart disease (Russell et al., 2012).

Traditionally, LV work is assessed through the pressure–volume relationship, which reflects myocardial oxygen consumption and overall LV performance (Bastos et al., 2019). However, since measuring the pressure–volume loop previously required invasive techniques, it was not commonly used in routine clinical practice. Echocardiographic-derived MW offers a non-invasive alternative (Russell et al., 2012), for evaluating cardiac mechanics and LV performance, as it incorporates both afterload and deformation, making it less dependent on load variations and able to demonstrate workload on a regional level. MW has been validated in patients with coronary artery disease (Edwards et al., 2019a) and heart failure, particularly those undergoing cardiac resynchronisation therapy (CRT) (Galli et al., 2018b, Duchenne et al., 2020).

6.5.2 The clinical utility of MW measures in predicting RV pacing related LV remodelling

MW reflects the workload of the heart in pumping blood and provides crucial insights into its functional efficiency. A patient's non-invasive blood pressure can be highly variable, making it challenging to rely solely on strain measurements to assess heart function during such serial assessments. MW potentially offers a more nuanced perspective.

The findings of this study show significant differences in GWI over time, with additional discrete measures suggesting this was driven by changes in GCW, and more specifically by changes within the septal MWI. These changes were seen whilst taking into account any changes in blood pressure, which may be particularly relevant given the patients were assessed at baseline were experiencing AVB and transferred to a paced rhythm during follow-up.

Therefore, measuring MW may be particularly pertinent in this patient population to uncover critical changes in cardiac function that may otherwise be masked by changes in the patient's haemodynamic status.

The integration of MW measurements into routine clinical practice could revolutionise the management of patients receiving pacemaker therapy. This might be particularly focussed on obtaining CW and MWIs measures. By providing objective data on LV function and workload, MW measurements can help clinicians in risk stratification, allowing for the identification of patients at higher risk for LVSD before significant deterioration occurs, thus enabling proactive management.

6.5.3 Contributory mechanisms of MW Changes

In my previous work, I already identified co-morbidities that may influence LV remodelling and not pacing requirement alone. LV remodelling is primarily driven by mechanical stretch, not only in pacing related pacemaker but various other factors, such as ischemia, hormonal changes, and vasoactive peptides, also play significant roles in influencing these processes (Heusch et al., 2014, Mahmood et al., 2014). In clinical settings, such as the complex patients included in this study, remodelling often occurs due to a combination of factors, including pressure overload, ischemia, stress from myocardial scarring, and elevated levels of circulating hormones and vasoactive peptides (Saunderson et al., 2021, Dadson et al., 2016, Mendoza-Torres et al., 2015, Hori and Nishida, 2009, Frantz et al., 2022, Sabbahy and Vaidya, 2011, Brenner et al., 2013)

For instance, LV remodelling after myocardial infarction (MI) is often accompanied by a gradual decline in LVEF, making it an important marker for assessing the extent of remodelling. In hypertensive heart disease, there is a clear relationship between increasing blood pressure and the development of concentric ventricular hypertrophy, which eventually leads to both systolic and diastolic dysfunction as the heart dilates (Messerli et al., 2017).

These compensatory processes are also seen in other organs following partial loss, such as the kidney or liver (Sabbahy and Vaidya, 2011, Brenner et al., 2013).

Interestingly, the present analysis did not show a significant relationship between IHD and the development of LVSD, which has previously been identified (Gierula et al., 2015) which may be due to several factors. IHD patients often exhibit a range of disease severity, with some experiencing subclinical ischemia or minimal ongoing damage (Heusch et al., 2014). Additionally, early compensatory mechanisms or stable stages of IHD could mask alterations in LV wall mechanics, especially in patients without recent ischemic events. Furthermore, regional effects of ischemia may not be fully captured by global MW measurements, few studies have included patients on more novel cardiac therapeutics and the expected outcomes of those patients in real-world practice is still relatively unknown, and a limited sample size might reduce the study's power to detect subtle changes (Butt et al., 2022). These factors likely contribute to the observed outcomes.

While MW measures have been explored as potential predictors of LV remodelling, the present analysis demonstrated their limited application in this regard but suggests that MW is more effective in describing changes in LV mechanics over time rather than serving as a predictive marker. Although, Duchene et al suggests that heterogeneous MW patterns have shown some prognostic relevance pre-cardiac resynchronization therapy (CRT), where a more uniform workload distribution post-CRT is associated with improved response (Duchenne et al., 2020).. The evidence base also shows limited application of MW as a predictive tool, instead it has been used to describe changes in cardiac mechanic over time and demonstrated potential in detecting subtle changes. Further investigations though, may permit the understanding required to reach a predictive measure.

6.5.3.1 Medications

Clinical trials have demonstrated that structural remodelling can be slowed or even reversed with specific treatments (Willenheimer, 2000). Vasoactive drugs, such as β-blockers, ACE inhibitors, and spironolactone, have been shown to improve outcomes by targeting the heart's biological function (Butt et al., 2022) . For instance, ACE inhibitors are particularly effective in reducing left ventricular mass and volume, highlighting their potential in treating cardiac remodelling (Konstam, 1995). In this cohort, one third of the population were receiving cardiovascular medical therapies, including β-blockers, ACE inhibitors or diuretic agents.

Additionally, SGLT2 inhibitors have demonstrated significant benefits by reducing the risk of major adverse cardiovascular events, including heart attack and stroke, while also lowering the risk of HFH. The CVD-REAL study, a large multinational observational study, included 153,078 adults with type 2 diabetes, with 13% having established cardiovascular disease (CVD). The study found that the initiation of SGLT2 inhibitor therapy was associated with a significantly lower risk of death (HR: 0.56; 95% CI: 0.44 to 0.70) and HF (HR: 0.72; 95% CI: 0.63 to 0.82) compared to other glucose-lowering drugs, regardless of the presence of CVD. This highlights the important role of SGLT2 inhibitors in managing cardiovascular risk in patients with type 2 diabetes. About 10% of the cohort was prescribed SGLT2 inhibitors.

Therefore, 6-months follow up may not be sufficient to allow for clinically relevant LV remodelling to occur with more modern therapeutics, even in the context of pacemaker related LV dyssynchrony.

6.6 Limitations

There are some limitations with this study. First of all, the sample sizes for MW analysis were small, limiting the statistical power and generalisability of the findings. There were limitations in the ability to perform echocardiography assessment on all participants by excluded about

40% of the original cohort. It was expected that pre discharge after pacemaker implantation are a challenge due to patient's discomfort post implantation. Generally, study population were older, and it was no surprise that they tend to be lost to follow up either they are too frail or died before following up invitation. For instance, given the limited number of adverse remodelling events (n = 12), the events-per-variable ratio was 3, which is below the commonly recommended threshold of 10, therefore multivariable regression model at increased risk of overfitting. As such, the multivariable findings should be considered exploratory and interpreted with caution.

The high standard deviations observed indicate a substantial spread of data, likely reflecting the variability in MW measurements due to both individual differences in myocardial response and the inherent heterogeneity of patient conditions within these small study groups. This is compounded by utilisation of a composite primary endpoint, which included multiple measurements or remodelling, possibly diluting the impact of any single measure and complicating interpretation. These limitations highlight the need for larger-scale studies to achieve a more representative sample and to strengthen the reliability of MW as an assessment tool.

Factors such as patient body habitus, arrhythmias particularly the presence of irregular heart rates such as atrial fibrillation and the quality of the acoustic window can significantly impact the resolution of echocardiographic images and the accuracy of strain measurements. Additionally, haemodynamic conditions, such as severe hypertension and aortic stenosis, are likely to influence MW calculations due to their effects on left ventricular (LV) function and the increased afterload they impose on the heart. In particular, aortic stenosis can lead to altered ventricular loading and myocardial adaptation, which may affect the accuracy of both strain and MW measurements. These variables may introduce measurement errors that could potentially influence the assessment of MW. Should MW demonstrate clinical utility, the

incorporation of advanced imaging modalities, such as 3D echocardiography, could provide enhanced resolution and greater accuracy.

Furthermore, considering a single centre was selected conducting the research, there may not have been sufficient variation in the patient group, which could influence how extensively the findings can be applied. Additionally, the follow-up period was somewhat short, which may lead to long-term trends and findings related to change in cardiac function being missed.

6.7 Conclusion

In summary, this study demonstrates that significant declines MW measures during early follow-up post pacemaker implantation, may indicate the presence of early LV remodelling. These findings highlight the potential of advanced echocardiographic techniques to detect subtle changes in cardiac function that may not be apparent through traditional measures. The observed reductions in MW underscore the importance of monitoring these parameters in serial assessment, particularly in patients with AVB whom at risk due to their high requirement of RVP.

Although I show no additional predictive value of incorporating MW measures prior to implant, in risk stratifying patients for the development of adverse LV remodelling related to RVP, changes in MW measurements were observed indicating early signs of left ventricular systolic dyssynchrony.

Therefore, ongoing analysis with increased patient numbers may provide additional insights and are worthwhile. Future research should also consider longer follow-up to further explore MW measurements potential in predicting pacemaker-related LV remodelling to aid clinicians to implement tailored interventions and alternative pacing strategies aimed at preserving LV function earlier.

6.8 Dissemination of findings

This review is being prepared for submission to the *European Heart journal – Cardiovascular imaging*.

Chapter 7 The effects of novel conduction system pacing compared to traditional right ventricular pacing on left ventricular mechanics

7.1 Abstract

Introduction

For the past sixty years, right ventricular pacing (RVP) has been the primary therapeutic choice for bradyarrhythmia, although it has been linked to unfavourable left ventricular (LV) remodelling and an increased risk of heart failure (HF). Conduction system pacing (CSP) is a possible alternate pacing strategy, however its effectiveness in reducing LV dyssynchrony is unknown. Echocardiography is a crucial tool for understanding LV function and mechanics and may provide some mechanistic insights.

Aim

To assess LV mechanics induced from CSP in comparison to RVP using echocardiographic derived MW measurements.

Methods

Patients with atrioventricular block who needed pacemakers were recruited prospectively from October 2022 to October 2024 at a single tertiary hospital (Leeds Teaching Hospitals – Leeds General Infirmary) in the United Kingdom. Patients receiving CSP and RVP were pair-matched at baseline according to age and gender. Data were obtained pre-implant, 0-6 weeks post-implant (acute), and 6 months post-implant (mid-term). The primary outcome was difference over time in septal and lateral MW measurements between the two groups.

Results

Twenty patients (CSP n=10, RVP n=10), 76% male with a mean age 65±11 years, were included for analysis. After a median follow-up of 27 (IQR: 23-31) weeks, myocardial work index for the septal region (MWI_S) significantly decreased in both groups, with a greater decline in the RVP group (CSP: 1540±687 mmHg% vs. RVP: 1270±594 mmHg%, p=0.02). Global myocardial work efficiency (GWE) and global work index (GWI) showed significant reductions in the CSP group, whereas the RVP group preserved relatively stable values (p=0.02 for both). Global wasted work (GWW) increased significantly in both groups throughout follow-up (CSP:360±292 mmHg% vs. RVP:393±206 mmHg%, p=0.04).

Conclusions

Regional myocardial work analysis is useful to identify early changes in LV mechanics after starting pacemaker therapy. The findings suggests that CSP protects septal MW better than RVP in age and sex matched patients, potentially providing mechanistic insights into the effects of emerging bradycardia pacing techniques.

