CHARLES UNIVERSITY IN PRAGUE

3rd FACULTY OF MEDICINE

A DISSERTATION

SUBMITTED TO THE DEPARTMENT OF CARDIOVASCULAR

SCIENCE OF CHARLES UNIVERSITY IN PRAGUE IN PARTIAL

FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

CHARLES UNIVERSITY IN PRAGUE

3rd FACULTY OF MEDICINE

Title: Pacing-induced cardiomyopathy and electro-mechanical ventricular dyssynchrony - novel non-invasive dyssynchrony assessment tools and biomarkers of collagen metabolism

Název: Stimulací indukované kardiomyopatie a elektro-mechanická komorová dyssynchronie – nové neinvazivní diagnostické metody a biomarkery metabolismu kolagenu

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May 2024

Prague

Declaration:

I hereby declare that I have worked on this thesis independently, based on the results of my research and available literature, which is properly cited, under the supervision of doc. MUDr. Ing. Karol Čurila, Ph.D.

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MIZNER, Jan. *Pacing-induced cardiomyopathy and electro-mechanical ventricular dyssynchrony - novel non-invasive dyssynchrony assessment tools and biomarkers of collagen metabolism.* Prague 2024. 82 pages. Dissertation thesis. Cardiology, Third Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady. Supervisor Čurila Karol.

Key words:
pacing-induced cardiomyopathy, conduction system pacing, ventricular dyssynchrony, UHF-ECG, echocardiography, collagen metabolism

Klíčová slova:
stimulací indukovaná kardiomyopatie, stimulace převodního systému, komorová dyssynchronie, ultra-vysoko frekvenční EKG, echokardiografie, metabolismus kolagenu

Acknowledgements:

Five years have passed by so quickly, and my studies are heading towards a finish line. I have met many inspiring people who have contributed to our work. First, I would like to mention my supervisor, mentor, and friend Karol Čurila. Your immersive energy and enthusiasm for research inspired me and encouraged me to pursue higher goals. Thank you for your patience and the time you spent on our projects, sometimes even until late at night. I am truly grateful, and I admire and appreciate your work.

My gratitude also belongs to all my colleagues at the hospital. Starting with the head of our cardiology department, Petr Toušek, who offered me a position in student research and brought me from a hockey locker room to academia. I also need to thank our dean, Prof. Petr Widimský, who supports research at our faculty and creates an excellent environment for researchers. Unfortunately, I cannot mention all my colleagues, but I respect each one of them for their work in the hospital.

I gained many experiences during my internships, and therefore, I would like to mention and thank the team of Pavel Jurak from the Institute of Scientific Instruments of the Czech Academy of Sciences for introducing me to the engineering aspect of cardiovascular science and showing me a different perspective. I must also mention my internship at the Cardiovascular Research Institute in Maastricht and thank Joost Lummens for the time that I was able to spend with biomedical engineers. I will forever keep the good memories of Maastricht and the friends I made there.

Finally, my greatest gratitude and love belong to my family, who supported me throughout the whole journey and gave me strength and motivation day after day, even when things did not look bright. Thank you Bára, Alice and Michaela.

Contents

1. List of abbreviations

3D – three-dimensional

AUC – area under curve

AV - atrioventricular

AVO – aortic valve opening

BBB – bundle branch block

BP – blood pressure

BPSM – body potential surface mapping

CAD – coronary artery disease

CMR – cardiac magnetic resonance

COVID – coronavirus disease

CRT – cardiac resynchronization therapy

CSP – conduction system pacing

CT – computed tomography

CZ – Czech Republic

DM – diabetes mellitus

DYS – dyssynchrony

ECG – electrocardiography

ECM – extracellular matrix

ELISA – enzyme-linked immunoassay

Fig. – figure

Gal-3 – Galectin 3

GCW – global constructive work

GE – General Electric

GLS – global longitudinal strain

GWE - global work efficiency

GWI – global work index

GWW – global wasted work

HB – his bundle

HBP – His bundle pacing

HF - heart failure

HV – his-ventricle

I^{123} MIBG – iodine-123 meta-iodobenzylguanidine

ICD – implantable cardioverter defibrillator

ID – identification

IVMD – interventricular mechanical delay

LAO – left anterior oblique projection

LBBB – left bundle branch block

LBBP – left bundle branch pacing

LK – levá komora

LTAT – left thorax activation times

LV – left ventricle

LVEDV – left ventricular end-diastolic volume

LVEF – left ventricular ejection fraction

LVESV – left ventricular end-systolic volume

LVLW – left ventricular lateral wall

LVLWd – left ventricular lateral wall delay

LVOT – left ventricular outflow tract

LVSP – left ventricular septal pacing

LVTAT – LV total activation time

M.D. – Doctor of Medicine

M.Sc. – Master of Sciences

MA – Massachusetts

MMP-9 – matrix metalloproteinase-9

MN –Minnesota

MRI – magnetic resonance imaging

MW – myocardial work

NIVCD – non-specific intraventricular conduction delay

NYHA – New York Health Association

PEP – pre-ejection period

Ph.D. – Doctor of Philosophy

PICM – pacing-induced cardiomyopathy

PPM - permanent pacemaker

Prof. – professor

Q1 – 1st quartile

Q3 – 2nd quartile

RAO – right anterior oblique projection

RBB – right bundle branch

RBBB – right bundle branch block

ROC – receiver operating characteristics

RV – right ventricle

RVLW – right ventricular lateral wall

RVLWd – right ventricular later wall delay

RVOT – right ventricular outflow tract

RVP – right ventricular myocardial pacing

SD – standard deviation

SDAT – standard deviation of activation times

ST2 – suppression of tumorigenicity 2 interleukin

TAT – total activation time

TDI – tissue Doppler imaging

TGF-β1 – transforming growth factor β1

TIMP-1 – tissue inhibitor of metalloproteinase-1

UHF – ultra-high frequency

USA – United States of America

VEU – ventricular electrical uncoupling

2. Background

2.1. Permanent pacemakers

Permanent cardiac pacing is now a standard, reliable, and widely available method of treating bradycardia.[1] It is a worldwide, guidelines-supported treatment for bradycardia symptoms, suitable for the full spectrum of conduction disorders, including sinus node disease and atrioventricular (AV) node disease.[2,3] Since the first permanent pacemaker (PPM) was implanted in 1958 by thoracic surgeon Åke Senning and engineer Rune Elmquist, cardiac pacing has undergone a dynamic technological revolution.[4]

Pacemaker and lead technology has developed rapidly, and modern pacemakers are now automatic and more reliable. Pacemakers got smaller and were programmed to detect underlying cardiac activity and deliver pacing only when needed. Epicardial leads have been replaced by transvenous leads, and the feasibility of leadless pacemakers is currently being studied intensively.[5] In addition to single-chamber and dual-chamber pacemakers used for bradycardia treatment, the concept of cardiac resynchronization therapy (CRT) emerged in the 1990s, and biventricular pacemakers were introduced for the treatment of heart failure (HF) and ventricular dyssynchrony.[6]

However, the increased life expectancy of the ever-growing elderly population has led to increased rates of PPM implantation,[7] and new challenges in the management of bradycardia have arisen as the evidence of harmful effects of right ventricular (RV) myocardial pacing has emerged.[7] This has prompted further efforts to achieve a more physiological approach with conduction system pacing (CSP).

2.2. Pacing-induced cardiomyopathy – definition and prevalence

Although PPMs have brought indisputable benefits to patients with symptomatic bradycardia, the constantly rising standards of patient well-being and better patient follow-up have revealed patients who do not tolerate conventional right ventricular pacing (RVP) well.[8–15] Some of these patients may develop a decline in left ventricular (LV) ejection fraction (LVEF) after pacing. This condition has been defined as pacing-induced cardiomyopathy (PICM). In the current literature, there are several working sets

of diagnostic criteria for identifying PICM, primarily based on changes in the LVEF - Table 1. Some studies also included different percentages of RV pacing in the definition.[16] In the author's review of published research, these were the four most common definitions of PICM based on LVEF:

1. Decreased LVEF by 10 % or more or below 50 % without regard to patient symptoms.[13,17]
2. Decreased LVEF below 45 % or a decline in LVEF that is greater than 10 % [18]
3. Decreased LVEF below 40 % or an indication to CRT upgrade.[12]
4. Decreased LVEF by 5 % or more with HF symptoms without any other etiology of HF.[19]

According to the recent meta-analysis performed by Somma et al., including 18 studies (both prospective and retrospective data), the PICM prevalence ranged from 6 % - 25 %, with an overall pooled prevalence of 12 % in the time range from 1 month to 16.9 years.[16] This wide range in prevalence is associated with (1) differences in PICM definitions, (2) the variability of the studied populations, (3) the variable lengths of follow-up, and (4) RV pacing percentage.[20] Moreover, there is a rising awareness that in some patients, permanent RV pacing can lead to symptoms of heart failure (HF) without significant changes in LVEF, a condition called PICM syndrome.[21] As shown recently, HF can often appear on a time scale of months, not years, after PPM implantation. A Danish national registry-based study including almost 28,000 patients undergoing PPM implantation found that nearly 11 % of patients manifested with HF. This was significantly more than in the control group of patients without PPM, and most of these events occurred within six months of PPM implantation.[15]

Study	Patients (n)	PICM Definition	Average follow-up (years)	PICM incidence	Risk factors for PICM development
Khurshid et al. 2014[13]	257	Decrease of the LVEF ≥ 10% resulting in LVEF < 50%	3,3	20%	Male gender, prolonged spontaneous QRSd, prolonged paced QRSd
Kim et al. 2018[17]	130	Decrease of the LVEF ≥ 10%, with a resultant LVEF < 50%	4.7	16%	Paced QRSd
Kiehl et al.2016[12]	823	Resultant LVEF ≤ 40% or CRT upgrade	4.3	12%	Lower baseline LVEF and ≥ 20% ventricular pacing burden.
Lee et al. 2016[19]	234	LVEF decrease > 5% with symptoms of HF without other etiology for HF	15,6	21%	Higher ventricular pacing burden Old age Prolonged paced QRSd Higher myocardial scar score
Kaye et al.2018[20]	118	Definition 1: Resultant LVEF ≤ 40% if baseline LVEF was ≥ 50% or an absolute reduction of the LVEF ≥ 5% if baseline LVEF was < 50% Definition 2: Resultant LVEF ≤ 40% if baseline LVEF was ≥ 50%, or an absolute reduction of the LVEF ≥ 10% if baseline LVEF was ≤ 50% Definition 3: An absolute reduction of the LVEF ≥ 10% irrespective of baseline LVEF	3,5	Definition 1: 9% Definition 2: 6% Definition 3: 39%	Higher ventricular pacing burden

Table 1 - Pacing-induced cardiomyopathy definitions and incidence.

2.3. Pathophysiology of pacing-induced cardiomyopathy

Physiological heart activation preserves AV, interventricular, and LV/RV intraventricular conduction via the heart's conduction system. This mechanism preserves the AV synchrony and synchronous ventricular contraction. RV pacing bypasses the physiological pathway, leading to slow myocyte-to-myocyte signal transmission, with a single electrical breakthrough in the RV apex or septum (depending on the stimulation site). The velocity of electrical signal transmission in Purkinje fibers varies between 2–4

m s^{-1}, as opposed to 0.4–0.8 m s^{-1} in ventricular muscle cells.[22] This results in disproportional RV, but most importantly, LV mechanical and electrical activation with the initial depolarization occurring at the pacing site followed by delayed depolarization of the remote LV segments.[23] These consequences of RV pacing are generally regarded as electro-mechanical ventricular dyssynchrony. Different types of ventricular dyssynchrony are recognizable, i.e., interventricular (between RV and LV) and intraventricular (within RV and LV) electro-mechanical dyssynchrony. Intraventricular LV dyssynchrony is understood as a delay of activation between the various LV segments. Depending on our diagnostic tool, we sometimes refer to dyssynchrony as either electrical (ECG-based) or mechanical. The mechanical ventricular dyssynchrony can be assessed using echocardiography, cardiac magnetic resonance (CMR), or scintigraphy.[24,25] Echocardiographic dyssynchrony assessment offers a wide variety of different tools, allowing both intraventricular and interventricular quantitative and qualitative dyssynchrony assessment. These include pulsed-wave (PW) Doppler imaging, tissue Doppler imaging (TDI), 2-dimensional radial or longitudinal speckle-tracking strain analysis, myocardial work, real-time-3-dimensional (3D) echocardiography and visual assessment of apical rocking and septal flashing.[26–34] Both electrical and mechanical dyssynchrony assessment tools are discussed in detail further in the chapter regarding dyssynchrony assessment tools.

The relationship between LV dyssynchrony and RV apical pacing in humans was first shown in 2006 by Tops et al. in patients with atrial fibrillation treated with PPM implantation and subsequent AV nodal ablation. In this study, LV dyssynchrony, measured using echocardiography and TDI, developed in almost 50% of patients after a mean follow-up of 3.8 years. Patients with LV dyssynchrony had a significant decline in the LVEF and worsened NYHA scores, whereas in patients without LV dyssynchrony, the LVEF remained unchanged, and the NYHA score improved.[35] As was shown soon after, RV apical pacing results in dyssynchronous LV contractions immediately after the start of pacing, even in patients with structurally normal hearts.[36] The presence of mechanical ventricular dyssynchrony, caused by RV pacing, was identified as the critical determinant of the detrimental effect of RV pacing on LV function.[29,37–39]

After time, the disproportionally delayed activation sequence of the individual LV segments leads to structural alteration and asymmetrical remodeling of the ventricles.

Early activated septum and late activated LV lateral wall cause asymmetrical workloads for the myocardium, specifically less workload for the septum and increased workload for the lateral wall. (Fig.1 and 2) This is followed by thinning of the septum and hypertrophy of the late-activated LV lateral wall segments.[40]

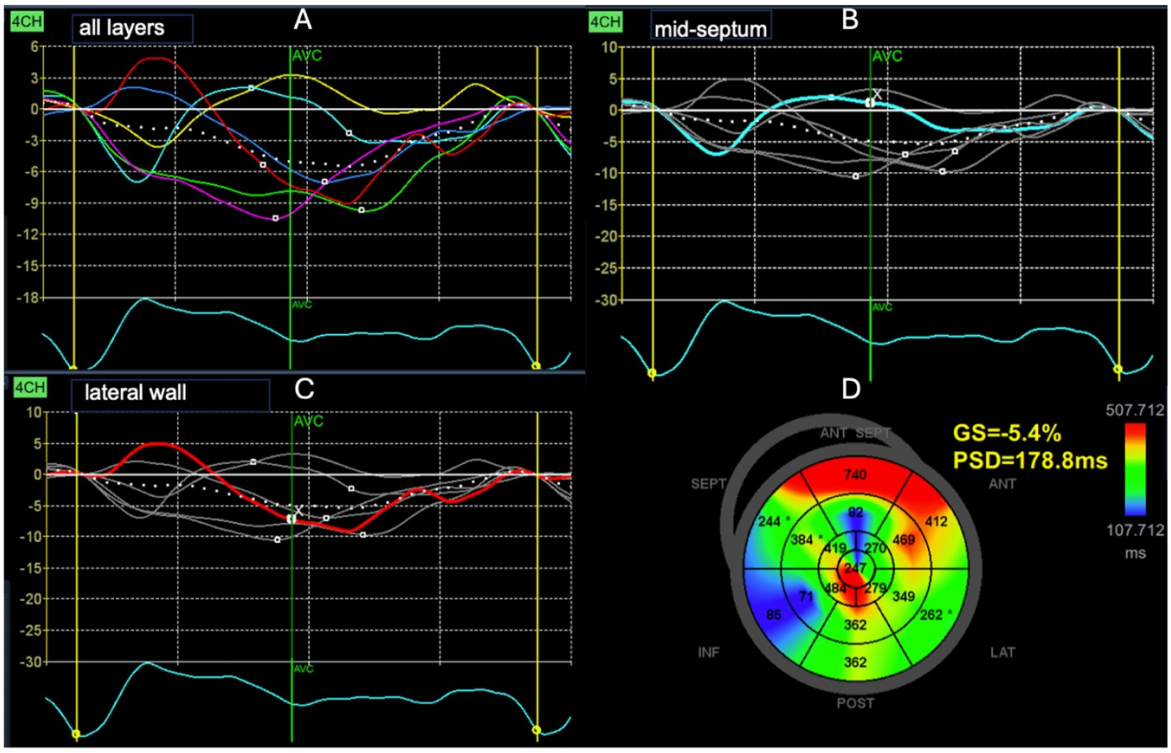

Figure 1 - Illustrative LV time to peak strain analysis of a patient with RV pacing and ventricular dyssynchrony. Panel A - All strain layers showing dyssynchronous activation. Panel B - Mid-septum strain (blue curve) with typical early activation; Panel C - Lateral wall strain (red curve) with a typical passive pre-stretch and late activation. Panel D - bull's–-eye plot with all regional time to peak strain values. GS = global strain, PSD = peak strain dispersion. Generated using EchoPAC Software only, version 206, GE Vingmed Ultrasound, Horten, Norway.

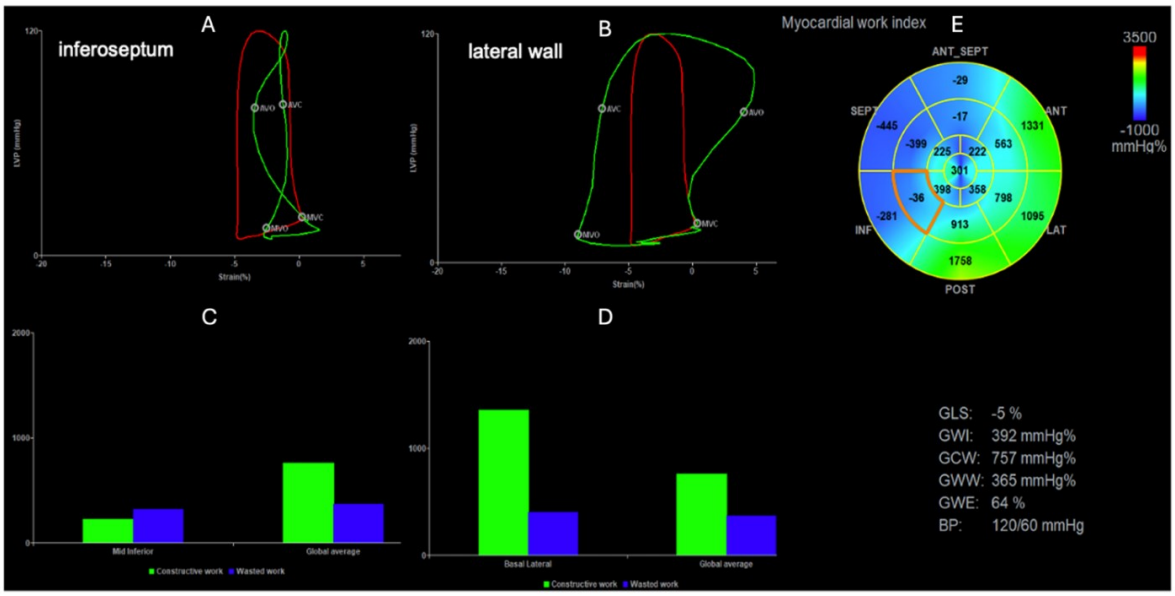

Figure 2 - Illustrative LV pressure–strain loop and myocardial work analysis in a patient with RV pacing and dyssynchronous contractions. Panels A and B show the pressure–strain loops, the area of which corresponds to the myocardial work index. The red profile shows the global myocardial work with normal clockwise looping but reduced global myocardial work. In panel A, the green profile depicts the LV mid-inferoseptal segment, showing counterclockwise looping. In panel B, the green profile depicts the LV lateral wall with normal clockwise looping and an enlarged area. The C and D panels show the relative extent of constructive work (green bars) and wasted work (blue bars), illustrating a high amount of wasted work and low amount of constructive work in the mid–inferoseptal segment (panel C) and increased constructive work for LV lateral wall (panel D). Panel E shows a bull's–eye plot with all regional myocardial work estimates - global longitudinal strain (GLS), global work index (GWI), global constructive work (GCW), global wasted work (GWW), global work efficiency (GWE) and blood pressure (BP). Generated using EchoPAC Software only, version 206, GE Vingmed Ultrasound, Horten, Norway.

