




ORIGINAL ARTICLE

Acute echocardiographic and hemodynamic response to his-bundle pacing in patients with first-degree atrioventricular block

Zak Loring MD^{1,2}  | Fredrik Holmqvist MD, PhD^{1,3}  | Edward Sze MD^{1,4} |
Fawaz Alenezi MD, MSc¹ | Kristen Campbell PharmD^{4,5} | Jason I. Koontz MD, PhD¹ |
Eric J. Velazquez MD^{1,6} | Brett D. Atwater MD^{1,7} | Tristram D. Bahnson MD¹ |
James P. Daubert MD¹ 

¹Division of Cardiology, Department of Medicine, Duke University, Durham, North Carolina, USA

²Duke Clinical Research Institute, Durham, North Carolina, USA

³Department of Cardiology, Lund University, Lund, Sweden

⁴Maine Medical Center, Portland, Maine, USA

⁵Department of Pharmacy, Duke University Medical Center, Durham, North Carolina, USA

⁶Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University, New Haven, Connecticut, USA

⁷Section of Cardiac Electrophysiology, Inova Heart and Vascular Institute, Fairfax, Virginia, USA

Correspondence

Zak Loring, Department of Medicine, Division of Cardiology, Duke University Medical Center, 2301 Erwin Rd, DUMC 3845, Durham, NC 27710, USA.
Email: zloring@gmail.com

Funding information

This study was funded by a grant from the Medtronic-Duke University Strategic Alliance

Abstract

Background: Atrial pacing and right ventricular (RV) pacing are both associated with adverse outcomes among patients with first-degree atrioventricular block (1°AVB). His-bundle pacing (HBP) provides physiological activation of the ventricle and may be able to improve both atrioventricular (AV) and inter-ventricular synchrony in 1°AVB patients. This study evaluates the acute echocardiographic and hemodynamic effects of atrial, atrial-His-bundle sequential (AH), and atrial-ventricular (AV) sequential pacing in 1°AVB patients.

Methods: Patients with 1°AVB undergoing atrial fibrillation ablation were included. Following left atrial (LA) catheterization, patients underwent atrial, AH- and AV-sequential pacing. LA/left ventricular (LV) pressure and echocardiographic measurements during the pacing protocols were compared.

Results: Thirteen patients with 1°AVB (mean PR 221 ± 26 ms) were included. The PR interval was prolonged with atrial pacing compared to baseline (275 ± 73 ms, $p = .005$). LV ejection fraction (LVEF) was highest during atrial pacing ($62 \pm 11\%$), intermediate with AH-sequential pacing ($59 \pm 7\%$), and lowest with AV-sequential pacing ($57 \pm 12\%$) though these differences were not statistically significant. No significant differences were found in LA or LV mean pressures or LV dP/dT. LA and LV volumes, isovolumetric times, electromechanical delays, and global longitudinal strains were similar across pacing protocols.

Conclusion: Despite pronounced PR prolongation, the acute effects of atrial pacing were not significantly different than AH- or AV-sequential pacing. Normalizing atrioventricular and/or inter-ventricular dyssynchrony did not result in acute improvements in cardiac output or loading conditions.

KEYWORDS

echocardiography, EP study, first-degree AV-block, His-bundle, pacing

Clinical Trial Registration: NCT01985802 (<http://www.clinicaltrials.org>).

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Annals of Noninvasive Electrocardiology* published by Wiley Periodicals LLC.

1 | INTRODUCTION

Direct pacing of the His-bundle (His-bundle pacing [HBP]) activates the ventricle through the heart's intrinsic conduction system and has been hypothesized to mitigate the detrimental effects of inter-ventricular dyssynchrony from left bundle branch block or right ventricular pacing (Kronborg et al., 2012; Vijayaraman et al., 2017; Zanon et al., 2011). Atrioventricular (AV) dyssynchrony may negatively impact ventricular hemodynamics and has been associated with worse outcomes among patients undergoing cardiac resynchronization therapy (CRT; Friedman et al., 2016; Kronborg et al., 2010). The optimal pacing strategy for patients with AV dyssynchrony remains unknown.