Keywords

Right ventricular pacing, conduction system pacing, left ventricular dyssynchrony, left ventricular mechanics, myocardial work

7.2 Introduction

Right ventricular pacing (RVP) has long been a standard effective treatment in managing symptomatic atrioventricular block (AVB) (Lamas et al., 1998, Members et al., 2008, Tracy et al., 2012), significantly improving patient longevity and quality of life (Shaw et al., 1985). Annually, over 550,000 pacemaker implants are performed across ESC countries, with 46,000 of these occurring in the UK alone, highlighting the widespread reliance on RVP (Raatikainen et al., 2017). Despite its benefits, chronic RVP is increasingly associated with mechanical dyssynchrony and adverse left ventricular (LV) remodelling (Lee et al., 1994, Begg et al., 2011a, Wilkoff et al., 2002), which can lead to LV systolic dysfunction (LVSD) and a heightened risk of heart failure (HF) in approximately 40% of patients (Lamas et al., 2002a, Gierula et al., 2015, Wilkoff et al., 2009). This progression is particularly concerning in those with significant ventricular pacing burden (VPB) and a history of ischemic heart disease (IHD) (Gierula et al., 2015). Additionally, the economic impact of HF is substantial, with direct costs to the NHS in England reaching £2 billion annually, representing 2% of the total NHS budget (UK, 2018).

Recent research has raised concerns about the long-term effects of RVP. Chronic RVP is linked to dyssynchronous LV activation, which can mimic left bundle branch block (LBBB) and result in disco-ordinated mechanical contraction (Sharma et al., 2005). In this scenario, the early-activated LV septum is minimally loaded, while the later-activated LV lateral wall endures greater stress (Duchenne et al., 2019c). This workload mismatch between the septal and lateral walls can lead to adverse LV remodelling and an increased risk of HF (Duchenne et al., 2019c, Sletten et al., 2021).

Advancements in pacing technology have introduced CSP, which targets the intrinsic electrical conduction system through pacing lead delivery through His-bundle pacing (HBP) or left bundle branch area pacing (LBBAP) (Chung et al., 2023). Among these, LBBAP has emerged as a preferred option due to its stability, effective sensing, and low capture thresholds, despite

variability in septal perforation rates compared to HBP (Cai et al., 2020, Chen et al., 2019). Preliminary studies suggest that CSP may lead to less impairment to LV systolic function and minimise HF events relative to standard RVP, while long-term evidence is limited (Chen et al., 2019, Cai et al., 2020, Mao et al., 2023, Zhang et al., 2019b) .This possible benefit is assumed to arise from the lesser introduction of electrical and mechanical dyssynchrony with CSP when compared to RVP, albeit present data consists primarily of observational and retrospective analyses (Cai et al., 2020, Chen et al., 2019, Mao et al., 2023, Zhang et al., 2019b).

In clinical practice, imaging assessments of LV function, particularly echocardiography, are crucial in defining pacing strategies (Flachskampf et al., 2015). Over the last two decades, various echocardiographic methods, including M-mode and tissue Doppler imaging, speckle tracking, and three-dimensional echocardiography, have been used to assess LV reverse remodelling and predict clinical outcomes (Cleland et al., 2005, Curtis et al., 2007, Paton et al., 2021, Kapetanakis et al., 2008, Pitzalis et al., 2002). However, a consistent approach to the timing of measurement and methodology remains elusive, resulting in variability in practice (Cvijic et al., 2018, Sutton and Keane, 2007)

I have shown in previous chapters that myocardial work (MW) may be an important measure in assessing cardiac function, providing a detailed understanding of the LV mechanical performance throughout different phases of the cardiac cycle (Papadopoulos et al., 2021). Recent investigations have highlighted the potential of advanced echocardiographic measurements in quantifying MW, facilitating a more comprehensive assessment of LV function, particularly in relation to different pacing strategies (Moya et al., 2023, Wang et al., 2023). MW analysis may reveal the implications of mechanical dyssynchrony associated with RVP, where the workload imbalance between the septal and lateral walls can result in adverse remodelling and dysfunction. In contrast, CSP, including approaches such as His bundle pacing (HBP) and left bundle branch area pacing (LBBAP), has the potential to optimise MW by maintaining a more physiological electrical conduction pattern, thereby mitigating

mechanical inefficiencies (Mao et al., 2023, Chen et al., 2023a, Chen et al., 2023b). This study aims to compare changes in MW to investigate the hypothesis that patients undergoing CSP exhibit less LV mechanical dyssynchrony compared to those undergoing RVP by assessing echocardiographic images collected prospectively, before, shortly after, and at medium-term follow-up after pacemaker implantation.

7.3 Method

7.3.1 Study population

From October 2022 to October 2023, data were gathered through a prospective observational study at a single tertiary centre (Leeds Teaching Hospitals – Leeds General Infirmary) in the UK. The study involved patients who were referred for pacemaker implantation due to atrioventricular block, in accordance with National Institute for Health and Care Excellence (NICE) and European guidance (NICE, 2005, Members et al., 2013).

In the observational cohort study, 17 patients who participated in the Predicting Pacemaker-Related LV Systolic Dysfunction clinical study, received CSP. Study sponsors allowed for dual recruitment. For this matched pilot study, CSP patients were included if they had echocardiographic images of sufficient quality and did not have a clinical condition known to significantly affect cardiac afterload (chronic uncontrolled hypertension and severe aortic stenosis). Eligible CSP patients were pair-matched to RVP patients at baseline according to age (matched within ±5 years) and sex (male with male) with RVP patients met the same inclusion criteria regarding image quality and absence of conditions affecting cardiac afterload. **(Figure 7.1).**

Prior to starting the trial, the Health Research Authority ethical permission (22/EE/0080) was obtained, and all patients supplied informed written consent. All research efforts followed the principles of the Declaration of Helsinki.

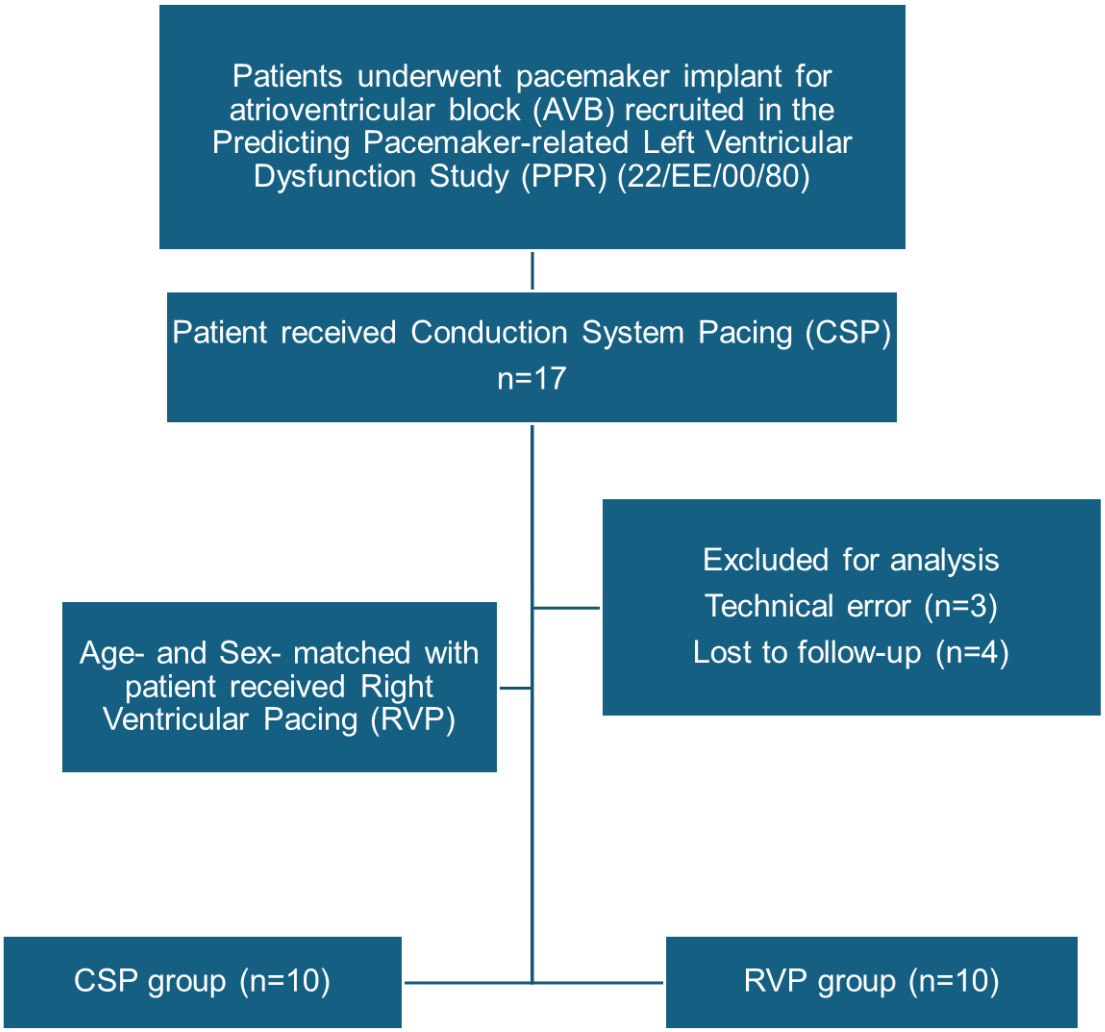


Figure 7.1 Study flowchart of methodology

7.3.2 Data collection

Study data were obtained during each follow-up visit to the National Institute for Health and Care Research (NIHR) Cardiovascular Clinical Research Facility. At the baseline visit, demographic and clinical data including age, sex, vital signs, height and weight, co-morbidities, past medical history, medical therapy, and blood chemistry were gathered.

Echocardiography was performed according to the British Society of Echocardiography minimum dataset, with the addition of global longitudinal strain (GLS) and myocardial work (MW) data at baseline (pre-implant), acute follow-up (0-6 weeks), and mid-term follow-up at 6 months post-implant. During the echocardiography procedure, the patient lay in the left lateral decubitus position (Ottenhoff et al., 2022) while a transducer was positioned on various areas of their chest and a non-invasive blood pressure (BP) was measured using an automatic sphygmomanometer. This recorded both systolic and diastolic readings at the beginning of each scan. The pacing programming remained unchanged throughout echocardiography assessment. Pacemaker mode, base rate, and cumulative pacing percentages were recorded at each follow-up.

All data were stored on a password-protected datasheet on an encrypted trust server. Echocardiographic images were analysed offline by a by a British Society of Echocardiography (BSE) accredited echocardiographer, blinded to patient data, using manufacturer-specific software (EchoPAC version 206, GE Vingmed).

Five investigations (25%) were dual reported by the same echocardiographer and another accredited echocardiographer to investigate intra and interobserver variability.

7.3.3 Outcome measures

The primary outcome was change in LV myocardial work patterns between patients who received CSP and RVP from baseline to acute follow up and to mid-term follow up, measured

via echocardiography. The secondary outcome was inter- and intra-observer variability in echocardiographic measures including Simpson's Biplane ejection fraction (EF), GLS, and MW.

7.3.4 Data analysis

Data were analysed with IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp, Armonk, NY, USA, 2020). Statistical significance was set as $p < 0.05$ with a 95% confidence interval (CI).

7.3.4.1 Descriptive analysis

Continuous data is reported as mean (± standard deviation) for variables with a normal distribution and median (interquartile range) for those that do not. Categorical variables are reported as percentages. LVEF, GLS, and MW changes were analysed with repeated measures ANOVA and Bonferroni correction.

7.3.4.2 Statistical analysis

The Interclass Correlation Coefficient (ICC) and Bland-Altman plots were used to characterise and illustrate the inter- and intra-observer reproducibility of echocardiographic parameters between two blinded echocardiographic readers. Based on the 95% confident interval of the ICC estimate, values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively (Koo and Li, 2016). Consistent with previous research (Oxborough et al., 2012), an ICC larger than 0.60 was deemed to be acceptable.

7.4 Result

7.4.1 Baseline characteristics

A total of twenty patients (10 age- and sex- matched pairs) were included in the analysis after being referred for a pacemaker implantation due to high degree AV block between October 2022 and October 2024, at a single tertiary hospital in the United Kingdom **(Table 7-1)**. Of these, 10 patients underwent CSP with left bundle branch area pacing (LBBAP), while the remaining 10 patients were treated with RVP.