It had been reported that the efficiency of the cardiac pump (the amount of stroke work generated by a unit of oxygen consumed) is approximately 30% lower in dyssynchronous compared to synchronous hearts.[41] As a result of non-physiological RV pacing, changes in ventricular blood perfusion, neuro-humoral innervation, and fatty acid metabolism have also been observed.

Dyssynchrony results in changes in local myocardium oxygen demand. Different effective workloads of particular ventricular segments cause changes in segmental myocardial perfusion and regional myocardial perfusion defects, even in the absence of coronary artery disease (CAD).[42,43] Moreover, cardiac pacing has been associated with increased noradrenaline levels in myocardial tissue; and in clinical research, early activated LV segments were associated with a redistribution of sympathetic activity that resulted in regional LV defects of ^{123}I-MIBG uptake.[44,45]

Altered myocardial metabolism can also contribute to myofibrillar disarray and changes in cardiac extracellular matrix (ECM) metabolism, resulting in fibrotic tissue formation. Adomian et al. identified myofibrillar disarray in 9 out of 12 canine hearts after three months of RV apical pacing.[46] Similar observations were confirmed in a clinical study of histological changes following RV pacing in humans. In this study, chronic RV pacing led to myofibrillar hypertrophy, fatty depositions, and an increased rate of cardiac interstitial fibrosis.[47]

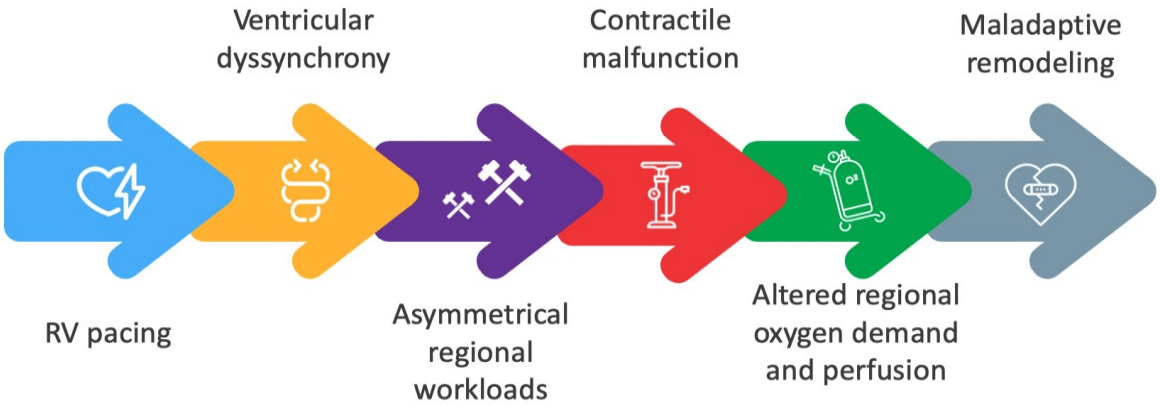

Figure 3 – Author´s schematic overview of the pathophysiology of PICM.

2.4. Potential role of selected laboratory biomarkers of ECM metabolism and fibrosis in pacing-induced cardiomyopathy

Biomarker is an objectively measurable parameter that indicates normal or pathological processes in living organisms. This chapter will focus on selected laboratory biomarkers with proven involvement in cardiovascular pathophysiology associated with ECM metabolism and fibrosis and their potential influence on PICM. Based on the previously mentioned pathophysiology of ventricular dyssynchrony, these biomarkers may play an important role in maladaptive ventricular remodeling following RV pacing.

Cardiac ECM is a sophisticated micro-environment that maintains the structural and functional integrity of the heart. It consists of a complex architectural network of structural (fibrillar collagen) and non-structural components (proteoglycans, glycoproteins, and glycosaminoglycans).[48] It regulates cardiomyocyte contractility through endomysium-myocyte coupling and calcium cycling.[49] It also directs micro-RNA expression, which is necessary for the synchronized continuous relaxation and contraction cycle of the heart. Furthermore, it provides a framework for the differentiation of cardiac progenitor cells, and ECM elasticity plays a pivotal role in lineage specification and heart self-renewal capacity.[50]

The continuous degradation of collagen and other proteins is executed by matrix-metalloproteinases (MMPs) and regulated by tissue inhibitor metalloproteinases (TIMPs). MMPs are a family of zinc-containing calcium-dependent endopeptidases (e.g., MMP-1, MMP-2, MMP-9, etc.) further divided into groups based on the substrate specificity.[51] TIMPs are specific inhibitors of MMPs in the tissue compartment. Four TIMPs have been identified in vertebrae (TIMP-1, TIMP-2, TIMP-3, TIMP-4). Balance between TIMPs and MMPs is essential for the proper ECM function and structure integrity.[50]

Disruption in constant remodeling of heart ECM plays a crucial role in HF development. Both sera and tissue concentration of MMP-9 and TIMP-1 are elevated in patients with HF (irrespective of the underlying condition) compared to healthy controls and higher sera levels of TIMP-1 and MMP-9 were associated with poor prognosis among HF patients.[52–54] Ablation of MMP-9 decreases cardiac fibrosis (collagen accumulation) and enhances survival and differentiation of cardiac stem cells in the heart of mice.[55]

RV apical pacing in dogs was associated with asymmetrical hypertrophy of the late-activated lateral wall segments and led to ECM remodeling and overexpression of the collagen type II gene. Additionally, the lateral wall exhibited increased amounts of matrix-metalloproteinases (MMP), MMP-2, MMP-9, TIMP-1, and tissue inhibitor metalloproteinases 3 (TIMP-3) expression.[56] MMP-9 and TIMP-1 concentrations were not studied in the human bradycardia population. However, based on current knowledge, they might provide useful information related to maladaptive ventricular remodeling caused by RV pacing.

Transforming growth factor (TGF) – βs are pleiotropic peptide growth factors with a crucial role in the regulation of inflammation, ECM deposition, cell growth, differentiation, and repair. Three isoforms of TGF- β have been identified in mammals (TGF-β 1,2,3), while TGF-β1 is the most prevalent isoform.[57]

TGF-β1 expression generally increases in tissue injury, repair, and scar formation. Induction of myocardial TGF-β1 expression has been proven in animal models of LV pressure overload, myocardial infarction, and angiotensin II infusion.[58] TGF-β signaling is highly complex and depends on a specific pathway. On one hand, it may promote collagen deposition and interstitial fibrosis, and the other way around, it may also promote cardiomyocyte apoptosis and hypertrophy, while both of these processes are crucial for myocardial scar formation.[59] The Importance of TGF-β signaling was intensively studied in animal models of CAD, where it was referred to as a "Master Switch" of cardiac fibrogenesis, as it may promote the transition from an inflammatory stage to a scar formation in an infarcted heart.[60]

Moreover, TGF-β1 was further studied in HF and cardiomyopathies with interesting conclusions. Patients with chronic HF have higher serum levels of TGF-β1 compared to healthy matched controls. Moreover, sera levels of TGF-β1 correlate with NYHA class.[61] Elevated myocardial and sera levels of TGF-β1 were also found in patients with DCMP and HCM and higher sera levels of TGF-β1 were positively associated with left ventricular mass in hypertensive patients.[62,63]

Due to the association of TGF- β1 and ventricular remodeling, clinical studies have been performed on the CRT population. It was shown that TGF- β1 serum levels are higher in CRT non-responders compared to responders. Multivariate analysis revealed that higher TGF-β1 levels before CRT administration were an independent predictor of death during the two years of follow-up.[64]

Progression of HF is closely related to systemic inflammatory response, which may even enhance heart damage. Non-surprisingly a high number of inflammatory markers have been studied in association with new heart failure onset prediction, prognosis, stratification, and even as a therapeutical target.[65] Galectin-3 (Gal-3) is a pleiotropic protein from the lectin family, which are beta-galactoside binding proteins. It is expressed in a broad spectrum of human tissues, including all types of immune cells. It participates

in cardiac remodeling and fibrosis by activating macrophages and fibroblasts. Therefore, it is sometimes referred to as a link between fibrosis and inflammation.[51]

Higher sera levels of Gal-3 were associated with increased risk of new HF development and all-cause mortality in the general population and Framingham Offspring Cohort (mean age 59 years, 53 % women).[66,67] Furthermore, Gal-3 has shown potential utility for the diagnosis of acute HF and short-term prognosis estimation. Kimmenade et al. showed that in patients presenting with dyspnea at the emergency department, Gal-3 levels were higher in those with HF compared to those without HF. In HF patients, Gal-3 was superior to NT-proBNP in 60-day mortality prediction (AUC 0.74, $p = 0.0001$). In multivariate logistic regression, elevated levels of Gal-3 were the strongest predictor of 60-day mortality (OR 10.3, $p < 0.01$) and of the combination of death and recurrent HF within 60 days (OR 14.3, $p < 0.001$).[68]

Gal-3 was approved by the American Food and Drug Administration, and guidelines support its use as a prognostic biomarker for patients with HF. Moreover, in patients with HF with preserved ejection fraction (HFpEF), higher Gal-3 levels were positively associated with higher LV stiffness and severity of LV diastolic dysfunction in both human and animal models.[69–71] Gal-3 and fibrosis on CMR were also studied in the cardiac resynchronization therapy (CRT) population. It was shown that higher pre-implant Gal-3 and LGE levels were negatively associated with response to cardiac resynchronization therapy, and higher Gal-3 levels correlated with higher levels of myocardial fibrosis in ventricular myocardium on preimplant CMR.[72] Based on previously mentioned studies, we believe that elevated Gal-3 levels and increased cardiac fibrosis may also be risk factors for PICM development; however, this has never been studied before.

On the other hand, there were also studies with conflicting results.[73] This showed an important fact that Gal-3 is neither a cardiac-specific biomarker nor a cardiac-specific protein. Therefore, it also reflects other pathologies linked with inflammation and fibrosis, e.g., end-stage kidney disease, pulmonic disease, and sepsis.[74–77] Gal-3 levels are gender-related; they are higher in women compared to men.[67]

Another potential biomarker for identifying patients prone to adverse cardiac remodeling could be the suppression of tumorigenicity-2 interleukin (ST2). ST2 is part of the Zoll-

like/Interleukin-1 receptor superfamily. It is expressed in hematopoietic organs in two isoforms: (I) a soluble isoform (further mentioned as ST2) and (II) a transmembrane form referred to as ST2 ligand (ST2L).[78] ST2 has a natural ligand identified as IRL-33. The IRL-33/ST2L plays a protective role for myocardium under mechanical strain as it prevents excessive cardiac hypertrophy and fibrosis. On the contrary, ST2 reduces the protective effect of the IRL-33/ST2L signaling pathway by binding to free IRL-33.

ST2 is overexpressed under conditions of myocardial stress, overload, and injury, and it is connected to fibrogenesis and immune and inflammatory response.[79–81] Higher sera levels of ST2 correlated with larger LV end-systolic volumes, worse LV and RV systolic function and higher long-term mortality in the PRIDE study (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) in patients with acute dyspnea.[82] Regarding chronic HF, a relatively recent meta-analysis (including seven trials and 6372 patients with HF) affirms the ST2 importance for prognostication. ST2 had an HR of 1.75 (95% CI 1.37–2.22) for all-cause death and 1.79 (95% CI: 1.22–2.63) for CV death (both P<.001).[83]

Due to robust evidence as a prognostic biomarker in both chronic and acute HF, ST2 gained a position in the 2013 AHA guidelines for risk assessment in these settings.[84] ST2 was also studied in the MADIT-CRT trial, where higher ST2 sera concentrations predicted cardiac death, and serial evaluation of ST2 predicted subsequent risk for ventricular arrhythmias in patients with mild symptoms of HF eligible for CRT.[85] Another benefit is that unlike natriuretic peptides, ST2 levels are less affected by age, BMI, gender, and renal functions.[86] However, the potential of ST2 in risk-stratification of bradycardia patients remained unknown until now.

2.5. Risk factors for pacing-induced cardiomyopathy development and tools for ventricular dyssynchrony assessment

There are known risk factors for PICM development in patients with frequent RV pacing, i.e., decreased pre-implant LVEF, older age, coronary artery disease (CAD), and wide spontaneous or paced QRS durations (QRSd). According to the latest research, the potentially harmful burden of RV pacing is even lower (around 20%) than previously suggested by results from the MOST trial.[10,12,19,20] The major problem in relying on these

risk factors is their limited predictive value; therefore, new, and better methods for PICM risk assessment are needed.

Echocardiography

LV systolic performance stands in the center of PICM definition, and measurement of the LVEF is the first-line tool for a systolic function assessment. A retrospective study by Kiehl et al. on bradycardia patients receiving RV pacing even showed that patients with lower pre-implant LVEF are more prone to PICM development.[12] Even though LVEF is the most widespread tool for LV systolic performance assessment, there are concerns about its limitations: (1) it is volume-derived and therefore load-dependent parameter which leads to lower reproducibility; (2) it is dependent on LV geometrical changes and does not reflect true LV contractility; (3) there is evidence that LVEF is poorly sensitive to slowly declining LV systolic function.[87]

These limitations led to prompted adoption of LV GLS into clinical practice as an alternative or support to LVEF. Speckle-tracking derived global longitudinal strain is a semi-automated method that decreases the intra- and inter-individual variability of myocardial performance assessment.[88,89] Moreover, GLS is more sensitive to subtle changes in LV function, which allows early identification of subclinical disease.[90] As shown by Ahmad et al., in patients with RV pacing, LV function measured using GLS deteriorates much sooner than when it is measured using LVEF. Furthermore, the study showed that GLS declines as soon as one month after the start of RV septal pacing. The same patients with worsening GLS later declined in the LVEF of $\geq$ 5% during the 12-month follow-up. In this study, lower GLS values were an independent predictor of an LVEF decline during follow-up.[31] Even though GLS improved LV function assessment, several studies demonstrated that it is a loading-dependent parameter; therefore, it is influenced by pre-load and after-load.

On the other hand, myocardial work (MW) by echocardiography is a new method incorporating myocardial strain and LV pressure (non-invasively derived from brachial blood pressure measurement). This provides loading-independent information about myocardial performance and allows both a general assessment of myocardial work and a segmental assessment of the LV. While the indices of global LV MW such as global work index (GWI) or global constructive work (GCW) correlate well with LVEF and GLS,

indices of segmental MW may also serve for mechanical LV dyssynchrony assessment in bradycardia patients.[91–93] Example of GLS and MW indices in a patient with RV myocardial pacing is shown in Fig. 4. Mao et al. have shown that in bradycardia patients LBBP preserves lower LV dyssynchrony than RV pacing using lateral wall to septal wall MW difference, and that this parameter also correlates with negative LV adverse remodeling and LV dysfunction induced by RV pacing.[94]

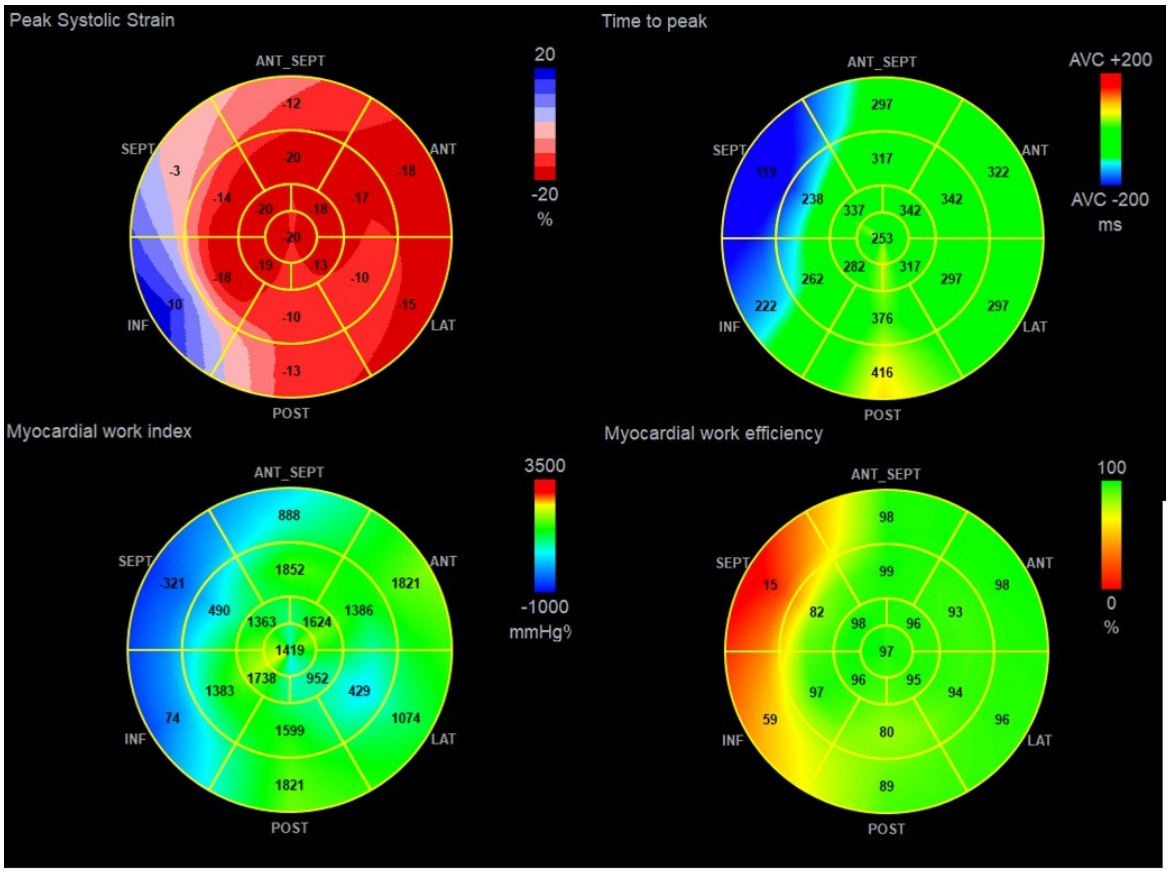

Figure 4 - Bull's eyes of a patient with RV myocardial pacing and mildly decreased LVEF. In septal segments, we can observe low peak systolic strain values, negative myocardial work index, and low myocardial work efficiency compared to the lateral wall. Generated using EchoPAC Software only, version 206, GE Vingmed Ultrasound, Horten, Norway

