Chronic effects of right ventricular pacing

The impact of right ventricular lead position

Fruelund, Patricia Zerlang

DOI (link to publication from Publisher):
10.54337/aau534290121

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

CHRONIC EFFECTS OF RIGHT VENTRICULAR PACING

THE IMPACT OF RIGHT VENTRICULAR LEAD POSITION

BY
PATRICIA ZERLANG FRUELUND

DISSERTATION SUBMITTED 2023

AALBORG UNIVERSITY
DENMARK

CHRONIC EFFECTS OF RIGHT VENTRICULAR PACING

THE IMPACT OF RIGHT VENTRICULAR LEAD POSITION

Patricia Zerlang Fruelund

AALBORG UNIVERSITY
DENMARK

Dissertation submitted February 2023

Dissertation submitted:	February 2023
PhD supervisor:	Professor Sam Riahi, MD, PhD; Department of Cardiology, Aalborg University Hospital; Department of Clinical Medicine, Aalborg University; Denmark
Assistant PhD supervisors:	Professor Claus Graff, PhD; Department of Health Science and Technology, Aalborg University; The Faculty of Medicine, Aalborg University; Denmark
	Professor Peter Søgaard, MD, PhD; Department of Cardiology, Aalborg University Hospital; Department of Clinical Medicine, Aalborg University; Denmark
	Tomas Zaremba, MD, PhD; Department of Cardiology, Aalborg University Hospital; Denmark
PhD committee:	Associate Professor Andreas Carus (chair) Aalborg University, Denmark
	Clinical Professor Henrik Wiggers Aarhus University, Denmark
	Professor Christian Wolpert RKH Klinikum Ludwigsburg, Germany
PhD Series:	Faculty of Medicine, Aalborg University
Department:	Department of Clinical Medicine

ISSN (online): 2246-1302
ISBN (online): 978-87-7573-755-0

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Stibo Complete, 2023

ACKNOWLEDGEMENTS

This dissertation is the culmination of an educational PhD journey, and I would like to thank my supervisors and collaborators for the help and support I have received throughout the process.

First and foremost, I would like to give a special thanks to my main supervisor Sam Riahi, who encouraged me to do research and without whom this PhD would not have been possible. You have been a great support throughout the whole process. You let me work independently and gave me the responsibility of realising my PhD and at the same time you nudged me forward and helped me keep focused when needed. It has been a privilege to have you as my main supervisor.

Furthermore, I would like to thank my three co-supervisors. Tomas Zaremba, thank you for sharing your knowledge and your many ideas on cardiac imaging. Our meetings have been both interesting and educational and together we have explored new ideas and found the needed solutions. Claus Graff, working with you has always been fun and inspiring. With your engineering background, you have contributed with out-of-the-box ideas and been an invaluable help with our research on electrocardiographic imaging. Peter Søgaard, you have been a great help on everything related to echocardiography. Furthermore, you have provided unreserved support when the publication process has seemed most challenging.

Søren Lundbye-Christensen, thank you for guiding me through the mysteries of statistics and for your generous moral support that is always offered when needed. Our meetings have never been boring. I would also like to thank Erik Berg Schmidt, you helped making my PhD a reality and you have been supportive throughout the process. I have always enjoyed our conversations and your experienced feedback has been much appreciated. Also, a great thanks to Anders Sommer, for your invaluable help with analysing the CT scans and for always providing relevant and constructive feedback.

I wish to thank my external collaborator Peter van Dam. Working with you has been exciting and intellectually challenging. The world of electrocardiographic imaging was completely new to me, and you have patiently guided me in the right direction. On the same note, I would also like to thank the rest of the Peacs team. Eelco van Dam and Martin Kastelein, thank you for all your patient technical support and for your great company during my visits to the office in Nieuwerbrug.

Michael Rangel Pedersen and Aksayan Arunanthy Mahalingasivam, you helped with data entry and reviewed an endless number of medical records. Thank you for your dedicated work. A great thanks to Britt Mejer Christensen for always helping with all kinds of issues and to Janni Margrethe Nielsen and Liselotte Bøgsted for their

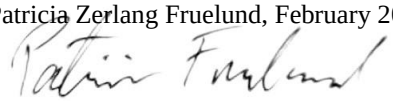
invaluable logistical and practical help with making the study visits possible. To my colleagues at the cardiology outpatient clinic, thank you so much for all you help and support with the logistics regarding the clinical examinations and your patient help with pacemaker interrogations. Pernille Veiss-Pedersen and Jens Brøndum Frøkjær, thank you for your important help with realising the CT scans. Søren Vraa, thank you for your big help with analysing a vast number of echocardiograms.

This work could not have been done without financial support. A special thanks to Helsefonden, Svend Andersen Fonden, Karl G. Andersen Fonden, Department of Cardiology at Aalborg University Hospital and Department of Clinical Medicine at Aalborg University for making this project possible.

The COVID-19 pandemic had a big impact on the course of my PhD, challenging both inclusion of study participants and collaboration with our external partner. Furthermore, the lockdowns emphasised the importance of good colleagues. Thank you to my fellow PhD students and colleagues at the Lipid Clinic for all the good times we have shared and for the moral support.

Finally, I would like to thank my friends and family for the support throughout the process. A huge thanks to my friend Søren, who has generously let me use his apartment as my second office. To the kids, Kjartan and Bjørk, thank you for keeping my feet on the ground, my sleep at a minimum, and for filling my life with love and fun. Last, but not least, I owe a special gratitude to my wife Sara for your inexhaustible love, patience, and encouragement.

Patricia Zerlang Fruelund, February 2023



ENGLISH SUMMARY

Due to dyssynchronous myocardial activation, right ventricular (RV) pacing may result in pacing-induced cardiomyopathy (PICM). The RV pacing site affects the pattern of dyssynchronous activation. Thus, research has focused on finding the optimal pacing site in the attempt to minimise the risk of PICM. However, results from prospective studies applying fluoroscopic assessment of RV lead position have been conflicting. Fluoroscopy is an inaccurate method for localising the lead position, and misclassification of exposure may have contributed to the conflicting results. This localisation inaccuracy is overcome when using computed tomography (CT).

This dissertation was based on three studies conducted within the same cohort of patients with chronic RV pacing due to high-degree atrioventricular block. In study I, we investigated the impact of different CT-verified RV lead positions on the risk of PICM. We found that RV lead position was not significantly associated with the risk of PICM when comparing septal and non-septal positions and when comparing anterior septal, posterior septal, apical, and free wall positions. However, though not statistically significant, a trend towards higher risk of PICM was observed in the posterior septum group. In study II, we investigated the association between left ventricular (LV) contractile dyssynchrony, quantified by a novel echocardiographic method, and the risk of PICM. Further, we assessed the impact of RV lead location on LV contractile dyssynchrony. Those with PICM had the highest degree of overall dyssynchrony and LV anterior-inferior dyssynchrony was independently associated with PICM. RV lead location significantly influenced the dyssynchronous activation pattern and pacing the posterior septum resulted in the highest degree of LV dyssynchrony. In study III, we investigated the accuracy of a novel non-invasive electrocardiographic imaging (ECGi) method to localise the RV pacing site and therefore potentially be a tool to guide RV lead implantation. We found that the method accurately and effectively localised the RV pacing site in relation to right ventricular anatomy.

The introduction of novel methods in this dissertation has provided the opportunity to investigate RV pacing from new perspectives, thus bringing new insights to a clinically important topic. Using CT to accurately localise RV lead position, allowed for true comparison of different RV lead positions. The evaluation of LV dyssynchrony contributed with new knowledge regarding the pathophysiological consequences of RV pacing and the impact of lead position. Finally, investigating ECGi as a potential method to guide pacemaker implantation was a minor, but important, step towards achieving implantation accuracy.

DANSK RESUME

Grundet dyssynkron aktivering ved pacing i højre ventrikel er der risiko for pacing-induceret kardiomyopati (PICM). Placeringen af pacemakerelektroden i højre ventrikel har betydning for den dyssynkrone aktivering og forskning har forsøgt at finde den optimale elektrodeplacering for at minimere risikoen for PICM. Desværre har resultaterne fra prospektive studier, som har brugt røntgengennemlysning til vurdering af elektrodeplaceringen, været modstridende. Røntgengennemlysning er en upræcis metode til bestemmelse af elektrodeplacering, og misklassifikation af eksponeringen kan have bidraget til de modstridende resultater. Brug af computertomografi (CT) kan sikre en mere præcis vurdering af elektrodeplaceringen.

Denne ph.d.-afhandling er baseret på tre studier med brug af data fra den samme kohorte inkluderende patienter med kronisk pacing i højre ventrikel grundet avanceret atrioventrikulært blok. I studie I undersøgte vi sammenhængen mellem forskellige CT-bestemte elektrodeplaceringer og risiko for PICM. Vi fandt ingen signifikant sammenhæng mellem elektrodeplacering og PICM ved sammenligning af septal of non-septal pacing og ved sammenligning af pacing i forreste septum, bageste septum, apex eller frivæg. Dog fandt vi en tendens mod større risiko for PICM ved pacing i bageste septum. I studie II undersøgte vi, med en ny ekkokardiografisk metode, sammenhængen mellem dyssynkron aktivering af venstre ventrikel og risiko for PICM. Ydermere undersøgte vi sammenhængen mellem elektrodeplacering og dyssynkroni. PICM-gruppen havde højere grad af dyssynkron aktivering sammenlignet med dem uden PICM. Særligt dyssynkroni mellem venstre ventrikels forreste og bageste væg var associeret med PICM. Elektrodeplacering påvirkede betydeligt det dyssynkrone aktiveringsmønster og pacing i den bageste del af septum resulterede i den højeste grad af dyssynkron aktivering. I studie III undersøgte vi en ny elektrokardiografisk (ECGi) metode til rekonstruktion af hjertets elektriske aktivering med potentiale til at guide pacemaker implantation. Vi fandt at metoden præcist og effektivt lokaliserede pacemakerlektroden i højre ventrikel.

I afhandlingen er der introduceret nye metoder som har bidraget med ny viden inden for kardiel pacing. Ved brug af hjerte-CT kunne vi mere præcist bestemme elektrodeplaceringen og dermed sikre en reel sammenligning af forskellige elektrodeplaceringer. Evaluering af venstre ventrikel dyssynkroni har bidraget med ny viden omkring patofysiologien ved pacing i højre ventrikel og betydningen af elektrodeplaceringen. Slutteligt så har studiet om ECGi været et lille men vigtigt skridt på vejen mod at opnå implantationspræcision.

LIST OF PAPERS

This dissertation is based on the following studies:

Study I

Fruelund PZ, Sommer A, Frøkjær JB, Lundbye-Christensen S, Zaremba T, Søgaard P, Graff C, Vraa S, Mahalingasivam AA, Thøgersen AM, Pedersen MR, and Riahi S. Risk of Pacing-Induced Cardiomyopathy in Patients with High-Degree Atrioventricular Block – Impact of Right Ventricular Lead Position Confirmed by Computed Tomography. *J Clin Med* 2022;11:7228.[1]

Study II

Fruelund PZ, Sommer A, Lundbye-Christensen S, Graff C, Søgaard P, Riahi S, and Zaremba T. The role of contractile dyssynchrony in pacing-induced cardiomyopathy: detailed assessment using index of contractile asymmetry. Submitted (in review).[2]

Study III

Fruelund PZ, Dam PM Van, Melgaard J, Sommer A, Lundbye-Christensen S, Søgaard P, Zaremba T, Graff C, and Riahi S. Novel non-invasive ECG imaging method based on the 12-lead ECG for reconstruction of ventricular activation: A proof-of-concept study. *Front Cardiovasc Med* 2023;10.[3]

ABBREVIATIONS

AV	Atrioventricular
CAMM	Curved anatomical M-mode
CI	Confidence interval
CRT	Cardiac resynchronisation therapy
CT	Computed tomography
ECG	Electrocardiogram
ECGi	Electrocardiographic imaging
HF	Heart failure
ICA	Index of contractile asymmetry
ICD	Implantable cardioverter defibrillator
IQR	Interquartile range
LE	Localisation error
LV	Left ventricular
LVEF	Left ventricular ejection fraction
PICM	Pacing-induced cardiomyopathy
RD	Risk difference
rICA	Relative index of contractile asymmetry
RR	Relative risk
RV	Right ventricular
TTE	Transthoracic echocardiogram
SD	Standard deviation
STE	Speckle tracking echocardiography
2CH	Two-chamber
3CH	Three-chamber
3D	Three-dimensional
4CH	Four-chamber

TABLE OF CONTENTS

CHAPTER 1. INTRODUCTION

There is a continuous increase in cardiac pacemaker implantations due to increasing life expectancy and new indications.[4] According to the latest report from the Danish Pacemaker and Implantable Cardioverter Defibrillator (ICD) Register, the Danish pacemaker population is continuously growing and more than 30,000 people were living with a pacemaker in 2020 in Denmark.[5] High-degree atrioventricular (AV) block remains the dominant indication for cardiac pacing in Denmark, resulting in 2,377 pacemaker implants in 2020.[5] Also globally, the number of pacemaker implantations has been steadily increasing and in 2009 there was an estimated one million pacemaker device implants.[6]

Right ventricular (RV) pacing is an efficient and life-saving treatment for patients with high-degree AV block.[4] However, RV pacing may also have detrimental effects on cardiac function, resulting in increased cardiovascular morbidity and mortality.[7–9] Deterioration in left ventricular (LV) systolic function following chronic frequent RV pacing with no other obvious aetiology is often referred to as pacing-induced cardiomyopathy (PICM).[10] Such untoward effects of RV pacing have been attributed to the pacing-induced abnormal and dyssynchronous electrical and mechanical biventricular activation.[11,12] The pattern of dyssynchronous activation is affected by the RV pacing site and for decades, extensive research to find the optimal RV lead position has emerged.[13–15] However, results have been conflicting and many questions about the role of RV lead position in PICM remain unanswered.[4] Traditionally, studies have applied fluoroscopy, possibly supported by QRS morphology from the 12-lead ECG, to guide pacemaker implantation and determine RV lead implantation site. However, current methods are known to be inaccurate, and misclassification of RV lead positions may have contributed to the inconsistent results.[16,17]

Therefore, the overall aim of this dissertation was to investigate the chronic effects of RV pacing and the impact of RV lead position on LV systolic function in patients with high-degree AV block. Contrast-enhanced computed tomography (CT) was applied to ensure precise localisation of the RV lead position and a novel strain rate based echocardiographic method was applied to evaluate patterns of dyssynchronous activation during RV pacing. Furthermore, a recently developed non-invasive electrocardiographic imaging (ECGi) method was evaluated for its future potential to guide RV lead positioning.

CHAPTER 2. BACKGROUND

2.1. CLINCIAL CONSEQUENSES OF RIGHT VENTRICULAR PACING

Chronic RV pacing may have deleterious effects on cardiac function resulting in PICM, with increased risk of heart failure (HF) and increased mortality.[7,9,18–20] Depending on outcome definition, inclusion criteria and duration of follow-up, the reported risk of PICM or HF varies between 10 to 40% among patients with preserved pre-implant LV ejection fraction (LVEF).[8,10,21–23]

The negative consequences of RV pacing cannot solely be ascribed to the underlying conduction system disease leading to the pacemaker implantation.[9,19] The Dual-Chamber and VVI Implantable Defibrillator (DAVID) trial included 506 patients referred for primary ICD implantation and randomised patients to receive either RV ventricular back-up pacing or dual-chamber pacing.[9] Looking at the composite endpoint of time to death or first HF hospitalisation, they observed a significantly higher outcome rate among those receiving dual-chamber pacing. Andersen *et al*. conducted a prospective trial randomising patients with sick sinus node syndrome to receive either single-chamber atrial pacing or single-chamber ventricular pacing. In line with the DAVID trial, they found a higher mortality and higher incidence of HF in the ventricular paced group.[20] Additionally, it has been reported that an increase in RV pacing burden is independently associated with adverse effects.[7,8,24] A pacing burden $\geq$ 40% has been reported to significantly increase the risk of adverse outcomes.[7,24]

The notion of dyssynchronous electrical and mechanical activation being the primary pathophysiological aetiology of PICM is supported by an improvement of LV function after upgrading to cardiac resynchronisation therapy (CRT) or conduction system pacing.[25–27] In addition, studies comparing RV pacing with de novo CRT or conduction system pacing have shown promising results in preservation of LV function.[28–37] However, CRT implantations are more expensive, have higher complication rates, and should be reserved for those who are most likely to benefit from it.[28,29,31,32,38] Though the pathophysiology of PICM is instigated by the pacing-induced dyssynchrony, multiple factors contribute to the negative effects. These factors include RV pacing burden and myocardial substrate for deterioration.[39] RV pacing is well tolerated in the majority of cases. Thus, numeral studies have investigated risk factors for developing PICM to identify patients in need of routine follow-up after pacemaker implantation or to identify candidates for de novo implantation of a CRT device.[8,21–23,40–42] Pre-implant decreased LVEF combined with

a high exposure to RV pacing has consistently been a strong predictor of PICM. Thus current guidelines recommend de novo implantation of CRT in patients with high-degree AV block and LVEF < 40%.[4] Furthermore, pre-implant characteristics such as male gender, pre-existing myocardial pathology, wider native QRS duration and ischemic heart disease have been associated with increased risk of PICM.[21–23] However, currently there are no recommendations on CRT implantations nor routine follow-up in high risk patients with normal pre-implant LVEF.[4,43]

2.2. PATHOPHYSIOLOGY OF PACING-INDUCED CARDIOMYOPATHY

The normal ventricular excitation starts from the AV node and is conducted through the specialised His-Purkinje system ensuring an effective and synchronous myocardial activation.[11,39,44] In contrast, RV pacing induces ectopic activation bypassing the His-Purkinje system. This results in an abnormal electrical and mechanical ventricular activation caused by the slow propagation of the electrical wavefront through the myocardium that is approximately four times slower than the specialised His-Purkinje system.[11,12] RV pacing induces initial early activation near the pacing site and pre-stretch in the later activated regions.[39] Consequently, this changes the LV activation pattern causing uncoordinated activation and contraction of the different ventricular segments.[11,12] Furthermore, delayed activation may be accompanied by an uncoupling between the ventricles, often with early RV activation and delayed LV activation, resulting in interventricular dyssynchrony.[12]