Of the total cohort, 8 (40%) patients were female, and the whole cohort had a mean age of 65 (±12) years at the time of implantation. The two groups were generally similar, although the rate of co-morbidities differed. One patient in the RVP group had a history of ischemic heart disease (IHD), atrial fibrillation (AF) with a history of a cerebrovascular event (1 (5%) patient whereas no patient in the CSP group had either IHD or AF. On the other hand, 6 people in the CSP group had a history of hypertension but only one patient in the RV group had a diagnosis of hypertension. While some differences were observed between the groups, none were statistically significant except history of hypertension, which was a comorbidity more present in with patients receiving CSP compared to RV (6 (60%) patients vs. 1 (10%) patient, p=0.02, respectively). Patients receiving CSP were less likely to have type II diabetes mellitus compared to those in the RVP group (1 [10%] patient vs. 5 [50%] patients, p=0.05). Conversely, the CSP group had higher baseline levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (515 pg/ml (IQR: 230-1490) vs. 590 pg/ml (IQR: 225-1820) vs. 510 pg/ml (IQR: 260-1160), p=0.85).

Table 7-1 Baseline characteristics of study population

	Total Cohort n=20	CSP n=10	RVP n=10	p-value
Age (years)	65 (±12)	63 (±13)	68 (±11)	0.39
Sex (female)	8 [40%]	4 [40%]	4 [40%]	1.00
Height (cm)	170 (±10)	169 (±12)	170 (±10)	0.89
Weight (kg)	87 (±25)	82 (±16)	92 (±32)	0.37
Resting Heart rate (bpm)	59 (±18)	60 (1±8)	57 (±18)	0.71
Systolic blood pressure	150 (±29)	150 (±33)	149 (±26)	0.88
Diastolic blood pressure	75 (±11)	76 (±11)	74 (±10)	0.72
Co-morbidities				
Hypertension	7 [35%]	6 [60%]	1 [10%]	0.02*
Atrial fibrillation	1 [5%]	0 [0%]	1 [10%]	-
Type II Diabetes Mellitus	6 [30%]	1 [10%]	5 [50%]	0.05
Cerebrovascular accident	1 [5%]	1 [10%]	0 [0%]	-
Overt ischaemic heart disease	1 [5%]	0 [0%]	1 [10%]	-
MI	0 [0%]	0 [0%]	0 [0%]	-
PCI	1 [5%]	0 [0%]	1 [10%]	-
CABG	0 [0%]	0 [0%]	0 [0%]	-
Blood investigation				
NT-proBNP (pg/ml)	515 (230-1490)	590 (225-1820)	510 (260-1160)	0.85
Medications				
Beta-blocker	6 [30%]	1 [10%]	5 [50%]	0.06
Ace-inhibitor	7 [35%]	4 [40%]	3 [30%]	0.50
MRA	0 [0%]	0 [0%]	0 [0%]	-
Diuretic	5 [25%]	3 [30%]	2 [20%]	0.50
SGLT2	3 [15%]	0 [0%]	3 [30%]	-
Pacing system				
Dual chamber pacing	10 [100%]	10 [100%]	10 [100%]	-
Pacing programming				
DDD (R)	14 [70%]	6 [60%]	8 [80%]	0.33
RV pacing avoidance algorithm (R)	6 [30%]	4 [40%]	2 [20%]	0.33
VVI (R)	0 [0%]	0 [0%]	0 [0%]	-
Rate response	0 [0%]	0 [0%]	0 [0%]	-
Base rate (bpm)	50 (±5)	50 (±5)	52 (±6)	0.57
Max tracking rate (bpm)	136 (±9)	137 (±11)	134 (±8)	0.50
Pacing requirement				
Atrial pacing burden (%)	13 (±22)	13 (±20)	12 (±25)	0.94
Ventricular pacing burden (%)	66 (±45)	64 (±47)	68 (±46)	0.85
Traditional echocardiographic measures				
LVEF (%)	54 (±5)	56 (±4)	52 (±5)	0.07
LVEDV (ml)	155 (±39)	154 (±38)	148 (±36)	0.21
LVESV (ml)	76 (±14)	76 (±11)	77 (±17)	0.21
Advanced echocardiographic measures				
GLS (%)	-17 (±4)	-18 (±5)	-15 (±3)	0.07
MWI_S (mmHG%)	1715 (±656)	1753 (±828)	1678 (±470)	0.81
MWI_L (mmHG%)	1852 (±878)	2114 (±802)	1590 (±911)	0.19
MWI_{S-L} (mmHG%)	-137 (±870)	-361 (±813)	87 (±908)	0.26
GWI (mmHG%)	2009 (±629)	2139 (±701)	1879 (±553)	0.37
GCW (mmHG%)	2333 (±702)	2498 (±686)	2168 (±713)	0.31
GWW (mmHG%)	266 (±128)	232 (±115)	299 (±137)	0.25
GWE (%)	88 (±8)	91 (±4)	86 (±11)	0.18

Continuous data are presented as mean (± standard deviation) or median (interquartile range) and categorical data are presented as n (%). A p-value ≤0.05 was considered significant.

MI; myocardial infarction, PCI; percutaneous coronary intervention, CABG; coronary artery bypass grafting, NT-proBNP; N-terminal pro-B-type natriuretic peptide, ACE inhibitor; Angiotensin-converting enzyme, MRA; Mineralocorticoid receptor antagonists, SGLT2; Sodium-glucose cotransporter-2,GLS; global longitudinal strain, MWI_S; myocardial work index at septal, MWI_L; myocardial work index at lateral, MWI_{S-L}; myocardial work index difference (septal-lateral), GWI; global work index, GCW; global constructive work, GWW; global wasted work, GWE; Global work efficiency,

7.4.1.1 Pacing indication, device prescription and requirement

All patients were fitted with a dual-chamber device. Those who received RVP were more likely to have DDD (R) programmed compared to those who received CSP (8 (80%) patients vs. 6 (60%) patients, p=0.33, respectively) and were less likely to have RV pacing avoidance algorithm (2 (20%) patients vs. 4 (40%) patients, p=0.33, respectively) although differences were non-significant. Mean base rate and maximum tracking rate were similar in both CSP and RVP groups (50±5 bpm vs 52±6 bpm, p=0.57 and 137±11 bpm vs 134±8 bpm, p=0.50), respectively). Average atrial and ventricular pacing burden were also similar in both CSP and RVP groups (13±20 % vs. 12±25 %, p=0.94, respectively) and (64±47 % vs 68±46%, p=0.85, respectively).

7.4.1.2 Medication

Medication at baseline was similar between CSP and RVP groups for angiotensin-converting enzyme (ACE) inhibitors (4 (40%) patients vs. 3 (30%) patients, p=0.50, respectively) and diuretics (3 (30%) patients vs. 2 (20%) patients, p=0.50). RVP patients were more likely to get β-antagonists (5 (50%) patients vs. 1 (10%) patient, p=0.06), although the differences were not statistically significant. Three patients in the CSP group got sodium-glucose cotransporter-2 (SGLT2) (3 (30%) patients compared to none in RVP group, and no one received mineralocorticoid receptor antagonists (MRAs) in both groups.

7.4.1.3 Baseline echocardiographic measures

The overall sample had a mean LVEF of 54±5%, LVEDV of 155±39 ml, and LVESV of 76±14 ml. Additionally, there was no statistically significant differences observed between CSP and RVP groups in terms of LVEF (56±4% vs. 52±5%, p=0.07), LVEDV (154±38 ml vs. 148±38 ml, p=0.21), and LVESV (76±11 ml vs. 77±17, p=0.21). GLS differed between the groups, with CSP had a higher baseline (pre implant) GLS compared to RVP, with no statistically significant difference (-18±5 mmHg% vs. -15±3 mmHg%, p=0.07, respectively).

At baseline, the CSP patients had higher measurements compared to RVP for global work efficiency (GWE) (91±4% vs. 86±11 mmHg%, p=0.18), GWI (2139±701 mmHg% vs. 1879±553 mmHg%, p=0.37), GCW (2498±686 mmHg% vs. 1879±553 mmHg%, p=0.31), and GWW (232±115 mmHg% vs. 299±137 mmHg%, p=0.25) although these were not statistically significant.

CSP also had a higher measurement compared to RVP for myocardial work index (MWI) at the LV septal wall (MWI_S) (1753±828 mmHg% vs. 1678±470 mmHg%, p=0.81) and MWI at LV lateral wall (MWI_L) (2114±802 mmHg% vs. 1590±911 mmHg%, p=0.19), but these were not statistically different. There were differences in septal to lateral MW differences between CSP and RVP groups at baseline (-361±813 mmHg% vs. 87±908 mmHg%, p=0.26, respectively), but these were also not statistically different.

7.4.2 Assessment of LV systolic function using traditional echocardiographic measurements throughout follow-up

In the CSP group, the LVEF minimally declined from baseline to six months post implant (56%±4 to 54%±5 to 52%±8) whereas in the RVP group, LVEF slightly increased from baseline to six month follow up (52±5 % to 51±5 % to 56±7 %). Nevertheless, this difference between group was not statistically significant (p=0.09) **(Table 7-2).**

Patients from both groups preserved relatively stable LVEDV values throughout follow up (CSP group: 154±38 ml to 148±22 ml to 155±37 ml vs. RVP group: 148±36 ml to 132±20 ml to 135±16 ml, p=0.26). Similarly, LVESV values were comparable between the two groups (CSP group: 76±11 ml to 74±12 ml to 76±11 ml vs. RVP group: 77±17 ml to 74±11 ml to 74±13 ml, p=0.63) with no statistically significant differences between groups. Over time, GLS was preserved in both the CSP group (-18±5 % to 16±3 % to -16±4 %), and the RVP group (-15±3 % to -14±4 % to -15±4 %, p=0.16).

7.4.3 Assessment of global LV mechanics throughout follow-up

The CSP group showed a reduction in GWE from baseline to acute and to mid-term follow up (6 months), while the RVP group have a lower efficiency throughout but measures remained relatively stable over time (91±4 % to 89±5 % to 83±10 %) vs. 86±11 % to 84±9 % to 84±10 % respectively, p=0.02) **(Figure 7.2,Table 7-2)**

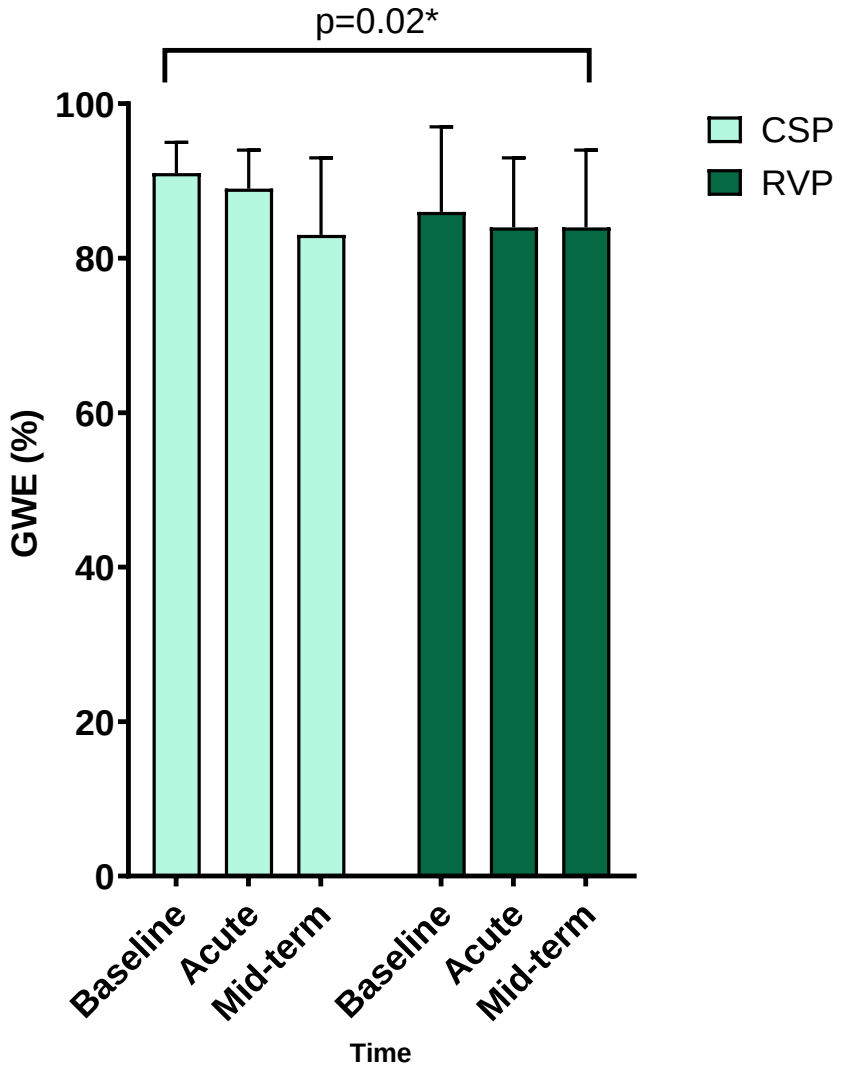


Figure 7.2 Global work efficiency (GWE) from baseline to acute and to mid-term follow up between conduction system pacing (CSP) and right ventricular pacing group (RVP) (p=0.02*).