Echocardiography can also express interventricular dyssynchrony. The most frequently used approach is interventricular mechanical delay (IVMD), also known as aortopulmonary ejection delay. It is an equivalent of interventricular mechanical dyssynchrony, and it can be measured using pulsed waved Doppler echocardiographic imaging as a time difference between LV pre-ejection period (time from QRS onset to aortic valve opening) and RV pre-ejection period (time from QRS onset to pulmonic valve opening).[27,28] IVMD was assessed as a risk factor for PICM in patients with RV pacing in

the study published by Bansal et al. This group demonstrated that patients with a significant aortopulmonary ejection delay (> 40 ms) were more prone to a decrease in the LVEF than patients with lower IVMD. Multivariate analysis showed that significant interventricular dyssynchrony and a high burden of RV pacing were the only predictors of an LVEF decrease >10% in this study.[29]

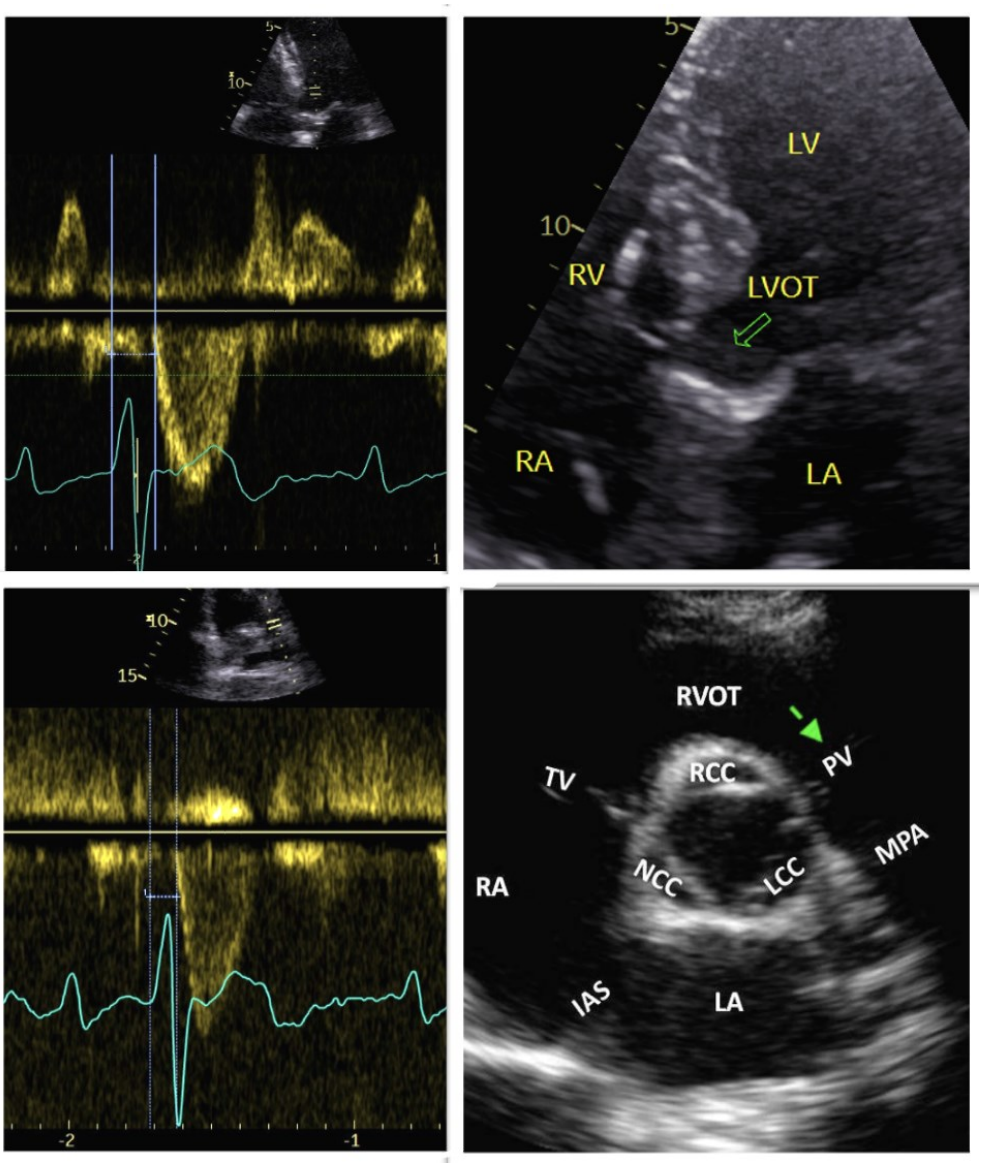

Figure 5. IVMD calculation A - LV-PEP measured from QRS onset to onset of trans-aortic flow; B - LVOT in apical 5 chamber view; C - RV-PEP measured from QRS onset to onset of trans-pulmonic flow; D - RVOT in parasternal short axis view.

As mentioned above, ventricular dyssynchrony and LV performance after pacemaker implantation can be readily assessed using echocardiography in very detailed approaches.

Echocardiography has been shown to better identify patients at the highest risk of developing PICM than other ECG and clinical parameters.[29,95]

However, it is important to mention the limitations as well. All the methods discussed above are either fully manual or only semi-automatic; they require time and experienced and trained specialists in cardiac imaging. Therefore, there will always be limited reproducibility and inter and intraindividual variability. Another major limitation is that in some patients, it is impossible even for trained specialists to acquire images of sufficient quality and to use advanced tools such as GLS or MW. Moreover, its use during the implant procedures is unfeasible in routine clinical practice, and therefore, they cannot be used as guidance during pacemaker implantations to detect non-physiological pacing.

ECG-based methods

The traditional tool for non-invasive dyssynchrony assessment has been the surface 12-lead electrocardiogram (ECG). The most often used parameter of synchronous ventricular activation is QRSd. It can be easily measured during implantation procedures, and for this reason, it appears to be an ideal parameter for ventricular dyssynchrony assessment. Although it was shown in some studies that a wider paced QRSd is an independent predictor for PICM development,[13,17,19] it was not confirmed in other studies.[12,29,95]

Its major limitation is that conventional ECG only visualizes the combined depolarization of both ventricles without the ability to assess their separate activation.[96] QRS morphology offers more insight into ventricular activation patterns; however, this assessment is subject to significant error. Additionally, several different definitions of LBBB have been introduced, and even the latest 2021 European Society of Cardiology definition of LBBB did not lead to better applicability in clinical praxis.[97,98]

Another ECG-based parameter of dyssynchrony is the QRS area (QRSa).[99] It is derived from orthogonal chest leads or calculated from a standard surface 12-lead ECG and converted to 3D vectorcardiography – Fig. 6.[100] The QRSa is an easily obtainable, reproducible parameter, which can be automatically calculated.[101] Large QRS areas have been positively associated with volumetric responses to cardiac resynchronization therapy (CRT) and are superior in predicting CRT responses over QRSd or QRS morphologies.[102] In CRT patients, a decrease in the QRSa was an independent predictor

of survival and reverse cardiac remodeling, especially in patients with larger baseline QRSa.[103] Also, in CRT patients, QRSa was shown to correlate better with LV lateral wall activation delay, measured by invasive electro-anatomical mapping, than did QRSd or QRS morphology.[104] In patients with bradycardia, QRSa was studied and compared during RV septal, deep septal, and left bundle branch area pacing.[104] Unfortunately, it had never been studied and compared in patients with various types of RV pacing.

Electrocardiographic imaging (ECGi) is a complex, non-invasive imaging tool based on body surface potential mapping (BSPM). It reconstructs electro-anatomical epicardial activation from a combination of approximately 240 surface electrodes and computed tomography (CT) acquired heart-torso geometry – Fig. 6. It creates over 2,500 epicardial unipolar electrocardiograms. From these, a variety of interventricular, as well as LV or RV dyssynchrony parameters can be calculated.[105] These are, for example: (1) ventricular electrical uncoupling (VEU), which is the difference between mean LV and RV activation times and thus, is an interventricular dyssynchrony parameter, (2) LV total activation time (LVTAT) or (3) the difference between the maximum and minimum activation times - total activation time (TAT) can be obtained.

It was used primarily in patients with heart failure and various types of ventricular conduction disorders or RV apical pacing.[106] These studies showed that the method provides detailed information about ventricular depolarization patterns and predicts the response of these patients to biventricular resynchronization therapy.[48,49] No study used ECGi to show the differences between various types of pacing in bradycardia patients or PICM prediction.

The ECG belt (Medtronic, Minneapolis, MN, USA) is a simplified BSPM system consisting of 40 body surface electrodes, which do not require a CT or MRI scan for dyssynchrony assessment. The data are processed offline and generate color-coded isochronal maps from the anterior and posterior chest view – Fig. 6. The most often used dyssynchrony parameters derived from the ECG belt are the standard deviation of activation times (SDAT) and left thorax activation times (LTAT). These parameters have been shown to be predictive of CRT response[107] and useful for optimizing CRT therapy.[108] Compared to ECGi, the method is less expensive, less time-consuming, and easier to operate, which enables its use during implant procedures. However, the need for

additional chest leads and the complexity of visualization of ventricular depolarization patterns make it less applicable in standard clinical care.

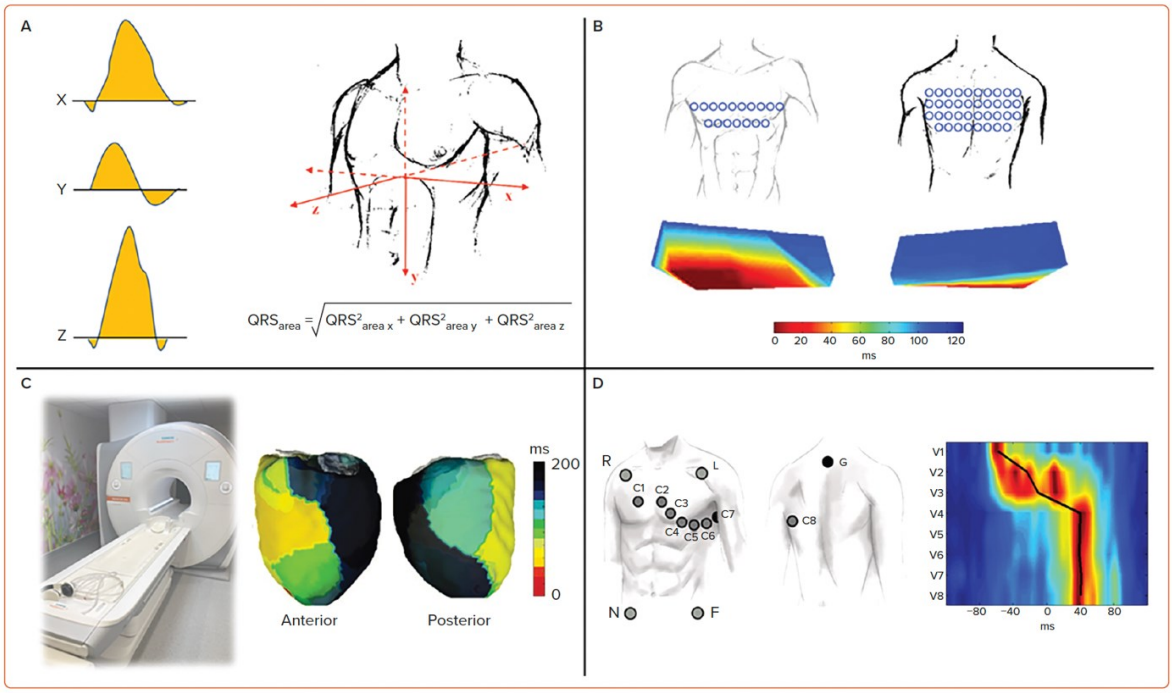

Figure 6 - Panel A – Schematic demonstration of QRSa calculation from orthogonal ECG leads; Panel B – Visualization of ventricular depolarization using ECG belt in patient with LBBB; Panel C – Visualization of ventricular depolarization using ECGi in patients with LBBB; Panel D Visualization of ventricular depolarization using UHF-ECG in patient with LBBB

Ventricular activation patterns and dyssynchrony parameters can also be derived from the UHF-ECG. It displays the ventricular activation sequence using an analysis of the ultra-high frequency components of ventricular myocyte action potentials in peri-myocardial tissue.[109,110] The ventricular activation sequence under standard chest leads (V1-V6 or V1-V8 configuration) is displayed in depolarization maps, usually in 1–3 minutes, making the method suitable for clinical practice.

The broad-band QRS complex is constructed as the average of the 16 normalized median amplitude envelopes of the 16 frequency bands (150-1000 Hz) and displayed as a colored map for chest leads. The local activation times under each of the used chest leads are calculated as the center of mass of the UHF-QRS above the 50 percent threshold of the baseline-to-peak amplitude for each chest lead. The parameter of LV electrical dyssynchrony, i.e., e-DYS, is calculated using the time difference between the first and

last local activation. Additional and more specific parameters, such as RV or LV lateral wall activation delay (RVLWd or LVLWd) as a distance from the first activated center of mass to V1 and V8, respectively, can be calculated in milliseconds (ms) – Fig. 7.

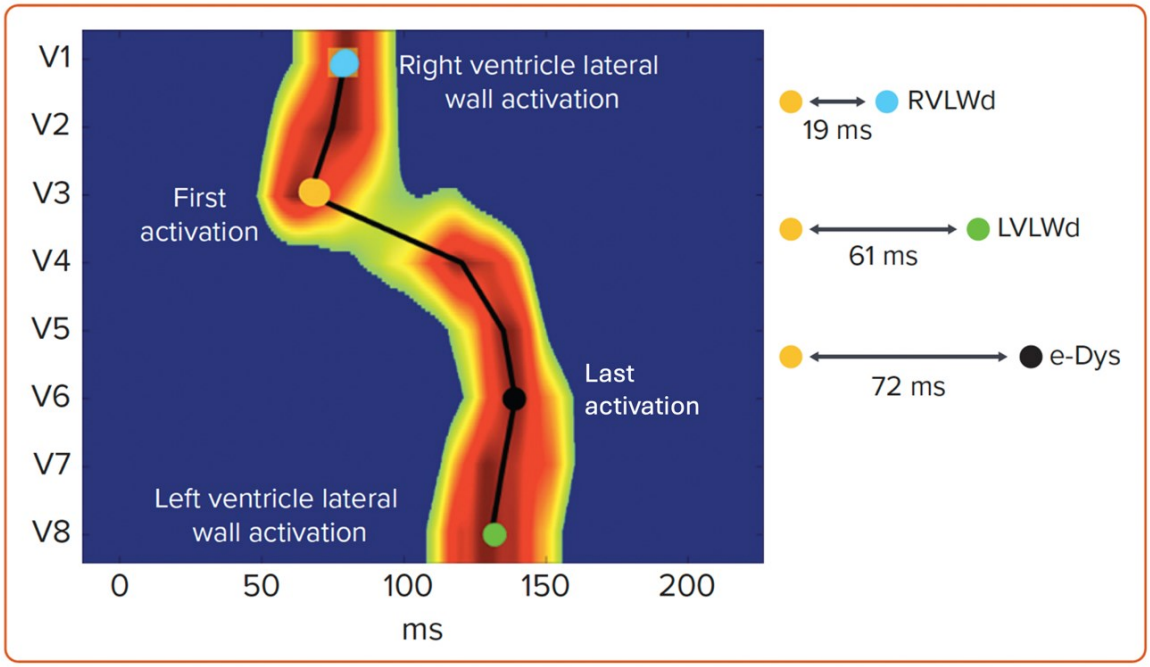

Figure 7 Ultra-high-frequency ECG map of a patient with right ventricular septal pacing. The calculation of parameter e-DYS (delay from the first activated lead to the latest), RVLWd (delay from the first activated lead to V1), and LVLWd (delay from the first activated lead to V8) are shown.

In recent years, our group has been studying electrical ventricular dyssynchrony using UHG-ECG in pacemaker patients. Both CSP and RV pacing were investigated in detail. We discovered that HBP is the most physiological method of ventricular pacing in bradycardia patients, and all other pacing techniques lead to the increase of ventricular electrical dyssynchrony.[111] It was shown that significant differences in RV and LV activation delays were present during pacing from the basal septum with myocardial and His bundle or proximal right bundle branch engagement (nsHB or RBBP), the pacing of the RV septum with pure myocardial capture, the pacing of the RV apex, and pacing of the RV anterior or RV lateral wall – Fig. 8.[112]

The shortest LVLWd was observed during nsHB or RBBp, while the longest LVLWd was observed during RV anterior and RV lateral wall pacing. LVLWd during RV septal and apical pacing was similar, although the latter caused a much longer QRSd.

Septal pacing of the RV inflow tract caused a significantly shorter LVLWd than the pacing of septal myocytes in the RV outflow tract, during which LVLWd values were very similar to values seen during RV apical pacing. Interestingly, RV apical capture was the only studied capture type that caused significant RV activation delays.

Measured variations in the RV and LV activation delay could be explained by differences between pacing locations and the character of the electrical wavefront propagation in both ventricles. When the velocity of depolarization wavefront propagation was measured in the leads placed above the LV lateral wall, it was found to be similar during RV apical, anterior, and lateral wall pacing, and all were significantly longer compared to RV septal pacing. This is likely a result of different types of electrical wave-front propagation. During RV septal pacing, the LV Purkinje system is utilized to activate LV lateral segments; however, during RV apical, anterior, and lateral wall pacing, slow myocardial cell-to-cell propagation plays a more significant role.

Although the averaged values showed significant differences between RV pacing sites, a closer review of the data revealed significant individual variability between the patients included in the study (data not published). There were patients with minimal LV and RV lateral wall delays during RV apical or RV septal pacing, but there were others in which pacing the same locations resulted in much greater ventricular dyssynchrony.