Changes in the activation pattern causing ventricular dyssynchrony have been associated with multiple adverse effects, which may ultimately result in impaired cardiac function and HF.[11,12] Chronic RV pacing may affect myocardial perfusion and cause changes in regional oxygen consumption with lower consumption in the early activated regions and higher consumption in the late activated regions.[11,45,46] Similarly, changes in myocardial work and strain have been observed with hypofunctioning myocardium near the pacing site and hyperfunctioning myocardium in the later activated regions.[47] Furthermore, the conduction delay seen with RV pacing is associated with functional mitral regurgitation and LV remodelling including dilatation and asymmetrical hypertrophy.[48–51] Finally, pacing may induce hemodynamic changes with a reduction in cardiac output and increased LV filling pressure.[13,52]

2.3. ASSESSMENT OF VENTRICULAR DYSSYNCHRONY

Over the years, several electrocardiographic and echocardiographic methods have been applied to estimate cardiac electrical and mechanical dyssynchrony.[53,54]

For decades, the 12-lead electrocardiogram (ECG) has been the primary modality for assessment of cardiac electrical activation. Measures such as QRS duration, QRS morphology and QRS area have been investigated as markers of electrical dyssynchrony.[53,55,56] Recently, more advanced non-invasive electrocardiographic methods have emerged, providing a more detailed evaluation of cardiac electrical activation and thus providing the potential for analysing a variety of novel dyssynchrony measures.[57–60] Non-invasive ECGi, often based on complex body surface potential mapping, is a comprehensive method for evaluation of cardiac electrical activation providing a three-dimensional (3D) reconstruction of cardiac activation.[61–63] ECGi derived measures of dyssynchrony include LV and RV total activation times and interventricular electrical uncoupling, which is calculated as the difference between the LV and RV total activation times.[59]

Several echocardiographic methods have been developed to assess and quantify mechanical dyssynchrony.[54,64] Many of these methods have been applied in studies assessing the impact of RV pacing, or in CRT studies assessing selection criteria.[64,65] Initial methods were based on Doppler and M-mode techniques.[54,66] Intraventricular activation delay has been evaluated using tissue Doppler imaging or pulsed/continuous Doppler by assessing the electromechanical delay defined as the time from QRS-onset to the onset of systolic myocardial motion or aortic/pulmonary flow.[66,67] Furthermore, pulsed/continuous Doppler of LV and RV outflow has been used to assess the timing between LV and RV activation as a measure of interventricular activation delay.[66,67] M-mode has been applied to assess LV dyssynchrony by measuring the septal-posterior wall motion delay.[68] Based on tissue Doppler imaging, cross-correlation analysis measures the correlation of myocardial acceleration between opposing segments and has been used to assess dyssynchrony in CRT candidates.[69,70] Assessment of myocardial strain, using tissue Doppler imaging or the newer speckle tracking echocardiographic (STE) technique has allowed further development of parameters of dyssynchrony.[64,71–73] The time-to-peak method measures the delay in peak systolic strain between two opposing wall segments. Expanding on this, mechanical dispersion is the standard deviation (SD) of time-to-peak in multiple LV segments.[64,73,74]

Thus, a broad range of measures have been developed and applied over the years assessing electrical and mechanical dyssynchrony in various patient categories and clinical situations. However, despite the access to detailed information on cardiac

electrical and mechanical activation, many of these measures provide only crude estimations of the overall degree of dyssynchrony and important information may therefore be lost. Recently, index of contractile asymmetry (ICA), a novel echocardiographic method for assessment of LV contractile dyssynchrony, has been developed.[75] In short, ICA quantifies and localises LV dyssynchrony using all data lines from each myocardial wall segment based on STE-derived strain-rates.[75] In contrast, other strain-based methods have included only a restricted number of strain curves.[76–78] Understanding the pathophysiology of dyssynchronous activation is important in the search for an optimal pacing site. However, detailed knowledge regarding ventricular activation during chronic RV pacing and the impact of RV lead position is currently lacking.

2.4. COMPARING RIGHT VENTRICULAR LEAD POSITIONS

The pattern of dyssynchronous myocardial activation is affected by the RV pacing site.[13,52,58,78–80] The RV apex has traditionally been the preferred site of RV lead implantation. However, due to compiling data on the negative consequences of RV apical pacing, the search for the optimal pacing site emerged.[81–87] It was hypothesised that RV leads positioned in close proximity to the conduction system would result in a more physiological activation and thus had the potential to mitigate the negative effects induced by pacing.[87–89] These alternative sites have included the RV outflow tract, the RV septum, the RV inflow tract and more recently, conduction system pacing has received much attention.[36,79,88,90–95] However, results have been conflicting and the optimal RV lead position remains debatable.[89] Consequently, current guidelines do not provide recommendations on RV lead position concerning conventional pacemaker treatment.[4,43]

Most studies comparing RV lead positions have applied fluoroscopy, possibly in combination with ECG criteria, to guide RV lead implantation and to determine the final insertion site. However, conventional methods have been proven unreliable for determination of the true RV lead position compared with cardiac CT.[16,96–100] The inaccuracy of current methods may have contributed to the conflicting results in previous studies comparing different pacing sites. Novel methods are needed to improve implantation accuracy and allow true randomisation in prospective studies. However, the inaccuracy of conventional implantation methods have provided the opportunity to retrospectively investigate the impact of pacing from various RV lead positions.[16,96–100]

Non-invasive ECGi may have the potential to guide pacemaker lead implantation more accurately.[101] Providing a 3D reconstruction of ventricular activation, ECGi is

not only useful for assessment of ventricular dyssynchronous activation, as described in the previous section, but also for identifying initial site of activation. Thus, ECGi has the potential to overcome some of the limitations of conventional implantation methods.[102] However, currently, the clinical applicability of ECGi is challenged by the need for detailed mapping of body surface potentials using a dense array of electrodes, a cumbersome process requiring specialised equipment.[62]

CHAPTER 3. AIMS AND HYPOTHESES

The overall aim of this dissertation was to investigate the chronic effects of RV pacing and the impact of RV lead position on LV systolic function in chronically paced patients with high-degree AV block. Furthermore, a novel ECGi method was evaluated for its future potential to guide RV lead positioning during implantation, by looking at the accuracy of localising the RV pacing site. Contrast-enhanced CT was applied to ensure precise localisation of RV lead position and a novel echocardiographic method was applied to evaluate the mechanical activation pattern during RV pacing.

Specifically, the three studies, on which this dissertation was based, had the following aims and hypotheses:

Study I

Aim: To investigate the impact of different CT-verified RV lead locations on the risk of PICM.
Hypothesis: The risk of PICM is lower with RV septal pacing compared with non-septal pacing.

Study II

Aim: To investigate the association between LV contractile dyssynchrony and the risk of PICM. Further, to assess the impact of RV lead location on LV contractile dyssynchrony.
Hypothesis: Increased LV contractile dyssynchrony is associated with PICM and RV pacing site impacts LV contractile dyssynchrony.

Study III

Aim: To investigate the accuracy of a novel non-invasive ECGi method to localise initial RV site of activation estimated from a reconstructed 3D electrical activation model.
Hypothesis: Non-invasive ECGi can accurately localise RV initial site of activation based on a reconstructed 3D electrical activation model.

CHAPTER 4. METHODS

4.1. STUDY DESIGN, POPULATION AND DATA SOURCES

Study design

Studies I and II were designed as retrospective cohort studies with active clinical follow-up at time of study inclusion for those eligible for final study participation.[2] Baseline was defined as date of pacemaker implantation (Figure 1). End of follow-up in both studies was defined as the date of the study-specific clinical follow-up visit. For patients upgraded to CRT during the follow-up period, end of follow-up was the date of CRT upgrade. Study III was solely based on the follow-up data (Figure 1).[3]

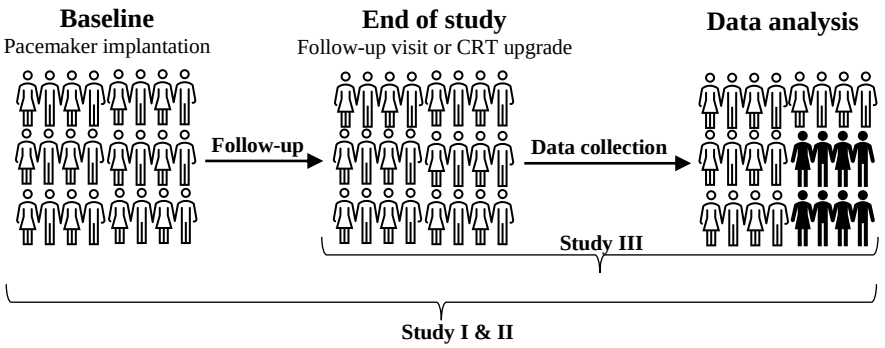


Figure 1. Schematic figure of the study designs applied in the three studies included in the dissertation.

Study population

The dissertation was based on three studies conducted within the same pacemaker cohort (n = 153). The description of the cohort in this section is based on paper I, II and III.[1–3] Eligibility for study participation was evaluated by screening consecutive patients undergoing routine fluoroscopy-guided dual-chamber pacemaker implantation due to high-degree AV block at Aalborg University Hospital between March 2012 and May 2020.

Inclusion criteria were high RV pacing burden (≥ 40%) and a transthoracic echocardiogram (TTE) documenting normal pre-implant LV systolic function (LVEF ≥ 50%). Patients were excluded if they were deemed unable to attend the study-specific follow-up visit (deceased, terminally ill, or no longer associated with the pacemaker outpatient clinic at Aalborg University Hospital). Furthermore, patients

with competing causes of decreased LVEF (severe ischemic and severe valvular heart disease), device complications with replacement of the RV lead ≥ 3 months after primary implantation or contraindication to contrast-enhanced cardiac CT were excluded. Finally, patients unable or unwilling to provide informed written consent were excluded.

Potential study candidates were identified from a search query in the Danish Pacemaker and ICD Register creating a list of all patients who had been implanted with a dual-chamber pacemaker at Aalborg University Hospital between March 2012 and May 2020. Subsequently, the eligibility assessment was based on detailed review of electronic medical records, pacemaker interrogation reports and analysis of available baseline TTEs performed prior to pacemaker implantation.

High-degree AV block was defined as second-degree AV block Mobitz type II, 2:1 AV block, AV block with ≥ 2 consecutive P-waves not conducted without complete loss of AV conduction, and third-degree AV block.[4] Severe ischemic heart disease was defined as acute myocardial infarction confirmed by coronary angiography, requiring revascularisation, or confirmed significant stenosis in ≥ 2 epicardial arteries requiring revascularisation.[103] Severe valvular heart disease was evaluated using guideline-recommended quantitative and semi-quantitative measures.[104]

Ethical considerations

The ethical review committee for the North Denmark Region determined that the project was exempt from formal ethical approval because it was a retrospective study. The use of clinical data was approved by the Danish Safety Authority and the North Denmark Region (31-1521-103).[1–3] All patients, who actively participated in the study, gave written informed consent at study inclusion. Participants were informed about any clinically significant findings during the study specific examinations and all findings were handled appropriately in accordance with current clinical guidelines.

Data sources

Data on study participants were collected from multiple sources (Figure 2). Baseline data were retrieved retrospectively. Follow-up data were obtained from the examinations performed during the study specific follow-up visit. The visit included a TTE examination, pacemaker interrogation, 12-lead ECG including a 3D photography of the thorax documenting the ECG electrode positions, and a contrast-enhanced cardiac CT scan. The TTE and 12-lead ECG was obtained during RV pacing. Information on patient characteristics was obtained from electronic medical records. Pacemaker interrogation reports were retrieved to assess the cumulative pacing burden. Contrast-enhanced cardiac CT scans were obtained to accurately determine RV lead position. Baseline and follow-up TTEs were analysed to assess

cardiac function. Finally, ECGs were obtained for assessment of the cardiac electrical activation.

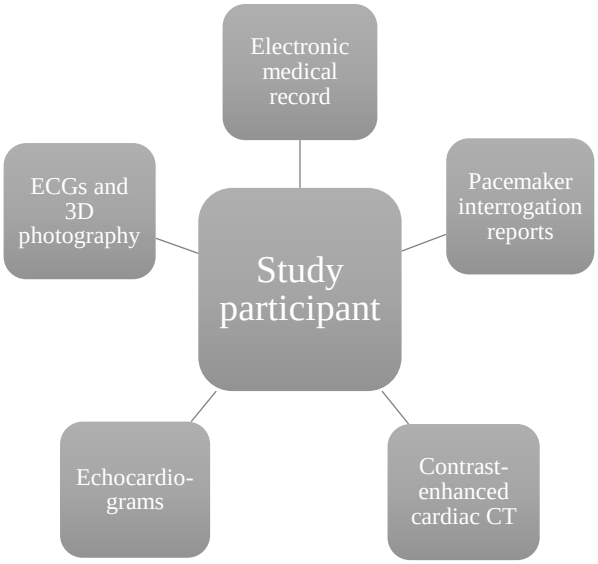


Figure 2. Schematic overview of the data sources used in the three studies. ECG, electrocardiogram; 3D, three-dimensional; CT, computed tomography.

4.2. COMPUTED TOMOGRAPHY – ACQUISITION AND ANALYSIS

This section is based on the CT method descriptions in paper I, II and III.[1–3] A contrast-enhanced CT scan showing the RV lead position was obtained for all patients. Some participants already had a high-quality contrast-enhanced CT scan with clear visualisation of the RV lead tip available (n = 42). If no such CT scan was available, a study-specific CT scan was performed at the follow-up visit (n = 111).

A study-specific CT scanning protocol was applied. The scans were performed using a second-generation dual source scanner (Siemens Somatom Definition Flash, Siemens Healthcare, Erlangen, Germany). The scans were ECG-synchronised and performed during breath hold at the end of inspiration. Administration of contrast was timed for optimal visualisation of both the right and left ventricles.

The CT scans were analysed using the commercially available image navigation and display DICOM software OsiriX (Pixmeo SARL, Bernex, Switzerland).[105] Two

physicians, who were blinded to the study outcomes, independently determined the RV lead position. If there was any disagreement, the RV lead position was determined by consensus. The RV lead position was analysed using a regional approach previously described by Sommer *et al*.[16] First, the RV lead position was evaluated in a long-axis view and categorised as basal, mid and apical based on dividing the LV long axis into equal thirds (Figure 3). Next, the images were analysed in a short axis view to determine RV septal or free wall implantation. The RV lead position was categorised as septal if located in the mid or basal septum or categorised as non-septal if located in the apical septum or free wall. Furthermore, for detailed analyses, the RV lead was categorised into anterior septum (mid and basal anterior septum), posterior septum (mid and basal posterior septum), apical septum, and free wall.

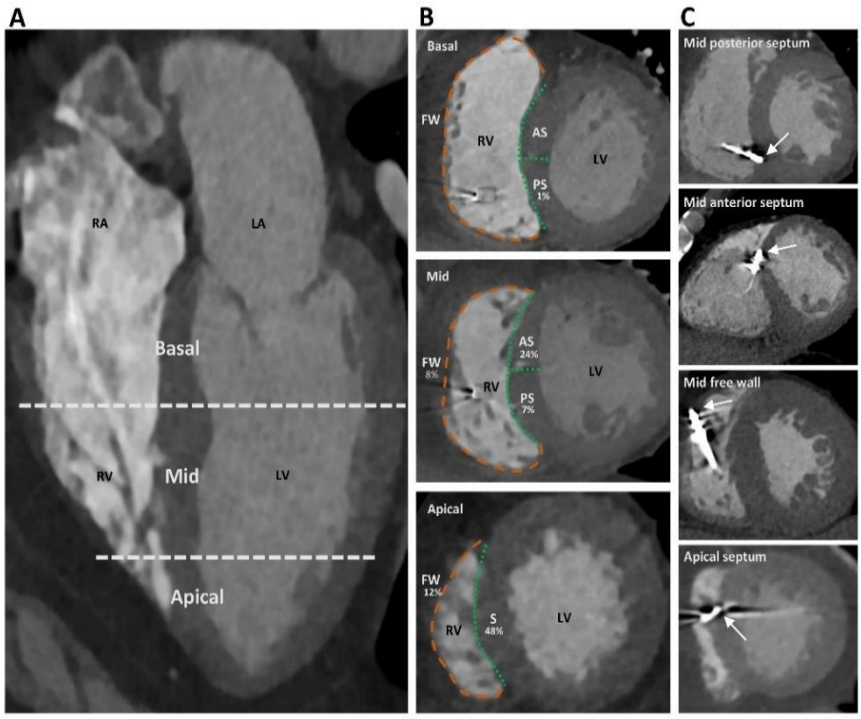


Figure 3. "*Assessment of right ventricular (RV) lead position. Panel (A): A simplistic approach was used dividing the left ventricular (LV) long axis into equal thirds (basal, mid, and apical). Panel (B): Septal (S) (green dashed lines) or free wall (FW) (orange dashed lines) positions were then analysed in short axis view. For primary outcome analysis, the RV lead position was categorised into septal (mid and basal septum) and non-septal (apical septum or free wall). Mid and basal septum were further divided into anterior septum (AS) and posterior septum (PS). The distribution of RV lead positions is shown for each segment. Panel (C): Examples of different RV lead tip positions (white arrows). LA, left atrium; RA, right atrium*." The figure is reused with permission from study I.[1]

4.3. ECHOCARDIOGRAMS – ACQUISITION AND ANALYSIS

This section is based on the TTE method descriptions in paper I and II.[1,2] Baseline two-dimensional TTEs, performed prior to pacemaker implantation, were retrieved together with all TTEs performed between baseline and end of follow-up. At the follow-up visit, a study specific TTE was performed using a 2.5-MHz transducer and the commercially available ultrasound system VIVID E95 (GE Healthcare, Milwaukee, USA). Recordings were ECG-gated and standard apical projections, including four-chamber (4CH) view, three-chamber (3CH) view and two-chamber (2CH) view, were obtained. For each image, three consecutive cardiac cycles during RV pacing were stored in a cine-loop format for offline analyses. Loops containing ectopic beats were excluded. Images for STE analyses were acquired at a high mean frame rate of $106 \pm 18\ s^{-1}$.

Blinded to the assessment of RV lead position, two experienced cardiologists assessed LVEF using the Simpson's biplane method. For aortic valve and mitral valve assessments, pulsed wave, continuous wave, and colour Doppler of the valves were performed. Presence and severity of valvular heart disease was evaluated using an integrative approach including quantitative and semi-quantitative measures.[104,106] Analyses were made offline using EchoPAC software (GE Healthcare, Milwaukee, USA).