First-degree atrioventricular block (1°AVB) has been considered a benign finding; however, recent studies suggest an independent association with increased risk of atrial fibrillation and all-cause mortality (Holmqvist & Daubert, 2013). In the Managed Ventricular Pacing (MVP) trial (Sweeney et al., 2010), there was an association between atrial pacing and death or heart failure (HF) hospitalization among patients with PR intervals ≥ 230 milliseconds (ms). The PR interval prolongs during atrial pacing at any rate (Sweeney et al., 2008), and it was hypothesized that increases in an already-prolonged PR interval may have increased AV dyssynchrony and driven the higher event rates. Canine studies have shown that ventricular hemodynamics are less impacted by AV dyssynchrony when the ventricle is activated via the intrinsic conduction rather than ventricular pacing (Kosowsky et al., 1968). It is unclear whether restoration of AV synchrony without introduction of inter-ventricular dyssynchrony through A-His (AH) sequential pacing would improve outcomes in patients with 1°AVB.

This study compared the acute hemodynamics and echocardiographic effects of three pacing strategies in patients with 1°AVB: (1) atrial pacing, (2) AH-sequential pacing, and (3) AV-sequential pacing. We hypothesized that AH-sequential pacing would be superior to atrial and AV-sequential pacing due to its preservation of both AV and inter-ventricular synchrony.

2 | METHODS

2.1 | Patient population

Patients undergoing clinically indicated pulmonary vein isolation (PVI) for atrial fibrillation using routine techniques at Duke University Medical Center were targeted for enrollment due to the need for left atrial (LA) access and pressure monitoring. Additional inclusion criteria were 1°AVB (PR ≥ 200 ms), QRS duration < 120 ms, and a normal left ventricular ejection fraction (LVEF $\geq 55\%$). Patients were excluded for participation in any concurrent research study, the presence of any bundle branch block, second- or third-degree AV-block, atrial fibrillation at the time of procedure, congestive heart failure, cardiomyopathy, myocardial infarction or recent major surgical procedure, or logistical issues (unavailability of echo lab staff at the time of procedure).

2.2 | Experimental protocol

The PVI was carried out according to the standard clinical routine under general anesthesia and at the discretion of the attending electrophysiologist. The experimental protocol was commenced before, during or after the LA ablation. The experimental protocol consisted of an electrophysiological study to assess the echocardiographic response to the three different pacing strategies (atrial, AH-sequential, and AV-sequential pacing). Catheters were positioned in the high right atrium, His-bundle region, and right ventricular (RV) apex to allow pacing at the desired positions. With each pacing strategy, pacing was performed at 10 to 15 beats per minute (bpm) above the basal rate or 5 to 10 bpm below the Wenckebach point, whichever was lower. For AV-sequential and AH-sequential pacing, a fixed AV delay of 150 ms was used. Echocardiographic evaluation (see below) was done during baseline without pacing, and during pacing at each of the pre-specified locations. Pacing from each site was maintained for at least one minute before echocardiographic recording to ensure that a steady-state had been obtained. The left atrial pressure was measured using the trans-septal sheath. The order of application of the three pacing protocols was varied across patients.

2.3 | Criteria to ensure para-hisian pacing

Selective His-bundle capture was confirmed by identifying (1) an isoelectric interval between pacemaker spike and QRS complex; (2) a QRS identical to that during normal sinus rhythm and (3) pacing from a fluoroscopic site similar to His recording (Zanon & Barold, 2012). Non-selective His-bundle pacing was confirmed if (1) an isoelectric interval between spike and QRS was not observed; (2) change in pacing output leading to transition of QRS morphology, proving the existence of fusion and (3) pacing from similar fluoroscopic site to His recording or slightly more ventricular (Burri et al., 2020).

2.4 | Echocardiographic evaluation

All study subjects underwent a comprehensive transthoracic echocardiogram. Two-dimensional views during five to ten beats were recorded digitally using the GE Vivid 7 system (GE Healthcare, Chicago, IL). Measurement of the electromechanical delay (time between stimulation and the tissue Doppler imaging [TDI] systolic wave onset; Bader et al., 2004) and electrosystolic delay (time between QRS onset and peak systolic contraction; Bax et al., 2003) using pulsed-wave TDI with sampling in the basal segments of opposing left ventricular walls (the midseptal and the midlateral wall) in the apical four-chamber view was also measured. Left ventricular ejection fraction (LVEF), LV dimensions, LA dimensions, isovolumetric contraction (IVCT), and relaxation (IVRT) times were collected. All measurements were conducted in accordance with American Society of Echocardiography (ASE) recommendations. LVEF was calculated by the percent change

in LV volume between systole (LV end-systolic volume [LVESV]) and diastole (LV end-diastolic volume [LVEDV]). Studies were uploaded to the vendor-independent TomTec image arena (Munich, Germany; REF-TTA2; LOT-20.01). This software was used to measure speckle-tracking echocardiography global longitudinal strain (GLS) for all cardiac chambers by manually tracing the endocardial border in end systole and the software automatically traced a region of interest including the entire myocardium. The patients, the investigators performing the echocardiographic procedure, and the physicians interpreting the echocardiographic images were blinded to pacing site; only the treating electrophysiologist who performed the electrophysiological study was aware of the pacing site.