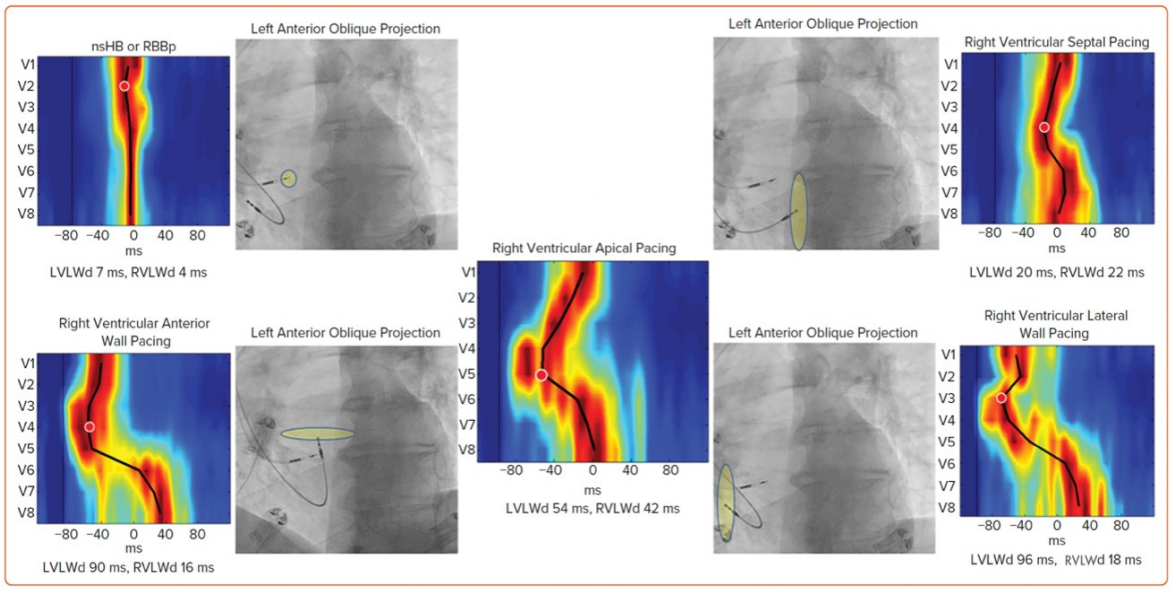

Figure 8 - Pacing locations and representative UHF-ECG maps for nsHB, RV septal pacing, RV apical pacing, RV anterior wall pacing, and RV lateral wall pacing. All myocardial captures of the RV produced more significant LVLWd and RVLWd than nsHB.

More recently, LBBP and LVSP were investigated using UHF-ECG. It was shown that both methods lead to some left-to-right ventricular activation delay (delayed activation under lead V1).[113] LBBP compared to HBP produced more interventricular dyssynchrony while preserving the same LV lateral wall activation and low LV dyssynchrony as seen during HBP. LVSP, on the other hand, did not lead to significantly increased interventricular dyssynchrony but prolonged LV lateral wall depolarization and led to higher LV dyssynchrony than HBP. Whether these findings on LVSP and LBBP have significant clinical consequences remains unknown.

In summary, UHF-ECG can visualize ventricular depolarization patterns in various types of ventricular pacing during the implant procedure. Significant differences were found between the studied pacing locations and individual patients using the same pacing locations. A multicenter prospective clinical trial was initiated to determine whether UHF-ECG dyssynchrony can serve as an additional tool for selecting patients with the highest risk of PICM – www.clinicaltrials.gov, NCT04908033.

Method and its measure(s) of dyssynchrony	Advantages	Disadvantages	Clinical utility in published literature
Vectorcardiography **(QRSarea)**	Feasible during the implantation, low-cost, fully automatic algorithm available, [101] reproducible.	Provides quantitative but not qualitative measurements. Does not offer a way to assess LV and RV activation separately	- CRT response prediction[102] - CRT optimization[114]
ECG belt **(SDAT, LTAT)**	Feasible during the implant procedure, without need for CT examination, less time consuming compared to ECGi	Multiple leads still make the system too complicated for everyday clinical use	- CRT response prediction[107] - CRT optimization[108,115]
ECGi **(VEU, LVTAT, RVTAT, TAT)**	Provides most detailed non-invasive electro-anatomical activation mapping of both LV and RV	CT or MRI scan required Time-consuming, expensive, and non-feasible in daily clinical praxis	- CRT response prediction[116] - CRT optimization[117] - Ventricular depolarization visualization in LBBB and IVCD patients[106]
UHF-ECG **(E-DYS, RVLWd, LVLWd)**	Feasible during implantation, fully automatic. Provide qualitative and quantitative information about LV and RV depolarization.	No validation study available until now; signal averaging is needed due to low amplitudes of analyzed signals; currently available only in few centers	- Describing the differences between various types of physiological or RV pacing.[111–113]

Table 2 Comparison of non-invasive ECG-based dyssynchrony assessment tools

2.6. Prevention and treatment of pacing-induced cardiomyopathy

The medical therapy is perceived to have limited or none curative effect on iatrogenically induced ventricular dyssynchrony. Therefore, the focus lies nowadays mainly on the etiology of PICM and correction or prevention of ventricular dyssynchrony using different methods of CRT, e.g., biventricular pacing (BiV) or conduction system pacing.

Initially, PICM development was thought to result from RV apical pacing, which produced wide QRS complexes. It was hypothesized that narrowing the paced QRS duration during RV septal pacing would reduce PICM development. Unfortunately, no clinical trial comparing RV septal to apical pacing showed any clinical benefit of RV septal pacing. [118,119]

However, some of these studies had important shortcomings, which limited the potential benefit of reduced ventricular dyssynchrony during RV septal over RV apical pacing. RV septal lead placement was based on unreliable ECG or X-ray criteria, which led to incorrect lead fixations towards the RVOT or anterior wall in a substantial percentage of patients, i.e., the pacing location that can produce based on UHF-ECG data to more delayed LV lateral wall depolarization than RV apical pacing.[120,121]

No clear differences in mortality or HF hospitalizations were observed in trials comparing RV and biventricular pacing in patients with preserved LV systolic function.[121,122] However, an upgrade to CRT or CRT-D in patients with PICM is a guideline-recommended treatment. A recent multicentric prospective RCT including 360 patients with symptomatic HFrEF, RVP burden > 20 %, and QRSd > 150ms showed that BiV-CRT-D upgrade reduces all-cause mortality and HF hospitalizations compared to ICD-only treatment.[123]

More recently, His-Purkinje conduction system pacing (CSP) techniques were introduced. These include HBP, left bundle branch pacing (LBBP), and left ventricular septal pacing (LVSP). It was proven, that these techniques better preserve physiological ventricular activation than RV pacing.[92,93,111–113,124,125]

The favorable effect on ventricular activation during HBP reduced HF hospitalizations in patients requiring more than 20% or 40% ventricular pacing compared to RV apical or

septal pacing.[126,127] Also, HBP seems to be effective in PICM treatment and even superior to BiV-CRT, according to some studies.[128,129] However, these were either retrospective or prospective cohort studies with a limited number of patients. Therefore, larger prospective trials need to be performed to confirm these results. But, as was shown subsequently, HBP pacing has its limitations, such as higher pacing thresholds that can lead to premature battery depletion, lower sensing values, and lower success rates in patients with bundle branch blocks; these limitations have limited its use in all patients.[130,131] Moreover, in some studies, the risk of re-intervention on pacing lead repositioning was unacceptably high.[132]

For that reason, more distal and intra-septal pacing lead placement (i.e., LBBP or LVSP) is now preferred by many specialists. Although these methods are less physiological than HBP, a recent multicenter, observational study showed that they reduce the incidence of death and HF hospitalizations compared to RV apical or septal pacing.[133] Also, small-sized retrospective trials suggested that upgrading from RV pacing to LBBP may improve LVEF and NYHA score in PICM patients.[134] But again, there is no prospective, randomized trial confirming these potential benefits of LBBP and LVSP. Even if these promising pacing methods prove effective, they are still more complex than RV pacing and require dedicated implant tools and advanced equipment in the operating room. Therefore, they may not be accessible to all patients, and selection based on PICM risk stratification might be necessary in the future.

3. Author's original research - part 1 - A randomized comparison of His bundle pacing versus RV pacing: effect on left ventricular function and biomarkers of collagen metabolism

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3.2. Abstract in English

Background:

Right ventricular pacing (RVP) may result in pacing-induced cardiomyopathy (PICM) in some patients. His bundle pacing (HBP) is a method of physiological pacing, which should not lead to PICM. There are some known risk factors, which are, however, not strong enough to reliably predict PICM development. It is unknown whether specific sera biomarkers of collagen metabolism reflect differences between His bundle pacing (HBP) and RVP or predict a decrease in left ventricular function during RVP.

Aims:

To compare the effect of HBP and RVP on the LV ejection fraction (LVEF) and on sera markers of collagen metabolism.

Methods:

Ninety-two high-risk PICM patients were randomized to HBP or RVP. Their clinical characteristics, echocardiography, and sera levels of TGF-β1, MMP-9, ST2, TIMP-1, and Gal-3 were studied before and six months after pacemaker implantation.

Results:

Fifty-three patients were randomized to HBP and 39 patients to RVP. HBP failed in 10 patients, who then crossed over to the RVP group. Both groups had the same clinical characteristics at the baseline, but patients with RVP had significantly lower LVEF compared to HBP after six months of pacing (−3 % and −3 % in *as-treated* and *intention-to-treat* analysis, respectively). Levels of TGF-β1 after six months were lower in HBP than RVP (mean difference −6 ng/mL, p = 0.009). Preimplant Gal-3 and ST2 levels were higher in RVP patients with a decline in the LVEF ≥ 5 % compared to those RVP patients with a decline of < 5 % (mean difference 3 ng/mL and 8 ng/mL, p = 0.02 for both)

Conclusion:

In patients at high risk of PICM, HBP was superior to RVP in providing enhanced physiological ventricular function, as reflected by higher LVEF and lower levels of TGF-β1 in patients with HBP after six months of pacing. Among RVP patients, LVEF declined more in those with higher baseline Gal-3 and ST2 levels than those with lower levels after six months of pacing.

3.3. Abstract in Czech

Úvod:

Pravokomorová stimulace (RVP, z anglického right ventricular pacing) může vyústit v rozvoj stimulací indikované kardiomyopatie. Stimulace Hisova svazku (HBP, z anglického His bundle pacing) je metodou fyziologickou a k rozvoji stimulací indikované kardiomyopatie by vést neměla. Doposud není známo, zdali specifické markery metabolismu kolagenu reflektují rozdíl HBP a RVP nebo zdali mohou predikovat pokles ejekční frakce levé komory srdeční (EFLK) vlivem RVP.

Cíle:

Cílem této studie bylo srovnání vlivu HBP a RVP na EFLK a na markery metabolismu kolagenu v krevním séru.

Metody:

92 pacientů s vysokým rizikem rozvoje stimulací indukované kardiomyopatie bylo randomizováno k HBP nebo RVP. Jejich klinické charakteristiky a sérové hodnoty TGF-β1, MMP-9, ST2, TIMP-1, a Gal-3 byly odebrány před a 6 měsíců po implantaci kardiostimulátoru. Echokardiografické vyšetření bylo provedeno a vyhodnoceno taktéž před a 6 měsíců po implantaci kardiostimulátoru.

Výsledky:

53 pacientů bylo randomizováno k HBP a 39 k RVP. HBP selhal u 10 pacientů, kteří poté přešli do skupiny RVP. Obě skupiny měly před implantací stejné klinické charakteristiky, ale pacienti ve skupině RVP měli po 6 měsících stimulace významně nižší EF než pacienti s HBP (–3 % a –3 % dle analýzy, jak byli léčeni, respektive jak bylo zamýšleno je léčit). Hladiny TGF-β1 byly po 6 měsících nižší ve skupině HBP než RVP (průměrný rozdíl –6 ng/ml; p = 0,009). Před implantací byly hladiny Gal-3 a ST2 vyšší u těch pacientů s RVP, kteří po 6 měsících poklesli s EF o více než 5 %, oproti těm, kterým EF nepoklesla (průměrný rozdíl 3 ng/ml; p = 0,02 pro oba).

Závěr:
HBP je u pacientů s vysokým rizikem rozvoje stimulací indukované kardiomyopatie více fyziologická než RVP, což bylo reflektováno vyšší EFLK a nižší sérovou hladinou TGF-β1 u pacientů s HBP po 6 měsících stimulace. Pacienti s RVP a vyšší předoperační hladinou Gal-3 a ST-2 měli výraznější pokles EFLK po 6 měsících stimulace než pacienti s jejich nízkou hladinou před implantací.

3.4. Background

Myocardial pacing of the right ventricle (RVP) is responsible for declining LV function and heart failure in some patients. The highest risk of these adverse consequences is seen in older patients with a high burden of RV pacing, decreased left ventricular function, CAD, and wider spontaneous or paced QRS complexes.[13] HBP preserves synchronous ventricular activation and represents the most physiological method of ventricular

pacing.[112,126] The pacing method is more complex, with longer procedure times and higher radiation doses, and requires more sophisticated equipment.[128]

For these reasons, HBP is best suited for patients who would gain the most from physiological ventricular activation. However, the benefit of HBP in high-risk populations has never been described.

Although the RVP is non-physiological, most patients tolerate it even for extended periods.[135] Currently, we cannot precisely identify (before pacemaker implantation) which patients will experience deterioration in ventricular function after RV pacing. The period after which PICM starts to develop is estimated to be 2–3 years. However, subtle changes in LV function (i.e., decline ≥ 5%) can present sooner, and these patients are at the highest risk of further heart failure.[136]

Remodeling and altered LV function are present together with changes in the ventricular microstructure. These changes are reflected by perfusion changes in particular ventricular segments, abnormal myocardial metabolism, increased fibrosis, and myocardial disarray.[137] It has already been shown that subtle myocardial microstructure changes in patients after myocardial infarction or heart failure could be evaluated using collagen metabolism biomarkers.[137] However, their significance in patients with a permanent pacemaker has never been established. Demonstrating their relevance to LV performance in these patients could be an important marker of increased risk of further heart failure.

Our study aimed to assess the effect of RVP and HBP on LV function in patients at high risk of heart failure after cardiac pacing. Another goal was to identify laboratory markers that can predict or detect the adverse effects of RVP on LV performance.

3.5. Methods

Patients

This was a prospective open-labeled randomized study with the anticipated recruitment of 120 patients. The project was approved by the Ethics Committee of the Faculty Hospital Kralovske Vinohrady, Prague, CZ; all subjects signed informed consent before enrollment. Only patients with conduction disease and an indication for permanent cardiac pacing per 2013 ESC Guidelines were enrolled. Patients had to have a permanent

conduction disease with an anticipated high burden of the RV pacing and a life expectancy greater than two years. Also, at least one of the following criteria had to be fulfilled:

a/ left ventricular ejection fraction ≤ 60%

b/ QRS duration > 115 ms

c/ presence of ischemic heart disease (defined as previous myocardial infarction or coronary intervention due to significant occlusion of coronary arteries or angina pectoris requiring pharmacologic treatment).

Exclusion criteria were as follows: a severe valvular disease with a planned intervention, cardiac surgery due to valvular disease or CAD in the last three months, permanent or persistent atrial fibrillation, dilated or hypertrophic cardiomyopathy, an indication for ICD or CRT implantation, and active myocarditis. Patients were randomized into the HBP or RVP arm with a 4:3 ratio; the anticipated His bundle pacing success rate was 80–90%. After randomization, patients were informed which arm of the study they were enrolled in. After pacemaker implantation, outpatient clinic follow-ups were at six weeks and six months. During these visits, the pacemaker was checked (with data collection), clinical status was assessed, and a physical examination was performed. Blood sampling and echocardiography were performed before pacemaker implantation and at the six-month follow-up visit.

Pacemaker implantation

His bundle pacing was performed using Select Secure leads (model 3830, 69 cm, Medtronic Inc., Minneapolis, MN, US) delivered through a fixed-curve sheath (C315 HIS, Medtronic, Minneapolis, MN, US) preferentially from the left subclavian approach. The end of the sheath was delivered to the tricuspid annulus over the guidewire, and then the pacing lead was advanced through the sheath 1–2 mm beyond the tip of the catheter. The His bundle area was mapped in unipolar settings using an electrophysiology system (Lab system Pro, Boston Scientific, Marlborough, MA, US) at a sweep speed of 200 mm/s. After the His bundle signal was identified, the lead was fixed by 3–5 clockwise rotations, and pacing from the lead tip was initiated. For the implant procedure to be considered successful, selective, or nonselective, His bundle capture had to be present during the pacing with a pacing output below 2.5 V at 1 ms.

RV septal pacing was performed using Tendril^{R} (Abbott, Little Canada, MN, US) or Ingevity^{R} (Boston Scientific, Marlborough, MA, US) pacing leads, preferably from the left subclavian approach. Once the lead was placed in the RV outflow tract/pulmonary artery, the stylet was pre-shaped, and the lead was fixed in the RV septum using the RAO projection and counterclockwise torque on the leads´ stylet. The lead tip septal position was verified in the RAO 30° and LAO 30° projections.

Echocardiography

Transthoracic echocardiographic examinations were performed on the baseline before the pacemaker implantation and after six months of follow-up, using a GE Vivid E95 Cardiovascular Ultrasound (GE Vingmed Ultrasound System, Horten, Norway). Images were acquired from the standard apical views with a minimum of 3 consecutive beats. Standard 2-dimensional data triggered to the ECG were digitally stored for offline analysis in the EchoPAC Software Only version 204 (GE Vingmed Ultrasound System, Horten, Norway). Two evaluators blinded to the studied groups measured and calculated end-diastolic and end-systolic volumes from the apical 4- and 2-chamber views, and LVEF was calculated using the formula: LVEF = [(LVEDV – LVESV) ÷ LVEDV] (modified Simpson´s method). The mean value of LVEF calculated by each evaluator was used for statistical analyses.

Blood sample collections and quantification of cytokines

Approximately four mL of peripheral venous blood were collected from each patient. Blood samples were centrifugated at 950 *g* for 20 minutes. Serum samples were aliquoted and stored at −80 °C. Samples were thawed prior to quantifying Transforming Growth Factor β1 (TGF-β1), Matrix Metalloproteinase 9 (MMP-9), Suppression of Tumorigenicity 2 Interleukin (ST2), Tissue Inhibitor of Metalloproteinase 1 (TIMP-1), and Galectin 3 (Gal-3) levels. Per the manufacturer's instructions, the measurements of the selected biomarkers were performed using specific Quantikine ELISA kits (R&D Systems, Minneapolis, MN, USA).

Statistical analysis

Statistical analysis was performed using Software: R version 4.0.5 (2021-03-31). Exploratory data analysis was performed for all variables. Categorical data are presented

as count with frequency and continuous data as mean with standard deviation (SD) or alternatively median with 1st and 3rd quartile (Q1; Q3) for nonparametric data. Kolmogorov and Smirnov tests were used for normality testing, and further statistical analysis included a linear mixed effect model with random intercept, Student's t-test, Fisher's exact test, and Chi-squared test.

For the linear mixed effect model, the fixed part of the model is represented by the interaction between two binary parameters: stimulation site (His vs. septum) and visitation (Day 0 vs. Day 180). The random part of the model is represented by the random intercept, which is the patient ID. A maximum likelihood estimator was used to fit models (function lmer of package lme4).[138]Post hoc analysis was performed using the emmeans package. Intention-to-treat and as-treated analyses were performed. For nonparametric data, the Wilcoxon test and Mann-Whitney U test were used. A $p < 0.05$ was considered statistically significant. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve was calculated for ST2 and Gal-3 to assess their predictive value for LVEF deterioration. The optimal cutting points of both markers were calculated using maximization of the Youden index (sensitivity + (specificity – 1)). This was a pilot feasibility trial, and no power calculation was performed prior to the initiation of the study.