4.4. RELATIVE INDEX OF CONTRACTILE ASSYMMETRY

This section is based the method description in paper II as well as the description in the paper from Zaremba and colleagues when first introducing the method in 2019.[2,75] ICA is a measure of contractile dyssynchrony between opposing walls that is calculated based on STE-derived strain rates. STE analyses were performed in the three standard apical views: 2CH, 3CH, and 4CH. In the EchoPAC analysis window, the systolic curved anatomical M-mode (CAMM) plot was exported for further analyses (Figure 4). Duration of systole was defined from the QRS onset to the closure of the aortic valve on continuous wave Doppler. The CAMM plot displays the myocardial strain rates from base to apex throughout the cardiac cycle in a pixelated image. The strain rate values were decoded from the pixels using the colour scale accompanying the CAMM plot in the EchoPAC window. Strain rate values from opposing pixels were pairwise subtracted creating a new table containing the strain rate differences.

Synchronous contraction results in pairwise strain rate differences close to zero as strain rate values will be similar in opposing segments. In contrast, dyssynchronous

contraction will result in increasing differences in strain rate values between opposing segments. This mismatch in the timing of contraction from opposing segments was quantified by the SD of the strain rate differences also referred to as ICA.

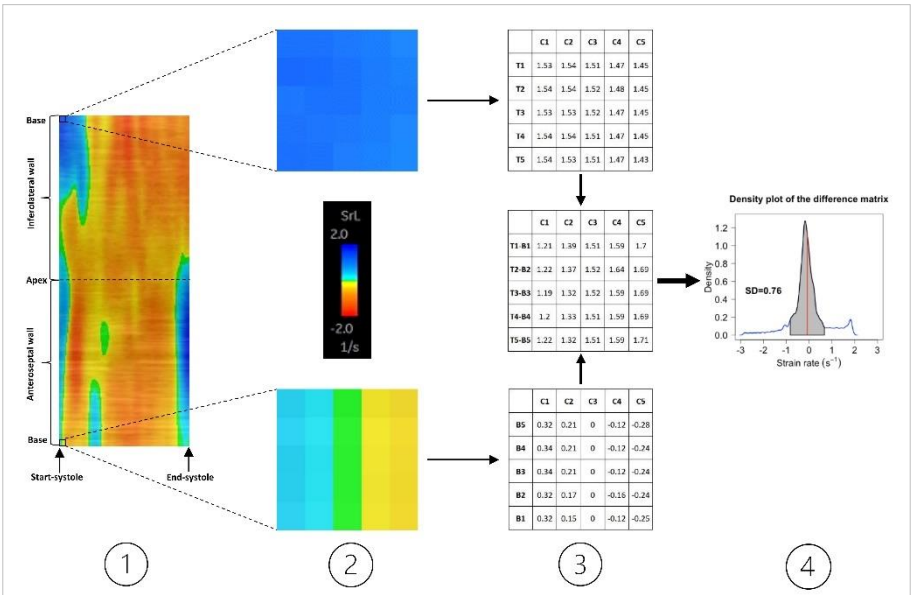


Figure 4. "*Schematic diagram of calculating ICA. Panel 1: CAMM plot showing the strain rate propagation throughout systole obtained by 3CH STE-analysis. Panel 2: Zoom on the CAMM plot illustrating the pixels and the colour scale used to decode the strain rate values. Panel 3: Extraction of strain rate values from the CAMM plot followed by pairwise subtraction of strain rate values of the opposing corresponding pixels [top rows (T) minus bottom rows (B)] for each column (C), creating a new table containing the strain rate differences (middle table). Panel 4: Density plot of the strain rate differences between the two opposing walls and the corresponding SD of those differences. This value is referred to as ICA. In this example, ICA in the 3CH view is 0.76 s^{-1}. 3CH, three-chamber; CAMM, curved anatomical M-mode; ICA, index of contractile asymmetry; SD, standard deviation; SrL, strain rate; STE, speckle tracking echocardiography.*" The figure is reused from study II.[2]

ICA is affected by the degree of myocardial contractility. Larger strain rate values are generated in a myocardium with preserved contractile function. This will produce larger strain rate differences during dyssynchronous contraction. In contrast, a myocardium with decreased contractile function will generate smaller strain rate values. This results in smaller strain rate differences during dyssynchronous contraction simply due to the lower strain rates. Therefore, the ICA measure was adjusted for the contractile properties by indexing ICA to the mean negative systolic strain rate. The strain rate adjusted ICA is referred to as relative ICA (rICA).

rICA was calculated for each of the apical views thus quantifying the degree of LV contractile dyssynchrony between the anterior and inferior opposing walls (2CH),

anteroseptal and inferolateral opposing walls (3CH), and inferoseptal and nterolateral opposing walls (4CH). Average rICA in the three views, termed rICA mean, was used as an overall measure of LV contractile dyssynchrony.

4.5. ELECTROCARDIOGRAPHIC IMAGING

The description of the ECGi method in this section is based the method description in paper III.[3] Reconstructing the electrical ventricular activation was done in a stepwise process starting with collection of input data, processing of input data, and finally application of the inverse ECG algorithm (Figure 5).

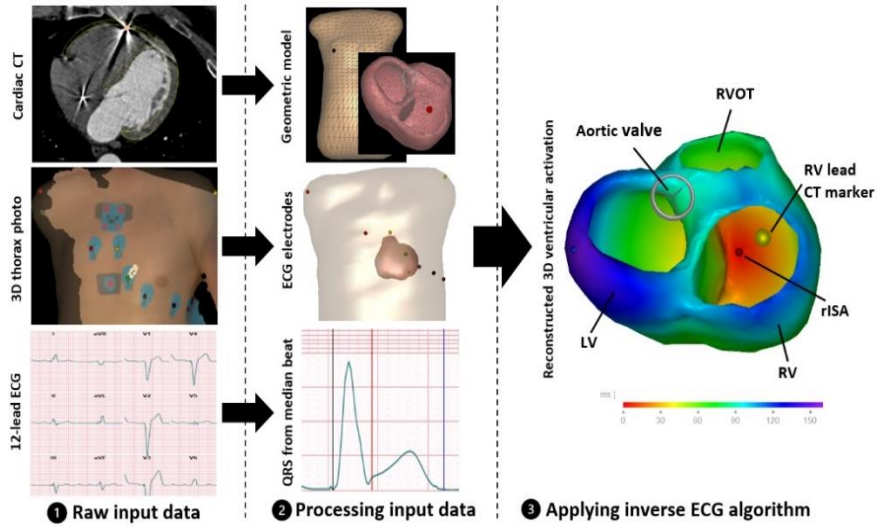


Figure 5. "*Summary of the stepwise process used for reconstructing 3D ventricular activation. (1) Collecting the raw input data including contrast-enhanced cardiac CT, 3D thorax photo documenting the ECG electrode positions and 12-lead ECG with right ventricular pacing. (2) Processing the input data including creation of a patient-specific geometric model with ECG electrodes correctly positioned on the thorax model and defining QRS onset and duration using the 12-lead ECG median beat. (3) Integration of processed input data using the inverse ECG algorithm creating the 3D ventricular activation model. LV, left ventricle; RV, right ventricle; RVOT, right ventricular outflow tract; rISA, reconstructed initial site of activation.*" The figure is reused with permission from study III.[3]

The ECGi method required input from a digitally recorded 12-lead ECG and a CT-derived heart-thorax geometry with correctly positioned ECG electrodes on the thorax model. At the follow-up visit, a new RV-paced 12-lead ECG was digitally recorded using the Cardiovit AT-102 plus resting ECG machine (Schiller, Baar, Switzerland).

A 3D thorax photography was recorded to document the location of the ECG electrodes (Figure 6).

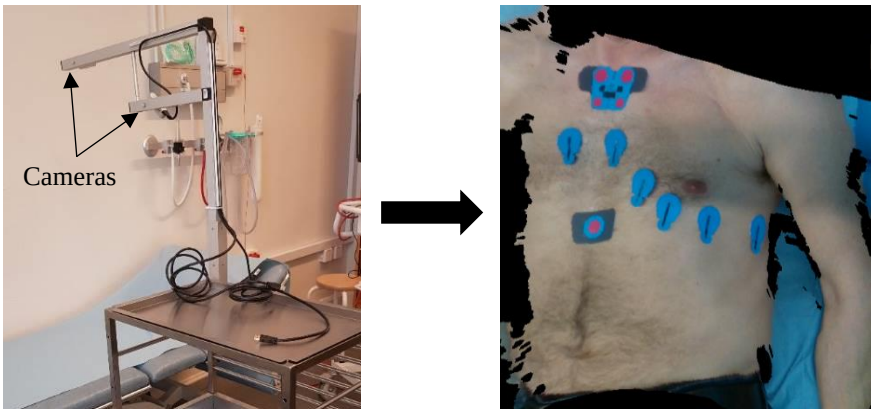


Figure 6. Two digital cameras (black arrows) were used to obtain the 3D photography of the thorax (left). Photography of the thorax documenting the ECG electrode positions (right).

Markers were positioned at the lower and upper extremes of the sternum to facilitate merging of the photo with the thorax geometric model. To exclude the pacing spike and effects of noise in the ECG analysis, QRS onset and duration were manually adjusted using the median beats.

Using the CT scans, patient-specific geometric models of the heart and thorax were created including a marker representing the RV lead insertion site at the RV endocardial border. The geometries were formed by a triangular surface mesh of discrete nodes defining the endocardial and epicardial ventricular myocardial surface and the location of the four heart valves. By merging the 3D thorax photography with the 3D thorax model, the ECG electrodes were subsequently correctly positioned on the thorax model.

The final step was the application of the automated inverse ECG algorithm. The algorithm is described in detail in paper III.[3] The algorithm combined several mathematical models describing electrophysiological rules. Through integration of information from the 12-lead ECG and the heart-thorax geometry, the biventricular electrical activation was reconstructed and visualised on the 3D heart model. The Fastest Route algorithm was applied to compute activation times between the discrete nodes in the heart geometry.[107] The myocardial propagation velocity was restricted to 0.7-0.8 m/s.[108] To account for the slower propagation perpendicular to the myocardial fibre direction compared to along the fibre direction, the transmural propagation

velocity was set to be 2.5 times slower than the propagation over the ventricular surface.[109] To synthesise ECGs based on the reconstructed activation times for the discrete nodes, the Equivalent Dipole Layer Model was applied.[110,111] Finally, The Boundary Element Method accounted for the volume conductor effects.[112,113] For the thorax and myocardium, the conductivity was set to 0.2 S/m and for the blood cavities it was set to 0.6 S/m. Using the set parameters, the algorithm reconstructed an activation sequence resulting in the synthesised ECG best matching the recorded ECG.

4.6. STATISTICAL ANALYSES

The statistical methods used in this dissertation are presented in the following sections, together with the rationale behind them. In paper I and II, a retrospective cohort study design with active clinical follow-up including echocardiography for outcome assessment was applied.[1,2] This design resulted in an increased incidence of outcomes at end-of follow-up, as subclinical cases may not have been recognised prior to this. In other words, we could determine if the outcome had occurred but not when it had occurred. Therefore, it was considered inappropriate to apply time-to-event analyses to investigate associations between exposures and outcomes. Descriptive statistics were the same in the three studies.[1–3] For continuous variables, the mean and SD or the median and interquartile range (IQR) were reported as appropriate based on the distribution. To compare differences, Student's *t*-test or Mann-Whitney test were used as appropriate. For categorical variables, numbers and percentages were reported, and Fisher's exact test was used for comparison.

In study I and II, modified Poisson regression with robust variance estimation was applied to analyse the relative risks (RR) of outcomes between groups.[1,2] This approach was chosen as the study design allowed estimation of risks. RR as the association measure was preferred over odds ratios for easier interpretation in case of frequent outcomes.[114]

To analyse the association between continuous variables and estimate the differences in means between binary or multiple categories, linear regression and one-way analysis of variance (ANOVA) were applied in paper I and II.[1,2] Standard errors were calculated applying bootstrap with 5000 replications.[115] This was done to accommodate potential violations of the normality and variance inhomogeneity assumptions.

To evaluate the linear correlation between two continuous variables in paper II and III, Pearson's correlation coefficient was calculated.[2,3] This was to measure both the

strength and direction of the association between the variables. In study II, receiver operation characteristics (ROC) analysis was applied.[2] The ROC analysis was used to evaluate the performance of a continuous variable as a predictor for the outcome. Cutoff values for prediction of the outcome were calculated based on maximising the Youden index (the difference between the true positive rate and the true negative rate).[116]

In study III, fractional polynomial regression was applied to analyse the association between continuous variables.[3] It is a more flexible method and was therefore used to accommodate potential non-linear association between continuous variables.[117]

CHAPTER 5. STUDIES

Study population

At baseline, a total of 608 patients met the inclusion criteria and 181 met one or more of the exclusion criteria leaving 427 eligible for follow-up. After baseline, an additional 274 patients met one or more of the exclusion criteria leaving 153 study participants (Figure 7).[1,2] Baseline characteristics for study participants as well as for those excluded are shown in Table 1. Generally, study participants were younger and had a lower prevalence of comorbidities compared with those excluded from the study.

Table 1. Pre-implant characteristics.

	Study participants (n = 153)	Excluded (n = 455)
Age (years)	72 (65-77)	79 (73-85)
Male	103 (67)	301 (66)
Comorbidities		
Ischemic heart disease	12 (8)	119 (26)
Valvular heart disease	12 (8)	145 (32)
Hypertension	106 (69)	330 (73)
Diabetes mellitus	35 (23)	103 (23)
History of smoking	65 (42)	252 (55)
eGFR (ml/min/1.73 m^2)	75 ± 15	60 ± 23

Continuous values are reported as mean ± SD or median (interquartile range) as appropriate. Categorical values are expressed as numbers (%). eGFR, estimated glomerular filtration rate.

For the study participants, the median duration of follow-up was 3.1 years (IQR 1.9-4.8 years), and the median cumulative pacing percentage was 96.5% (IQR 85.8-99.8%).[1,2]

CT determined RV lead position

Primary CT analysis showed that 48 (31%) leads were implanted in the mid or basal septum and thus categorised as septal, and 105 (69%) leads were implanted in the apical septum or in the free wall and thus categorised as "non-septal" (Figure 3).[1–3] Based on detailed analysis of RV lead implantation sites, 37 (24%) leads were implanted in the anterior septum, 11 (7%) in the posterior septum, 31 (20%) in the free wall, and 74 (48%) in the apical septum.[1,2]

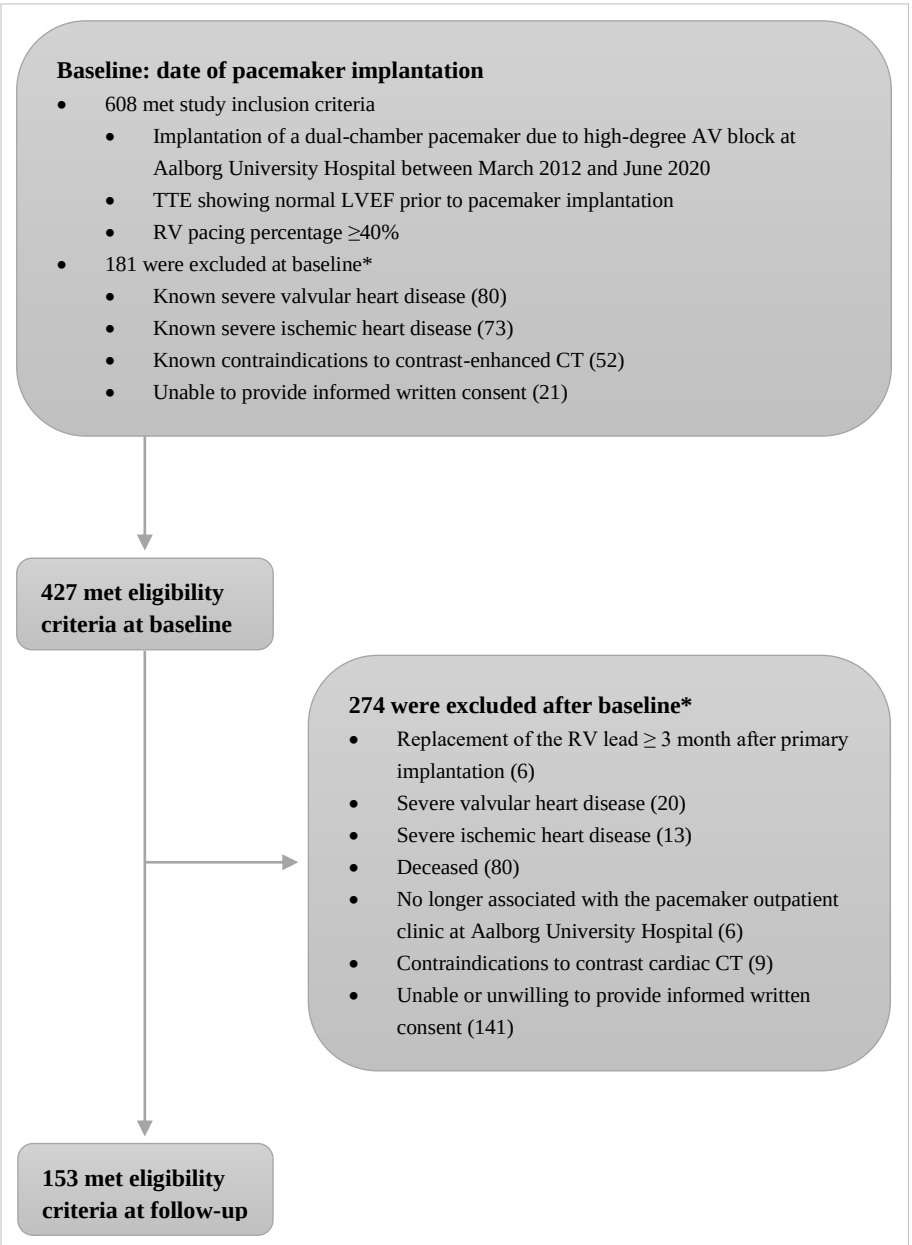


Figure 7. Flowchart of the study population used in the three studies. *The sum of those who meet the different exclusion criteria is larger than the number excluded as some met more than one exclusion criterion. AV, atrioventricular; TTE, transthoracic echocardiogram; LVEF, left ventricular ejection fraction; CT, computed tomography; RV, right ventricular.