Table 7-2 Echocardiographic measurements at baseline and follow-up between CSP and RVP group (absolute values)

	CSP group *n=10*			RVP group *n=10*			
	Baseline	**Acute**	**Mid-term**	**Baseline**	**Acute**	**Mid-term**	**p-value**
LVEF (%)	56±4	54±5	52±8	52±5	51±5	56±7	0.09
LVEDV (ml)	154±38	148±22	155±37	148±36	132±20	135±16	0.26
LVESV (ml)	76±11	74±12	76±11	77±17	74±11	74±13	0.63
GLS (%)	-18±5	-16±3	-16±4	-15±3	-14±4	-15±4	0.16
GWE (%)	91±4	89±5	83±10	86±11	84±9	84±10	0.02*
GWI (mmHG%)	2139±702	1853±558	1718±669	1879±553	1476±463	1480±547	0.02*
GCW (mmHG%)	2498±686	2231±480	2079±877	2168±714	1914±457	1930±508	0.10
GWW (mmHG%)	232±115	260±116	360±292	260±116	388±326	393±206	0.04*
MWI_S (mmHG%)	1752±828	1542±675	1540±687	1678±471	1415±458	1270±594	0.02*
MWI_L (mmHG%)	2114±802	2039±767	1943±441	1590±911	1703±794	2010±741	0.54
MWI_{S-L} (mmHG%)	-361±813	-496±674	-293±658	87±908	-288±918	-740±499	0.09

Values are presented as mean (± standard deviation) A p-value ≤0.05 was considered significant.
LVEF; left ventricular ejection fraction, LVEDV; left ventricular end-diastolic volume, LVESV; left ventricular end-systolic volume, GLS; global longitudinal strain, GWE; global myocardial work efficiency, GWI; global work index, GCW; global constructive work, GWW; global wasted work, MWI_S; myocardial work index septal, MWI_L; myocardial work index lateral, MWI_{S-L}; myocardial work index septal-lateral.

Global work index (GWI) in the CSP group demonstrated a decline from baseline across follow up, whereas the RVP group had consistently lower GWI values, stabilising by mid-term follow up (2139±702 mmHg% to 1853±558 mmHg% to 1718±669 mmHg% vs. (1879±553 mmHg% vs 1476±463 mmHg% to 1480±547 mmHg%, respectively, p=0.02)). These absolute values over time were statistically different between groups **(Table 7.2, Figure 7.3)**.

Global constructive work (GCW) decreased in both CSP and RVP groups (2498±686mmHg% to 2231±480 mmHg% to 2079±877 mmHg%) vs 2168±714 mmHg% to 1914±457 mmHg% to 1930±508 mmHg%, p=0.10) **(Table 7.2, Figure 7.4).**

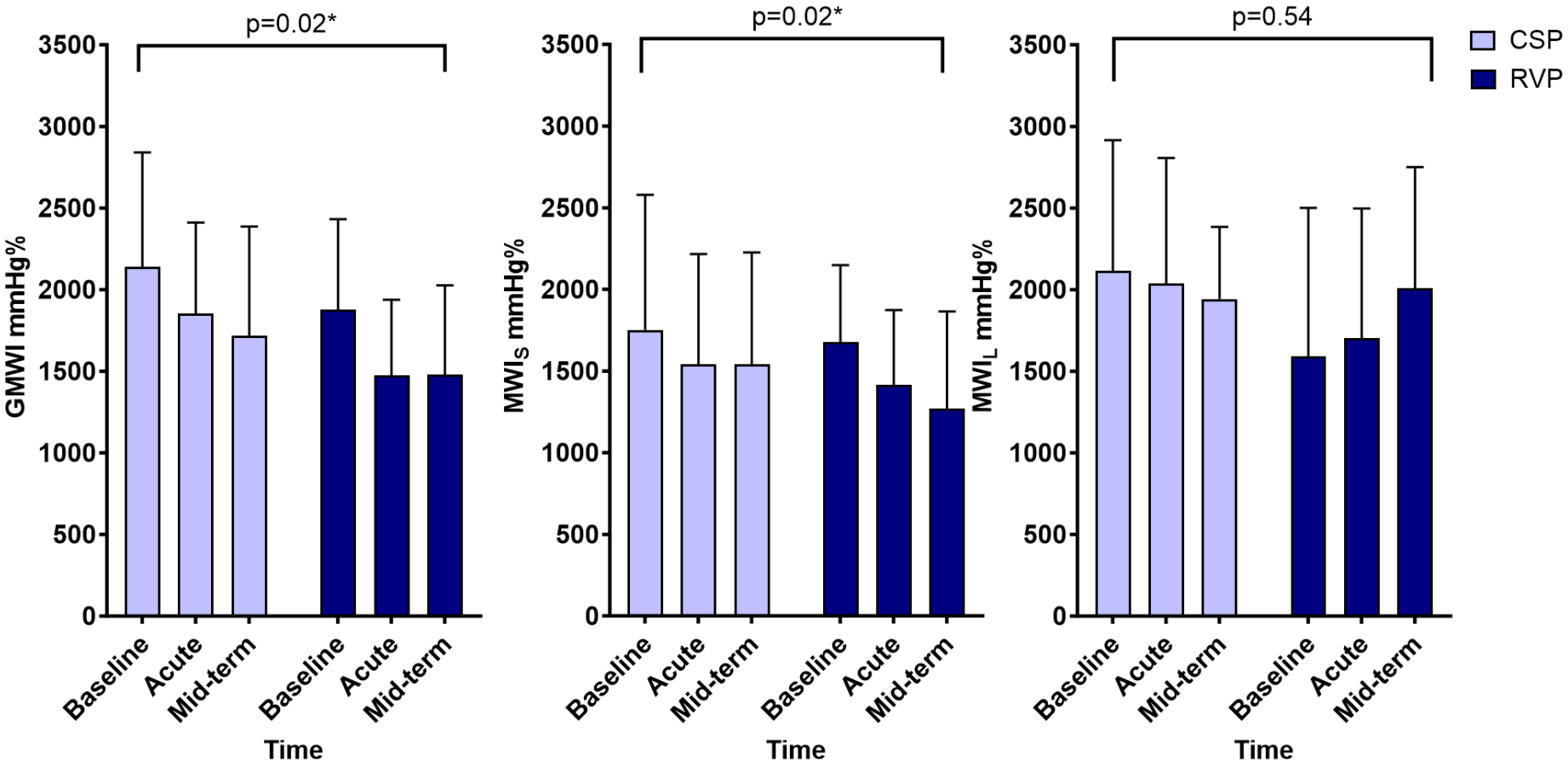


Figure 7.3 Distribution of work index at global (GWI), regional work index at septal (MWI_S) and lateral (MWI_L)

Global wasted work (GWW) increased significantly over time in both groups, with the CSP group showing a slower deterioration over follow-up, whilst GWW in the RVP group rose acutely and progressively (232±115 mmHg% to 260±116 mmHg% to 360±292 mmHg% vs. 260±116 mmHg% to 388±326 mmHg% to 393±206 mmHg%, respectively) with a statistically significant difference between the groups (p=0.02**) (Table 7.2, Figure 7.4).**

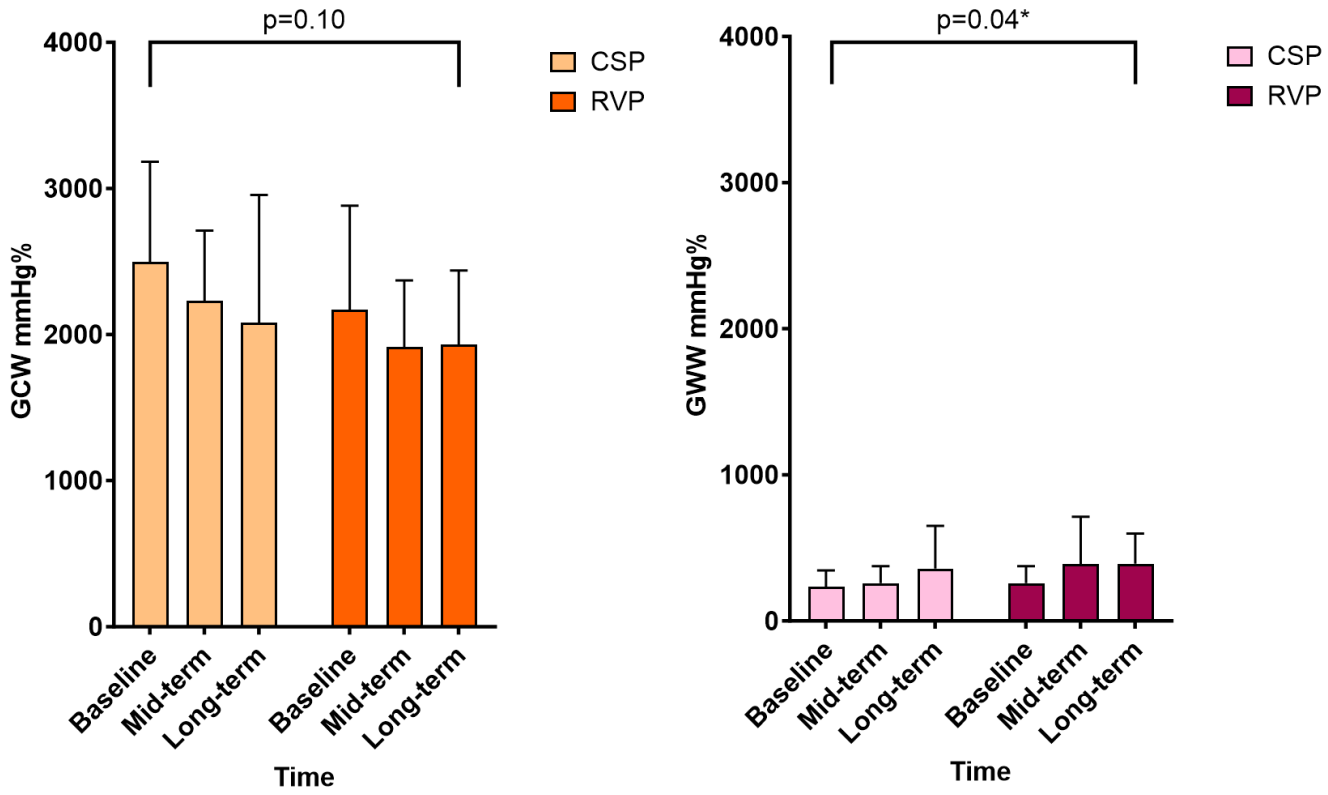


Figure 7.4 Distribution of global constructive work (GCW) and global wasted work (GWW)

7.4.4 Regional assessment of LV mechanics

In the CSP group, MWI_S decreased from baseline acutely, with stabilisation between acute and mid-term, whilst in the RVP group, MWI_S decreased more progressively from baseline to mid-term (1752±828 mmHg% to 1542±675 mmHg% to 1540±687 mmHg% vs. 1678±471 mmHg% to 1415±458 mmHg% to 1270±594 mmHg%, p=0.02) **(Table 7.2, Figure 7.3)**.