3.6. Results

Ninety-two patients were randomized into the study. The mean age was 78 years, and they all had AV conduction disease as the pacing indication. Planned patient recruitment was not reached, and randomization was stopped due to challenges during the COVID-19 pandemic. Fifty-three patients were randomized to HBP, and 39 were randomized to RVP. Lead placement in the HB region failed in 10 of 53 patients (19 %) randomized to the HBP group. The lead was then successfully placed in the RV with myocardial capture in all patients. However, two of these patients (20 %) required ventricular lead revision due to a pacing threshold rise. The reasons for lead implant failure in the HB region were as follows: (1) in two patients, the HB signal was not found, (2) in four patients, the distal HV block could not be corrected by HB pacing, and (3) in four patients, pacing the HB region did not lead to conductive tissue capture with QRS narrowing.

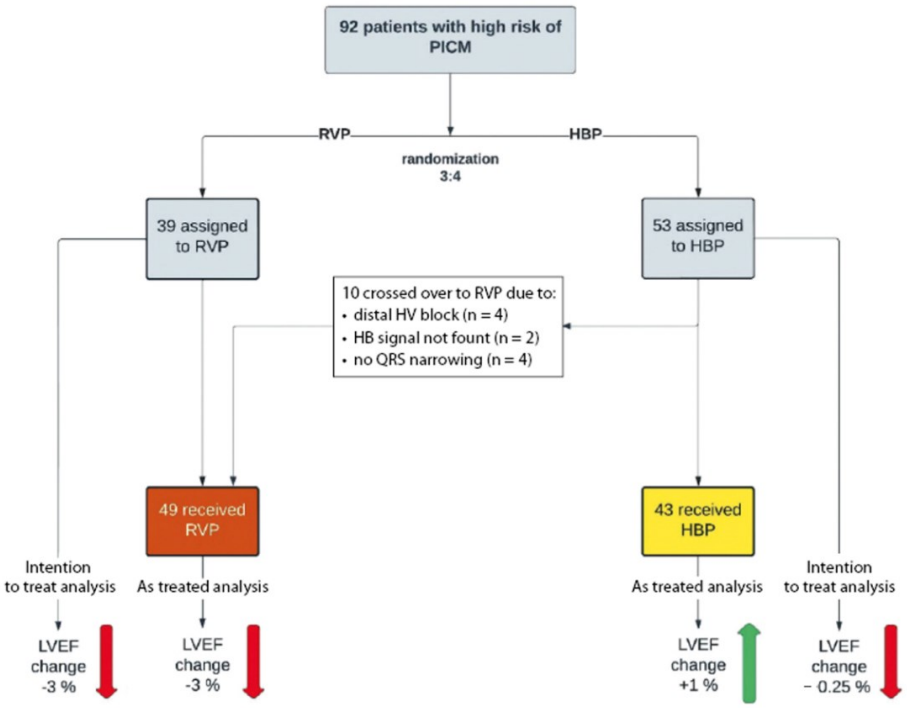

Figure 9 Central illustration: The study flow-chart and the effect of right ventricular pacing and His bundle pacing on left ventricular ejection fraction after six months of pacing in intention-to-treat and as-treated analyses.

As a result, 49 patients had RVP (47 septal and two apical lead positions), and 43 had HBP. No difference in baseline clinical characteristics was observed between groups relative to *intention-to-treat* and *as-treated* analyses. Patients in both groups did not differ with respect to age, gender, preimplant LVEF, QRS duration during spontaneous rhythm, the prevalence of CAD, myocardial infarction, hypertension, or DM - Table 3.

	Intention-to-treat			As-treated		
	RVP (n = 39)	HBP (n = 53)	*P*-value	RVP (n = 49)	HBP (n = 43)	*P*-value
Age, years, mean (SD)	78 (7)	78 (8)	0.99	79 (7)	77 (8)	0.33
Male sex, n (%)	39 (80)	38 (88)	0.26	33 (85)	44 (83)	0.84
LVEF, %, mean (SD)	58 (7)	60 (5)	0.27	59 (6)	59 (4)	0.54
Arterial hypertension, n (%)	38 (97)	51 (96)	0.75	48 (98)	41 (95)	0.49
Diabetes mellitus, n (%)	16 (41)	20 (38)	0.75	18 (37)	18 (42)	0.62
CAD, n (%)	15 (38)	23 (43)	0.64	18 (37)	20 (47)	0.34
Myocardial infarction in history, n (%)	5 (14)	14 (27)	0.15	8 (17)	11 (26)	0.32
Spontaneous QRSd, (ms) mean (SD)	126 (27)	125 (25)	0.80	126 (26)	126 (27)	0.98
Spontaneous QRS morphology, n (%)						
BBB	16 (41)	20 (38)	0.78	19 (39)	17 (40)	0.66
Narrow (<115 ms)	12 (31)	20 (38)		16 (33)	17 (40)	
NIVCD	11 (28)	13 (24)		14 (28)	9 (20)	
Pacing indication, n (%)						
AV block I. degree	5 (13)	7 (13)	0.95	6 (12)	6 (14)	0.94
AV block II. degree	16 (41)	25 (47)		21 (43)	20 (47)	
AV block III. degree	16 (41)	19 (36)		20 (41)	15 (35)	
BBB + syncope	2 (5)	2 (4)		2 (4)	2 (4)	

Abbreviations: AV block, atrioventricular block; BBB, bundle branch block; CAD, coronary artery disease; NIVCD, non-specific intraventricular conduction delay; other — see Central illustration

Table 3: Baseline clinical characteristics of the study population

HBP required a longer fluoroscopy time (in *intention-to-treat* analysis), higher acute and chronic pacing thresholds, and presented with lower acute and chronic ventricular sensing than RVP. However, there was no difference in rates of lead repositions due to higher pacing thresholds between the HBP and RVP groups (Table 4).

		Intention-to-treat			As-treated		
		RVP	HBP	*P*-value	RVP	HBP	*P*-value
Pacing thresholds (V) at 0.4 ms, mean (SD)	D1	0.7 (0.3)	1.4 (0.6)	<0.001	0.8 (0.4)	1.5 (0.6)	<0.001
	D180	0.9 (0.6)	1.7 (1.1)	0.004	1.1 (0.7)	1.7 (1.1)	0.005
	D1 vs. D180 *P*-value	0.35	0.11		0.40	0.21	
Ventricular sensing, mV, mean (SD)	D1	9.4 (3.5)	4.5 (3.3)	<0.001	9.3 (3.7)	3.5 (2.0)	<0.001
	D180	9.5 (2.9)	4.3 (3.2)	<0.001	9.3 (3.1)	3.2 (2.0)	<0.001
	D1 vs. D180 *P*-value	0.91	0.75		0.98	0.54	
Fluoroscopy time, sec, median (IQR)		242 (171; 413)	505 (270; 835)	<0.001	329 (190; 553)	399 (249; 679)	0.34
Burden of ventricular pacing after 180 days, mean (SD)		92 (18)	98 (4)	0.02	95 (17)	98 (4)	0.09
Threshold rise requiring lead revision, n (%)		2 (5)	4 (8)	0.64	4 (8)	2 (5)	0.50

Table 4: Procedural and follow-up pacing characteristics.

There was no difference between HBP and RVP groups in the preimplant LVEF in both *intention-to-treat* and *as-treated* comparisons. However, the LVEF significantly decreased after six months of RVP but remained the same in the HBP group. Also, the LVEF was significantly lower in RVP than in the HBP group after six months of follow-up in both *as-treated* ($p < 0.001$) and *intention-to-treat* analysis ($p = 0.008$) - Fig. 10.

A decline in the LVEF of ≥ 5 % after six months of pacing was observed in 13 of 46 patients (28 %) in the RVP group and none in the HBP group. Among patients with RVP, a decline in LVEF ≥ 10 % was observed in nine patients (20 %), and in eight patients (17 %), the resultant LVEF was ≤ 45 % after six months of pacing.

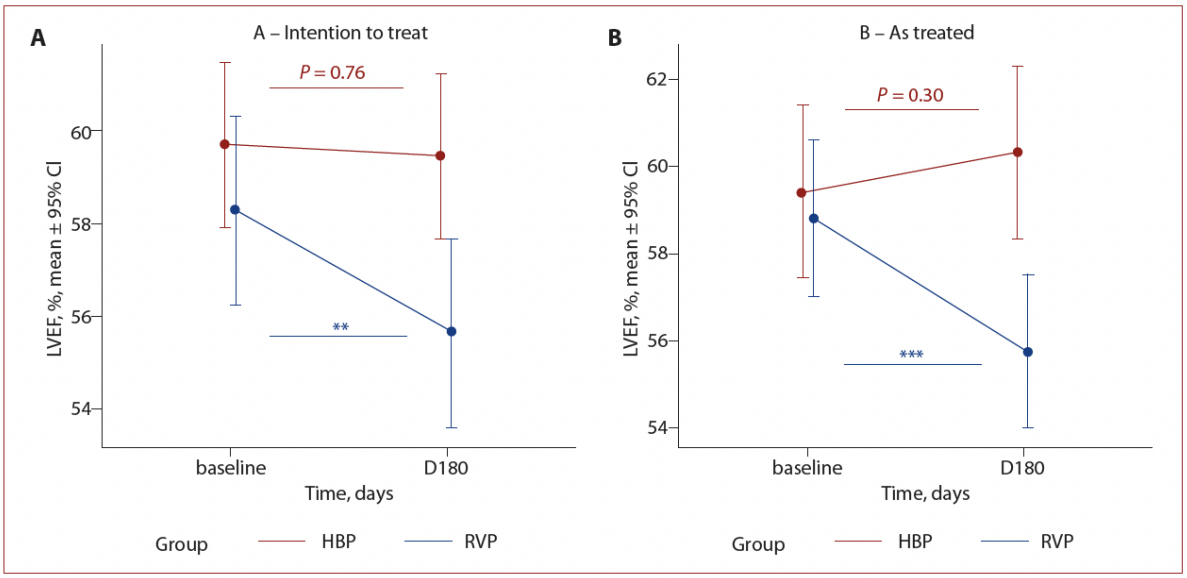

*Figure 10 – Comparison of LVEF in the HBP and RVP groups per intention-to-treat (A) and as-treated (B) analyses. ** means p < 0.01, *** means p < 0.001*

There was no significant difference in baseline serum levels of TGF-β1, MMP-9, ST2, TIMP-1, and Gal-3 between patients with HBP vs. patients with RVP (both *as-treated* and *intention-to-treat* comparison). In the RVP group, in an *as-treated* comparison, a significant decline in the levels of ST2 and TIMP-1 was observed after six months of pacing, but no difference in the serum levels of TGF-β1, MMP-9, and Gal-3 was detected. In the HBP group, a significant decline in the serum level of ST2, MMP-9, and TGF-β1 was seen after six months of pacing; the levels of Gal-3 and TIMP-1 remained statistically the same.

When comparing differences in serum levels of studied biomarkers between HBP and RVP six months after the pacemaker implantation, the only difference was observed in the levels of TGF-β1, which were significantly lower in the HBP group than in the RVP group - Fig. 11.

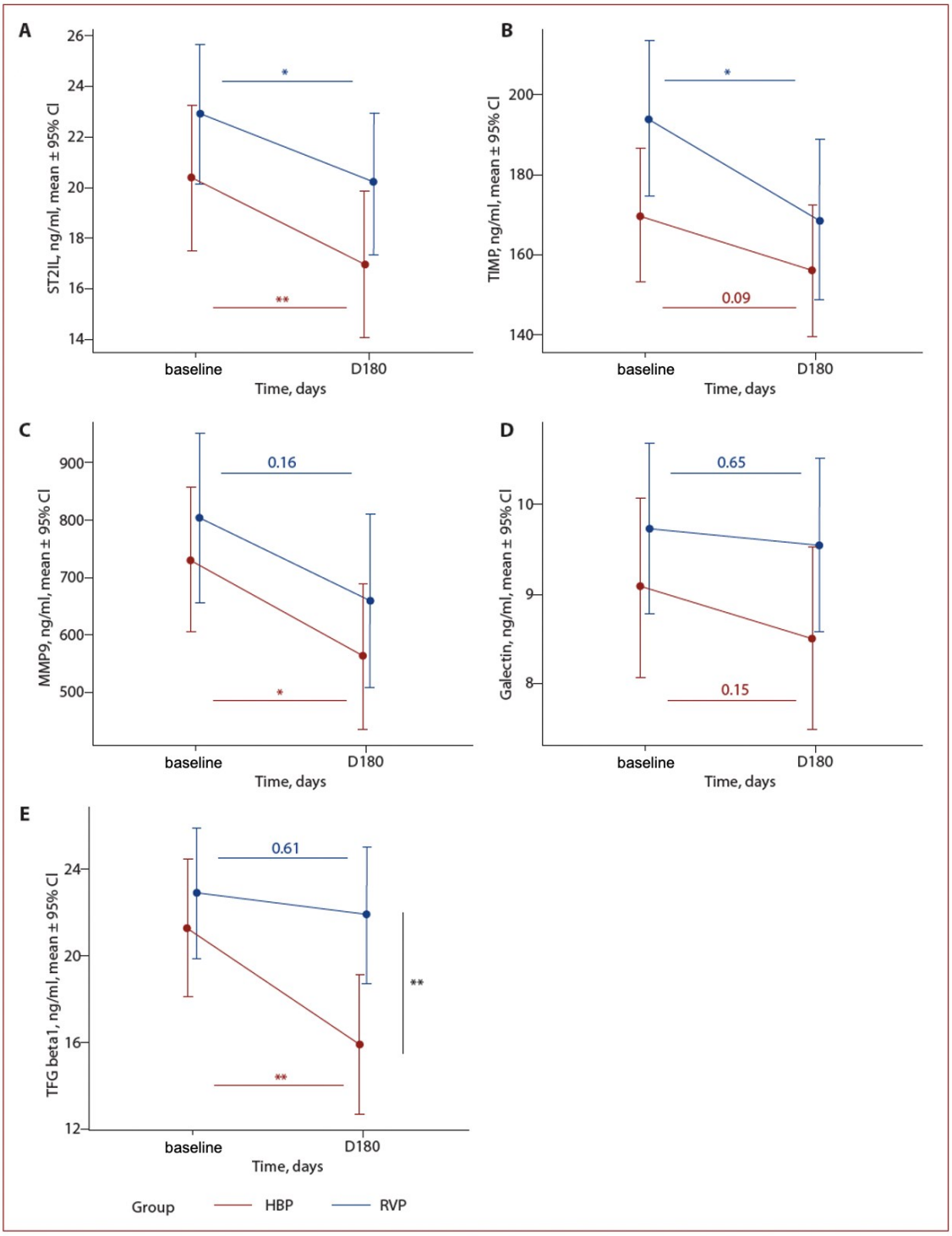

*Figure 11 – Comparison of serum levels of ST2, TIMP-1, MMP-9, Galectin 3, and TGF-β1 at baseline and after six months of pacing in HBP vs. RVP group per as-treated analysis. * Means $p < 0.05$, ** means $p < 0.01$.*

To determine whether cytokine levels before pacemaker implantation could predict an LVEF decline of ≥ 5 %, we compared cytokine levels in patients with RVP and an LVEF decline of ≥ 5% (13 patients) vs. cytokine levels in patients with RVP and LVEF decline < 5% (36 patients).

Patients with an LVEF decline ≥ 5 % after six months of RVP had higher baseline levels of Gal-3 and ST2. After six months, the elevations of both markers persisted and were higher than in patients with an LVEF decline < 5 % in the primary analysis and after adjustment to the baseline levels of both molecules – Fig. 12. During RVP, a decline in TIMP-1 was observed in patients without deterioration of LVEF ($p = 0.04$). No difference in serum levels of the other studied biomarkers was found before and after six months of RVP - Fig. 11.

The ROC analysis showed an AUC of 0.79 for Gal-3 and 0.71 for ST2 relative to the prediction of a decline in LVEF ≥ 5 % (Fig. 13). Gal-3 serum concentrations ≥ 8.88 ng/mL was 100% sensitive and 61% specific, with a positive predictive value of 45%, a negative predictive value of 100%, and an accuracy of 72 %; ST2 concentrations ≥ 19 ng/mL showed 90% specificity and 52 % specificity, with a positive predictive value of 38 %, a negative predictive value of 94 %, and an accuracy of 71 % for detection of patients with a decline in LVEF ≥ 5 % after six months of RVP.

In the HBP group, patients with higher baseline Gal-3 (> 8.88 ng/ml) and ST2 (> 19 ng/mL) levels did not differ in LVEF change after six months of follow-up in comparison to patients with lower baseline Gal-3 and ST2 levels (LVEF change 1 vs. 1 % and 1 vs. 1 %, $p= 0.66$ and $p= 0.72$, respectively).