5.1. STUDY I

Study I "*Risk of Pacing-induced Cardiomyopathy in Patients with High-Degree Atrioventricular Block – Impact of Right Ventricular Lead Position Confirmed by Computed Tomography"* was published in *Journal of Clinical Medicine*.[1] The paper was authored by Patricia Zerlang Fruelund, Anders Sommer, Jens Brøndum Frøkjær, Søren Lundbye-Christensen, Tomas Zaremba, Peter Søgaard, Claus Graff, Søren Vraa, Aksayan Arunanthy Mahalingasivam, Anna Margrethe Thøgersen, Michael Rangel Pedersen, and Sam Riahi.

Aim

To investigate the impact of different CT-verified RV lead locations on the risk of PICM in chronically paced patients with high-degree AV block.

Key methods

The primary outcome was development of PICM, defined as ≥ 10% decrease in LVEF resulting in LVEF < 50% at any timepoint between implant and end of follow-up. Secondary outcomes were upgrade to a CRT device and absolute changes in LVEF.

Exposure was RV lead position. For the primary analysis, RV lead position was categorised as septal (RV leads positioned at the mid or basal septum) or non-septal (RV leads positioned at the apical septum or free wall). For comprehensive analysis, the RV lead position was divided into four categories: anterior septum, posterior septum, apex, and free wall.

Main results

In total, 47 (31%) developed PICM and 9 (6%) were upgraded to a CRT device during the study period. When comparing outcomes between the non-septal and septal groups, no significant differences were found (Table 2).

Table 2. Comparison of outcomes between RV non-septal and RV septal lead position.

Outcomes	All (n = 153)	Non-septal (n = 105)	Septal (n = 48)	RR	95% CI	*p* value
PICM	47 (30.7)	31 (29.5)	16 (33.3)	0.89	0.54;1.46	0.63
CRT upgrade	9 (5.9)	6 (5.7)	3 (6.3)	0.91	0.23;3.52	0.90

Values are given as numbers (%). CI, confidence interval; CRT, cardiac resynchronisation therapy; PICM, pacing-induced cardiomyopathy; RR, relative risk; RV, right ventricular.

In the PICM group, an absolute reduction in LVEF of 19% (95% confidence interval [CI]: 17–22%) was found. LVEF ≤ 40% after pacemaker implantation was observed in 20 (13%) patients.

In a detailed analysis, risk of PICM and absolute changes in LVEF was compared between the four RV lead position groups (Figure 8). There were no significant differences between the four groups for any of the outcomes. However, looking at absolute change in LVEF and risk of PICM, a trend towards a worse outcome in the posterior septal group was observed.

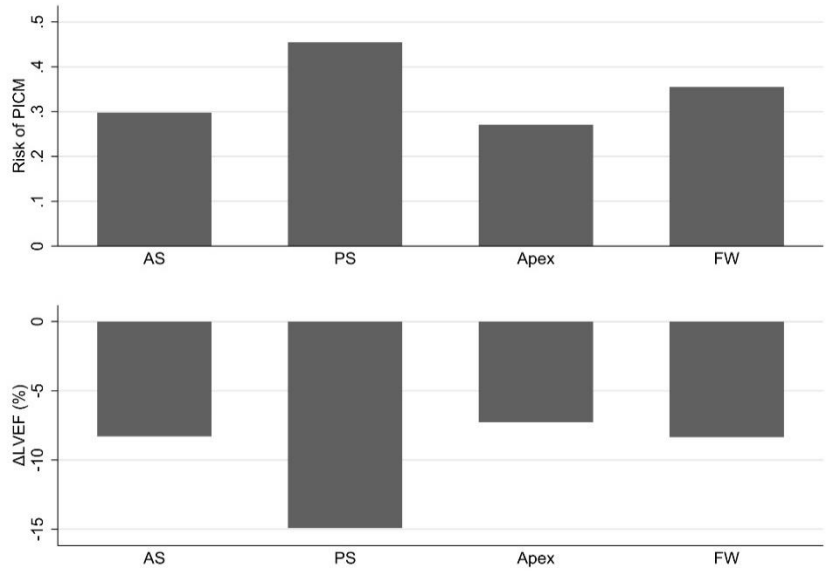


Figure 8. "*Comparison between anterior septal (AS), posterior septal (PS), apical and free wall (FW) RV lead position. Upper panel: Risk of pacing-induced cardiomyopathy (PICM). Lower panel: Decrease in left ventricular ejection fract (ΔLVEF) after pacemaker implantation.*" The figure is partially reused with permission from study I.[1]

In the septal group, a non-significant increase in the risk of PICM with increased duration of pacemaker treatment was observed (p = 0.41) (Figure 9). In the non-septal group, there was a borderline significant decrease in the risk of PICM with increased duration of pacemaker treatment (p = 0.066). The associations were borderline significantly different between the two groups (p = 0.064).

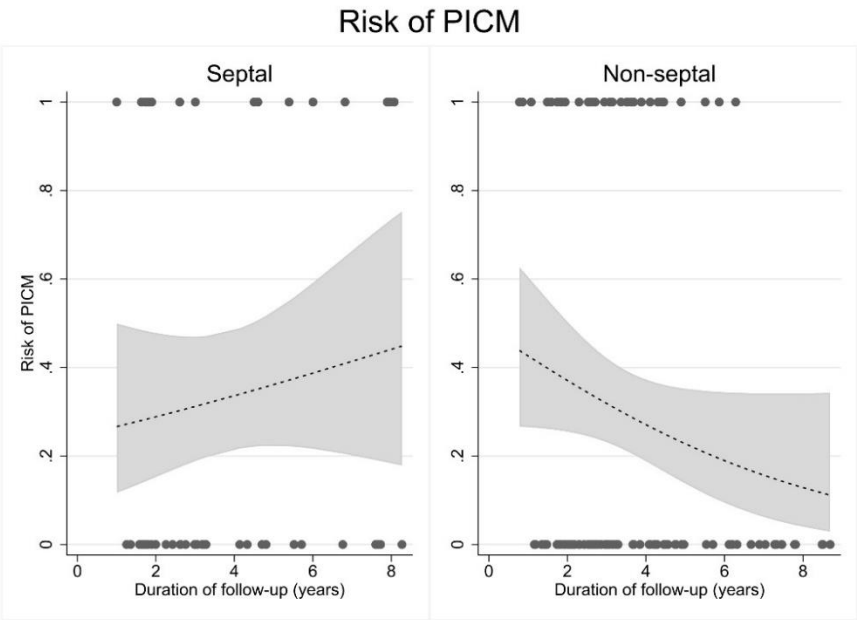


Figure 9. Graphs showing the association between duration of follow-up and risk of pacing-induced cardiomyopathy (PICM) in the septal group (left) and in the non-septal group (right).

Main conclusions

CT-verified RV lead position was not significantly associated with risk of PICM nor CRT-upgrade. However, though not statistically significant, a trend towards higher risk of PICM and a larger reduction in LVEF was observed in those paced in the posterior septum. Importantly, the study demonstrated an overall high risk of PICM (31%) in a relatively young population with normal pre-implant LVEF during a median follow-up of 3.1 years.

5.2. STUDY II

Study II "*The role of mechanical dyssynchrony in pacing-induced cardiomyopathy: detailed assessment using index of contractile asymmetry*" is currently submitted for publication.[2] The paper was authored by Patricia Zerlang Fruelund, Anders Sommer,

Søren Lundbye-Christensen, Claus Graff, Peter Søgaard, Sam Riahi, and Tomas Zaremba.

Aims

To investigate the association between LV contractile dyssynchrony, quantified by rICA, and the risk of PICM. Furthermore, to assess the impact of RV lead location on LV contractile dyssynchrony.

Key methods

Development of PICM was defined as ≥ 10% decrease in LVEF resulting in LVEF < 50% at any timepoint between implant and end of follow-up. The RV lead position was categorised into four groups: anterior septum, posterior septum, apex, and free wall.

Contractile dyssynchrony was assessed by rICA in follow-up TTEs from all study participants. Furthermore, rICA was assessed from TTEs acquired from 10 healthy individuals for comparison.

Main results

Location and degree of LV contractile dyssynchrony was significantly associated with PICM (Figure 10, Table 3). In univariable analyses, rICA was consistently and significantly higher in all three apical views, resulting in a rICA mean significantly higher in those with PICM compared to those without PICM.

Table 3. rICA for the PICM and non-PICM group.

	PICM (n = 47)	Non-PICM (n = 106)	rICA difference (95% CI)	*p* value
rICA 2CH	1.04 ± 0.30	0.81 ± 0.25	0.23 (0.14-0.32)	< 0.001*
rICA 3CH	1.28 ± 0.24	1.15 ± 0.27	0.12 (0.03-0.21)	0.005*
rICA 4CH	1.26 ± 0.23	1.13 ± 0.24	0.12 (0.04-0.20)	0.002*
rICA mean	1.19 ± 0.21	1.03 ± 0.19	0.15 (0.10-0.22)	< 0.001*

rICA, relative index of contractile asymmetry; CI, confidence interval; 2CH, two-chamber; 3CH, three-chamber; 4CH, four-chamber; *, $p < 0.05$.

The largest rICA difference was observed between the LV anterior-inferior walls (2CH view). rICA 2CH was independently associated with PICM in a multivariable analysis including rICA in all three views ($p < 0.001$). However, rICA 3CH ($p = 0.64$) and rICA 4CH ($p = 0.25$) were not independently associated with PICM.

Thus, rICA 2CH was chosen for further investigation. ROC analysis showed that a cutpoint of rICA 2CH > 0.90 was the best predictor of having PICM yielding a RR of PICM of 3.4 (95% CI 2.0-5.8). Clinically relevant, rICA 2CH > 0.90 yielded a RR of 12.9 (95% CI 3.1-53.7) for having a follow-up LVEF ≤ 40%.

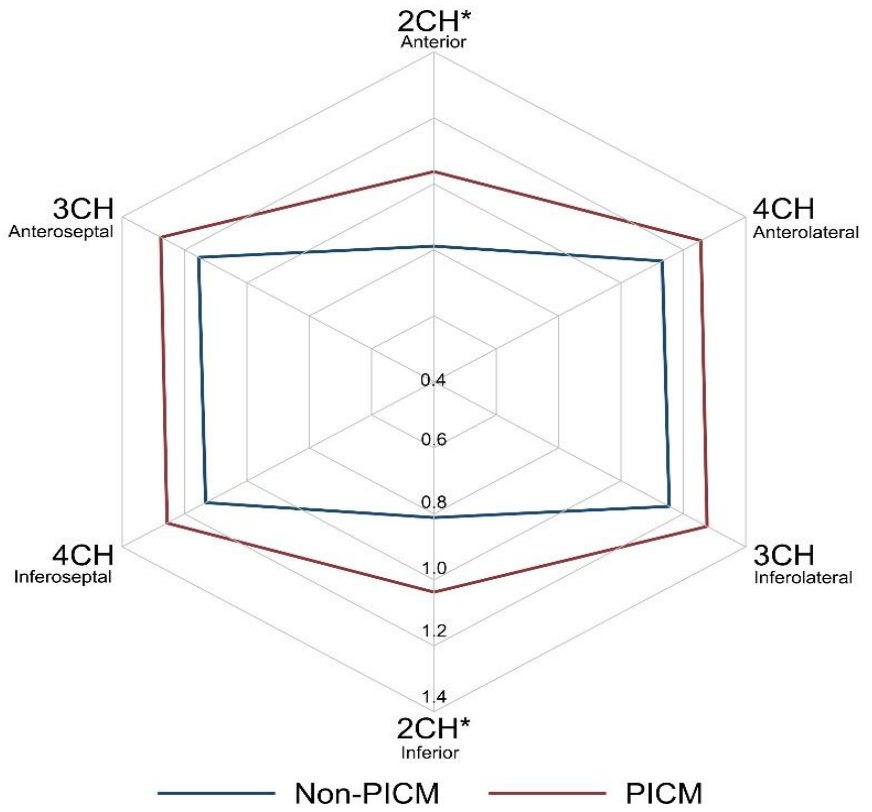


Figure 10. *"Illustration of the degree and location of LV dyssynchrony. The radar plot shows the 2CH, 3CH and 4CH rICA values for the PICM group (red) and non-PICM group (blue). rICA, relative index of contractile asymmetry; PICM, pacing-induced cardiomyopathy; 2CH, two-chamber; 3CH, three-chamber; 4CH, four-chamber; *, p < 0.05 when comparing rICA between the PICM and non-PICM group in a multi variable analysis.*" The figure is reused from study II.[2]

Looking at rICA in the four RV lead position groups, the anterior septal, apical, and free wall groups showed a similar rICA pattern with low rICA in the 2CH view and high rICA in the 3CH and 4CH view (Figure 11). In the posterior septum group, rICA was high in all apical views. rICA 2CH was significantly different between the four RV lead groups ($p < 0.01$), with the highest value observed in the posterior septum

group. rICA in the 3CH and 4CH views were not significantly different between the four groups. Compared with the four RV lead groups, the control group showed significantly lower rICA in all apical views.

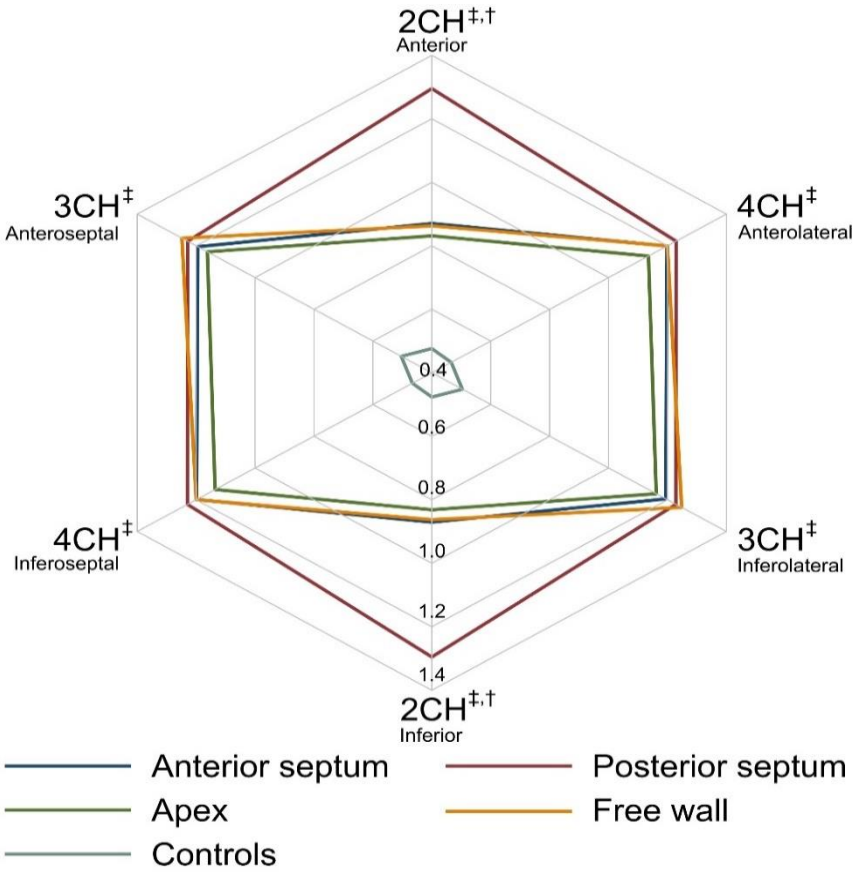


Figure 11. *"Radar plot illustrating the degree and location of LV contractile dyssynchrony by showing the 2CH, 3CH and 4CH rICA for each of the four RV lead groups and the controls. rICA, relative index of contractile asymmetry; 2CH, two-chamber; 3CH, three-chamber; 4CH, four-chamber; †, $p < 0.05$ when comparing rICA between the four RV lead groups; ‡, $p < 0.05$ when comparing rICA between the four RV lead groups and controls.*" The figure is reused from study II.[2]

Main conclusions

PICM was significantly associated with both location and degree of LV contractile dyssynchrony assessed by rICA. Those with PICM had the highest degree of overall dyssynchrony quantified by rICA mean. Dyssynchrony in the anterior-inferior direction, assessed by rICA in the 2CH view, was independently and significantly associated with PICM. RV lead location significantly influenced the contractile dyssynchronous activation pattern. Pacing the posterior septum resulted in the highest rICA mean and rICA 2CH.

5.3. STUDY III

Study III "*Novel non-invasive ECG imaging method based on the 12-lead ECG for reconstruction of ventricular activation: A proof of concept study*" was published in *Frontiers in Cardiovascular Medicine*.[3] The paper was authored by Patricia Zerlang Fruelund, Peter van Dam, Jacob Melgaard, Anders Sommer, Søren Lundbye-Christensen, Peter Søgaard, Tomas Zaremba, Claus Graff, and Sam Riahi.

Additionally, as a supplement to the published study III, data on the remaining study participants have recently been analysed and the results are presented in this section.

Aim

To investigate the accuracy of a novel non-invasive ECGi method to localise initial site of activation estimated from the reconstructed biventricular activation model.

Key methods

Additional exclusion criteria for this study were suspected fusion pacing in the follow-up ECG and prior upgrade to CRT. Results from the published study are based on data from the first 34 patients included in the pacemaker cohort eligible for this study. Recently, data has been analysed for the remaining patients in the cohort meeting the additional eligibility criteria. Therefore, extra results are presented in this dissertation, based on all eligible patients (n = 137).

The 12-lead ECG-based ECGi method was used to reconstruct biventricular activation. This method was based on an inverse-ECG algorithm applying electrophysiological rules as described in the methods section (Figure 5). The algorithm generating the results for the 137 patients was based on a subsequent optimisation of the fitted ECG after the initial estimation, whereas the results for the 34 patients was based on the initial estimation.

Primary validation of the method was done by comparing the geodesic distance between the reconstructed initial site of activation and the known RV lead insertion site estimated from CT. This distance is referred to as the localisation error (LE) (Figure 12). Furthermore, to assess the reconstructed activation sequence, it was compared to the activation sequence generated when forced to initiate from the known RV lead implantation site.