Myocardial work index at the lateral region (MWI_L) was preserved in the CSP group whilst it slightly increased in the RVP group overtime (2114±802 mmHg% to 2039±767 mmHg% to 1943±441 mmHg% vs. 1590±911 mmHg% to 1703±794 mmHg% to 2010±741 mmHg%), with a non-significant trend over time between groups (p=0.54) **(Table 7.2, Figure 7.3)**. However, relatives change in MWI_L towards approached statistically significant between CSP and RVP group (Δ Mid-Baseline; -313±1104 vs -394±741, p=0.61, relatively).

The septal-lateral difference (MWI_{S-L}) approached statistical significance (p=0.09), suggesting a trend towards differential septal-lateral work distribution between the CSP and RVP group. In the CSP group, there was increased lateral work compared to septal work from baseline which homogenised during follow-up. In the RVP group, there was less lateral work compared to septal from baseline, however increased lateral work was observed by six month follow-up with increased heterogeneity between regions, which trended towards statistical significance (-361±813 mmHg% to -496±674 mmHg% to -293±658 mmHg% vs 87±908 mmHg% to -288±918 mmHg% to -740±499 mmHg%, p=0.09) **(Table 7.2, Figure 7.5).**

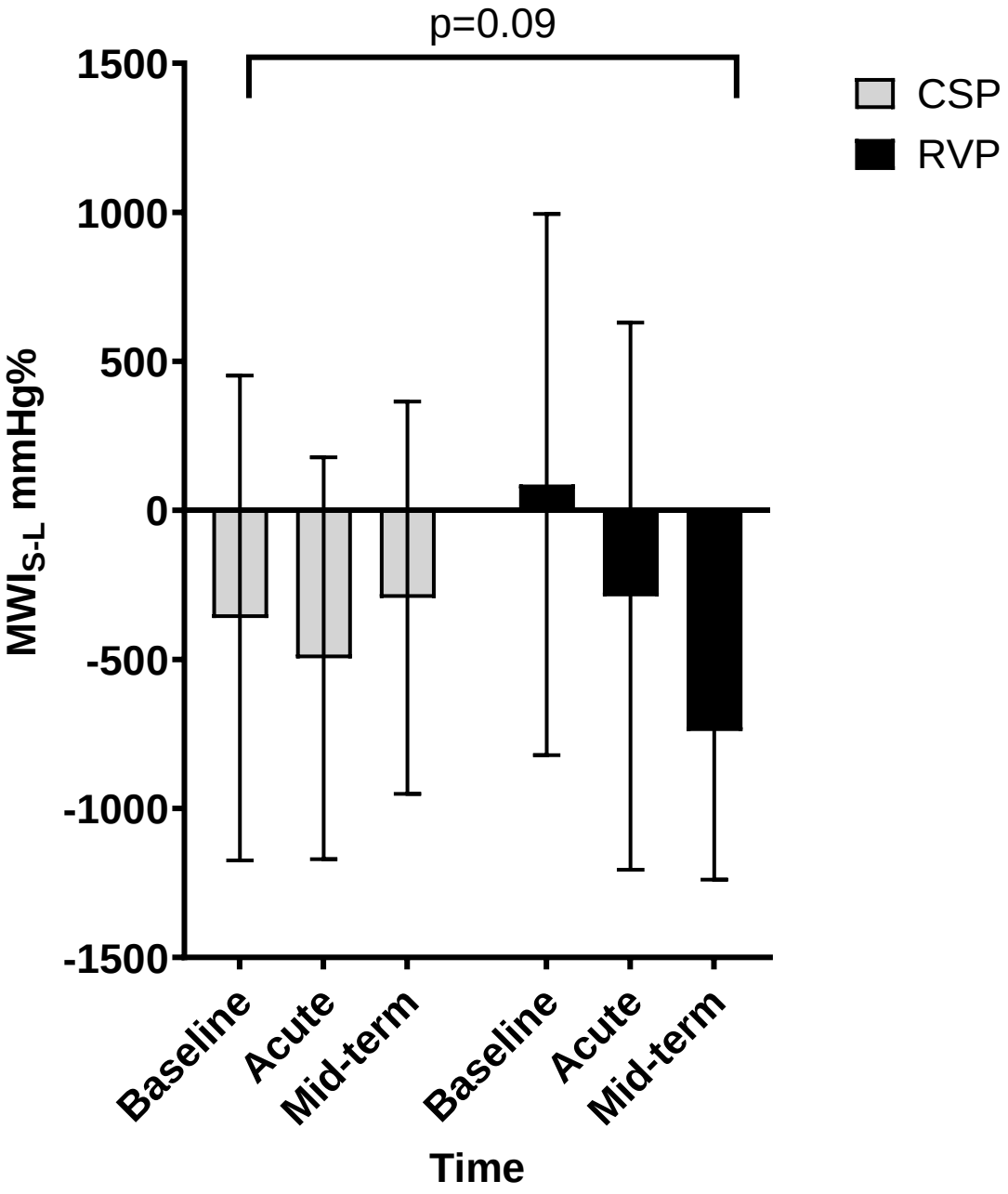


Figure 7.5 The septal-lateral difference (MWI_{S-L})

7.4.5 Evaluation of observer variability in echocardiographic measures

Inter-observer reliability indicated some variability across measurements. A moderate reproducibility was observed for LVEDV (ICC: 0.73, 95% Limits of agreement (LOA) -0.65 to 0.97, p=0.10), LVESV (ICC: 0.51, 95% LOA -8.70 to 0.95, p=0.27) and LVEF (ICC: 0.56, 95% LOA -41.80 to 0.95, p=0.25) measurements indicating considerable inconsistency across observers. In contrast, GLS had an excellent reliability (ICC: 0.92, 95% LOA 0.21 to 0.99, p=0.02) when taken by different observers For myocardial work measures, GWE measurements had a moderate reliability (ICC: 0.73, 95% LOA -4.98 to 0.97, p=0.14), whilst GWI (ICC: 0.80, 95% LOA, p=0.08), GCW (ICC: 0.81, 95% LOA, p=0.08), and GWW (ICC: 0.81, 95% LOA, p=0.08) measurements showed a good reliability, when taken by different observer.

In comparison, all ICC values for intra-observer reliability were "good" or "excellent" **(Table 7-3, Figure 7.6)**. Excellent reliability was observed when measured LVEDV (ICC of 0.91, 95% LOA: 0.29 to 0.99, p=0.02), LVESV (ICC of 0.95, 95% LOA: 0.64 to 0.99, p=0.00), LVEF (ICC of 0.89, p=0.02) and GLS (ICC: 0.99, 95% LOA: 0.92 to 0.99, p<0.01) respectively, demonstrating that measurements were consistent when taken by the same observer. Similarly for advanced echocardiographic measurements, global work index (GWI) (ICC: 0.97, 95% LOA 0.81 to 0.99, p=0.01), global constructive work (GCW) (ICC: 0.99, 95% LOA 0.93 to 0.99, p<0.01) and global wasted work (GWW) (ICC: 0.85, 95% LOA 0.01 to 0.98, p=0.03) showed an excellent reliability, respectively. However, GWE (ICC: 0.74, 95% LOA -0.64 to 0.97, p=0.09) had a moderate reliability and not statistically significant when taken by the same observer.

Table 7-3 Repeatability and reproducibility of echocardiographic data

Variables	Mean (±SD)	Mean (±SD)	Bias	p-value	ICC	95% LOA
Inter-observer						
LVEDV (ml)	155±45	174±25	-19	0.10	0.73c	-0.65 to 0.97
LVESV (ml)	73±31	80±11	-7	0.27	0.51c	-8.70 to 0.95
LVEF (%)	54±10	54±4	1	0.25	0.56c	-4.18 to 0.95
GLS (%)	-16±5	-16±4	0	0.02*	0.92c	0.21 to 0.99
GWE (mmHg%)	89±7	89±3	0	0.14	0.73c	-4.98 to 0.97
GWI (mmHg%)	2047±781	1895±418	152	0.08	0.80c	-1.03 to 0.97
GCW (mmHg%)	2402±875	2171±458	232	0.07	0.81c	-0.49 to 0.98
GWW (mmHg%)	277±158	261±114	15	0.08	0.81c	-1.62 to 0.98
Intra-observer						
LVEDV (ml)	164±32	172±54	-8	0.02*	0.91c	0.29 to 0.99
LVESV (ml)	77±22	83±29	-6	0.00*	0.95c	0.64 to 0.99
LVEF (%)	53±7	52±6	1	0.02*	0.89c	0.13 to 0.98
GLS (%)	-16±5	-16±6	0	<0.01*	0.99c	0.92 to 0.99
GWE (mmHg%)	89±7	92±3	-3	0.09	0.74c	-0.64 to 0.97
GWI (mmHg%)	2060±818	1933±943	127	0.01*	0.97c	0.81 to 0.99
GCW (mmHg%)	2302±917	2206±1005	97	<0.01*	0.99c	0.93 to 0.99
GWW (mmHg%)	254±14)	205±86	50	0.03*	0.85c	0.01 to 0.98

Continuous data are presented as mean (± standard deviation) and median (interquartile range). A p-value ≤0.05 was considered significant. LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dysfunction; LVEDD, left ventricular end-diastolic diameter; GLS, global longitudinal strain; GWE, global work efficiency; GWI, global work index; GCW, global constructive work; GWW, global wasted work; SD, standard deviation; ICC, intraclass correlation; LOA, lower limits of agreement.

