Charles University

3rd Faculty of Medicine

# Autoreport of a dissertation

**English title:** Pacing-induced cardiomyopathy and electro-mechanical ventricular dyssynchrony – novel non-invasive dyssynchrony assessment tools and biomarkers of collagen metabolism

**Czech title:** Stimulací indukovaná kardiomyopatie a elektro-mechanická komorová dyssynchronie – nové neinvazivní diagnostické metody a biomarkery metabolismu kolagenu

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# Table of Contents

# 1.Introduction

Right ventricular pacing (RVP) is well tolerated by some patients; however, others may experience worsening of left ventricular (LV) function and develop pacing-induced cardiomyopathy (PICM). This is mainly a consequence of non-physiological ventricular activation bypassing the conduction system and leading to electro-mechanical ventricular dyssynchrony.[1]

Adverse LV remodeling due to RVP involves changes in global LV function and in the ventricular microstructure. This is reflected in extra-cellular matrix (ECM) metabolism and increased myocardial fibrosis.[2] However, it is unknown whether biomarkers of collagen metabolism could reflect adverse effects of RVP. The highest risk of PICM was documented in patients with a high burden of RVP, decreased LV function, coronary artery disease, and wider spontaneous or paced QRS complexes.[3]

On the other hand, conduction system pacing (CSP) preserves relatively synchronous ventricular activation and therefore represents the more physiological method of ventricular pacing.[4,5] However, CSP methods are complex, require more time, higher radiation doses and trained electrophysiology specialists with dedicated tools. Therefore, CSP is not currently available for all bradycardia patients now, and it is desirable to improve the PICM risk stratification to preselect the high-risk patients.[6]

Mechanical ventricular dyssynchrony can be readily assessed by echocardiography. Echocardiographic dyssynchrony indices such as interventricular mechanical delay (IVMD) and left ventricular dyssynchrony were proven to be an independent risk factor for PICM development.[7–9] However, they never entered common clinical practice due to their limitations. Therefore, we are still lacking rapid and reliable methods of interventricular dyssynchrony assessment, not only before and after, but also during the implantation procedures.

Advanced tools for electrical dyssynchrony assessment were also intensively studied since it became evident that conventional ECG parameters such as QRS duration and QRS morphology are insufficient. Among others, ultra-high-frequency electrocardiography (UHF-ECG) is a non-invasive imaging tool that visualizes ventricular activation patterns during the spontaneous and paced rhythms.[10] It analyzes electrical signals in frequencies above 100 Hz and enables the calculation of ventricular dyssynchrony in a matter of minutes with standard surface chest leads.[11]

UHF-ECG was used to intensively study ventricular dyssynchrony associated with His bundle pacing (HBP), RVP, biventricular, LV septal pacing (LVSP) and left bundle branch area pacing (LBBAP).[4,10,12,13] However, until now, no studies have compared electrical dyssynchrony assessed by UHF-ECG with mechanical dyssynchrony assessed by echocardiography.

# 2. A randomized comparison of His bundle pacing versus RV pacing: effect on left ventricular function and biomarkers of collagen metabolism

## 2.1. 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 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 6 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.

## 2.2. 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 signifikantně 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 nízkou hladinou před implantací.

## 2.3. Hypothesis and aims

We hypothesized that HBP will preserve LV systolic function in patients at high risk of PICM, while RVP will cause its deterioration. Moreover, we hypothesized that adverse LV remodeling will be reflected in sera levels of biomarkers of collagen metabolism. Therefore, this study aimed to assess the effect of RVP and HBP on LVEF in patients at high risk of PICM. Another goal was to identify laboratory markers of collagen metabolism which could predict or detect the adverse effects of RV pacing on LV performance. This has never been studied before.

## 2.4. Methods

This was a single-center, prospective, open-labeled, randomized study. Only patients with atrioventricular (AV) conduction disease and an indication for permanent cardiac pacing with anticipated high burden of the RVP were enrolled. Patients also had to have at least one more risk factor for PICM development, e.g. decreased LV systolic function, QRS duration > 115 ms or coronary artery disease.

Exclusion criteria were as follows: severe valvular disease, 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. Blood sampling and echocardiography were performed before pacemaker implantation and at the six-month follow-up visit. LV ejection fraction was calculated using Simpson's biplane method. Serum analysis of 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 was performed using specific Quantikine ELISA tests.

Statistical analysis was performed using Software R version 4.0.5. Intention-to-treat and as-treated analyses were performed. Repeated measurement comparisons were made using a linear mixed effect model. 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. Further methods included Student’s t-test, Fisher’s exact test, and a Chi-squared test; for nonparametric data the Wilcoxon test and Mann-Whitney U test were used.

## 2.5. Results

Fifty-three patients were randomized to the HBP, and 39 were randomized to RVP. Lead placement in the HB region failed in 19 % patients randomized to the HBP group. As a result, 49 patients had RVP and 43 had HBP. The mean age was 78 years. No difference in baseline clinical characteristics was observed between groups relative to *intention-to-treat* and *as-treated* analyses.