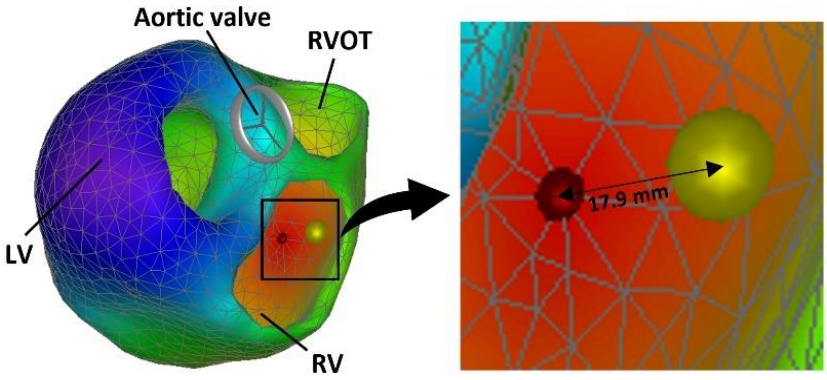


Figure 12. "*Reconstructed 3D ventricular electrical activation sequence showing the estimated initial site of activation (red marker) and the marker indicating right ventricular (RV) lead position assessed from computed tomography (CT) (yellow marker). The localisation error is the geodesic distance between the centre of the CT marker and the estimated initial site of activation. LV, left ventricle; RV, right ventricle; RVOT, right ventricular outflow tract.*" The figure is reused with permission from study III.[3]

Main results based on the 34 patients

The mean LE was 13.9 ± 5.6 mm. For 30 (82%) of the patients, the LE was < 20.0 mm. Four patients had an LE > 20.0 mm and there was one outlier with an LE of 28.6 mm. Figure 13 shows the reconstructed activation sequences for all 34 patients including the reconstructed initial site of activation and the RV lead insertion site.

There was a high correlation between the initial reconstructed biventricular activation and the activation forced to initiate from the RV lead insertion site with a mean r = 0.92 ± 0.06 (range 0.73-0.99). Increasing LE was significantly and negatively associated with the correlation (p = 0.01). Comparison between the recorded ECG and

the initially fitted ECG showed an overall high correlation with a median r = 0.88 (range 0.62-0.99).

The mean computation time, after having loaded the input data (12-lead ECG and patient geometry) into the research software, was 1.1 ± 0.4 s per ECG using a standard laptop (Intel CORE i7 central processing unit).

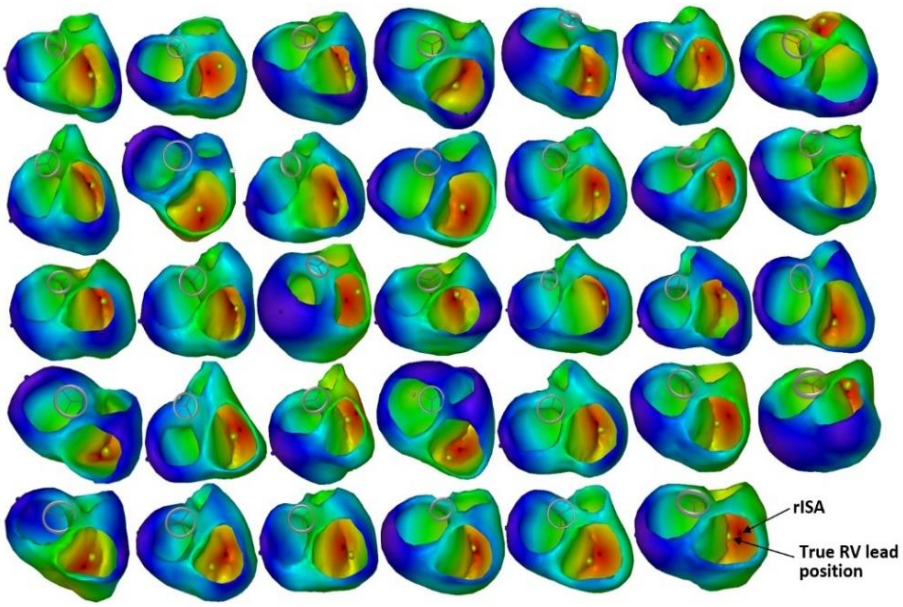


Figure 13. "*Reconstructed 3D ventricular activation models for all 34 patients. The red marker indicates the reconstructed initial site of activation (rISA), and the yellow marker indicates the true right ventricular (RV) lead position determined by computed tomography*." The figure is reused with permission from study III.[3]

Main results based on the 137 patients

The mean LE was 13.7 ± 6.7 mm. For 116 (85%) of the patients, the LE was < 20.0 mm and 132 (96%) had an LE < 25 mm. There were 5 outliers with an LE > 25 mm (range 26-42 mm).

There was a high correlation between the initial reconstructed biventricular activation and the activation forced to initiate from the RV lead insertion site with mean r = 0.94 ± 0.05 (range 0.73-0.99). Increasing LE was significantly and negatively associated with the correlation ($p < 0.01$) (Figure 14). Comparison between the recorded ECG and the optimised fitted ECG showed an overall high correlation with median $r = 0.98$ (range 0.90-0.99).

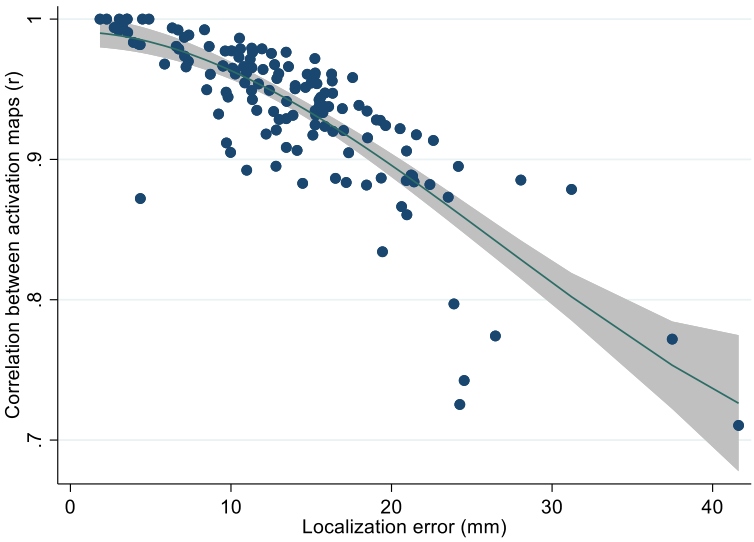


Figure 14. Fractional polynomial plot showing the association between the localisation error and the correlation between activation maps. r, Pearson's correlation coefficient.

Main conclusions

This study demonstrated a novel ECGi method based on the 12-lead ECG for reconstruction of biventricular activation and estimation of initial site of activation. On average, the method accurately localised initial site of activation in relation to right ventricular anatomy. Furthermore, the method effectively fitted the reconstructed ECG to the recorded ECG.

CHAPTER 6. DISCUSSION

In this dissertation, the chronic effects of RV pacing and the impact of RV lead position was investigated, followed by an assessment of a novel ECGi method with the potential to guide RV lead implantation.

In study I, we found a high risk of PICM in a pacemaker cohort with normal pre-implant LVEF.[1] Comparing CT-determined septal and non-septal RV lead position, we found no statistically or clinically significant difference in risk of PICM. However, when further dividing the RV lead position into four categories, we found a trend towards a worse outcome among those paced in the posterior septum. In conclusion, our results did not support the hypothesis of decreased risk of PICM with septal pacing compared with non-septal pacing.

In study II, both location and overall degree of LV contractile dyssynchrony was significantly associated with PICM.[2] Interestingly, dyssynchrony between the LV anterior and inferior walls was an independent predictor of having PICM. Furthermore, we found that the RV lead location was highly associated with the location and degree of contractile dyssynchrony. Supporting the results in study I, we found that pacing the posterior septum resulted in the highest degree of overall dyssynchrony as well as highest degree of dyssynchrony between the LV anterior and inferior walls. Thus, study II supported our hypotheses of RV pacing site having an impact of LV dyssynchrony and LV dyssynchrony being associated with PICM.

In study III, a novel non-invasive ECGi method was evaluated for its potential to guide RV lead implantation.[3] Supporting our hypothesis, the reconstructed activation sequence accurately localised the RV pacing site in relation to RV anatomy.

6.1. METHODOLOGICAL CONSIDERATIONS

The retrospective design with active clinical follow-up has several limitations including the potential of introducing significant selection bias. Ideally, we would have conducted a prospective, randomised trial and included more study participants. However, currently there are no methods providing the opportunity for true randomisation of RV lead position and prospective trials are time-consuming and expensive. Thus, conducting a randomised controlled trial did not seem feasible. The chosen design with active clinical follow-up ensured a thorough follow-up assessment including CT for precise localisation of RV lead implantation site providing novel clinically relevant insights. The availability of electronic medical records and access

to stored echocardiograms ensured that high-quality data could be obtained retrospectively. However, it is important to be aware of the study limitations to ensure a correct interpretation of the results. In the following sections, important methodological considerations and limitations are discussed.

Patient selection

Due to the design of this study, there is a risk of post-treatment selection bias favouring those who survived long enough and who were willing to participate in the study.[118] Bias may arise because retrospectively selecting the population based on variables that might possibly be affected by the treatment and outcome itself. If the exposure was associated with the outcome and the outcome was associated with the selection criterion, there is a risk of such bias. In this case, the association observed might reflect an association between the exposure and the selection criterion and not between the exposure and the outcome. For significant selection bias to occur, strong associations between the variables need to be present.[119] Using causal diagrams, each selection criterion was evaluated for its potential to induce bias.[120] Selecting patients based on information known at baseline should not induce selection bias and only those excluded after pacemaker implantation are likely to cause bias (Figure 7). Selecting patients on having to be alive, able, and willing to participate in the study, have the potential to cause such bias. Examples of the potential pathways for bias when selecting on death and lack of consent are shown in Figure 15.

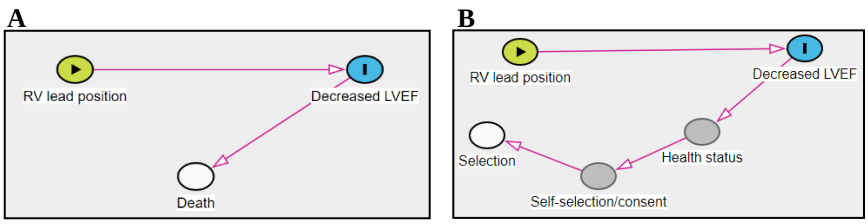


Figure 15. The pathway of potential selection bias due to excluding those who died prior to study follow-up (A) or due to excluding those unable or unwilling to participate in the study (B). RV, right ventricular; LVEF, left ventricular ejection fraction.

If a certain RV lead position is strongly related to the risk of PICM, patients with the detrimental lead position may be less likely to participate in our study. Furthermore, those with the detrimental RV lead position who have survived and are willing to participate may represent a group who are less prone to the negative effects of that RV lead position, so called super survivors. Their outcomes may therefore not be representative of all patients having been exposed to that RV lead position.[121] The remaining selection criteria have resulted in exclusion of only a few patients after

baseline and the association with both exposure and outcome is likely to be weak. Therefore, those criteria are not believed to cause significant bias.

Looking at our data, there were indications of selection bias. Though not statistically significant, we found that the risk of PICM increased with longer duration of follow-up in the septal group and the opposite was seen for non-septal group. This is an indication of deselection of patients with PICM and a non-septal lead position with longer duration of follow-up (Figure 9). Furthermore, no PICM outcomes occurred in the non-septal group among those with > 6.2 years of follow-up. This is counter-intuitive as longer duration of pacemaker treatment should lead to an increased risk of PICM.[18] Post-treatment selection is an inherent problem in many retrospective studies, and studies on the impact of RV pacing are no exeption.[8,10,21–23,122,123] Several methods have been developed to overcome the issue of selection bias.[120,124] However, attempts to mitigate the possible selection bias in our study using G-methods were unsuccessful due to violation of the statistical assumptions.[119]

Confounding

Confounding is a systematic bias due to common causes of treatment and outcome.[120] The RV lead was considered positioned at random, due to the inaccuracy of fluoroscopy-guided implantation, and confounding through association with both outcome and RV lead position was therefore considered unlikely. Thus, no adjusted analyses were performed when the RV lead position was the exposure variable.[1]

Classification of right ventricular lead position

In study I and II, the RV lead position was defined and analysed as an exposure variable.[1,2] Classification of the RV lead position was based on analyses of CT scans using a regional approach. Several limitations to this method may lead to misclassification of the exposure. Though generally providing a good visualisation of cardiac anatomy and the RV lead, some CT scans were challenging to analyse. Signal noise around the RV lead tip as well as suboptimal contrast filling in the RV cavity, resulting in poor definition of the myocardial border, made the assessment of RV leads positioned in the area of the septal-free wall junction difficult. This may have resulted in a misclassification of septal or free wall position. Furthermore, RV leads located on the border between the lower third and the upper two thirds of the LV long-axis or on the border between the anterior or posterior septum may also have been misclassified.

In general, the arbitrary segmental approach used to classify the RV lead position, may not have resulted in a clinically relevant comparison. As the exposure was analysed using the same method for all patients included, a potential misclassification would be non-differential, meaning the exposure would be equally misclassified in

cases and non-cases.[125] Therefore, such misclassification is expected to bias the result towards null.

Defining pacing-induced cardiomyopathy

The purpose of defining the outcome often is to separate the diseased from the non-diseased. However, many disease processes represent a continuum, and thus defining a clinically relevant binary outcome can be challenging and potentially misleading. In study I and II, we chose PICM as the primary outcome, defined as a decrease in LVEF $\geq$ 10% resulting in LVEF < 50%.[1,2] This definition was chosen to identify all with a significant decrease in LVEF. However, this outcome was based on TTE measurements with no consideration of the clinical significance. Furthermore, LVEF is a crude measure of cardiac function providing only a limited perspective on the many consequences of RV pacing.[12] However, LVEF continues to be the most utilised measure of cardiac function and importantly, the measure upon which guidelines are made.[4,126] There is no universal definition of PICM, and the definition of choice has a major impact on the reported incidence.[10] To overcome the limitations of a binary outcome, absolute change in LVEF was also reported in study I and II.[1,2]

Assessment of LVEF using two-dimensional TTE is known to be subject to both interobserver and intraobserver variability, especially when evaluating dyssynchronous ventricles, and the accuracy of the LVEF assessment is also affected by varying quality of the TTE examinations.[127–129] Inaccurate assessment of LVEF may also have resulted in misclassification of the PICM outcome. Again, this misclassification is non-differential and may be expected to bias the result towards null.[125]

Relative index of contractile asymmetry

In study II, LV contractile dyssynchrony, quantified by rICA, acted both as an exposure and an outcome variable in different analyses.[2] In general, using continuous variables increase the statistical power to detect the relationship between exposure and outcome compared with using binary variables.[130] Dichotomising data, like choosing a cutoff point, will inevitably result in loss of information. Using rICA as a continuous variable allowed for examination of a dose-dependent relationship between dyssynchrony and PICM.[130] rICA has previously been shown to be a robust parameter with a good intraobserver agreement in the study by Zaremba and colleagues.[75] However, rICA is based on STE-analyses and was therefore affected by the varying image quality in the follow-up echocardiograms. Such inaccurate rICA assessment may have the potential to bias the result towards null.[125]

External validity

External validity concerns the generalisability of the results.[131] Are the results applicable only to the included population or can we extrapolate these results to other settings or other study samples? The external validity of our results may be limited due to the study eligibility criteria. Comparison of baseline characteristics between those included and those excluded from our study are shown in Table 1. Patients excluded from the study were older and had more comorbidities compared with those included in the study. Thus, the results from our studies are not necessarily representative for the entire pacemaker population.

6.2. CLINICAL RELEVANCE OF PACING-INDUCED CARDIOMYOPATHY

In study I, we found that more than 30% of the patients developed PICM despite having a normal pre-implant LV systolic function.[1] A decrease in LVEF of ≥ 10% resulting in a post-implant LVEF < 50% may not be clinically relevant for all but does indicate an important negative effect on cardiac function after chronic RV pacing. This was supported by an absolute decrease in LVEF of 8% for the entire cohort. According to the HF guidelines, medical treatment is indicated when LVEF is < 40% and CRT upgrade when LVEF is ≤ 35%.[126] However, though an LVEF ≥ 40% may not prompt initiation of guideline-recommended treatment, deterioration in cardiac function after pacemaker implantation is important to identify, as cardiac function may continue to worsen. Thus, regular follow-up can ensure early initiation of relevant treatment.[4,126]

Comparing risk of PICM between studies is challenged by the lack of a universal definition of PICM.[10] Multiple definitions have been applied in previous studies, all trying to separate those whose conditions deteriorate as a result of RV pacing from those who tolerate RV pacing.[10,132] Some studies have been looking at clinical outcomes including HF hospitalisation, CRT upgrade, or mortality.[7,8,21,122,133] Often, however, as in this dissertation, PICM has been defined based on deterioration in LVEF after pacemaker implantation.[1,2,8,10,21]

Using the same PICM definition as applied in this dissertation, Khurshid *et al*. found a 19% risk of PICM during 3.3 years of follow-up of 277 patients.[1,2,21] Similarly, Abdin *et al*. found a risk of PICM of 16% during 40 months of follow-up of 198 patients.[123] The lower PICM occurrence in the two studies compared to our findings may partly be explained by a lower RV pacing burden and differences in patient selection. Kiehl *et al*. applied a more strict definition, limiting PICM to those with a follow-up LVEF < 40% and based on 823 patients, they found that 12% developed PICM during 4.3 years of follow-up.[8] This is comparable to our findings, where 13%

deteriorated to LVEF ≤ 40% during the study period.[1] Dor *et al*. conducted a study including 203 patients with normal baseline LVEF and a pacing burden ≥ 70%.[133] Defining PICM as a > 10% decrease in LVEF after pacemaker implantation, they found a risk of PICM of 25% with 11% deteriorating to LVEF ≤ 40% after pacemaker implantation. Upgrade to CRT was performed in 4% of patients in the study by Kiehl *et al*., 5% in the study by Khurshid *et al*., and 7% in the study by Dor *et al*. With 6% upgraded to CRT in our study, the results are comparable.[1]

Overall, our results on the risk of PICM are in line with published research including patients with normal pre-implant systolic function. Currently, clinical guidelines offer no recommendations on measures to mitigate the high risk of PICM in this population.[4,43]

6.3. IMPACT OF LEAD POSITION ON CLINICAL OUTCOMES

In study I, we compared the risk of PICM between groups with different RV lead implantation sites.[1] As in many previous studies, we chose a binary exposure categorisation and compared septal with non-septal RV lead position for the primary analysis.[1,90,91,95,134,135] However, unlike other studies, we applied post-implant contrast-enhanced cardiac CT for accurate assessment of RV lead position, to overcome the inaccuracy of exposure assessment by fluoroscopy.[1,16,96–100] Using CT, we found no clinically relevant or statistically significant differences in outcomes between septal and non-septal RV lead positions.[1]

Clinical outcome studies, applying CT for accurate localisation of RV lead position are scarce, and only one other similar study has been identified for comparison.[122] In a retrospective study from 2019, Hattori *et al*., compared RV septal and free wall lead positions. Looking at the combined endpoint of cardiac death and HF hospitalisations, they found that free wall pacing was significantly associated with cardiovascular events (hazard ratio 2.93, $p = 0.018$) during 41 months of follow-up. Unfortunately, neither our study nor the study by Hattori *et al*. provide any final answers on optimal RV lead position. The choice of comparing septal with free wall implantation in the study by Hattori *et al*. perhaps seems less clinically relevant, as there already exists a general consensus to avoid free wall implantation.[4] However, it does underline the importance of avoiding free wall implantation. Importantly, both studies exposed the shortcomings of relying on fluoroscopy for assessment of RV lead position. To continue the search for optimal RV lead position, it is essential to develop new methods that will ensure implantation accuracy and thus allow for true randomisation in prospective studies.