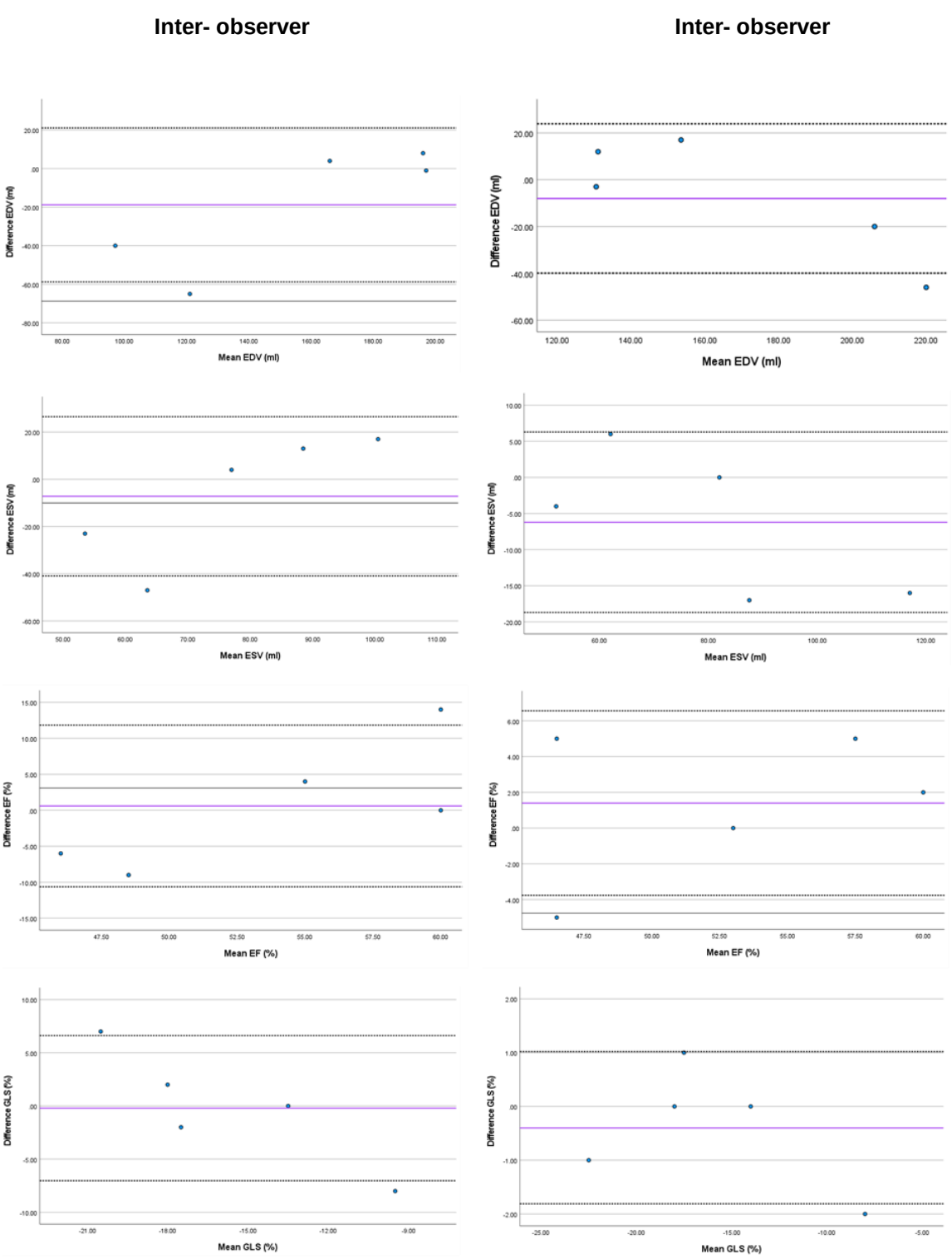


Figure 7.6 Inter- and intra-observer reliability of traditional echocardiographic measures by Bland-Altman plots

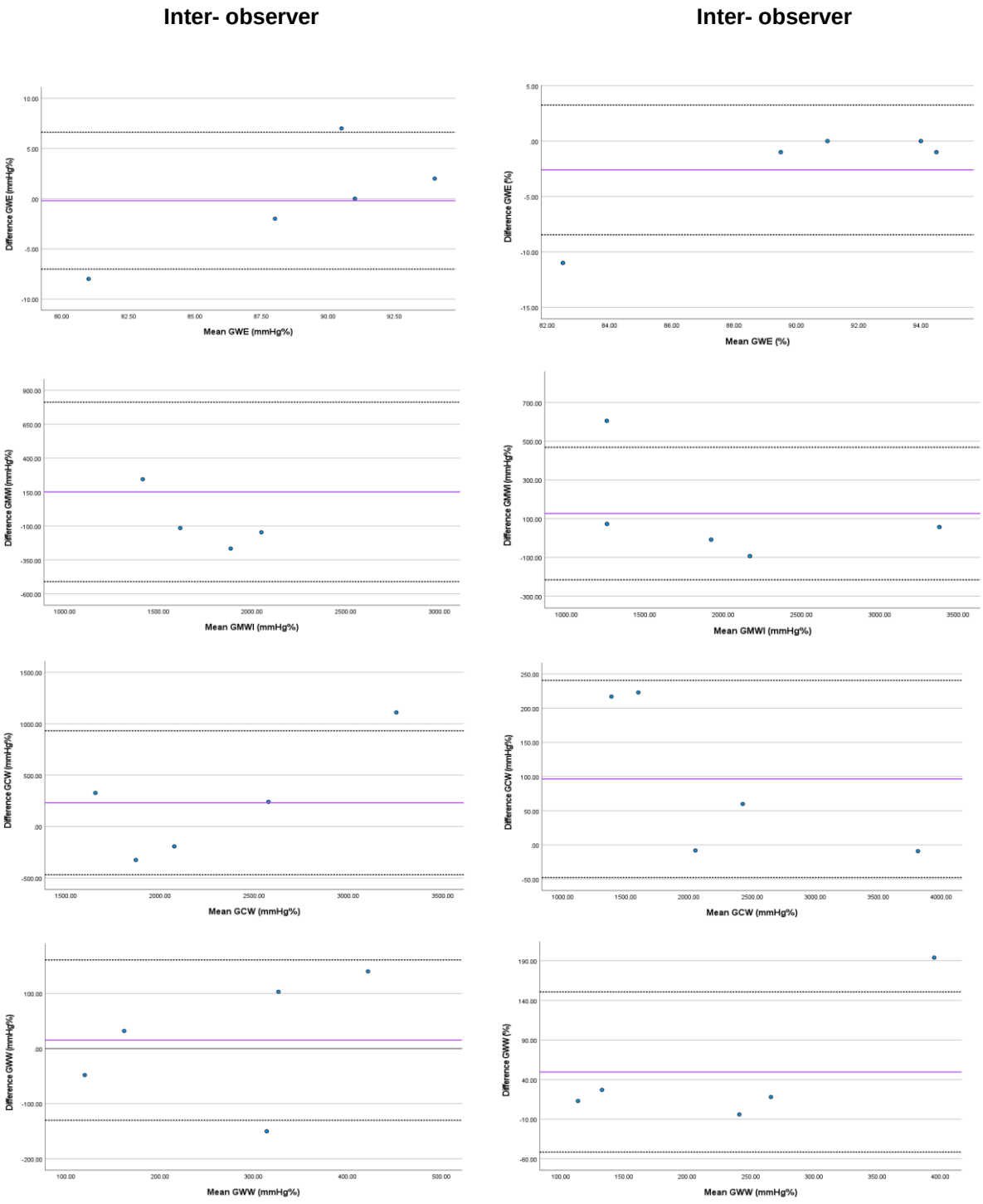


Figure 7.7 Inter- and intra-observer reliability of myocardial work measures echocardiographic measures by Bland-Altman plots

7.5 Discussion

This study assessed LV mechanics in patients receiving device therapy with novel CSP approaches compared to traditional RVP using echocardiography. The study revealed a number of significant findings between the two pacing strategies, with CSP being shown to preserve more homogenous workload distribution and a higher degree of myocardial work than RVP. These remodelling effects were apparent within the six months follow-up after pacemaker implantation.

The observed differences in global MW index (GWI) and global MW efficiency (GWE) over time between CSP and RVP offer mechanistic insights into how these pacing modalities effect LV performance. When broken down into the discrete components which determine MW index and efficiency, GCW represents the work contributing to effective LV contraction, whilst GWW represents inefficient energy use. Both CSP and RVP groups showed GCW reduction, but the slower decline in the CSP group suggests better preservation of constructive myocardial function within the six months of follow-up. This is reinforced by the slower increase in GWW in the CSP group, suggesting that CSP maintains better synchronisation of contraction, whereas the sharp rise in GWW in the RVP group demonstrates worsening mechanical inefficiency.

Again, septal and lateral region interactions seem important in determining the longer-term outcome of the patients. Septal myocardial work index (MWI_S) decreased but stabilised at 6 months in patient receiving CSP, and lateral myocardial work index (MWI_L) was preserved throughout follow-up. The RVP group, however, showed progressive decline in MWI_S across follow-up intervals and a slight increase in MWI_L, causing septal deterioration and lateral overcompensation, leading to a septal-lateral work (MWI_{S-L}) imbalance, mechanical inefficiency and increasing wasted work of the LV. This trend supports the hypothesis that CSP helps preserve regional mechanical co-ordination compared to RVP (Vassallo et al., 1986, Gierula et al., 2015, Paton et al., 2021, Sharma et al., 2005, Duchenne et al., 2019b,

Sletten et al., 2021, Ghani et al., 2011, Sweeney et al., 2003, Catanzariti et al., 2013, Lamas et al., 2002b).

While the exploratory analysis primarily focused on absolute values of myocardial work measurements, a secondary assessment of relative changes was also undertaken to explore temporal dynamics. Interestingly, the trend toward reduced septal work and compensatory increases in lateral work in RVP patients reinforces the concept of regional imbalance. These findings, though not conclusive, add nuance to the understanding of pacing-related remodelling and highlight the need for larger studies to explore its clinical relevance.

7.5.1 CSP as a strategy to preserve LV function

Alternative pacing techniques including HBP and LBBAP, collectively referred to as CSP, have been developed due to RVP-related ventricular dyssynchrony. Despite its potential advantage of maintaining physiological ventricular activation, HBP is technically challenging and linked to increased rates of complications (Heckman et al., 2020). LBBAP represents a fundamental change in pacing therapy and requires specialised knowledge (Padala and Ellenbogen, 2020). LBBAP procedure first describes by Huang et al where the procedure involves advancing the pacing lead through the interventricular septum, mapping the His bundle region, and then advancing the lead 1 to 2 cm into the septum (Huang et al., 2017). During the procedure, unipolar pacing configuration and peak LV activation times are monitored, and pacing thresholds are assessed by the transition from nonselective to selective left bundle branch capture, resulting in a ventricular activation that is more physiological compared to RVP (Li et al., 2019, Chan et al., 2019, Cano and Vijayaraman, 2021, Huang et al., 2017). Whilst this requires additional training and expertise, according to a recent study (Hua et al., 2020), LBBAP had a higher success rate, shorter procedure and fluoroscopy times, lower pacing thresholds, and larger R-wave amplitudes than HBP, and therefore may be the more viable option for clinical adoption.

Reducing mechanical dyssynchrony and preserving physiological pacing may adverse cardiac remodelling, LV systolic dysfunction and ultimately HF clinical events in the longer term compared to RVP approaches (Heckman et al., 2020). Thus, assessment of LV mechanics, such as via MW, may be potential surrogate marker of adverse outcomes in this patient cohort, which may allow for more rapid assessment of CSP effectiveness. (Hua et al., 2020).

In the current study, the CSP group exhibited less LV remodelling from baseline to mid-term follow up than the RVP group, and their septal and lateral wall MW load was more equally distributed. Interestingly, similar to Mao et al. (Mao et al., 2023), RVP patients had considerably worse septal work compared to lateral wall work. I show LBBAP may be a more protective pacing approach, thereby preventing pacemaker-related LVSD and the development of HF (Whinnett, 2023).

7.5.2 Role of echocardiography in the assessment of mechanical dyssynchrony

Should CSP be proven beneficial, it would require a paradigm shift in cardiac pacing which would require the retraining of all current implanters and cardiac scientists, as well as pacing equipment provision. Therefore, until this is available widely, it may be required to identify patients at increased risk and direct them for CSP at specialist centres. In order to investigate predictive variables, potential predicters must first be identified.

I have shown advanced echocardiographic measures of LV mechanics, may detect more subtle localised abnormalities than traditional echocardiographic measures, which may in the future allow a more tailored therapeutic strategy (Russell et al., 2013).This work shows dyssynchronous LV activation during RVP causes abnormal and heterogenous timing of LV regional contraction, especially in the septal and lateral regions, resulting in additional wasted MW, whereby there is misaligned contraction across LV regions or inefficient contraction (Russell et al., 2013, Duchenne et al., 2020). Increased wasted MW was also seen in a study of patients with left bundle branch block compared to controls (controls: 0.09±0.03, LBBB:

0.36±0.16) and interestingly, wasted work was substantially reduced with the application of CRT in the study cohort (from 0.36±0.16 to 0.17±0.07, P<0.001) (Russell et al., 2013).

The present study also found MWI and GWE were better preserved in those receiving CSP pacing. A comparative study evaluated MW in HF patients, exploring LBBAP as a promising alternative to traditional CRT in 62 patients. The results also showed that LBBAP led to greater improvements in global work index (GWI) and global work efficiency (GWE), as well as better mechanical synchronisation, compared to CRT (Liu et al., 2021).In addition, the prospective, single-centre EMPATHY observational study (Malagù et al., 2022) found that RVP worsened myocardial function for all MW measures compared to spontaneous.