After six months of pacing, LVEF significantly decreased in the RVP group but remained the same in the HBP group. 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* analyses ($p = 0.008$).

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

Patients with an LVEF decline ≥ 5% after six months of RVP had higher baseline levels of Gal-3 and ST2 than those RVP patients with LVEF decline ≤ 5%. 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%. 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% sensitivity 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 RV pacing.

## 2.6. Conclusions

In patients at high risk of PICM, RVP led to a decline in LVEF compared to HBP, which preserved LV function after six months of pacing. Gal-3 and ST2-IL have the potential to better identify patients in which RVP does not pose a significant risk of PICM development. However, studies with larger numbers of participants are needed to verify their predictive powers relative to PICM.

# 3. Electrical and mechanical interventricular dyssynchrony coupling in bradycardia patients; a UHF-ECG validation trial

## 3.1. 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:**

53 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.

## 3.2. 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

randomizováno 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 elektrickou 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.

## 3.3. Hypothesis and aims

Our hypothesis was that mechanical dyssynchrony assessed by echocardiography and electrical dyssynchrony assessed by UHF-ECG will be comparable in patients with preserved LV and RV function undergoing pacemaker implantation. The aim of this study was to establish and compare interventricular dyssynchrony assessed by UHF-ECG and echocardiography in patients with bradycardia treated by RVP or CSP.

## 3.4. Methods

The population consisted of patients enrolled in the ´´Ultra-high-frequency ECG for Prediction of Left Ventricular Remodeling´´ trial. This is a currently ongoing prospective, multi-centric, in part randomized, clinical trial enrolling patients with an AV conduction disease and an indication for permanent pacing. Patients were assigned into two groups and received either RVP or CSP.

Exclusion criteria were as follows: planned cardiac surgery; hypertrophic cardiomyopathy; an indication for implantable cardioverter-defibrillator or 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 one-year follow-up were screened for electrical and mechanical dyssynchrony assessment. From these patients only patients with preserved LV and RV systolic function were included. Both echocardiography and UHF-ECG were performed before pacemaker implantation and after one year of follow-up during the pacing.

Echocardiographic interventricular mechanical delay (IVMD) was measured as a time difference between LV and RV pre-ejection periods. Measurements were performed by two experienced and blinded examinators using pulsed wave Doppler imaging. A positive value indicates right-to-left activation delay, and a negative value indicates left-to-right activation delay.

A ventricular dyssynchrony imaging (VDI) monitor (ISI Brno, Cardion, FNUSA, Czech Republic) was used to record and analyze the UHF-ECG signals. Standard V1-V7 chest lead positions were used. UHF-ECG data for all captures were collected during 5-10minutes of DDD pacing with prespecified AV delays.

Median amplitude envelopes were computed for 16 frequency bands 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 50% threshold of the baseline-to-peak amplitude in each chest lead.

Interventricular dyssynchrony (interventricular e-DYS) was measured as the time difference in the local activation between the V7 and V1 lead. A positive value indicates right-to-left activation delay pattern, and a negative value indicates left-to-right activation delay.

Statistical analysis was performed in Software: R version 4.0.5. Correlations were assessed using Spearman's and Pearson's tests. Repeated measurement comparisons were made using a linear-mixed effects model. Further methods used Student's t-test, Fisher's exact test, a Chi-squared test; for nonparametric data, the Wilcoxon test and Mann-Whitney U test were used.

## 3.5. Results

From the 53 analyzed patients, 21 received CSP and 32 RVP. The median age was 75 years. There were no clinical differences between the two groups.

IVMD and automatic interventricular e-DYS were similar 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 automatic interventricular e-DYS in all paced and spontaneous rhythms showed moderately strong correlation ($R = 0.74$; $p < 0.0001$). Manual re-assessment of the interventricular e-DYS to the latest V1 activations led to an improved correlation between IVMD and interventricular DYS ($R = 0.78$, $p < 0.0001$).

Both the CSP and the RVP groups had comparable IVMD at the baseline (−6 [−17, 5] ms for CSP vs 2 [−7, 10] ms for RVP; $p=0.22$), but while there was a distinct 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 the

CSP group (mean change −2 [−12, 9] ms; p = 0.74). 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).

The interventricular e-DYS was also similar for the CSP and the RVP groups at the baseline −5 [−14, 4] ms for CSP vs. 2 [−5, 10] ms for RVP; 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 the CSP group (mean change 0 [−8, 8] ms; p = 0.98). Interventricular e-DYS was significantly higher in the RVP group than in the CSP group after one year of pacing (RVP 26 [19, 33] ms vs CSP −5 ± [−12, 2] ms; p <0.0001).

## 3.6. Conclusions

This work showed that UHF-ECG could be used for dyssynchrony assessment in patients with bradycardia and pacemakers. It expressed the interventricular dyssynchrony non-invasively by measuring the delays between standard chest ECG leads, and the results were similar to those of echocardiography measurements of IVMD. Both methods showed that CSP preserves low interventricular dyssynchrony, while RVP leads to its increase. Whether the UHF-ECG can be used in a clinical setup to predict clinical outcomes needs to be investigated further.