Comparing multiple pacing sites

As the use of CT allowed for a more detailed assessment, that might be of clinical relevance, the RV lead position was further divided into apical, free wall, anterior septum, and posterior septum.[1,2] In study I, analyses of clinical outcomes between the four exposure groups again showed no statistically significant differences though a trend towards higher risk of PICM in the posterior septum group was observed.[1] However, subdividing the RV lead position into four groups reduced the statistical power and the posterior septum group consisted of only 11 (7%) patients.

Studies investigating the effect of pacing from multiple RV locations including the posterior septum are few. In a study from 2013 including eight patients, Vančura *et al*. investigated the acute impact of RV pacing from 18 different RV locations.[52] The outcomes were acute LV hemodynamic measures determined invasively. The CARTO system (Biosense Webster, Inc., Irvine, USA) was used to accurately guide RV lead positioning. The authors found great variations in hemodynamic outcomes between the different RV pacing sites. Consistently, worse outcomes were seen when pacing the RV posterior regions regardless of free wall or septal position. The authors concluded that RV mid or high septal pacing was superior to apical pacing. However, looking at the systolic index measure, anterior apical pacing performed better compared with most mid and high anterior septal pacing sites.

In 2003, Peschar *et al*. conducted a study on open chest anesthetised dogs, looking at the hemodynamic effects of different RV and LV pacing sites.[80] They found that pacing the LV posterior or lateral wall significantly reduced both systolic and diastolic function. In contrast, pacing the LV septum or LV apex maintained systolic function compared with sinus rhythm despite longer duration of activation time (wider QRS). There were no significant differences in systolic function between RV apical and RV septal pacing. The results from each of the experiments showed that pacing different RV sites including the apex, low, mid, mid-high, and high septum consistently resulted in worse hemodynamic outcomes compared with sinus rhythm with very few exceptions.

The results from these two acute studies are in line with our results from study I.[1] However, this is, to our knowledge, the first study investigating the clinical consequences of chronic pacing in the posterior RV septum. Despite the lack of statistical power, our results exposed a potential clinically important risk of worse outcome with chronic posterior septal pacing. These results should be regarded as hypothesis generating and tested in future clinical studies. Though our study does not reveal one optimal implantation site, the exposure of less favourable implantation sites is important as efforts could then be made to avoid such implantation.

Categorical comparison of right ventricular lead position

Most clinical studies comparing RV lead positions have applied a simplistic, often binary, categorisation of RV lead locations.[41,91,136] However, as shown by Vančura *et al*., any crude categorisation of RV lead location may demonstrate large intragroup variations in hemodynamic outcomes.[52] The authors reported a great heterogeneity in outcomes even within often targeted implantations areas such as the RV outflow tract, RV septum, and apex. Furthermore, they found that the optimal pacing site varied from patient to patient and included both apical and free wall segments as well as the expected septal segments. The RV endocardium including the conduction system is complex with large interindividual electro-anatomical differences.[137] Consequently, this arbitrary categorisation of RV lead position may lead to an unintentional grouping of patients with very different responses to being paced in the same overall RV segment. Inappropriate categorisation of the RV lead position is likely to contribute to the neutral results in studies comparing pacing sites.

Risk of free wall pacing

Worth mentioning, we found 20% unintended RV free wall implantations. Other studies have similarly found high incidences of RV free wall implantations in patients undergoing fluoroscopy-guided pacemaker implantation.[16,17,98,100,122,138] Using dedicated contrast-enhanced cardiac CT, Sommer *et al*. found a 48% incidence of RV free wall implantations and Moore *et al*. found an even higher incidence of 61%.[16,100] Using incident clinical CT scans with or without contrast-enhancement, Hattori *et al*. found an 8% risk of RV free wall implantations.[122] The lower incidence in the latter study might be explained by the quality of the CT scans. The use of a dedicated scanning protocol with contrast-enhancement and ECG-gating ensures an optimal visualisation of cardiac anatomy and clear separation of the RV septum and free wall that are not easily separated in non-contrast scans. The high incidence of unintended free wall implantations is highly clinically relevant as free wall screw-in implantations may also be associated with myocardial perforation and possible damage to the left anterior descending artery and should therefore be avoided.[4,135,139]

6.4. PACING-INDUCED DYSSYNCHRONY

Right ventricular lead position and dyssynchronous activation

In study II, a novel echocardiographic method was applied to assess LV contractile dyssynchrony during RV pacing.[2] RV lead position was found to be significantly associated with both degree and location of dyssynchronous activation. Those with RV anterior septal, apical, and free wall implantations exhibited similar activation patterns the with highest degree of dyssynchrony in the 3CH and 4CH view, and the lowest degree of dyssynchrony in the 2CH view. In contrast, pacing the posterior

septum resulted in a high degree of dyssynchrony in all three apical views. This is the first study, to our knowledge, evaluating dyssynchrony knowing the true RV lead position determined from CT.

The similar activation pattern observed in the apical, free wall and anterior septum groups might be explained by a general tendency of pacing leads to be positioned anteriorly during implantation.[16,100] Though not further divided into anterior or posterior, it is likely that the majority of apical and free wall implantations were anterior, thus exhibiting a mean activation pattern similar to anterior septal pacing with early anterior LV activation. This will also explain the similar outcomes in the three groups. However, this is hypothetical and needs to be confirmed.

Importantly, compared with the control group, all RV pacing sites resulted in significantly higher degree of dyssynchrony. Suggesting that RV pacing, regardless of pacing site, will inevitably induce some degree of slow and dyssynchronous myocardial activation. It has been hypothesised that RV septal leads positioned in close proximity to the conduction system would result in a more physiological activation and thus had the potential to mitigate the negative effects induced by RV pacing.[87–89] However, the conduction system is electrically isolated from the myocardium except at the Purkinje terminals, which are mainly located in the RV apical region.[11] Consequently, conventional septal pacing may primarily induce slow myocardial propagation despite the proximity to the conduction system thus gaining no or only limited advantage of the conduction system.[140]

Clinical consequences of dyssynchronous activation

In study II, we found that LV contractile dyssynchrony was significantly associated with PICM.[2] Of interest, not only the overall degree of dyssynchrony but also the location of dyssynchrony was found to be an important factor. Increased dyssynchrony between the LV anterior and inferior walls (2CH view) was independently associated with PICM.

Using various methods, other studies have investigated the association between clinical outcomes and dyssynchrony.[11,12,39] In a study from 2008, using QRS duration as a measure of electrical dyssynchrony, Zhang *et al*. found that a wider paced QRS duration was a predictor of HF.[23] However, in a large study from 2016, including 823 patients, an association between QRS duration and PICM could not be reproduced.[8] In a study from 2007, Tops *et al*. evaluated mechanical dyssynchrony by calculating time-to-peak based on STE-derived radial strain in RV paced patients.[72] The authors found that the presence of dyssynchrony, after a mean 3.8 years of pacemaker treatment, was associated with a significant decrease in LVEF and deterioration in New York Heart Association functional class. In a prospective study published in

2015, Fang *et al*. evaluated the presence of mechanical dyssynchrony using time-to-peak based on colour-coded tissue Doppler imaging.[141] They found that the early presence of pacing-induced dyssynchrony, was significantly associated with subsequent deterioration in LVEF and increased end-systolic volumes during 4.8 years of follow-up.

However, many studies have applied only crude estimations of dyssynchrony, often reducing dyssynchrony to being present or not or being a one-dimensional parameter with no consideration for location or direction of the dyssynchronous activation. Pacing-induced dyssynchrony is complex and affected by several factors including pacing site, individual electroanatomical variations and pre-existing myocardial pathologies. It is essential to better understand the dyssynchronous activation during pacing to identify those at risk of deterioration after pacemaker implantation. The use of rICA provided the opportunity to evaluate LV activation during RV pacing in detail by assessing both location and degree of dyssynchrony.[2] Furthermore, using all data lines throughout systole from the strain rate derived CAMM plot, rICA measured discrepancies in activation between entire opposing walls. This ensured that dyssynchronous activation along the entire LV long axis view was captured and contributed to a comprehensive evaluation. We found that only dyssynchrony assessed in the 2CH view was independently associated with PICM. This underlines the importance of a thorough TTE evaluation, as restricting the evaluation to the 3CH or 4CH view might result in loss of important information.

The highest levels of dyssynchrony were observed in the 3CH and 4CH views. However, high degrees of 3CH and 4CH dyssynchrony were not independently associated with PICM. This underlines the importance of the location of dyssynchrony and thus the activation sequence in the pathophysiology of pacing. This finding is in line with Peschar *et al*., who argued that a good activation sequence is more important to maintain LV systolic function than overall dyssynchrony or duration of activation.[80] Hypothetically, pacing the RV posterior septum likely induces a detrimental activation sequence with early activation of the LV inferoseptal and inferior wall with pre-stretch of the anterior wall.[11] This initial activation may not generate sufficient force to open the aortic valve, and the initial myocardial work is wasted. Subsequently, the pre-stretched LV anterior wall is activated, forcing the blood flow away from the anteriorly positioned LV outflow tract and back towards the prematurely relaxed inferior region. Ultimately, this may result in lower myocardial efficiency, premature closure of the aortic valve and decreased cardiac output.[11,52,80] In contrast, pacing the anteriorly may result in an activation sequence mimicking intrinsic activation, even though the overall activation may be slower. This hypothesis should be investigated in future studies.

6.5. CLINICAL APPLICATION OF ELECTROCARDIOGRAPHIC IMAGING

In study III, we evaluated the accuracy of a novel ECGi method based on the 12-leads ECG to localise the RV pacing site and reconstruct biventricular activation.[3] We found that the new method localised RV pacing site with a mean LE of 14 mm. This result is comparable with previous ECGi studies also validating the method using the distance between a known stimulation site and the reconstructed initial site of activation. The majority of ECGi studies have applied body surface potential mapping using up to 256 electrodes, together with a subject specific geometric heart and thorax model to reconstruct the ventricular activation.[62,142–144]

Thus in 2016, Oosterhoff et. al conducted an ECGi study on four pigs (55-65 kg).[142] Using 64-lead body surface potential mapping for the reconstruction, the authors found a distance of 18 mm between the stimulation site and the estimated initial site of activation. In a study from 2012, also using 10 pigs, Liu *et al*. applied 100 leads for the body surface potential mapping and found a mean LE of 6 mm.[145] Similarly, Han *et al*. found a LE of 5 mm in a study on 13 healthy rabbits with the use of 64 leads.[143] In a study from 2015 including 29 pacemaker patients, Revishvili *et al*. applied 224 leads for body surface potential mapping and found a mean 8 mm distance between the known pacing site and the reconstructed initial site of activation.[144] Similar to our study, using only the 12-lead-ECG, Pezzuto *et al*. conducted an ECGi study in 2021 including 11 HF patients.[101] A detailed patient-specific geometric anatomical model based on cardiac magnetic resonance images was constructed and included information on myocardial scarring and a detailed thorax model encompassing lungs, blood masses, myocardial fibre orientation, connective tissue, muscle and skin. By performing invasive intracardiac mapping for comparison, they found a distance of 14 mm between the reconstructed and the invasively measured endocardial breakthrough point during intrinsic activation.

To our knowledge, our study using clinical data from 137 patients, is the largest study conducted to date and only one other study has tested an ECGi method including pacemaker patients.[144] Furthermore, our method was based on the 12-lead ECG, a method only few other and small studies have investigated.[101,146] In contrast to the study by Pezzuto *et al*., our method was based on a simple patient-specific model without information on myocardial scarring and the thorax model included only information on the thoracic border.[3] Despite the use of a simple geometric model and applying only the 12-lead ECG, our method accurately localised the RV pacing site in a very heterogenous and comorbid pacemaker cohort.

The gold standard for validating ECGi methods is the use of invasive electrocardiographic mapping as ground truth data for comparison.[102] However, this

was unfortunately not available in our study.[3] However, the CT scans provided accurate knowledge on the RV lead position, serving as ground truth data for validation of the reconstructed initial site of activation. Validation of the reconstructed activation sequence using ground truth data was not possible and this validation should be performed in future studies applying invasive mapping for comparison.

It is important to remember that ECGi provides only an estimate of cardiac electrical activity based on an algorithmic reconstruction and thus it is not a direct recording of cardiac activation. The algorithm makes many assumptions including assumptions on the propagation of the electrical wavefront throughout the myocardium and the conduction of the electrical impulses to the body surface. Violations of the algorithm assumptions may likely affect the accuracy of the method. For example, the algorithm applied in our study assumed a uniform propagation velocity throughout the myocardium, an assumption that is unlikely to be fully met in an elderly population with comorbidities such as ischemic heart disease, valvular heart disease, diabetes mellitus and hypertension.[3,147,148] However, a non-uniform myocardial propagation velocity was indirectly accounted for, as the reconstructed QRS duration was matched to the recorded QRS duration.[3] Despite potential violations of algorithm assumptions, the method accurately localised RV leads implanted throughout the RV endocardium.

The results from our study as well as other studies on ECGi are promising and show the potential of ECGi as a tool to guide intraprocedural pacemaker implantation. However, further work is needed to improve the accuracy of the method and its clinical applicability. Currently, ECGi is a research tool with the disadvantage of requiring the creation of a patient specific model, a time-consuming process requiring a cardiac CT or magnetic resonance scan. However, despite the use of a fairly simple geometric model in the study, our results were comparable to those from the study by Pezzuto *et al*. using a more complex model.[3,101] Future studies on the feasibility of using a generic geometric model or model library, making the method manageable in a clinical setting, seem encouraging. Another disadvantage of ECGi is the need for extensive body surface potential mapping, which is time-consuming and requires special technical equipment.[149] Importantly, our study showed, that the use of a standard 12-lead ECG is feasible thus taking a step further towards making ECGi a useful clinical tool.[3]

Importantly, the applicability of ECGi is not limited to localising pacing sites and guide pacemaker implantation but may have a wide range of potential applications.[102,150,151] So far, ECGi has been evaluated as a tool to improve patient selection in CRT, guide and optimise CRT implantation and localise arrhythmogenic substrate for atrial and ventricular arrhythmias.[59,102,146,150,152] Furthermore, ECGi has

been used to improve risk stratification of malignant ventricular arrhythmias in patients with Brugada and arrhythmogenic right ventricular cardiomyopathy.[153–155]

CHAPTER 7. CONCLUSIONS AND PERSPECTIVES

The aim of this dissertation was to investigate the chronic effects of RV pacing and the impact of RV lead position. Additionally, we aimed to investigate a novel ECGi method with a potential to guide pacemaker lead implantation.

In study I, we found a high risk of PICM despite normal pre-implant LV systolic function.[1] Importantly, RV lead position was not found to be associated with the risk of PICM though a trend towards a worse outcome was observed for those paced in the posterior septum. Of further importance, we found 20% unintended RV free wall implantations after routine fluoroscopy-guided RV lead implantation.[1] This underlines the necessity of new methods to more accurately guide pacemaker lead implantation thus minimising the risk of complications.

In study II, we found that location and degree of LV contractile dyssynchrony was indeed associated with PICM and furthermore, that LV dyssynchrony was associated with RV lead position.[2] Thus, indicating that RV lead position does play a role in PICM despite the neutral results from study I.[1] Of interest, the highest degree of dyssynchrony was observed in those paced from the posterior septum supporting the results from the first study.

In study III, we presented a novel ECGi method that reconstructed biventricular activation and accurately localised initial site of activation as a proxy for RV lead position.[3] ECGi could be a future solution to overcome the shortcomings of current implantation methods with the potential to, not only visually guide pacemaker lead implantation in relation to cardiac anatomy, but also ensure that the RV lead position results in the optimal activation pattern for the individual patient.

Despite decades of research, the problem of significant deterioration following pacemaker implantation has not been solved. So far, efforts to find the optimal RV lead position have not been fruitful. Our results on the impact of RV lead position, are based on a highly selected pacemaker cohort, and can merely be regarded as hypothesis generating. A true benefit of high or mid septal pacing needs to be established to justify the potential increased implantation procedure duration, radiation exposure, and a high risk of unintended free wall implantations using current implantations methods.[16,91] Prospective, randomised trials with true randomisation of RV lead position are therefore needed. However, accurate comparison of RV lead positions is challenged by the limitations of current implantation methods.

Furthermore, the currently used segmental approach, comparing implantation sites with no consideration of individual electroanatomical variations, may not provide any valid answers to the search for optimal lead position.

Perhaps the "one size fits all" approach is too simple. We showed, that regardless of the pacing site, significant LV contractile dyssynchrony was induced compared with intrinsic activation.[2] This indicates that RV pacing, regardless of the pacing site, is likely to induce significant dyssynchrony with increased risk of PICM, potentially only mitigated by CRT or conduction system pacing. However, long-term safety and efficacy need to be established, as challenges including elevated pacing thresholds leading to exit block or premature depletion of the battery and problems with sensing have been observed.[38,156–158] Consequently, widespread use of these implantation strategies may have long prospects and the majority of patients continues to receive conventional pacemaker treatment. Thus, it is important to continue the research on how to improve pacemaker treatment for the benefit of the many patients in a growing pacemaker population. Furthermore, it is important that guidelines clearly address the negative consequences of RV pacing and provide recommendations on treatment and follow-up of patients at risk.[4,43]

The introduction of novel methods in this dissertation, including the use of CT, rICA and ECGi, has provided the opportunity to investigate RV pacing from new perspectives, bringing new insights to a clinically important topic. Using CT to accurately localise RV lead position, allowed for true comparison of different RV lead positions. A comprehensive evaluation of LV dyssynchrony was made possible by using rICA, thus contributing with new knowledge regarding the pathophysiology of PICM and consequences of pacing from different RV lead positions. Finally, investigating ECGi as a potential method to guide pacemaker implantation was a minor, but important, step towards achieving implantation accuracy, ensuring the optimal treatment for each pacemaker patient.