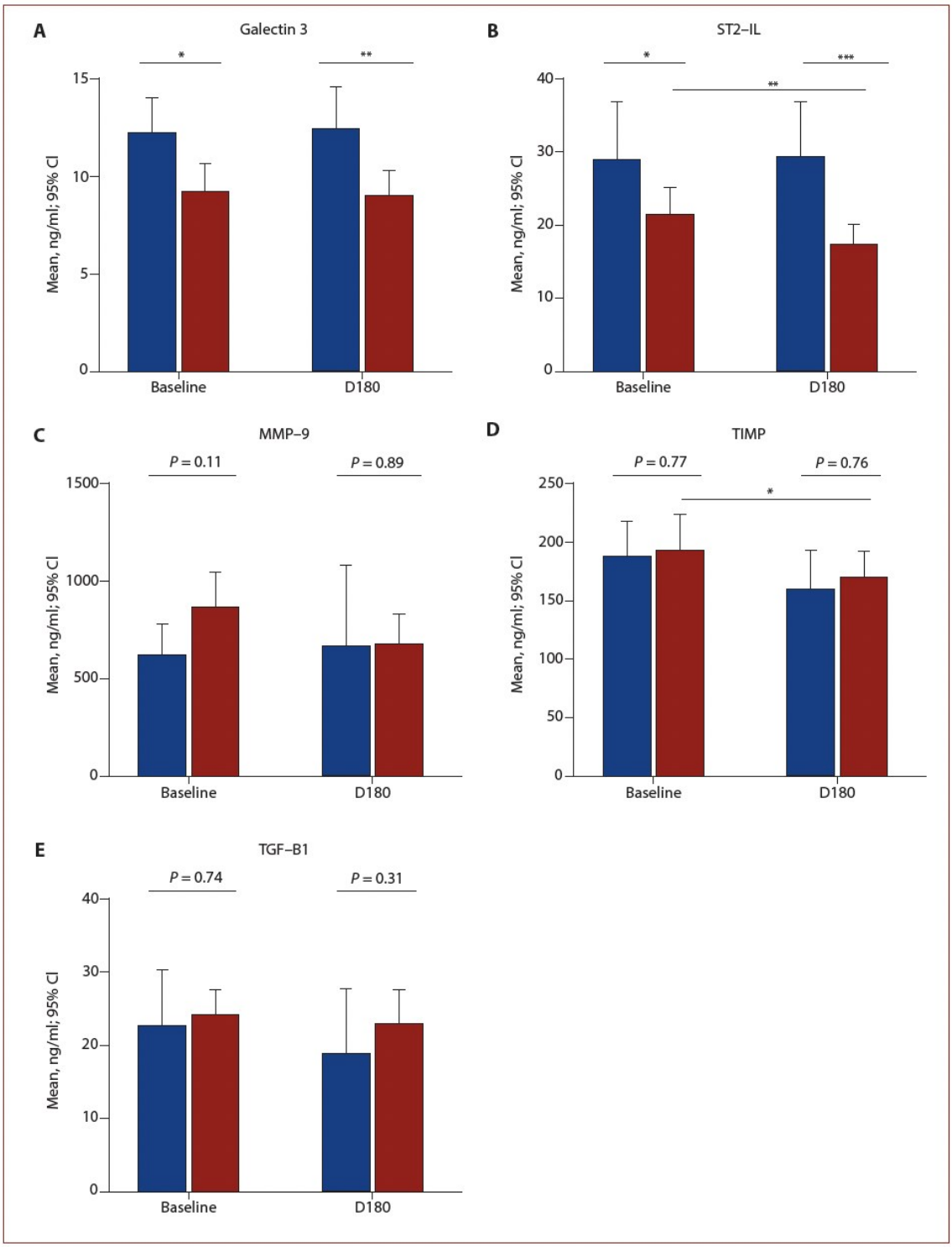

Figure 12 – Comparison of serum levels of Gal-3, ST2, MMP-9, TIMP-1, and TGF-beta1 before implant and after six months of pacing in patients with RVP and preserved LVEF vs. declined in LVEF ≥ 5 %.

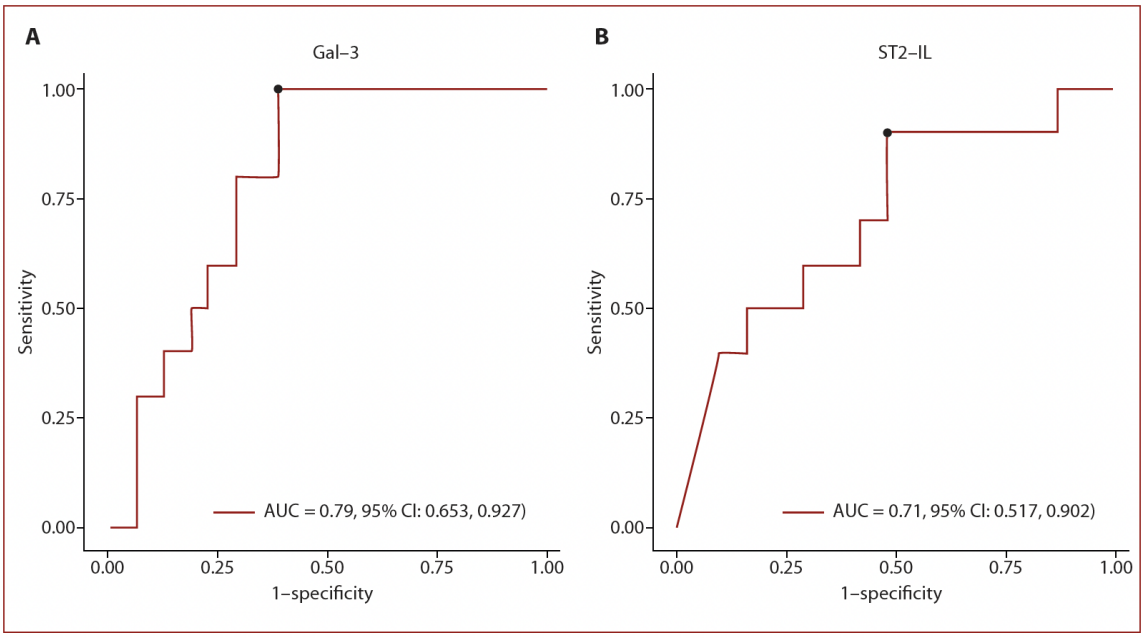

Figure 13 – Receiver operating characteristic (ROC) curves of Gal-3 (Panel A) and ST2 (Panel B) in patients with and without the decline in the LVEF ≥ 5% after six months of RVP.

3.7. Discussion

This study compared the effect of His bundle pacing and RVP on the LVEF in patients at high risk of pacing-induced cardiomyopathy. Also, this is the first trial studying fibrosis biomarkers in patients with pacemakers. We showed that adverse effect on LV function with a decline in LVEF ≥ 5 % after pacing was not uncommon and affected almost 1/3 of patients with RVP, with the LVEF falling below 45 % in 17 % of the group. Contrary to this, HBP preserved LV function in all patients.

We also showed that initiation of permanent cardiac pacing resulted in changes in the serum levels of the studied biomarkers, with serum TGF-β1 levels reflecting different ventricular activation during HBP and RVP. Lastly, patients with a decline in the LVEF ≥ 5% due to non-physiological RVP had significantly higher serum levels of Gal-3 and ST2 than patients with a < 5% decline in LVEF, both at the baseline and after six months of RVP.

HBP vs. RVP

His bundle pacing is well established, and guidelines supported treatment option in selected patients with bradycardia.[139] However, data from randomized trials supporting its use in the broader spectrum of patients are missing. So far, only one randomized trial

comparing His bundle pacing to right ventricular septal pacing in patients with conduction disease has been published.[140] It used a crossover design, with HBP and RV pacing being utilized in the same patient for 12 months, and the number of randomized patients was small. Moreover, the studied population differed from our group, e.g., only patients with narrow QRS complexes (the average was 93 ms), and most were without coronary artery disease.

The study showed that HBP preserved LVEF and ventricular synchrony better than right ventricular septal pacing, which resulted in a significant decline in the LVEF (mean decline of 4 ± 1%). A similar level of LVEF deterioration during RVP occurred in a shorter period in our study, possibly reflecting the higher risk profile of our patients. CAD was present in 1/3 of our patients, and the average QRS duration was 126 ms; both have been associated with a higher risk of adverse LV remodeling during pacing.[13]

Considering the relationship between the severity of the LVEF decline and the duration of non-physiological RVP, it is possible that the difference in LVEF between HBP and RVP would be even greater with a longer follow-up. In our study, a decrease of LVEF ≥ 5% was seen only in patients with RVP. Although a 5% decline in LVEF could be considered clinically negligible, it was previously shown that patients who demonstrate a slight decrease in LVEF soon after the pacemaker implantation were at the highest risk of further PICM.[141] It is often defined as a decline in the LVEF of more than 10 % and/or an LVEF < 50 %.[13]

Using this definition, 20 % of patients in our high-risk population developed PICM after six months of pacing. This agrees with the numbers reported by other investigators; however, it occurred earlier after pacemaker implantation in our study.[13]

The difference in serum levels of studied cytokines between HBP vs. RVP

In patients with bradycardia and pacemaker implantation, we studied serum levels of collagen metabolism and fibrosis biomarkers, which were already shown to play a role in adverse ventricular remodeling in different clinical scenarios.[66,142–144] Right ventricular myocardial pacing corrects the atrioventricular dyssynchrony and bradycardia. However, it may lead to non-physiological ventricular activation with adverse remodeling and LVEF deterioration in some patients.[137] These changes should be reflected in serum levels

of biomarkers of fibrosis, although they have yet to be studied in patients with pacemakers.

We showed that cardiac pacing (HBP) led to a decline in the serum levels of ST2, MMP-9, TGF- β1, and we can observe a trend of decline also in Gal-3 and TIMP-1, although it did not reach a statistical significance. However, after six months of pacing, the groups differed only in the levels of TGF-β1. TGF-β1 is a pleiotropic cytokine critically involved in cardiac injury, repair, remodeling, and fibrogenesis. It also exerts potent matrix-preserving actions by suppressing the activity of MMPs and by inducing the synthesis of protease inhibitors, such as TIMP-1. Elevated TGF-β1 levels in experimental *in vivo* models of heart failure were associated with increased myocardial stiffness, fibrosis, and LV diastolic dysfunction.[145]

We found that TGF-β1 declined after the institution of HBP but remained the same in RVP patients. This may reflect the normalization of atrioventricular synchrony with truly physiological ventricular activation in HBP patients.[146] In RVP patients, AV synchrony was also normalized, but at the cost of non-physiological ventricular activation due to RVP, which is associated with worsening LV performance.[147]

Similarly, TGF-β1 was also studied in the CRT population by Osmancik et al. They found that levels of TGF-β1 decreased significantly in CRT responders compared to non-responders, in which it even increased after six months of follow-up.[64]

Gal-3 has strong evidence in HF prognostication; however, the power of Gal-3 repeated measurements showed no usefulness in clinical events prediction in some studies.[73] Systemic levels of Gal-3 rather represent long-going chronic processes, and they are not strongly affected by rapid changes in HF clinical status (acute decompensations or hemodynamic changes).[51] This might explain why the change of Gal-3 did not reach statistical significance in the six months of follow-up in the HBP group.

New pacing strategies, such as His bundle pacing and left bundle branch area pacing, reduce the risk of adverse LV remodeling and heart failure in bradycardia patients.[126,148] However, these techniques may be best suited for those with the highest risk of PICM because they are more complex. This remains a challenge because we still cannot accurately predict which patients will have a decline in LVEF due to RVP.

Our theory was that the detrimental effect of RVP would be seen mostly in patients susceptible to the harmful impact of RVP, i.e., with a pre-existing condition, like increased myocardial fibrosis, which could be reflected in serum levels of studied biomarkers. Therefore, we compared these biomarkers in patients with an LVEF decline of ≥ 5 % vs. those with preserved LVEF during RVP (i.e., < 5 %). The only cytokines that showed different preimplant levels were Gal-3 and ST2. Both are known as prognostic biomarkers in heart failure patients and are involved in collagen metabolism and ventricular remodeling.[66,144] Data on their significance in patients with pacemakers are scarce.

However, it was already shown that higher preimplant Gal-3 levels were negatively associated with response to cardiac resynchronization therapy and higher levels of myocardial fibrosis in ventricular myocardium, as seen on preimplant CMR.[72] It is possible that increased levels of Gal-3 and ST2 in our patients with a more significant decline in LVEF during RVP reflected a higher degree of pre-implant myocardial fibrosis, which led to a more harmful effect of RVP on LV performance. On the other hand, patients without significant myocardial fibrosis can better compensate for dyssynchronous ventricular activation during RVP while maintaining the LVEF.

3.8. Limitations

This was a single-center study with echocardiographic follow-up restricted to six months, which prohibited tracking LVEF changes and clinical outcomes over a more extended period. Potential bias could have been present during the evaluation of echocardiographic measurements. Although the evaluators were blinded to the randomization of patients in the studied groups, the position of the pacing lead in the His bundle or RV septal region could be seen during the evaluation. An LVEF decline of 5%, which was used to compare groups, is relatively small and difficult to measure precisely, especially in patients with LV dyssynchrony due to pacing.

We did not study LV diastolic function, which could correlate more with ventricular fibrosis rather than systolic function. The absence of BNP measurements did not allow for advanced multi-marker assessment. The burden of ventricular pacing was taken from the programmer's printouts, and we did not study the incidence of fused pacing beats during Holter-ECG monitoring, which could lead to a higher burden of ventricular pacing as was, in fact, present.

Finally, the number of patients in the RVP group, specifically those with a decline in the LVEF after pacing, was small, preventing more robust conclusions about the PICM prediction based on specific levels of studied molecules.

3.9. Conclusion

In patients at high risk of PICM, right ventricular pacing led to a decline in left ventricular ejection fraction compared to His bundle pacing, which preserved LV function after six months of pacing. Patients with HBP had lower sera levels of TGF-β1 after six months of pacing compared to patients with RVP. In the RVP group, LVEF declined more in patients with higher baseline Gal-3 and ST2 levels than in those with lower levels after six months of pacing. Based on that, we concluded that Gal-3 and ST2 have the potential to identify patients in which right ventricular pacing does not pose a significant risk. Further studies with more patients, longer follow-up, and clinical endpoints are needed to verify their predictive powers relative to pacing-induced cardiomyopathy.

4. Author's original research - part 2 - Electrical and mechanical interventricular dyssynchrony coupling in bradycardia patients; a UHF-ECG validation trial

4.1. Authors and Institutions

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4.2 Abstract in English:

Background:

Permanent cardiac pacing may cause various types of ventricular dyssynchrony. Ultra-high-frequency ECG (UHF-ECG) is a diagnostic tool for non-invasive visualization of the ventricular activation sequence. It has never been compared to other methods assessing mechanical dyssynchrony.

Aims:

To compare UHF-ECG electrical interventricular dyssynchrony (interventricular e-DYS) and echocardiographic interventricular mechanical delay (IVMD) in bradycardia patients with right ventricular pacing (RVP) or conductive system pacing (CSP).

Methods:

Fifty-three patients with advanced AV conduction disease, no structural heart disease, and preserved left ventricular systolic function were prospectively randomized to RVP (n=32) or CSP (n=21). IVMD was measured as a difference between LV and RV pre-ejection periods by two examinators. Interventricular e-DYS was calculated automatically and manually as a time difference between activation in V7 and V1 chest electrodes using UHF-ECG.

Results:

The median patients age was 75 years, and both groups had similar clinical characteristics. After one year of pacing, the patients with CSP preserved similar levels of both IVMD (mean change –2 ± 5 ms, p = 0.74) and interventricular e-DYS (mean change 0 ± 4 ms, p = 0.95) compared to a spontaneous rhythm before pacemaker implantation. By contrast, in the RVP group, both IVMD interventricular e-DYS increased (IVMD by 27 ± 5 ms and interventricular e-DYS by 24 ± 5 ms; p <0.0001 for both compared to the baseline. There was a moderate overall correlation between IVMD and interventricular e-DYS in all studied ventricular rhythms (R = 0.73).

Conclusion:

UHF-ECG expresses interventricular dyssynchrony noninvasively by measuring the activation difference between V7-V1 chest leads. RVP increases interventricular dyssynchrony, while CSP preserves synchronous ventricular activation.

4.3. Abstract in Czech:

Úvod:

Trvalá kardiostimulace může způsobit různé druhy komorové dyssynchronie. Ultra-vysokofrekvenční EKG (UHF-ECG) je nástroj sloužící k neinvazivnímu zobrazení sekvence komorové aktivace. Ještě nikdy nebyl použit ke srovnání mechanické a elektrické komorové dyssynchronie.

Cíl:

Srovnání elektrické mezikomorové dyssynchronie (e-DYS) získané z ultra-vysokofrekvenčního EKG a echokardiograficky změřené mechanické mezikomorové dyssynchronie (IVMD, z anglického interventricular mechanical delay) u pacientů s pravokomorovou myokardiální stimulací a stimulací převodního systému.

Metodika:

53 pacientů bez strukturálního onemocnění srdce se zachovalou systolickou funkcí LK a pokročilou poruchou AV vedení bylo prospektivně určeno buď k myokardiální pravokomorové stimulaci (32), nebo stimulaci převodního systému srdečního (21). IVMD bylo manuálně měřeno 2 zaslepenými hodnotiteli jako rozdíl pre-ejekčních period LK a PK. Mezikomorový e-DYS byl hodnocen automaticky softwarem i manuálně jako rozdíl mezi aktivačními časy svodu V7 a V1.

Výsledky:

Medián věku námi studované populace byl 75 let a obě studované skupiny měly stejné klinické charakteristiky. Po jednom roce stimulace převodního systému nedošlo oproti pre-implantačním hodnotám k nárůstu IVMD (průměrná změna −2 ± 5 ms, p = 0,74) ani mezikomorového e-DYS (průměrná změna 0 ± 4 ms, p = 0,95). Naproti tomu po jednom roce pravokomové stimulace vzrostlo oproti předimplantačním hodnotám jak IVMD (27 ± 5 ms, p <0,0001), tak i mezikomorový e-DYS (průměrná změna 24 ± 5 ms; p < 0,0001). Při srovnání všech studovaných komorových rytmů byla zaznamenána významná korelace mezi IVMD a mezikomorovým e-DYS (R = 0,73).

Závěr:

Ultra-vysokofrekvenční EKG neinvazivně zobrazuje elektro-mechanickou mezikomorovou dyssynchronii, ta je výsledkem rozdílu mezi aktivačními časy svodu V7 a V1. Pravokomorová stimulace vede k nárůstu mezikomorové dyssynchronie, zatímco stimulace převodního systému zachovává nízkou mezikomorovou dyssynchronii.

4.4. Background:

Right ventricular (RV) pacing is well tolerated by some patients; however, others manifest heart failure (HF) after pacemaker implantation and develop pacing-induced cardiomyopathy (PICM).[12,13,20,149] This is a consequence of non-physiological ventricular activation bypassing the conduction system and leading to ventricular dyssynchrony[41], which was identified as the main factor of PICM development.[29,35]

One method for assessing interventricular dyssynchrony is using echocardiography to measure interventricular mechanical delay (IVMD). Despite IVMD being proven to be an independent and robust risk factor for PICM development or CRT outcome prediction[29,150], it never entered common clinical practice, and we still lack rapid and reliable methods of interventricular dyssynchrony assessment, not only before and after but also during the implant procedures.

Ultra-high-frequency electrocardiography (UHF-ECG) is a non-invasive imaging tool that assesses ventricular activation patterns during spontaneous and paced rhythms. It analyzes electrical signals in frequencies above 150 Hz and allows ventricular dyssynchrony to be calculated in a few minutes by using standard ECG chest leads. Although it was intensively used to study ventricular dyssynchrony associated with His bundle pacing (HBP), RV myocardial, biventricular, and left bundle branch pacing (LBBAP), [111–113,151] there are no data that would compare electrical interventricular dyssynchrony assessed by UHF-ECG to mechanical dyssynchrony assessed by echocardiography.

The aim of our study was to understand the relationship between interventricular dyssynchrony assessed by UHF-ECG and echocardiography in patients with bradycardia treated by RV myocardial or conduction system pacing.

4.5. Methods:

Population:

The population comprised patients from the ´´Ultra-high-frequency ECG for Prediction of Left Ventricular Remodeling´´ - UHF Predict trial. (ClinicalTrials.gov Identifier: NCT04908033).