# 4. Author's list of publications

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

2. **Mizner J**, Waldauf P, Grieco D, et al. A randomized comparison of HBP versus RVP: Effect on left ventricular function and biomarkers of collagen metabolism. *Kardiol Pol*. 2023;81(5):472-481. doi:10.33963/KP.a2023.0065

3. Curila K, Jurak P, Halamek J, Prinzen F, Waldauf P, Karch J, Stros P, Plesinger F, **Mizner J**, Susankova M, Prochazkova R, Sussenbek O, Viscor I, Vondra V, Smisek R, Leinveber P, Osmancik P. Ventricular activation pattern assessment during right ventricular pacing: Ultra-high-frequency ECG study. *J Cardiovasc Electrophysiol*. 2021 May;32(5):1385-1394. doi: 10.1111/jce.14985. Epub 2021 Mar 11. PMID: 33682277.

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.

5. Čurila K, Štros P, **Mizner J**, et al. Stimulace Oblasti Levého Raménka Je Fyziologická Alternativa Pravokomorové/ Biventrikulární Stimulace-Výsledky Registru Implantačního Centra. Vol 21.; 2022. *Intervenční a akutní kardiologie*

*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

# 5. Cited literature


1. Prinzen FW, Lumens J, Duchenn J, Vernooy K. Electro-energetics of Biventricular, Septal and Conduction System Pacing. *Arrhythm Electrophysiol Rev*. 2021;10(4):250-257. doi:10.15420/aer.2021.30

2. Ahmed FZ, Khattar RS, Zaidi AM, Neyses L, Oceandy D, Mamas M. Pacing-induced cardiomyopathy: Pathophysiological insights through matrix metalloproteinases. *Heart Fail Rev*. 2014;19(5):669-680. doi:10.1007/s10741-013-9390-y

3. Khurshid S, Epstein AE, Verdino RJ, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy. *Heart Rhythm*. 2014;11(9):1619-1625. doi:10.1016/j.hrthm.2014.05.040

4. Curila K, Jurak P, Halamek J, et al. Ventricular activation pattern assessment during right ventricular pacing: Ultra-high-frequency ECG study. *J Cardiovasc Electrophysiol*. 2021;32(5):1385-1394. doi:https://doi.org/10.1111/jce.14985

5. Abdelrahman M, Subzposh FA, Beer D, et al. Clinical Outcomes of His Bundle Pacing Compared to Right Ventricular Pacing. *J Am Coll Cardiol*. 2018;71(20):2319-2330. doi:10.1016/j.jacc.2018.02.048

6. Vijayaraman P, Herweg B, Dandamudi G, et al. Outcomes of His-bundle pacing upgrade after long-term right ventricular pacing and/or pacing-induced cardiomyopathy: Insights into disease progression. *Heart Rhythm*. 2019;16(10):1554-1561. doi:10.1016/j.hrthm.2019.03.026

7. Bansal R, Parakh N, Gupta A, et al. Incidence and predictors of pacemaker-induced cardiomyopathy with comparison between apical and non-apical right ventricular pacing sites. *Journal of Interventional Cardiac Electrophysiology*. 2019;56(1):63-70. doi:10.1007/s10840-019-00602-2

8. Tops LF, Suffoletto MS, Bleeker GB, et al. Speckle-Tracking Radial Strain Reveals Left Ventricular Dyssynchrony in Patients With Permanent Right Ventricular Pacing. *J Am Coll Cardiol*. 2007;50(12):1180-1188. doi:10.1016/j.jacc.2007.06.011

9. Tops LF, Schalij MJ, Holman ER, van Erven L, van der Wall EE, Bax JJ. Right Ventricular Pacing Can Induce Ventricular Dyssynchrony in Patients With Atrial Fibrillation After Atrioventricular Node Ablation. *J Am Coll Cardiol*. 2006;48(8):1642-1648. doi:10.1016/j.jacc.2006.05.072

10. 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

11. Jurak P, Curila K, Leinveber P, et al. Novel ultra-high-frequency electrocardiogram tool for the description of the ventricular depolarization pattern before and during cardiac resynchronization. *J Cardiovasc Electrophysiol*. 2020;31(1):300-307. doi:10.1111/jce.14299

12. Curila K, Prochazkova R, Jurak P, et al. Both selective and nonselective His bundle, but not myocardial, pacing preserve ventricular electrical synchrony assessed by ultra-high-frequency ECG. *Heart Rhythm*. 2020;17(4):607-614. doi:10.1016/j.hrthm.2019.11.016

13. Curila K, Jurak P, Jastrzebski M, et al. Left bundle branch pacing compared to left ventricular septal myocardial pacing increases interventricular dyssynchrony but accelerates left ventricular lateral wall depolarization. *Heart Rhythm*. 2021;18(8):1281-1289. doi:10.1016/j.hrthm.2021.04.025