LITERATURE LIST

1. Fruelund PZ, Sommer A, Frøkjær JB, Lundbye-Christensen S, Zaremba T, Søgaard P, *et al.* Risk of Pacing-Induced Cardiomyopathy in Patients with High-Degree Atrioventricular Block—Impact of Right Ventricular Lead Position Confirmed by Computed Tomography. *J Clin Med* 2022;**11**:7228.

2. Fruelund PZ, Sommer A, Lundbye-Christensen S, Graff C, Søgaard P, Riahi S, *et al.* The role of contractile dyssynchrony in pacing-induced cardiomyopathy – detailed assessment using index of contractile asymmetry [submitted].

3. Fruelund PZ, Dam PM Van, Melgaard J, Sommer A, Lundbye-Christensen S, Søgaard P, *et al.* Novel non-invasive ECG imaging method based on the 12-lead ECG for reconstruction of ventricular activation: A proof-of-concept study. *Front Cardiovasc Med* 2023;**10**.

4. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, *et al.* 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;**42**:3427–520.

5. Johansen JB on behalf of the steering committee. Danish Pacemaker and ICD Register Annual Report 2020. 2020.

6. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: Calendar year 2009 - A world society of Arrhythmia's project. *PACE - Pacing Clin Electrophysiol* 2011;**34**:1013–27.

7. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, *et al.* Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003;**107**:2932–7.

8. Kiehl EL, Makki T, Kumar R, Gumber D, Kwon DH, Rickard JW, *et al.* Incidence and predictors of right ventricular pacing-induced cardiomyopathy in patients with complete atrioventricular block and preserved left ventricular systolic function. *Hear Rhythm* 2016;**13**:2272–8.

9. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, *et al.* Dual-Chamber Pacing or Ventricular With an Implantable Defibrillator. *Jama* 2002;**288**:3115–23.

10. Kaye G, Ng JY, Ahmed S, Valencia D, Harrop D, Ng ACT. The Prevalence of Pacing-Induced Cardiomyopathy (PICM) in Patients With Long Term Right Ventricular Pacing - Is it a Matter Of Definition? *Heart Lung Circ* 2019;**28**:1027–33.

11. Prinzen FW, Peschar M. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. *Pacing Clin Electrophysiol* United States; 2002;**25**:484–98.

12. Tops LF, Schalij MJ, Bax JJ. The Effects of Right Ventricular Apical Pacing on Ventricular Function and Dyssynchrony. *J Am Coll Cardiol* 2009;**54**:764–76.

13. Lieberman R, Padeletti L, Schreuder J, Jackson K, Michelucci A, Colella A, *et al.* Ventricular Pacing Lead Location Alters Systemic Hemodynamics and Left Ventricular Function in Patients With and Without Reduced Ejection Fraction. *J Am Coll Cardiol* 2006;**48**:1634–41.

14. Alhous MHA, Small GR, Hannah A, Hillis GS, Broadhurst P. Impact of temporary right ventricular pacing from different sites on echocardiographic indices of cardiac function. *Europace* 2011;**13**:1738–46.

15. Verma AJ, Lemler MS, Zeltser IJ, Scott WA. Relation of right ventricular pacing site to left ventricular mechanical synchrony. *Am J Cardiol* 2010;**106**:806–9.

16. Sommer A, Kronborg MB, Nørgaard BL, Gerdes C, Mortensen PT, Nielsen JC, *et al.* Left and right ventricular lead positions are imprecisely determined by fluoroscopy in cardiac resynchronization therapy: A comparison with cardiac computed tomography. *Europace* 2014;**16**:1334–41.

17. Osmancik P, Stros P, Herman D, Curila K, Petr R. The insufficiency of left anterior oblique and the usefulness of right anterior oblique projection for correct localization of a computed tomography-verified right ventricular lead into the midseptum. *Circ Arrhythmia Electrophysiol* 2013;**6**:719–25.

18. Tayal B, Fruelund P, Sogaard P, Riahi S, Polcwiartek C, Atwater BD, *et al.* Incidence of heart failure after pacemaker implantation: a nationwide Danish Registry-based follow-up study. *Eur Heart J* 2019;1–8.

19. Nielsen JC, Andersen HR, Thomsen PEB, Thuesen L, Mortensen PT, Vesterlund T, *et al.* Heart failure and echocardiographic changes during long-term follow-up of patients with sick sinus syndrome randomized to single-chamber atrial or ventricular pacing. *Circulation* 1998;**97**:987–95.

20. Andersen HR, Nielsen JC, Thomsen PEB, Thuesen L, Mortensen PT,

Vesterlund T, *et al.* Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. *Lancet* 1997;**350**:1210–6.

21. Khurshid S, Epstein AE, Verdino RJ, Lin D, Goldberg LR, Marchlinski FE, *et al.* Incidence and predictors of right ventricular pacing-induced cardiomyopathy. *Hear Rhythm* 2014;**11**:1619–25.

22. Cho SW, Gwag H Bin, Hwang JK, Chun KJ, Park K-M, On YK, *et al.* Clinical features, predictors, and long-term prognosis of pacing-induced cardiomyopathy. *Eur J Heart Fail* 2019;**21**:643–51.

23. Zhang XH, Chen H, Siu CW, Yiu KH, Chan WS, Lee KL, *et al.* New-onset heart failure after permanent right ventricular apical pacing in patients with acquired high-grade atrioventricular block and normal left ventricular function. *J Cardiovasc Electrophysiol* 2008;**19**:136–41.

24. Sharma AD, Rizo-Patron C, Hallstrom AP, O'Neill GP, Rothbart S, Martins JB, *et al.* Percent right ventricular pacing predicts outcomes in the DAVID trial. *Hear Rhythm* 2005;**2**:830–4.

25. Kabutoya T, Mitsuhashi T, Hata Y, Hashimoto T, Nakagami R, Osada J, *et al.* Beneficial Effects of Upgrading from Right Ventricular Pacing to Cardiac Resynchronization Therapy in Patients with Heart Failure Compared to de Novo Cardiac Resynchronization Therapy. *J Arrhythmia* 2010;**26**:16–20.

26. Fröhlich G, Steffel J, Hürlimann D, Enseleit F, Lüscher TF, Ruschitzka F, *et al.* Upgrading to resynchronization therapy after chronic right ventricular pacing improves left ventricular remodelling. *Eur Heart J* 2010;**31**:1477–85.

27. Vijayaraman P, Herweg B, Dandamudi G, Mittal S, Bhatt AG, Marcantoni L, *et al.* Outcomes of His-bundle pacing upgrade after long-term right ventricular pacing and/or pacing-induced cardiomyopathy: Insights into disease progression. *Hear Rhythm* 2019;**16**:1554–61.

28. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, *et al.* Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013;**368**:1585–93.

29. Doshi RN, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, *et al.* Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol* 2005;**16**:1160–5.

30. Kindermann M, Hennen B, Jung J, Geisel J, Böhm M, Fröhlig G. Biventricular Versus Conventional Right Ventricular Stimulation for Patients With Standard Pacing Indication and Left Ventricular Dysfunction. The

Homburg Biventricular Pacing Evaluation (HOBIPACE). *J Am Coll Cardiol* 2006;**47**:1927–37.

31. Yu C-MM, Chan JY-SS, Zhang Q, Omar R, Yip GW-KK, Hussin A, *et al.* Biventricular Pacing in Patients with Bradycardia and Normal Ejection Fraction. *N Engl J Med* 2009;**361**:2123–34.

32. Stockburger M, Gómez-Doblas JJ, Lamas G, Alzueta J, Fernández-Lozano I, Cobo E, *et al.* Preventing ventricular dysfunction in pacemaker patients without advanced heart failure: Results from a multicentre international randomized trial (PREVENT-HF). *Eur J Heart Fail* 2011;**13**:633–41.

33. Orlov M V., Gardin JM, Slawsky M, Bess RL, Cohen G, Bailey W, *et al.* Biventricular pacing improves cardiac function and prevents further left atrial remodeling in patients with symptomatic atrial fibrillation after atrioventricular node ablation. *Am Heart J* 2010;**159**:264–70.

34. Brignole M, Botto G, Mont L, Iacopino S, Marchi G De, Oddone D, *et al.* Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: A randomized trial. *Eur Heart J* 2011;**32**:2420–9.

35. Albertsen AE, Nielsen JC, Poulsen SH, Mortensen PT, Pedersen AK, Hansen PS, *et al.* Biventricular pacing preserves left ventricular performance in patients with high-grade atrio-ventricular block: A randomized comparison with DDD(R) pacing in 50 consecutive patients. *Europace* 2008;**10**:314–20.

36. Abdelrahman M, Subzposh FA, Do DB, Do BD, Naperkowski A, Ceps RN, *et al.* Clinical Outcomes of His Bundle Pacing Compared to Right Ventricular Pacing. *J Am Coll Cardiol* 2018;**71**:2319–30.

37. Sharma PS, Patel NR, Ravi V, Zalavadia D V., Dommaraju S, Garg V, *et al.* Clinical outcomes of left bundle branch area pacing compared to right ventricular pacing: Results from the Geisinger-Rush Conduction System Pacing Registry. *Hear Rhythm* 2022;**19**:3–11.

38. Arenas IA, Jacobson J, Lamas GA. Routine Use of Biventricular Pacing Is Not Warranted for Patients with Heart Block. *Circ Arrhythmia Electrophysiol* 2015;**8**:730–7.

39. Sweeney MO, Prinzen FW. Ventricular pump function and pacing: physiological and clinical integration. *Circ Arrhythm Electrophysiol* 2008;**1**:127–39.

40. Mazza A, Bendini MG, Leggio M, Riva U, Ciardiello C, Valsecchi S, *et al.* Incidence and predictors of heart failure hospitalization and death in

permanent pacemaker patients: a single-centre experience over medium-term follow-up. *Europace* 2013;**15**:1267–72.

41. Bansal R, Parakh N, Gupta A, Juneja R, Naik N, Yadav R, *et al.* Incidence and predictors of pacemaker-induced cardiomyopathy with comparison between apical and non-apical right ventricular pacing sites. *J Interv Card Electrophysiol* 2019;**56**:63–70.

42. Kim JH, Kang KW, Chin JY, Kim TS, Park JH, Choi YJ. Major determinant of the occurrence of pacing-induced cardiomyopathy in complete atrioventricular block: A multicentre, retrospective analysis over a 15-year period in South Korea. *BMJ Open* 2018;**8**:1–7.

43. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, *et al.* 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhyth. *Circulation* 2019;**140**.

44. Durrer D, Dam RT van, Freud GE, Janse MJ, Meijler FL, Arzbaecher RC. Total excitation of the isolated human heart. *Circulation* 1970;**41**:899–912.

45. Tse HF, Yu C, Wong KK, Tsang V, Leung YL, Ho WY, *et al.* Functional abnormalities in patients with permanent right ventricular pacing: The effect of sites of electrical stimulation. *J Am Coll Cardiol* 2002;**40**:1451–8.

46. Tse HF, Lau CP. Long-term effect of right ventricular pacing on myocardial perfusion and function. *J Am Coll Cardiol* 1997;**29**:744–9.

47. Prinzen FW, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: Experimental study using magnetic resonance imaging tagging. *J Am Coll Cardiol* 1999;**33**:1735–42.

48. Vernooy K, Dijkman B, Cheriex EC, Prinzen FW, Crijns HJGM. Ventricular remodeling during long-term right ventricular pacing following His bundle ablation. *Am J Cardiol* 2006;**97**:1223–7.

49. Oosterhout MFM Van, Prinzen FW, Arts T, Schreuder JJ, Vanagt WYR, Cleutjens JPM, *et al.* Asynchronous electrical activation induces asymmetrical hypertrophy of the left ventricular wall. *Circulation* 1998;**98**:588–95.

50. Prinzen FW, Cheriex EC, Delhaas T, Oosterhout MFM van, Arts T, Wellens HJJ, *et al.* Asymmetric thickness of the left ventricular wall resulting from

asynchronous electric activation: A study in dogs with ventricular pacing and in patients with left bundle branch block. *Am Heart J* 1995;**130**:1045–53.

51. Erlebacher JA, Barbarash S. Intraventricular conduction delay and functional mitral regurgitation. *Am J Cardiol* 2001;**88**:83–6.

52. Vančura V, Wichterle D, Melenovský V, Kautzner J. Assessment of optimal right ventricular pacing site using invasive measurement of left ventricular systolic and diastolic function. *Europace* 2013;**15**:1482–90.

53. Mizner J, Jurak P, Linkova H, Smisek R, Curila K. Ventricular Dyssynchrony and Pacing-induced Cardiomyopathy in Patients with Pacemakers, the Utility of Ultra-high-frequency ECG and Other Dyssynchrony Assessment Tools. *Arrhythmia Electrophysiol Rev* 2022;**11**.

54. Satish P, Narasimhan B, Hagendorff A, Tayal B. Evolving concept of dyssynchrony and its utility. *J Geriatr Cardiol* 2022;**19**:44–51.

55. Heckman LIB, Luermans JGLM, Curila K, Stipdonk AMW Van, Westra S, Smisek R, *et al.* Comparing ventricular synchrony in left bundle branch and left ventricular septal pacing in pacemaker patients. *J Clin Med* 2021;**10**:1–13.

56. Lee KH, Cho JG, Park HW, Yoon NS, Kim SS, Kim MR, *et al.* QRS morphology and ventricular dyssynchrony in patients with chronic right ventricular pacing. *Int J Cardiol* 2014;**176**:962–8.

57. Varma N, Ploux S, Ritter P, Wilkoff B, Eschalier R, Bordachar P. Noninvasive mapping of electrical dyssynchrony in heart failure and cardiac resynchronization therapy. *Card Electrophysiol Clin* 2015;**7**:125–34.

58. Curila K, Jurak P, Halamek J, Prinzen F, Waldauf P, Karch J, *et al.* Ventricular activation pattern assessment during right ventricular pacing: Ultra-high-frequency ECG study. *J Cardiovasc Electrophysiol* 2021;**32**:1385–94.

59. Ploux S, Lumens J, Whinnett Z, Montaudon M, Strom M, Ramanathan C, *et al.* Noninvasive electrocardiographic mapping to improve patient selection for cardiac resynchronization therapy: Beyond QRS duration and left bundle branch block morphology. *J Am Coll Cardiol* 2013;**61**:2435–43.

60. Eschalier R, Ploux S, Lumens J, Whinnett Z, Varma N, Meillet V, *et al.* Detailed analysis of ventricular activation sequences during right ventricular apical pacing and left bundle branch block and the potential implications for cardiac resynchronization therapy. *Hear Rhythm* 2015;**12**:137–43.

61. Strik M, Ploux S, Bordachar P. What Body Surface Mapping Has Taught Us

About Ventricular Conduction Disease Implications for Cardiac Resynchronization Therapy and His Bundle Pacing. *Card Electrophysiol Clin* 2022;**14**:213–21.

62. Bear L, Cuculich PS, Bernus O, Efimov I, Dubois R. Introduction to Noninvasive Cardiac Mapping. *Card Electrophysiol Clin* 2015;**7**:1–16.

63. Bear LR, Huntjens PR, Walton RD, Bernus O, Coronel R, Dubois R. Cardiac electrical dyssynchrony is accurately detected by noninvasive electrocardiographic imaging. *Hear Rhythm* 2018;**15**:1058–69.

64. Tayal B, Sogaard P, Risum N. Why Dyssynchrony matters in Heart Failure. *Card Electrophysiol Clin* 2019;**11**:39–47.

65. Tayal B, Sogaard P. Role of echocardiography in CRT. *Aging (Albany NY)* 2018;**10**:3641–2.

66. Galderisi M, Cattaneo F, Mondillo S. Doppler echocardiography and myocardial dyssynchrony: a practical update of old and new ultrasound technologies. *Cardiovasc Ultrasound* 2007;**5**:28.

67. Bordachar P, Garrigue S, Lafitte S, Reuter S, Jaïs P, Haïssaguerre M, *et al.* Interventricular and infra-left ventricular electromechanical delays in right ventricular paced patients with heart failure: Implications for upgrading to biventricular stimulation. *Heart* 2003;**89**:1401–5.

68. Pitzalis MV, Iacoviello M, Romito R, Massari F, Rizzon B, Luzzi G, *et al.* Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J Am Coll Cardiol* 2002;**40**:1615–22.

69. Olsen NT, Mogelvang R, Jons C, Fritz-Hansen T, Sogaard P. Predicting Response to Cardiac Resynchronization Therapy with Cross-Correlation Analysis of Myocardial Systolic Acceleration: A New Approach to Echocardiographic Dyssynchrony Evaluation. *J Am Soc Echocardiogr* 2009;**22**:657–64.

70. Tayal B, Gorcsan J, Delgado-Montero A, Marek JJ, Haugaa KH, Ryo K, *et al.* Mechanical Dyssynchrony by Tissue Doppler Cross-Correlation is Associated with Risk for Complex Ventricular Arrhythmias after Cardiac Resynchronization Therapy. *J Am Soc Echocardiogr* 2015;**28**:1474–81.

71. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation* 2006;**113**:960–8.

72. Tops LF, Suffoletto MS, Bleeker GB, Boersma E, Wall EE van der, Gorcsan J, *et al.* Speckle-Tracking Radial Strain Reveals Left Ventricular Dyssynchrony in Patients With Permanent Right Ventricular Pacing. *J Am Coll Cardiol* 2007;**50**:1180–8.

73. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, *et al.* Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;**369**:1395–405.

74. Haugaa KH, Goebel B, Dahlslett T, Meyer K, Jung C, Lauten A, *et al.* Risk assessment of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy by strain echocardiography. *J Am Soc Echocardiogr* 2012;**25**:667–73.

75. Zaremba T, Tayal B, Riahi S, Thøgersen AM, Bruun NE, Janus K, *et al.* Index of contractile asymmetry improves patient selection for CRT : a proof-of-concept study. *Cardiovasc Ultrasound* 2019;1–11.

76. Tops LF, Delgado V, Bax JJ. The role of speckle tracking strain imaging in cardiac pacing. *Echocardiography* 2009;**26**:315–23.