This is an ongoing prospective, multi-centric, in part randomized, clinical trial enrolling patients with bradycardia due to the AV conduction disease and an indication for permanent pacing. Patients are assigned into two arms: in one arm, patients receive RV myocardial pacing, and in the second arm, His bundle or left bundle branch area pacing. The inclusion and exclusion criteria for this study are as follows:

Inclusion Criteria:

1. expectation of permanent right ventricular pacing with atrio-ventricular delay set to 150/180 ms (130/160 for CSP) for sensed/paced atrial events during a follow-up
2. sufficient echocardiography window quality for measuring LVEF by a Simpson method
3. willingness to attend clinical check-ups in the implanting center for at least two years.
4. life expectancy of at least two years

Exclusion criteria are planned cardiac surgery or transcatheter aortic valve implantation, hypertrophic cardiomyopathy, an indication for implantable cardioverter-defibrillator, biventricular implantable cardioverter-defibrillator, or biventricular pacemaker, active myocarditis, cardiac surgery or coronary revascularization in the last ten days, persistent/permanent atrial fibrillation during randomization, severe aortic stenosis, mitral valvular disease with an indication to intervention.

The first 60 patients with completed 1-year follow-up were screened for enrollment in this study. From these patients, only patients with LVEF ≥ 50 % and RV fractional area change ≥ 35 % entered this study. As a result, seven patients were excluded from the study due to: (1) LV systolic dysfunction (n=3), (2) RV systolic dysfunction (n=2), and (3) third-degree AV block with alternating ventricular rhythm, leading to different rhythms during the echocardiography and UHF-ECG acquisitions (n=2).
The project was approved by the Ethics Committee of the Faculty Hospital Kralovske Vinohrady, Prague, CZ; all subjects signed informed consent before enrollment.

Echocardiography:

Transthoracic echocardiographic examinations were performed on the baseline before the pacemaker implantation and after one year of follow-up during the pacing, using a GE Vivid E95 Cardiovascular Ultrasound (GE Vingmed Ultrasound System, Horten, Norway). Images were acquired in the standard parasternal and apical views with at least three consecutive beats. Standard 2-dimensional and Doppler data triggered to the ECG were digitally stored for offline analysis in the EchoPAC Software Only version 204 (GE Vingmed Ultrasound System, Horten, Norway). Interventricular mechanical delay (IVMD) was measured as a time difference between the onset of the QRS (or the peak of

the first QRS amplitude if the onset was unclear) and the onset of the flow through LVOT and RVOT. In each control, the same point of the QRS complex was selected for both RV and LV PEP measurements to minimize the measurement error. Measurements were performed using pulsed wave (PW) Doppler imaging in the RVOT in parasternal short-axis view or the LVOT in apical 5-chamber view to acquire RV pre-ejection period (PEP) and LV PEP respectively - Figure 1. A positive value indicates a right-to-left activation delay, and a negative value indicates a left-to-right activation delay. Two experienced examiners blinded to the patient's allocation performed measurements.

Pacemaker implantation:

The left subclavian approach was preferred in all pacing approaches. RV septal pacing was performed using Tendril^{R} (Abbott, Little Canada, MN, US) or Ingevity^{R} (Boston Scientific, Marlborough, MA, US) pacing leads. Once the lead was placed in the RV outflow tract/pulmonary artery, the stylet was pre-shaped, and the lead was fixed in the RV septum using the RAO projection and counterclockwise torque on the lead´s stylet. The RAO 30° and LAO 30° projections verified the lead tip septal position. If the RV septal pacing was unsuccessful, placing the lead in the RV apex was allowed per protocol.

His bundle pacing was performed using SelectSecure lead (model 3830, 69 cm, Medtronic Inc., Minneapolis, MN, US) delivered through a fixed curve sheath (C315 HIS, Medtronic) as described previously.[152] s-HB and ns-HB capture were defined according to published criteria.[153]

For the left bundle branch area pacing (LBBAP), the location of His bundle was identified by a pacing lead, or septal leaflet of the tricuspid valve was visualized by a dye. Then, Medtronic Select Secure 3830 lead (Medtronic Inc., Minneapolis, MN, US) was moved towards the right ventricle (RV), along the line between the His-bundle region and the RV apex and screwed deep into the septum to obtain a position in the left side of the interventricular septum showing a paced QRS morphology of RBBB/pseudo-RBBB in lead V_1 and proof of LVSP or LBBP as described in detail in European Heart Rhythm Association´s clinical consensus statement on CSP implantation.[154]

UHF-ECG acquisition and calculations:

A ventricular dyssynchrony imaging (VDI) monitor (ISI Brno, Cardion, FNUSA, Czech Republic) was used to record and analyze the 5-kHz, 14-lead ECG signals with 3-nV resolution and a frequency range of 1.5 kHz. Standard V1-V8 chest lead positions were used. UHF-ECG data for all captures were collected during 5-10 minutes of DDD pacing with prespecified AV delays.

Signal processing and UHF-ECG map construction were described previously (VDI Scientific Software, VDI Technologies, Inc.).[155] Briefly, median amplitude envelopes were computed for 16 frequency bands (150–1000 Hz) for each chest lead. The broad-band QRS complex (UHF-QRS) was constructed as the average of the 16 normalized median amplitude envelopes and displayed as a color map for each lead. Local activation times were calculated as the center of mass of UHF-QRS above the 50% threshold of the baseline-to-peak amplitude in each chest lead. Interventricular dyssynchrony (interventricular e-DYS) was measured as the time difference between the local activation in the V7 and V1 lead – Fig. 1. A positive value indicates right-to-left activation delay, and a negative value indicates left-to-right activation delay.

Global QRS duration (QRSd) was measured automatically (VDI Scientific Software, VDI Technologies, Inc.) from the first to the last deflection of any of the V1-V6 chest leads during the spontaneous rhythm or from the pacing artifact to the last QRS deflection for the paced rhythms.

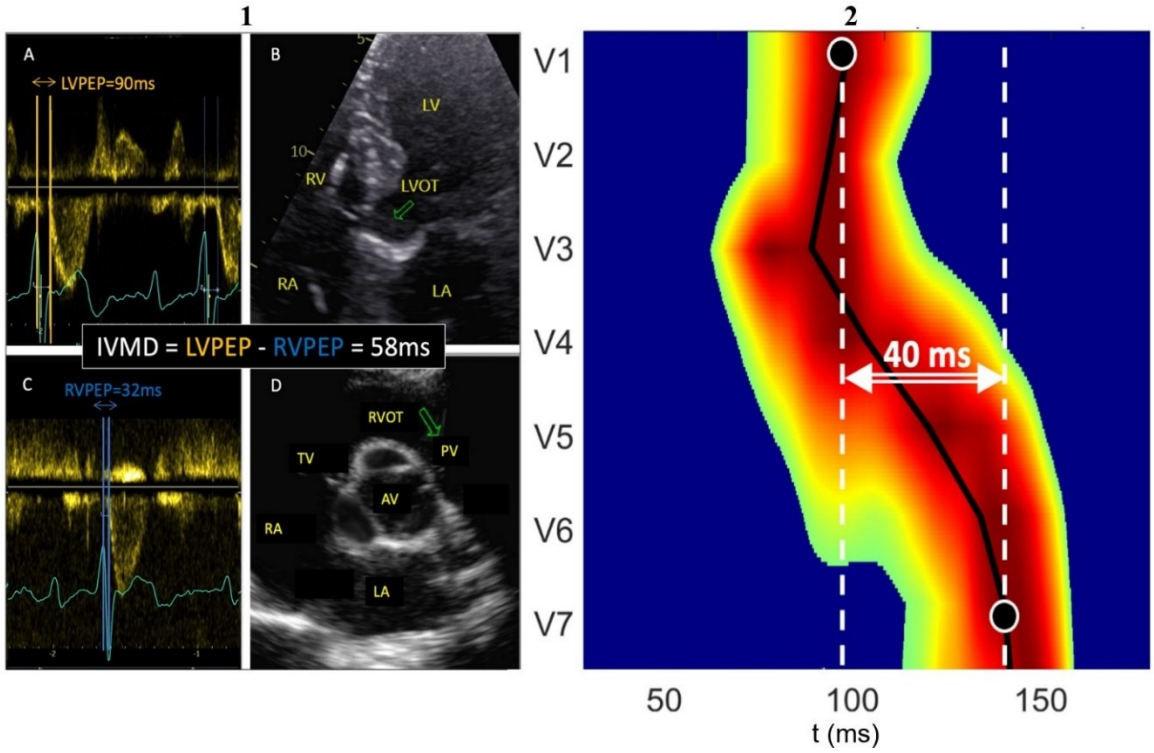

Figure 1: Panel 1: Interventricular dyssynchrony measurement using echocardiography; A - Left ventricular pre-ejection period (LVPEP) measurement; B - apical 5-chamber view; C - Right ventricular pre-ejection period (RVPEP) measurement; D parasternal short axis view; interventricular mechanical delay (IVMD) calculation: LVPEP-RVPEP=IVMD. Panel 2: Interventricular dyssynchrony measurement in a patient with RVSP using Ultra-High-Frequency ECG: Ventricular depolarization map with visualization of the local activation times under V1-V7 (they are connected by a black line) and interventricular dyssynchrony visualization as the time difference between V7-V1 leads (interventricular e-DYS). Leads are displayed on the y-axis, and time in ms during QRS complex is displayed on the x-axis.

Statistics:

Statistical analyses and graph plotting were performed using Software: R version 4.0.5 and Prism 9 version 9.5.0. Exploratory data analysis was performed for all parameters. The correlation was assessed using Spearman's and Pearson's correlation tests for nonparametric and parametric data, respectively. Repeated measurement comparisons were made using a linear mixed effect model (LMEM). Further statistical analysis included the Chi-squared test and two-tailed Student's t-test, and the Wilcoxon test and Mann-Whitney U test were used for nonparametric data.

A $p < 0.05$ was considered statistically significant. Inter-observed reliability was tested by intra-class correlation coefficient (ICC) estimate and 95% confidence interval based on a mean-rating ($k = 2$), absolute-agreement, 2-way random-effects model. If not specified, the results are presented as means with confidence intervals and comparisons

as mean differences with confidence intervals. This was a proof-of-concept study, and no power calculation was performed.

4.6. Results:

Of the 53 enrolled patients, 21 received CSP, and 32 received RVP. In the CSP group, five patients received HBP, and 16 received LBBAP. In the RVP group, 31 patients had RV septal pacing, and only 1 received RV apical pacing. 106 UHF-ECG recordings and 86 echocardiographic recordings were analyzed (including both baseline and one-year controls). Twenty echocardiographic recordings were not analyzed either due to insufficient quality of PW-Doppler signals in LVOT/RVOT (n = 16) or insufficient ECG quality during echocardiography recording (n = 4) – Figure 2.

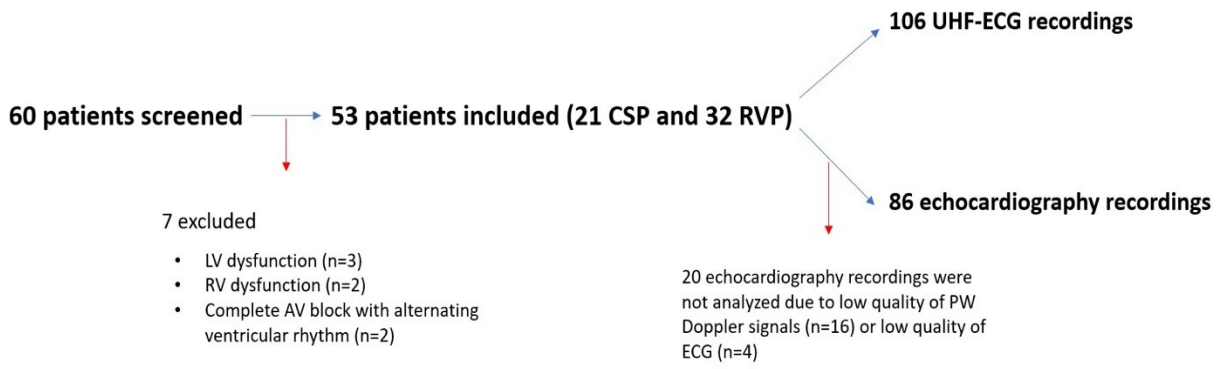

Figure 2: Study flow-chart

The median age of all included patients was 75 (72; 80) years. There were no clinical differences between patients receiving RVP vs. those with CSP (Table 1). Also, pacing thresholds at implant were comparable between the two groups, while procedure and fluoroscopy times were significantly higher in the CSP group (Table 1).

	All N = 53	RVP N = 32	CSP N=21	P-value
Age (years), median, IQR	75 (72; 80)	75 (72; 78)	74 (72; 77)	0.67
Male, n (%)	36 (68)	22 (69)	14 (66)	0.87
BMI (kg/m2), mean, 95 % CI	27 (27; 28)	27 (25; 28)	28 (27; 30)	0.09
DM, n (%)	29 (55)	16 (50)	13 (62)	0.39
HT, n (%)	35 (66)	21 (66)	14 (67)	0.94
CAD, n (%)	16 (30)	12 (38)	4 (19)	0.15
LVEF (%), mean, 95 % CI	64 (62; 65)	64 (62; 65)	64 (61; 66)	0.88
Baseline QRSd (ms), mean, 95 % CI	111 (105; 118)	112 (103; 121)	110 (101; 120)	0.84
Paced QRSd D360 (ms), mean, 95 % CI	130 (125; 136)	139 (133; 146)	116 (110; 122)	<0.0001
QRS morphology, n (%) • **Narrow, n (%)** • **NIVCD, n (%)** • **RBBB, n (%)** • **LBBB, n (%)**	 30 (57) 7 (13) 12 (23) 4 (7)	 17 (53) 4 (13) 8 (25) 3 (9)	 13 (62) 3 (14) 4 (19) 1 (5)	0.86
Pacing threshold (V), median, IQR	0.50 (0.50; 0.75)	0.60 (0.50; 0.75)	0.50 (0.50; 0.95)	0.33
Procedure duration (min.), mean, 95 % CI	49 (44; 54)	38 (34; 42)	66 (60; 73)	< 0.0001
Fluoroscopy time (sec.), mean, 95 % CI	396 (315; 477)	245 (182; 308)	518 (402; 634)	< 0.0003

Table 5 Clinical and procedural characteristics.

Interventricular mechanical and electrical dyssynchrony in patients with RV myocardial pacing and conduction system pacing

Both RVP and CSP groups had comparable IVMD at the baseline (2 [−7, 10] ms for RVP vs. −6 [−17, 5] ms for CSP; p=0.22), but while there was an increase of IVMD in the RVP group after one year of pacing (mean change + 27 [17, 36]ms; p <0.0001), it remained the same in CSP group (mean change −2 [−12, 9] ms; p = 0.74) – Figure 3, panels A and C. IVMD in the RVP group after one year of pacing was significantly higher than in the

CSP group (RVP 28 [23, 33] ms vs. CSP −7 ± 18 ms; p <0.0001). A comparison of the IVMD values from both examiners showed excellent agreement (ICC 0.93 [0.89, 0.96]).

The interventricular e-DYS was also similar for RVP and CSP groups at the baseline (2 [−5, 10] ms for RVP vs. −5 [−14, 4] ms for CSP; p = 0.59), and it markedly increased in RVP patients after one year of pacing (mean change + 24 [14, 34] ms; p <0.0001), while it remained the same in CSP group (mean change 0 [−8, 8] ms; p = 0.98) – Figure 3, panels B and D. Interventricular e-DYS was significantly higher in the RVP group than the CSP group after one year of pacing (RVP 26 [19, 33] ms vs CSP -5 ± [−12, 2] ms; p <0.0001).

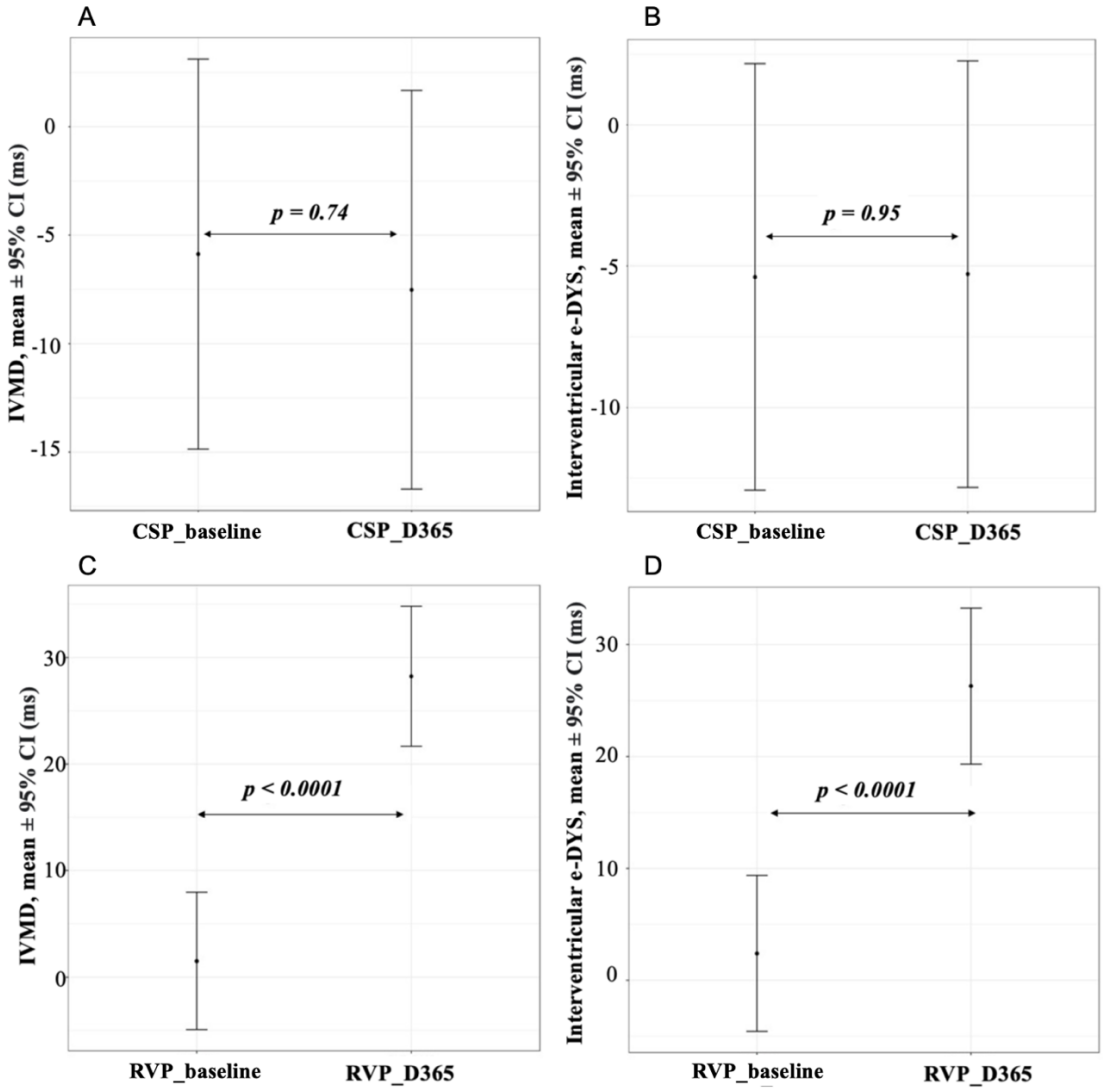

Figure 3 - Linear mixed-effect models comparing baseline and 1-year (D365) interventricular mechanical delay (IVMD) - panels A and C, and interventricular e-DYS (panels B and D) during conduction system pacing (CSP) and right ventricular pacing (RVP).