My investigation, therefore, builds on the growing evidence surrounding LBBAP and CSP as potential alternatives to traditional RVP for patients requiring pacemaker therapy. Similar to findings by Wang et al. and Mao et al which demonstrated that LBBAP maintains a more physiological electrical conduction pattern with less mechanical dyssynchrony compared to RVP, our study shows that CSP significantly better preserves septal MW overtime compared to RVP (Wang et al., 2023, Mao et al., 2023). However, Mao's study had limited MW assessments, was performed retrospectively, and only at specific time points where data were available, whilst Wang's study had a small sample size of only 20 patients and a short follow-up duration of only 7 days, which may limit the generalisability and long-term applicability of the findings. Additionally, Azzolini et al. found no significant differences in GWI between His bundle pacing (HBP) and LBBAP, suggesting both modalities can mimic intrinsic contraction effectively (Azzolini et al., 2023).

Echocardiographic derived MW may provide early mechanistic insights for larger clinical trials testing CSP, which may take years to report. An ongoing double-blinded PROTECT-HF trial (NCT05815745) compares classic RVP with new CSP (LBBAP and HBP). This critical investigation will not publish until 2030, leaving clinical practice without definitive knowledge

of whether physiological pacing can protect pacemaker patients from long-term mortality and morbidity. Early echocardiographic assessment, including MW analysis in this group may aid therapeutic guidance and cardiac rhythm management strategy. Whatsmore, we have shown that MW measures are feasible in clinical practice and have comparable reproducibility to similar echocardiographic measures.

7.6 Limitations

This exploratory analysis of prospective non-randomised data reflects the experience of a single centre, limiting statistical power. Post-hoc matching was based only on age and sex, potentially introducing bias. Despite this, I adopted a pragmatic approach to match the group and given the limited data comparing CSP and RVP approaches impact on myocardial performance, the results offer valuable insights. However, future research should consider baseline echocardiographic measurements as a matching strategy. Echocardiography provides an objective assessment of myocardial performance before intervention, helping to control for pre-existing differences in LVEF, GLS and MW measurements. Since pacing strategies directly influence myocardial performance, incorporating baseline echocardiographic data would enhance the validity of comparisons and strengthen conclusions regarding the effects of CSP and RVP on LV mechanics.

The 6-month follow-up restricts long-term analysis, but differences in MW between the septal and lateral LV regions appeared within 3 months of RVP initiation in patients who developed LVSD (LVEF <50%), aligning with previous findings (Duchenne et al., 2019b). Therefore, MW changes can be detected earlier than traditional remodelling measures. Nevertheless, longer-term observational cohorts and multi-centre clinical trial data are needed to confirm the findings.

7.7 Conclusion

This study demonstrates that CSP preserves LV mechanics compared to RVP within six months of pacemaker implantation. GWI and GWE declined more significantly and persistently in RVP patients, indicating greater deterioration in global myocardial function. Regional measures, including MWI_{S-L} difference, further revealed that CSP preserved a better balance between regional work distributions, minimising mechanical regional dyssynchrony. In contrast, RVP caused progressive septal dysfunction and lateral overcompensation. These findings suggest that CSP potentially offers a more physiologically favourable pacing strategy compared to RVP.

7.8 Dissemination of findings

A manuscript is being prepared for publication

Chapter 8 Conclusion

Overall, the present thesis describes studies that aim to risk stratify patients who need long term right ventricular pacing, assessing their risks of left ventricular systolic dyssynchrony. To date, the cardiac community are still unable to identify those at risk using clinical characteristics and traditional diagnostics. The challenge is to evaluate the efficacy of novel echocardiography measures in identifying patients who subsequently aversely remodel in order to utilise this data prior to pacemaker implantation to direct protective therapeutic strategies.

8.1 The relationship of cardiovascular comorbidities and right ventricular pacing requirement: a cohort study

This study highlights the high prevalence of left ventricular systolic dysfunction (LVSD) in patients undergoing pacemaker therapy for bradycardia, particularly in those receiving right ventricular pacing. The findings demonstrate that a significant proportion (37%) of the cohort exhibited LVSD, with higher rates observed in patients receiving a new implant compared to those undergoing pacemaker generator replacement. Key risk factors associated with LVSD included male gender, a history of ischemic heart disease, and a high ventricular pacing burden >80%.

Additionally, over a median follow-up period of 30 months, one-third of the patients experienced heart failure requiring hospitalisation or death, with pacing generator replacement patients showing worse outcomes compared to NI patients. Independent predictors of adverse outcomes included age, presence of atrial fibrillation, and reduced left ventricular ejection fraction <50%.

This study suggests that ventricular pacing burden is associated with a considerable risk of LVSD and adverse clinical outcomes, but indicated it is not responsible in isolation. Therefore, simple taking as detailed clinical history to ascertain if a patient has a diagnosis of ischaemic

heart disease, atrial fibrillation and hypertension, along with a high requirement for ventricular pacing, may direct targeted screening and management strategies to patients at high-risk to prevent adverse left ventricular remodelling and ultimately the progression to heart failure.

8.2 Left ventricular mechanics in patients receiving right ventricular pacing: a retrospective analysis

This study reveals that right ventricular pacing significantly influences left ventricular function in patients with atrioventricular block receiving pacemaker therapy in a retrospective analysis. Over a mean follow-up period of 26 months, 28% of patients developed left ventricular systolic dys (defined as left ejection fraction <50%).

Analysis of myocardial work measurements revealed that global and regional work index may be associated with the development of left ventricular systolic dysfunction (defined left ejection fraction <50%). There was difference in in between patients who preserved a left ventricular ejection fraction ≥50% to those who did not (left ventricular ejection fraction <50%). highlighting the distinct impact of right ventricular pacing on LV mechanics.

These findings suggest that regional myocardial work measurements have prognostic value in identifying early signs of emerging LVSD. However, further research is needed to assess their predictive value for future LVSD. Early identification of patient at risk could enable timely intervention with alternative pacing strategies, such as conduction system pacing or cardiac resynchronisation therapy, to mitigate adverse remodelling and improve long-term outcomes.

8.3 Predicting left ventricular systolic dyssynchrony and adverse remodelling using measures of left ventricular mechanics

This study prospectively investigated the effects of right ventricular pacing on left ventricular mechanics in patients with atrioventricular block undergoing pacemaker implantation. While left ejection fraction remained stable from baseline to six-month follow-up, significant declines

in global longitudinal strain and myocardial work (MW) measurements were observed, indicating early signs of left ventricular systolic dyssynchrony.

Specifically, reductions in both the septal myocardial work index and global work index, along with a decrease in global constructive work, suggest that even in the absence of overt left ventricular systolic dyssynchrony, subtle changes in left ventricular mechanics can occur early post-implantation. Regression analysis identified age and ventricular pacing burden as significant predictors of post-implant left ventricular systolic dyssynchrony. However, myocardial work measurements, were not significant predictors of left ventricular systolic dyssynchrony. This may be attributed to the relatively short follow-up period, which could limit the ability to detect meaningful associations with longer-term outcomes. Although these measurements can identify subtle changes in left ventricular function, their predictive potential prior to implant for right ventricular pacing-related left ventricular systolic dyssynchrony may require further investigation with extended follow-up.

Overall, the findings emphasise the potential role of advanced echocardiographic measurements in identifying patients who subsequently develop RVP related left ventricular systolic dyssynchrony and remodelling. However, given no baseline MW measurements demonstrated value in predicting future LVSD, further research is needed before any changes in clinical practice can be recommended. Future studies should investigate whether these imaging measurements can reliably predict future adverse LV remodelling and ultimately inform individualised patient management.

8.4 The effects of novel conduction system pacing compared to traditional right ventricular pacing on left ventricular mechanics

In this study, the impact of conduction system pacing (CSP) versus right ventricular pacing (RVP) on left ventricular mechanics in patients with atrioventricular block were evaluated. The results indicate that while both pacing strategies lead to a decrease in the left ventricular

myocardial work index for the septal region, the decline is significantly greater in the right ventricular pacing group, suggesting a detrimental effect on septal myocardial function. Similarly, both groups showed a significant reduction in global work index overtime, with the right ventricular group experiencing a more marked early decline. Global wasted work increased significantly in both groups, suggesting that both strategies lead to inefficiency in LV work post-procedure.

Overall, the findings highlight the potential role of advanced echocardiographic assessments in evaluating the cardiac mechanical performance prior to, and after pacemaker implantation. While the data suggest that CSP may offer protective benefits against LV remodelling compared to RVP in appropriately selected patients, these observations remain preliminary. Further research is needed to confirm whether CSP truly offers protective benefits against left ventricular dyssyhncrony and adverse remodelling and clarify its role in future pacing strategies for bradycardia management.

8.5 Future directions

A number of keys messages can be drawn from these findings, which are outlined below:

1. Ventricular pacing burden is not an isolated driver of left ventricular dysfunction in pacing patients. Important clinical characteristics associated with adverse clinical events includes ischaemic heart disease, atrial fibrillation, and number of comorbidities could guide clinicians in identifying patients at higher risk.

2. Right ventricular pacing (RVP) in AV block patients leads to reduced LV function and altered LV mechanics distribution. Patients with preserved LVEF >50% show more normally distributed LV mechanics

3. Myocardial work index difference is because of constructive work contributions, particularly at septal region. Although no additional predictive value, but significant declines in LV mechanics, suggest potential for detecting early LV remodelling post-implantation.

4. Global myocardial work index declined more significantly in RVP patients. RVP causes a reduction at septal work and lateral work overcompensation. Conduction system pacing (CSP) better preserve LV mechanics compared to RVP within 6 months post-implant. However, the long-term recovery and potential impact on clinical outcomes remain uncertain.

Taken together, these findings suggest that ventricular pacing effects on LV mechanics are multifactorial and not solely dependent on pacing burden. Future research should consider more patients and longer-term follow-up to clarify the predictive value of LV mechanics analysis in pacing related LV remodelling. Such insights may guide pacing strategies toward preserving ventricular function and improving patient outcomes.

List of abbreviation

2D	:	two dimensions
3D	:	three dimensions
AAI	:	atrial demand pacing
ACE-inhibitor	:	angiotensin-converting-enzyme-inhibitor
AF	:	atrial fibrillation
AHA	:	American Heart Associations
ANOVA	:	analysis of variance
ANP	:	atrial natriuretic peptide
APB	:	atrial pacing burden
AS	:	aortic stenosis
ASE	:	American Society of Echocardiology
AUC	:	area under curve
AV	:	atrioventricular block
AVB	:	atrioventricular block
BHRS	:	British Heart Rhythm

BNP	:	brain natriuretic peptide
BP	:	blood pressure
BSE	:	British Society of Echocardiography
CABG	:	coronary artery bypass grafting
CI	:	confidence interval
CIED	;	cardiovascular implantable electronic devices
CMR	:	cardiac magnetic resonance
CRF	:	Cardiovascular Research Facility
CRT	:	cardiac resynchronisation therapy
CSP	:	conduction system pacing
CVA	:	cerebrovascular accident (stroke)
CVD	:	cardiovascular disease
CW	:	constructive work
CWIS	:	constructive work at septal
CWL	:	constructive work at lateral
DDD	:	dual chamber sensing and dual response

DDDR : dual chamber universal rate-responsive mode

DDI : Dual-chamber sensing, dual-chamber pacing, inhibited response

DM : diabetes mellitus

EACVI : European Associations of Cardiovascular Imaging

ECG : electrocardiogram

EF : ejection fraction

EHRA : European Heart Rhythm Associations

ERP : Echo Research Practice

ESC : European Society of Cardiology

GCS : Global constructive work

GCW : Global constructive work

GLS : Global longitudinal strain

GWE : Global work efficiency

GWI : Global work index

GWW : Global wasted work

HBP : His Bundle pacing

HF	:	Heart failure
HFH	:	heart failure hospitalisation
HR	:	hazard Ratio
HRS	:	Heart Rhythm Associations
ICC	:	interclass correlation coefficient
ICD	:	Implantable cardioverter defibrillator
IHD	:	ischaemic heart disease
IQR	:	interquartile range
LA	:	left atrial
LBBAP	:	left bundle branch area pacing
LBBB	:	left bundle branch block
LOA	:	limits of agreement
LV	:	left ventricular
LVEDD	:	left ventricular end diastolic diameter
LVEDV	:	left ventricular end diastolic volume
LVEF	:	left ventricle ejection fraction