77. Inoue K, Okayama H, Nishimura K, Ogimoto A, Ohtsuka T, Saito M, *et al.* Right Ventricular Pacing from the Septum Avoids the Acute Exacerbation in Left Ventricular Dyssynchrony and Torsional Behavior Seen with Pacing from the Apex. *J Am Soc Echocardiogr* 2010;**23**:195–200.

78. Saito M, Kaye G, Negishi K, Linker N, Gammage M, Kosmala W, *et al.* Dyssynchrony, contraction efficiency and regional function with apical and non-apical RV pacing. *Heart* 2015;**101**:600–8.

79. Wang F, Shi H, Sun Y, Wang J, Yan Q, Jin W, *et al.* Right ventricular outflow pacing induces less regional wall motion abnormalities in the left ventricle compared with apical pacing. *Europace* 2012;**14**:351–7.

80. Peschar M, Swart H De, Michels KJ, Reneman RS, Prinzen FW. Left ventricular septal and apex pacing for optimal pump function in canine hearts. *J Am Coll Cardiol* 2003;**41**:1218–26.

81. Varma N. Alternative site pacing: accessing normal precordial activation: is it possible? *J Electrocardiol* 2012;**45**:660–2.

82. Shimony A, Eisenberg MJ, Filion KB, Amit G. Beneficial effects of right ventricular non-apical vs. apical pacing: a systematic review and meta-analysis of randomized-controlled trials. *Europace* 2012;**14**:81–91.

83. Lieberman R, Grenz D, Mond HG, Gammage MD. Selective site pacing:

Defining and reaching the selected site. *PACE - Pacing Clin Electrophysiol* 2004;**27**:883–6.

84. Weizong W, Zhongsu W, Yujiao Z, Mei G, Jiangrong W, Yong Z, *et al.* Effects of right ventricular nonapical pacing on cardiac function: A meta-analysis of randomized controlled trials. *PACE - Pacing Clin Electrophysiol* 2013;**36**:1032–51.

85. Hussain MA, Furuya-Kanamori L, Kaye G, Clark J, Doi SAR. The Effect of Right Ventricular Apical and Nonapical Pacing on the Short- and Long-Term Changes in Left Ventricular Ejection Fraction: A Systematic Review and Meta-Analysis of Randomized-Controlled Trials. *Pacing Clin Electrophysiol* 2015;**38**:1121–36.

86. Kaye G. The quest for physiological pacing—Does one size fit all? *J Cardiovasc Electrophysiol* 2019;**30**:2977–80.

87. Kaye G. Pacing site in pacemaker dependency: is right ventricular septal lead position the answer? *Expert Rev Cardiovasc Ther* 2014;**12**:1407–17.

88. Hillock RJ, Mond HG. Pacing the right ventricular outflow tract septum: Time to embrace the future. *Europace* 2012;**14**:28–35.

89. Kaye G. The desire for physiological pacing: Are we there yet? *J Cardiovasc Electrophysiol* 2019;**30**:3025–38.

90. Cano O, Osca J, Sancho-Tello MJ, Sánchez JM, Ortiz V, Castro JE, *et al.* Comparison of Effectiveness of Right Ventricular Septal Pacing Versus Right Ventricular Apical Pacing. *Am J Cardiol* 2010;**105**:1426–32.

91. Kaye GC, Linker NJ, Marwick TH, Pollock L, Graham L, Pouliot E, *et al.* Effect of right ventricular pacing lead site on left ventricular function in patients with high-grade atrioventricular block: results of the Protect-Pace study. *Eur Heart J* 2015;**36**:856–62.

92. Rosso R, Medi C, Teh AW, Hung TT, Feldman A, Lee G, *et al.* Right ventricular septal pacing: a comparative study of outflow tract and mid ventricular sites. *Pacing Clin Electrophysiol* 2010;**33**:1169–73.

93. Flevari P, Leftheriotis D, Fountoulaki K, Panou F, Rigopoulos AG, Paraskevaidis I, *et al.* Long-term nonoutflow septal versus apical right ventricular pacing: Relation to left ventricular dyssynchrony. *PACE - Pacing Clin Electrophysiol* 2009;**32**:354–62.

94. Kronborg MB, Mortensen PT, Poulsen SH, Gerdes JC, Jensen HK, Nielsen JC. His or para-His pacing preserves left ventricular function in

atrioventricular block: A double-blind, randomized, crossover study. *Europace* 2014;**16**:1189–96.

95. Riahi S, Nielsen JC, Hjortshoj S, Thomsen PE, Hojberg S, Moller M, *et al.* Heart failure in patients with sick sinus syndrome treated with single lead atrial or dual-chamber pacing: no association with pacing mode or right ventricular pacing site. *Europace* 2012;**14**:1475–82.

96. Sommer A, Kronborg MB, Witt CT, Nørgaard BL, Nielsen JC, Norgaard BL, *et al.* The paced electrocardiogram cannot be used to identify left and right ventricular pacing sites in cardiac resynchronization therapy: Validation by cardiac computed tomography. *Europace* 2015;**17**:432–8.

97. Rowe MK, Moore P, Pratap J, Coucher J, Gould PA, Kaye GC. Surface ECG and Fluoroscopy are Not Predictive of Right Ventricular Septal Lead Position Compared to Cardiac CT. *Pacing Clin Electrophysiol* 2017;**40**:537–44.

98. Shenthar J, Rai MK, Chakali SS, Pillai V, Delhaas T. Computed tomography validated right ventricular mid-septal lead implantation using right ventricular angiography. *J Arrhythmia* 2021;**37**:1131–8.

99. Sharma G, Salahuddin S, Sanders P, Gupta H, Gulati G, Jagia P, *et al.* Inadequacy of fluoroscopy and electrocardiogram in predicting septal position in RVOT pacing - Validation with cardiac computed tomography. *Indian Heart J* 2016;**68**:174–80.

100. Moore P, Coucher J, Ngai S, Stanton T, Wahi S, Gould P, *et al.* Imaging and Right Ventricular Pacing Lead Position: A Comparison of CT, MRI, and Echocardiography. *Pacing Clin Electrophysiol* 2016;**39**:382–92.

101. Pezzuto S, Prinzen FW, Potse M, Maffessanti F, Regoli F, Caputo ML, *et al.* Reconstruction of three-dimensional biventricular activation based on the 12-lead electrocardiogram via patient-specific modelling. *Europace* 2021;**23**:640–7.

102. Cluitmans M, Brooks DH, MacLeod R, Dössel O, Guillem MS, Dam PM Van, *et al.* Validation and opportunities of electrocardiographic imaging: From technical achievements to clinical applications. *Front Physiol* 2018;**9**:1–19.

103. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, *et al.* 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.

104. Baumgartner H, Falk V, Bax JJ, Bonis M De, Hamm C, Holm PJ, *et al.* 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–91.

105. Rosset A, Spadola L, Ratib O. OsiriX: An open-source software for navigating in multidimensional DICOM images. *J Digit Imaging* 2004;**17**:205–16.

106. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, *et al.* Recommendations on the echocardiographic assessment of aortic valve stenosis: A focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2017;**18**:254–75.

107. Dam PM van, Oostendorp TF, Oosterom A van. Application of the fastest route algorithm in the interactive simulation of the effect of local ischemia on the ECG. *Med Biol Eng Comput* 2009;**47**:11–20.

108. Draper MH, Mya-Tu M. A COMPARISON OF THE CONDUCTION VELOCITY IN CARDIAC TISSUES OF VARIOUS MAMMALS. *Q J Exp Physiol Cogn Med Sci* 1959;**44**:91–109.

109. Dam PM Van, Oostendorp TF, Linnenbank AC, Oosterom A Van. Non-invasive imaging of cardiac activation and recovery. *Ann Biomed Eng* 2009;**37**:1739–56.

110. Oosterom A Van. The dominant T wave. *J Electrocardiol* 2004;**37**:193–7.

111. Oosterom A Van. Genesis of the T wave as based on an equivalent surface source model. *J Electrocardiol* 2001;**34**:217–27.

112. Meijs JW, Weier OW, Peters MJ, Oosterom A van, Oosterom AVAN. On the Numerical Accuracy of the Boundary Element Method. *IEEE Trans Biomed Eng* 1989;**36**:1038–49.

113. Geselowitz DB. Description of cardiac sources in anisotropic cardiac muscle. Application of bidomain model. *J Electrocardiol* 1992;**25**:65–7.

114. Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. *Am J Epidemiol* 2004;**159**:702–6.

115. Gonçalves S, White H. Bootstrap standard error estimates for linear regression. *J Am Stat Assoc* 2005;**100**:970–9.

116. Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. *Biometrical J* 2005;**47**:458–72.

117. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* 1999;**28**:964–74.

118. Elwert F, Winship C. Endogenous Selection Bias: The Problem of Conditioning on a Collider Variable. *Annu Rev Sociol* 2014;**40**:31–53.

119. Hernán MA, Robins JM. Causal Inference - what if. Found. Agnostic Stat. 2020.

120. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004;**15**:615–25.

121. Elston DM. Survivorship bias. *J Am Acad Dermatol* 2021;

122. Hattori M, Naruse Y, Oginosawa Y, Matsue Y, Hanaki Y, Kowase S, *et al.* Prognostic impact of lead tip position confirmed via computed tomography in patients with right ventricular septal pacing. *Hear Rhythm* 2019;**16**:921–7.

123. Abdin A, Yalin K, Zink MD, Napp A, Gramlich M, Marx N, *et al.* Incidence and predictors of pacemaker induced cardiomyopathy: A single-center experience. *J Electrocardiol* 2019;**57**:31–4.

124. Hernán MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health* 2006;**60**:578–86.

125. Delgado-Rodríguez M, Llorca J. Bias. *J Epidemiol Community Health* 2004;**58**:635–41.

126. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution. *Eur J Heart Fail* 2016;**18**:891–975.

127. Lenell J, Lindahl B, Karlsson P, Batra G, Erlinge D, Jernberg T, *et al.* Reliability of estimating left ventricular ejection fraction in clinical routine: a validation study of the SWEDEHEART registry. *Clin Res Cardiol* 2022;

128. Marwick TH. Ejection Fraction Pros and Cons: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2018;**72**:2360–79.

129. Pickett CA, Cheezum MK, Kassop D, Villines TC, Hulten EA. Accuracy of cardiac CT, radionucleotide and invasive ventriculography, two- and three-dimensional echocardiography, and SPECT for left and right ventricular ejection fraction compared with cardiac MRI: a meta-analysis. *Eur Hear journal Cardiovasc Imaging* 2015;**16**:848–52.

130. Altman DG, Royston P. The cost of dichotomising continuous variables. *BMJ* England; 2006;**332**:1080.

131. Kukull WA, Ganguli M. Generalizability: The trees, the forest, and the low-hanging fruit. *Neurology* 2012;**78**:1886–91.

132. Merchant FM, Mittal S. Pacing induced cardiomyopathy. *J Cardiovasc Electrophysiol* 2020;**31**:286–92.

133. Dor O, Haim M, Barrett O, Novack V, Konstantino Y. Incidence and Clinical Outcomes of Pacing Induced Cardiomyopathy in Patients With Normal Left Ventricular Systolic Function and Atrioventricular Block. *Am J Cardiol* 2020;**128**:174–80.

134. Ng ACT, Allman C, Vidaic J, Tie H, Hopkins AP, Leung DY. Long-Term Impact of Right Ventricular Septal Versus Apical Pacing on Left Ventricular Synchrony and Function in Patients With Second- or Third-Degree Heart Block. *Am J Cardiol* 2009;**103**:1096–101.

135. Domenichini G, Sunthorn H, Fleury E, Foulkes H, Stettler C, Burri H. Pacing of the interventricular septum versus the right ventricular apex: A prospective, randomized study. *Eur J Intern Med* 2012;**23**:621–7.

136. Muto C, Calvi V, Botto GL, Pecora D, Porcelli D, Costa A, *et al.* Chronic Apical and Nonapical Right Ventricular Pacing in Patients with High-Grade Atrioventricular Block: Results of the Right Pace Study. *Biomed Res Int* 2018;**2018**.

137. Gopalan D. Right heart on multidetector CT. *Br J Radiol* 2011;**84 Spec No**:S306-23.

138. Pang BJ, Joshi SB, Lui EH, Tacey MA, Ling LH, Alison J, *et al.* Validation of conventional fluoroscopic and ECG criteria for right ventricular pacemaker lead position using cardiac computed tomography. *Pacing Clin Electrophysiol* 2014;**37**:495–504.

139. Teh AW, Medi C, Rosso R, Lee G, Gurvitch R, Mond HG. Pacing from the right ventricular septum: Is there a danger to the coronary arteries? *PACE - Pacing Clin Electrophysiol* 2009;**32**:894–7.

140. Myerburg RJ, Nilsson K, Gelband H. Physiology of canine intraventricular conduction and endocardial excitation. *Circ Res* 1972;**30**:217–43.

141. Fang F, Luo X-X, Zhang Q, Azlan H, Razali O, Ma Z, *et al.* Deterioration of left ventricular systolic function in extended Pacing to Avoid Cardiac Enlargement (PACE) trial: the predictive value of early systolic dyssynchrony. *Europace* 2015;**17**:ii47–53.

142. Oosterhoff P, Meijborg VMF, Dam PM Van, Dessel PFHM Van, Belterman

CNW, Streekstra GJ, *et al.* Experimental Validation of Noninvasive Epicardial and Endocardial Activation Imaging. *Circ Arrhythmia Electrophysiol* 2016;**9**:1–10.

143. Han C, Pogwizd SM, Killingsworth CR, He B. Noninvasive imaging of three-dimensional cardiac activation sequence during pacing and ventricular tachycardia. *Hear Rhythm* 2011;**8**:1266–72.

144. Revishvili AS, Wissner E, Lebedev DS, Lemes C, Deiss S, Metzner A, *et al.* Validation of the mapping accuracy of a novel non-invasive epicardial and endocardial electrophysiology system. *Europace* 2015;**17**:1282–8.

145. Liu C, Eggen MD, Swingen CM, Iaizzo PA, He B. Noninvasive mapping of transmural potentials during activation in swine hearts from body surface electrocardiograms. *IEEE Trans Med Imaging* 2012;**31**:1777–85.

146. Misra S, Dam P van, Chrispin J, Assis F, Keramati A, Kolandaivelu A, *et al.* Initial validation of a novel ECGI system for localization of premature ventricular contractions and ventricular tachycardia in structurally normal and abnormal hearts. *J Electrocardiol* 2018;**51**:801–8.

147. Kléber AG, Rudy Y. Basic Mechanisms of Cardiac Impulse Propagation and Associated Arrhythmias. *Physiol Rev* 2004;**84**:431–88.

148. King JH, Huang CLH, Fraser JA. Determinants of myocardial conduction velocity: Implications for arrhythmogenesis. *Front Physiol* 2013;**4 JUN**:1–14.

149. Pereira H, Niederer S, Rinaldi CA. Electrocardiographic imaging for cardiac arrhythmias and resynchronization therapy. *Europace* 2020;**22**:1447–62.

150. Sedova K, Repin K, Donin G, Dam P Van, Kautzner J. Clinical utility of body surface potential mapping in CRT patients. *Arrhythmia Electrophysiol Rev* 2021;**10**:113–9.

151. Issa ZF, Miller JM, Zipes DP. Advanced Mapping and Navigation Modalities. *Clin Arrhythmology Electrophysiol* 2019;155–205.

152. Melgaard J, Dam PM Van, Sommer A, Fruelund P, Nielsen JC, Riahi S, *et al.* Non-invasive estimation of QLV from the standard 12-lead ECG in patients with left bundle branch block. *Front Physiol* 2022;

153. Boonstra MJ, Hilderink BN, Locati ET, Asselbergs FW, Loh P, Dam PM Van. Novel CineECG enables anatomical 3D localization and classification of bundle branch blocks. *Europace* 2021;**23**:I80–7.

154. Andrews CM, Srinivasan NT, Rosmini S, Bulluck H, Orini M, Jenkins S, *et al.* Electrical and Structural Substrate of Arrhythmogenic Right Ventricular Cardiomyopathy Determined Using Noninvasive Electrocardiographic Imaging and Late Gadolinium Magnetic Resonance Imaging. *Circ Arrhythmia Electrophysiol* 2017;**10**:1–12.

155. Zhang J, Sacher F, Hoffmayer K, O'Hara T, Strom M, Cuculich P, *et al.* Cardiac electrophysiological substrate underlying the ECG phenotype and electrogram abnormalities in brugada syndrome patients. *Circulation* 2015;**131**:1950–9.

156. Sharma PS, Vijayaraman P, Ellenbogen KA. Permanent His bundle pacing: shaping the future of physiological ventricular pacing. *Nat Rev Cardiol* 2020;**17**:22–36.

157. Bhatt AG, Musat DL, Milstein N, Pimienta J, Flynn L, Sichrovsky T, *et al.* The Efficacy of His Bundle Pacing: Lessons Learned From Implementation for the First Time at an Experienced Electrophysiology Center. *JACC Clin Electrophysiol* 2018;**4**:1397–406.

158. Fang F, Sanderson JE, Yu C-M. Should all patients with heart block receive biventricular pacing? All heart block patients with a pacemaker indication should receive biventricular pacing: one move, double the gains? *Circ Arrhythm Electrophysiol* 2015;**8**:722–9.

APPENDICES

Appendix A

Fruelund PZ, Sommer A, Frøkjær JB, Lundbye-Christensen S, Zaremba T, Søgaard P, Graff C, Vraa S, Mahalingasivam AA, Thøgersen AM, Pedersen MR, and Riahi S. Risk of Pacing-Induced Cardiomyopathy in Patients with High-Degree Atrioventricular Block – Impact of Right Ventricular Lead Position Confirmed by Computed Tomography. *J Clin Med* 2022;11:7228.

Appendix B

Fruelund PZ, Sommer A, Lundbye-Christensen S, Graff C, Søgaard P, Riahi S, and Zaremba T. The role of mechanical dyssynchrony in pacing-induced cardiomyopathy: detailed assessment using index of contractile asymmetry. Submitted (in review).

Appendix C

Fruelund PZ, Dam PM Van, Melgaard J, Sommer A, Lundbye-Christensen S, Søgaard P, Zaremba T, Graff C, and Riahi S. Novel non-invasive ECG imaging method based on the 12-lead ECG for reconstruction of ventricular activation: A proof-of-concept study. *Front Cardiovasc Med* 2023;10.

ISSN (online): 2246-1302
ISBN (online): 978-87-7573-755-0

AALBORG UNIVERSITY PRESS