The relationship between interventricular mechanical and electrical dyssynchrony

The values of IVMD and interventricular e-DYS were the same in the whole study population both before the pacemaker implantation (−2 [−8, 5] ms for IVMD vs. −1 [−6, 5] ms for interventricular e-DYS; p = 0.31) and after one year of pacing (14 [7, 21] ms for IVMD vs. 14 [7, 20] ms for UHF; p = 0.70).

Comparison of IVMD and interventricular e-DYS calculated automatically by software in all 53 patients (including both baseline and one-year control) showed moderate to strong correlation (R=0.74; p <0.0001) - Fig. 4.

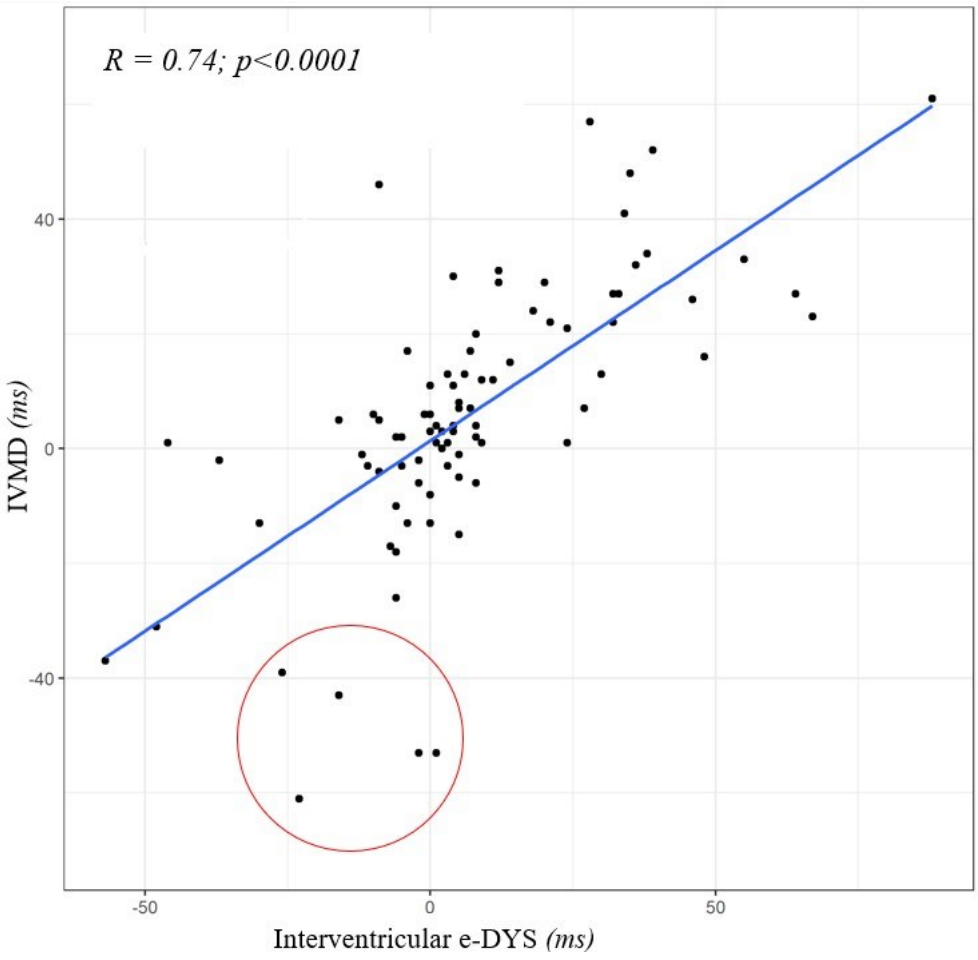

Figure 4 – The relationship between IVMD vs interventricular e-DYS; IVMD on the y-axis and interventricular e-DYS on the x-axis. The red circle highlights the cases in which automatic interventricular e-DYS measurements failed. R = Spearman´s correlation coefficient; p = p-value.

Visual re-assessing of the UHF-ECG maps identified 5 cases in which the automated interventricular e-DYS algorithm failed. They all had RBBB during the spontaneous

rhythm and are situated in the lower left quadrant of the graph in Fig. 4 – red circle. We show an example of one of these patients in Figure 5. In this case, the automated algorithm incorrectly identified the RV lateral wall activation because UHF-ECG visualized two activation centers under the lead V1 – black and white crosses. The one with the stronger signal (black cross) occurring 68 ms ahead of the weaker one (white cross) was incorrectly taken as the reference point for interventricular e-DYS calculation. The same phenomenon was observed in all other four patients, visualized by the red circle in Figure 4. Manual re-assessment of the interventricular e-DYS to the latest V1 activations in those five patients improved the correlation between IVMD and interventricular DYS (R= 0.78, p <0.0001) – Fig. 5.

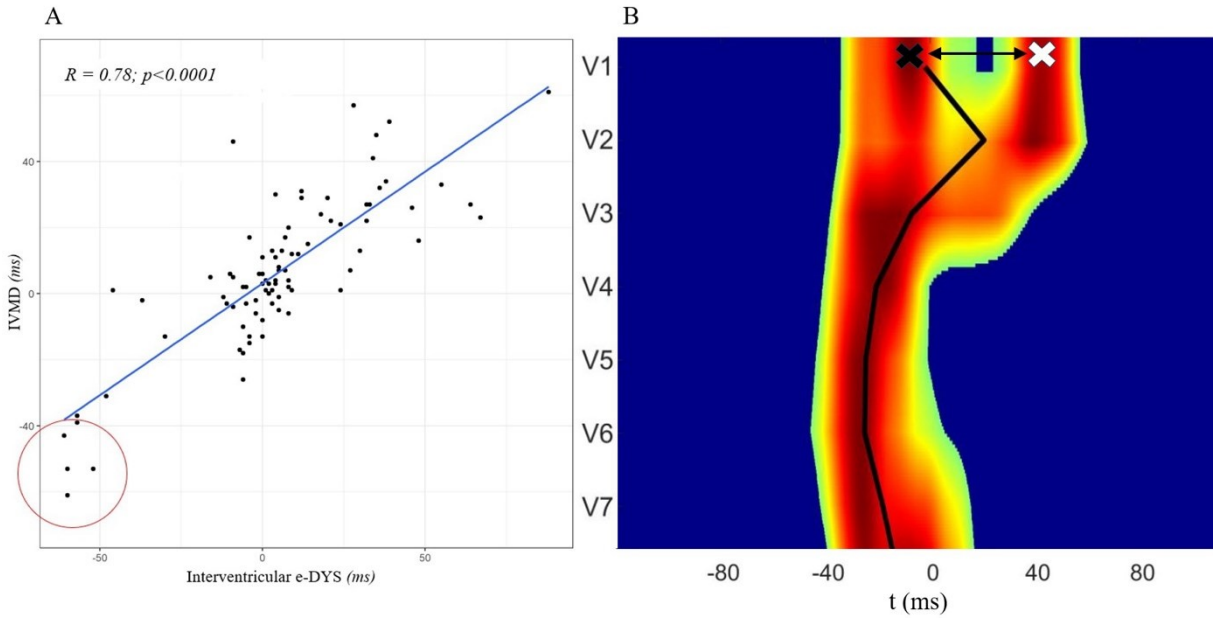

Figure 5: A – The relationship of IVDM vs manually corrected interventricular e-DYS; IVMD on the y-axis and interventricular e-DYS on the x-axis. The red circle highlights the cases with manually corrected interventricular e-DYS. R = Spearman´s correlation coefficient; p = p value. B - An example of automated interventricular e-DYS calculation failure in the patient with RBBB. Under the V1 lead, two distinct activations are visualized. The first activation (black cross) had a higher intensity and was 45 before (black cross) the second one (white cross). The automated algorithm calculated interventricular e-DYS as the difference between the maximal activation in V7 and V1 (-16ms). However, manual measurement of the interventricular e-DYS as the difference between maximal activation in V7 and the latest activation in V1 led to the correction of the interventricular e-DYS to a value of -61ms. IVMD was -43ms in this case.

4.7. Discussion

This study showed that both echocardiography and UHF-ECG reflected changes in interventricular dyssynchrony during RVP and CSP in bradycardia patients. Both methods

of dyssynchrony assessment showed similar results, i.e., while CSP preserves interventricular dyssynchrony, RV myocardial pacing leads to its increase.

Ventricular dyssynchrony, i.e., bigger-than-normal time delay between the activation of various ventricular segments, was identified as the main reason for PICM development.[41] The easiest way to assess ventricular electrical dyssynchrony during pacing is to measure paced QRS duration (QRSd). It was, however, shown that paced QRSd is only poorly associated with PICM development,[13] and its main weakness is that it cannot assess the activations of the right and left ventricles separately. Better predictors of PICM development are echocardiographic markers of ventricular dyssynchrony. Of those, both LV dyssynchrony and right-to-left interventricular dyssynchrony were much stronger predictors of PICM than any other ECG or clinical indicators.[29,35]

Time differences between the activation of particular ventricular segments could be, however, easily assessed by UHF-ECG.[155] In recent years, our group has been studying electrical ventricular dyssynchrony using UHG-ECG in bradycardia patients. We have shown that HBP is the most physiological method of ventricular pacing, and all other pacing types from RV and the left bundle branch area led to an increase in ventricular electrical dyssynchrony.[111–113] Pacing locations with myocardial capture in the RV were associated with the right-to-left activation pattern and delayed activations of ventricular segments under V6-V8.[111,156] LBBP and LVSP led to left-to-right ventricular activation patterns, with more delayed activation under the V1 leads during LBBP.[113] Data in the current work confirm previous observations, i.e., RV myocardial pacing increased right-to-left interventricular electrical dyssynchrony (+ 26 ms). In contrast, interventricular e-DYS was negative (– 5 ms) in the CSP group.

The main finding of our study, however, is that there was no difference between mean values of interventricular electrical dyssynchrony measured by UHF-ECG and mechanical interventricular dyssynchrony measured by echocardiography. Mechanical interventricular dyssynchrony for prediction of PICM during the RVP has already been studied by Bansal et al.[29] The average values of IVMD during RVP in their study (25 ms during RV septal and 32 ms during the RV apical pacing) were similar to those observed in our group of patients with RV pacing. Most importantly, they demonstrated that interventricular dyssynchrony > 40 ms is a stronger predictor of PICM development than paced QRSd, pre-implant LVEF, RV pacing location, or any other studied clinical

characteristics. To determine whether the UHF-ECG electrical dyssynchrony is a similarly strong predictor of the PICM is the goal of the currently undergoing clinical trial (www.clinicaltrials.gov - NCT04908033).

Data on the relationship between mechanical and electrical dyssynchrony in bradycardia patients are scarce. We identified only one study examining the relationship between IVMD and LV lateral wall delay (assessed as a time between pacing artifact and R wave peak time in lead V5, i.e., Sti-LVAT) in patients with HBP, RVP, and LBBP. [157] They studied 20 patients with complete AV block and found that RV septal and apical pacing led to increased IVMD (23 ms and 35 ms, respectively) compared to HBP (5 ms) and LBBP (– 19 ms). There was a significant but weak correlation between IVMD and Sti-LVAT during all studied captures (R = 0.39). In our study, we were able to show a much stronger relationship between IVMD and UHF-ECG-derived parameters of interventricular dyssynchrony when using a fully automated method of the assessment of electrical delays between V1 and V7 activations.

We have also observed that UHF-ECG failed to calculate interventricular dyssynchrony correctly in some RBBB patients. The assessment of the local ventricular activation by UHF-ECG relies on measuring the current amplitudes produced by the closest ventricular segments under the specific lead. Due to anatomical reasons, the V1 lead may be placed close to both the RV lateral wall and the proximal part of the interventricular septum. It is very likely that in those patients with failed interventricular dyssynchrony assessment, the septal rather than RV lateral wall activation was taken as the reference point for the interventricular e-DYS calculation. However, the correct value of interventricular electrical dyssynchrony assessment was correctly calculated after the visual assessment of the UHF-ECG maps and manual correction of the marker to the latest V1 activation, which should represent the RV lateral wall depolarization.

4.8. Limitations:

This was a proof-of-concept study with a limited number of participants. Although the echocardiographers were blinded to the patient group allocation, the position of the pacing lead could be revealed during the evaluation. Successful assessment of IVMD was limited in some patients due to the poor quality of the PW Doppler signal in LVOT or RVOT. This resulted from the project's inclusion criteria that specified only sufficient

echocardiography window quality for LVEF calculation but not for interventricular dyssynchrony assessment. The study's results shouldn't be generalized for all patients with bradycardia treated by RVP and CSP, as only patients with preserved LV and RV systolic function were included. The reason for this decision was that published research shows that mechanical and electrical interventricular dyssynchrony do not correspond well in patients with RV or LV systolic dysfunction.[158,159]

4.9. Conclusion:

Our work showed that UHF-ECG-derived measure of interventricular electrical dyssynchrony could be used for the dyssynchrony assessment in bradycardia patients with preserved LV and RV functions, both during spontaneous rhythms and pacing. It expressed the interventricular dyssynchrony by measuring the delays from standard chest ECG leads with similar results as echocardiography by measuring IVMD. Both methods showed that conduction system pacing preserves low interventricular dyssynchrony, while RV myocardial pacing leads to its increase. The question of whether the UHF-ECG-derived interventricular dyssynchrony could be used in a clinical setup to predict PICM or clinical events in all patients with bradycardia needs to be investigated further.

5. General conclusion

Declining LV performance and development of HF are relatively common complications in patients receiving RV myocardial pacing. These complications occur due to non-physiological ventricular activation, resulting in dyssynchronous ventricular contractions that are detectable soon after initiation of RV pacing. Conventional ECG and echocardiographic tools for assessing dyssynchrony are either insufficient to reliably predict PICM or are not feasible in routine clinical practice. Therefore, better imaging and laboratory tools for risk stratification, prevention, and detection of PICM are desired.

Several methods based on the processing of signals generated by ventricular depolarization (ECGi and BSPM) or echocardiography can assess ventricular dyssynchrony. However, most of these are complex, time-consuming, and cannot be readily performed during standard implant procedures. Alternatively, this information can be obtained using UHF-ECG, which can be used to visualize ventricular depolarization

patterns. This method analyzes high-frequency ECG signals in a 12-lead ECG. It uses standard chest leads and provides information on ventricular activation in less than three minutes. Until now, no research has been published regarding the relationship between mechanical dyssynchrony derived from echocardiography and electrical dyssynchrony derived from UHF-ECG.

In the first study presented, we showed that 17 % of patients with RVP developed PICM within six months of pacing, while none with HBP developed PICM. RVP resulted in a decrease in LVEF compared to HBP, which preserved normal LV function. In addition, we were able to show that the beneficial effect of HBP on LV remodeling was also reflected in biomarkers of collagen metabolism. HBP was associated with lower serum levels of TGF-β1 after six months of pacing compared to patients with RVP. LVEF decreased more in RVP patients with higher baseline levels of Gal-3 and ST2 than in those with lower baseline levels after six months of pacing. Therefore, we concluded that Gal-3 and ST2 have the potential to identify patients in whom RVP does not pose a significant risk. To verify their power in predicting PICM, further studies with more patients, longer follow-ups, and clinical endpoints are needed.

In the second study presented, we showed that interventricular dyssynchrony derived from echocardiography correlates well with interventricular dyssynchrony derived from UHF-ECG. Both methods showed that CSP preserves low interventricular dyssynchrony, whereas RVP leads to increased interventricular dyssynchrony. Therefore, we concluded that UHF-ECG can be used for rapid and non-invasive assessment of interventricular dyssynchrony in patients with preserved ventricular function and without structural heart disease before and after pacemaker implantation. However, the clinical impact of UHF-ECG has yet to be established. Therefore, it is desirable to perform randomized prospective trials to verify whether the dyssynchrony parameters derived from UHF-ECG predict adverse clinical outcomes of cardiac pacing, or whether UHF-ECG guidance during pacemaker implantation could be used to select a pacing site that would avoid ventricular dyssynchrony.

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1. **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. *Arrhythm Electrophysiol Rev*. 2022;11. doi:10.15420/aer.2022.01
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4. Curila K, Jurak P, Vernooy K, Jastrzebski M, Waldauf P, Prinzen F, Halamek J, Susankova M, Znojilova L, Smisek R, Karch J, Plesinger F, Moskal P, Heckman L, **Mizner J**, Viscor I, Vondra V, Leinveber P, Osmancik P. Left Ventricular Myocardial Septal Pacing in Close Proximity to LBB Does Not Prolong the Duration of the Left Ventricular Lateral Wall Depolarization Compared to LBB Pacing. *Front Cardiovasc Med.* 2021 Dec 7;8:787414. doi: 10.3389/fcvm.2021.787414. PMID: 34950718; PMCID: PMC8688808.
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6. *Unpublished research:* **Mizner J**, Beela A, Curila K et. al., Electrical and mechanical interventricular dyssynchrony coupling in bradycardia patients; a UHF-ECG validation trial. Prague 2024. Manuscript in preparation.

7. Author´s list of conference abstracts:

1. **J Mizner**, K Curila, P Stros, R Prochazkova, J Vesela, J Karch, D Herman, P Osmancik, P Widimsky, His bundle pacing preserves left ventricular ejection fraction in patients with conduction disease and high risk of development pacing induced cardiomyopathy, ESC main congress Amsterdam, *European Heart Journal*, Volume 41, Issue Supplement_2, November 2020, ehaa946.0774, https://doi.org/10.1093/ehjci/ehaa946.0774
2. **J. Mizner**, P. Jurák, H. Línková, P. Štros, O. Süssenbek, J. Veselá, A. Beela, J. Lumens, K. Čurila, Conduction system pacing preserves both electrical and mechanical interventricular synchrony – a UHF-ECG validation study, EHRA 2024, Berlin
3. **J. Mizner**, P. Jurák, H. Línková, P. Štros, J. Veselá, O. Süssenbek, A. Beela, J. Lumens, K. Čurila, Conduction system pacing preserves both electrical and mechanical interventricular synchrony – a UHF-ECG validation study, xx. české a slovenské sympozium o arytmiích a kardiostimulaci 2023, Ostrava
4. **J. Mizner**, P. Jurák, H. Línková, P. Štros, O. Süssenbek, J. Veselá, A. Beela, J. Lumens, K. Čurila, Conduction system pacing preserves both electrical and mechanical

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8. **J. Mizner**, K Curila, P Stros, R Prochazkova, J Karch, J Vesela, D Herman, P Osmancik, Identifikace prediktorů úspěchu stimulace Hisova svazku u pacientů s převodní poruchou, XVII. slovenské a české sympozium o arytmiích a kardiostimulaci 2019, Bratislava

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