LVESD : left ventricular end systolic diameter

LVESV : left ventricular end systolic volume

LVSD : left ventricular systolic dysfunction

LW : lateral wall

MI : myocardial infarction

MRA_S : mineralocorticoid receptor antagonists

MRI : magnetic resonance imaging

MVP : minimised ventricular pacing

MW : myocardial work

MWE : myocardial work efficiency

MWEL : myocardial work efficiency at lateral

MWES : myocardial work efficiency at septal

MWI : myocardial work index

MWIL : myocardial work index at lateral

MWIS : myocardial work index at septal

NHS : National Health Service

NI	:	new implant
NICE	:	National Institute of Health and Care Excellence
NIHR	:	National Institute for Health and Care Research
NSVT	:	non-sustained ventricular tachycardia
NYHA	:	New York Heart Association
OR	:	odds ratio
PGR	:	pacemaker generator replacement
PRISMA	:	Preferred Reporting Items for Systematic Review and Meta-Analyses
PSL	:	pressure-strain loop
QOL	:	quality of life
RA	:	right atrium
RAA	:	right atrium appendage
RV	:	right ventricle
RVA	:	right ventricle apex
RVAP	:	right ventricular apical pacing
RVHS	:	right ventricular high septum

RVOT	:	right ventricular outflow tract
RVA	:	right ventricle apex
RVS	:	right ventricle septum
RVSP	:	right ventricle septal pacing
SD	:	standard deviation
SDI	:	systolic dyssynchrony index
STE	:	speckle tracking echocardiography
SVC	:	superior vena cava
SW	:	septal wall
TDI	:	tissue Doppler imaging
TTE	:	transthoracic echocardiography
UK	:	United Kingdom
USA	:	United States of America
UTR	:	upper tracking rate
VBP	:	ventricular pacing burden
VDD	:	ventricle pacing, dual-chamber sensing, inhibited response

VOO	:	asynchronous ventricle pacing
VVI	:	ventricle pacing, ventricle sensing, inhibited response
VVIR	:	ventricle pacing, ventricle sensing, rate responsive mode
WHO	:	World Health Organisation
WW	:	wasted work
WWL	:	wasted work at lateral
WWS	:	wasted work at septal
ΔLVEF	:	change in left ventricular ejection fraction
ΔLVGLS	:	change in left ventricular global longitudinal strain
ΔLW	:	change in left wall

Appendix A: The relationship of cardiovascular comorbidities and right ventricular pacing requirement: a cohort study - new implant (NI group) (Ethical Approval)

NHS
Health Research Authority
NRES Committee Yorkshire & The Humber - South Yorkshire
Millside
Mill Pond Lane
Meanwood
Leeds
LS6 4RA

Telephone: 0113 3050122
Facsimile: 0113 8556191

31 October 2012

Dr Klaus Witte
Senior Lecturer and Consultant Cardiologist
University of Leeds
LIGHT building,
Clarendon Road
Leeds
LS2 9JT

Dear Dr Witte

Study title: **Optimising pacemaker therapy (OPT-PACE)**
REC reference: **12/YH/0487**

The Research Ethics Committee reviewed the above application at the meeting held on 25 October 2012.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non NHS sites

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of

the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

The participant information sheet should have references to vitamin D removed and should state the correct Research Ethics Committee.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Evidence of insurance or indemnity		
GP/Consultant Information Sheets	1.0 - Leeds - new implant study	24 September 2012
Investigator CV	Witte K, abbreviated CV	12 January 2012
Other: GP letter	1.0 - Leeds	24 September 2012
Other: GP letter	1.0 - Bradford	24 September 2012
Other: GP letter	1.0 - Harrogate	24 September 2012
Other: OPT-PACE flow chart	1.0	24 September 2012
Participant Consent Form: OPT-PACE	1.0	24 March 2012
Participant Consent Form: OPT-PACE (Bradford)	1.0	24 March 2012
Participant Consent Form: OPT-PACE (Harrogate)	1.0	24 March 2012
Participant Information Sheet: new implants	1.0	24 September 2012
Participant Information Sheet: Leeds WP2	1.0	24 September 2012

Participant Information Sheet: Bradford WP2	1.0	24 September 2012
Participant Information Sheet: Harrogate WP2	1.0	24 September 2012
Protocol	1.0	24 September 2012
REC application		

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/YH/0487 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp
Ms Jo Abbott
Chair

Email: nrescommittee.yorkandhumber-southyorks@nhs.uk

Appendix B: The relationship of cardiovascular comorbidities and right ventricular pacing requirement: a cohort study - new implant (NI group) (LTHT & R&D Approval)

The Leeds Teaching Hospitals NHS
NHS Trust

Ref: Amanda Bird

12/04/2013

Research & Development
Leeds Teaching Hospitals NHS Trust
34 Hyde Terrace
Leeds
LS2 9LN

Tel: 0113 392 2878
Fax: 0113 392 6397

r&d@leedsth.nhs.uk
www.leedsth.nhs.uk

Dr Klaus Witte
Consultant Cardiologist
University of Leeds
LIGHT building,
Clarendon Road
Leeds
University of Leeds
LS2 9JT

Dear Dr Klaus Witte

Re: NHS Permission at LTHT for: Optimising pacemaker therapy (OPT-PACE)
LTHT R&D Number: CD12/10554 (116334/WY)
REC: 12/YH/0487

I confirm that *NHS Permission for research* has been granted for this project at The Leeds Teaching Hospitals NHS Trust (LTHT). NHS Permission is granted based on the information provided in the documents listed below. All amendments (including changes to the research team) must be submitted in accordance with guidance in IRAS. Any change to the status of the project must be notified to the R&D Department.

Permission is granted on the understanding that the study is conducted in accordance with the *Research Governance Framework for Health and Social Care*, ICH GCP (if applicable) and NHS Trust policies and procedures available at http://www.leedsth.nhs.uk/sites/research_and_development/.

This permission is granted only on the understanding that you comply with the requirements of the *Framework* as listed in the attached sheet "Conditions of Approval".

If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

Indemnity Arrangements

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust only accepts liability for research activity that has been managerially approved by the R&D Department.

The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm to cover you as investigator and the researchers listed on the Site Specific Information form. Should there be any changes to the research team please ensure that you inform the R&D Department and that s/he obtains an appropriate contract, or letter of access, with the Trust if required.

Yours sincerely

Dr D R Norfolk
Associate Director of R&D

Approved documents
The documents reviewed and approved are listed as follows

Document	*Version*	*Date of document*
NHS R&D Form	3.4	12/02/2013
SSI Form	3.4	06/01/2013
Directorate Approval		20/03/2013
REC Letter confirming favourable opinion		31/10/2012
Insurance with Indemnity		N/A
Protocol	1.0	24/08/2012
Patient information sheet (REC approved); Implants	1.1	24/09/2012
Consent form (REC aporoved)	1.1	31/10/2012
Patient Information Sheet - Leeds	1.1	31/10/2012
Flow Chart	1.0	24/08/2012
GP/Consultant information sheets (REC approved)	1.0	24/08/2012

Appendix C: The relationship of cardiovascular comorbidities and right ventricular pacing requirement: a cohort study – pacemaker generator replacement (PGR group) and (Ethical Approval)

NHS
National Research Ethics Service
Leeds (West) Research Ethics Committee
A/B Floor, Old Site
Leeds General Infirmary
Great George Street
Leeds
LS1 3EX

Telephone: 0113 3923181
Facsimile: 0113 392 2863

20 February 2008

Dr Klaus K Witte
Senior Lecturer in cardiology
University of Leeds
LIGHT building

Dear Dr Witte

Full title of study: **The prevalence and effects on exercise tolerance of left ventricular dysfunction in the Leeds pacemaker population.**
REC reference number: **08/H1307/12**

Thank you for your letter of 13 February 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA. There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Application	2	16 January 2008
Investigator CV	Klaus K Witte	19 December 2007
Investigator CV	J Gierula	
Protocol	1.1	13 February 2008

Covering Letter		19 December 2007
Summary/Synopsis	V1 (In Protocol)	19 December 2007
GP/Consultant Information Sheets		19 December 2007
Participant Information Sheet	1.1	13 February 2008
Participant Consent Form	1.1	13 February 2008
Response to Request for Further Information		13 February 2008
Evidence of Insurance	University of Leeds	24 September 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from http://www.rdforum.nhs.uk/rdform.htm.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.
b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk .

08/H1307/12	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Laura Sawiuk
REC Co-ordinator
On Behalf of
Mr Jon Silcock
Chair

Email: laura.sawiuk@leedsth.nhs.uk

Enclosures: *Standard approval conditions*

Copy to: Mr Clare Skinner, University of Leeds

R&D, Leeds Teaching Hospitals NHS Trust

Appendix D: The relationship of cardiovascular comorbidities and right ventricular pacing requirement: a cohort study– pacemaker generator replacement (PGR group) and (LTHT & R&D Approval)

The Leeds Teaching Hospitals NHS
NHS Trust

30/01/2008

Research & Development Directorate
A/B Corridor, Old Site
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Tel: 0113 392 2878
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www.leedsteachinghospitals.com

Dr Klaus Witte
Senior Lecturer in Cardiology
LIGHT Building
University of Leeds

Dear Dr Klaus Witte

Re: LTHT R&D Approval of CD08/8474: The prevalence and effects on exercise tolerance of left ventricular dysfunction in the Leeds pacemaker population.

I write with reference to the above research study. I can now confirm that this study has R&D approval and the study may proceed at The Leeds Teaching Hospitals NHS Trust (LTHT). This organisational level approval is given based on the information provided in the documents listed below.

As principal investigator you have responsibility for the design, management and reporting of the study. In undertaking this research you must comply with the requirements of the *Research Governance Framework for Health and Social Care* which is mandatory for all NHS employees. This document may be accessed on the Department of Health website at http://www.dh.gov.uk/research

R&D approval is therefore given on the understanding that you comply with the requirements of the *Framework* as listed in the attached sheet "Conditions of Approval".

If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

Indemnity Arrangements

The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust only accepts liability for research activity that has been managerially approved by the R&D Department.

The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm to cover you as principal investigator and the researchers listed on the R&D approval form provided that each member of the research team has an employment contract (substantive or honorary) with the Trust. Should there be any changes to the research team please ensure that you inform the R&D Department and that s/he obtains an employment contract with the Trust if required.

Yours sincerely

Dr D R Norfolk
Associate Director of R&D

Approved documents
The documents reviewed and approved are listed as follows

Document	*Version*	*Date of document*
Protocol	1.0	19/12/07
SSI Form	5.5	17/01/08
CMT Approval		21/01/08
NHS REC Application Form	5.5	17/01/08

Appendix F: Predicting left ventricular systolic dyssynchrony and adverse remodelling using measures of left ventricular mechanics (Ethical Approval)

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Maria Paton
NIHR Clinical Lecturer
University of Leeds
Cardiovascular Research Facility
F Floor, Jubilee Wing, Leeds General Infirmary
Leeds
LS1 3EX

Email: approvals@hra.nhs.uk

11 May 2022

Dear Dr Paton

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Predicting pacemaker-related left ventricular systolic dysfunction**
IRAS project ID:	**309289**
REC reference:	**22/EE/0080**
Sponsor	**University of Leeds**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

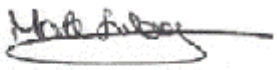
- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **309289**. Please quote this on all correspondence.

Yours sincerely,



Mark Sidaway
Approvals Specialist
Email: approvals@hra.nhs.uk

Copy to: *Ms Jean Uniacke*

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