2.5 | Impedance catheter procedures

In a subset of the study population ($n = 4$) a CD Leycom pressure sensor catheter (CD Leycom, 7556 BP Hengelo, The Netherlands) was used to obtain cardiac output measurements and real-time LV pressure measurements. The pressure sensor catheter was inserted through a trans-septal sheath (positioned for the ablation procedure) to access the LA and advanced through the mitral valve to access the LV. Cardiac output and real-time LV pressures were obtained in each pacing configuration.

2.6 | Statistics

Data are presented as mean \pm standard deviation or as a percentage of the total (categorical variables). For comparisons between atrial pacing and AV- or AH-pacing, paired t-tests or Wilcoxon's signed-rank test was used based on the results of the Shapiro-Wilk test. Fisher's exact test was used for categorical variables. All tests were two-sided and an adjusted $p < .05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Mac, Version 25.0. Armonk, NY: IBM Corp) and R (R Core team, 2017, Vienna, Austria).

3 | RESULTS

Between April 2015 and October 2017, 561 patients were screened for enrollment. An ECG demonstrating sinus rhythm, a PR >200 ms, and QRS <120 ms was present in 95 patients. Exclusion criteria were present in 75 patients resulting in 20 patients being enrolled in the study (Figure 1). An additional seven patients were excluded due to having a normal PR at the time of the procedure ($n = 2$), having inadequate echo images ($n = 4$), or being in atrial fibrillation at the time of the procedure ($n = 1$). A total of 13 patients underwent the pacing protocols and constitute the study population.

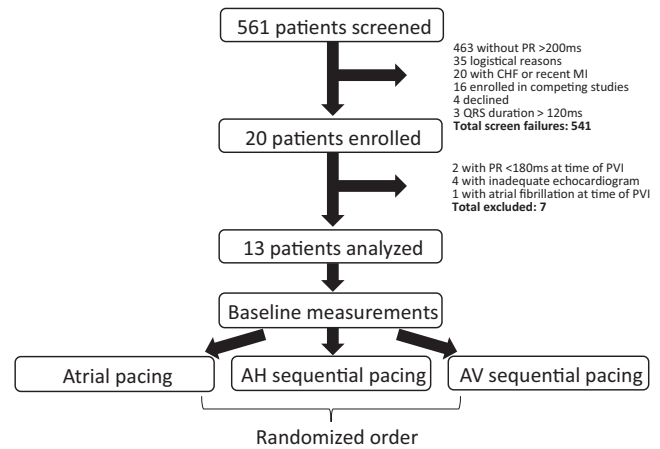


FIGURE 1 CONSORT diagram of patient enrollment: Description of screening and exclusion of patients approached for inclusion in this study. AH, atrial-His; AV, atrial-ventricular; CHF, congestive heart failure; MI, myocardial infarction; PVI, pulmonary vein isolation

Baseline characteristics of the study population are shown in Table 1. The mean age of the studied patients was 65 ± 9 years and the majority (69%) were male. The mean PR interval on the screening ECG at enrollment was 221 ± 26 ms (range 200–278 ms). Prior to the procedure, seven patients (54%) were using beta-blockers, three were using calcium channel blocker (23%) and nine patients (69%) were using Class I or III antiarrhythmic drugs. All but one patient (92%) were using one or more of these drugs. Of note, for 11 out of the 12 patients treated with one of these drugs, at least one drug was held for one or more days prior to ablation.

ECG intervals at the time of the procedure are shown in Table 2. The mean baseline PR was 221 ± 26 ms. With atrial pacing, the mean PR interval significantly increased compared to baseline (275 ± 73 ms; $p = .005$). All but one patient showed an increase in PR interval with atrial pacing. The QRS durations during atrial and AH-sequential pacing were similar (95 ± 16 and 105 ± 22 ms, $p = .19$), but substantially prolonged with AV-sequential pacing (157 ± 20 ms, $p < .0001$). Selective His-capture was achieved in nine (69%) patients and non-selective His-capture in the rest.

Hemodynamic data for each of the pacing protocols is shown in Table 2. There were no significant differences in blood pressure, mean LA pressure, or the magnitude of the LA V wave across pacing protocols. Four of the included patients had invasive LV hemodynamic measurements done including LV end-diastolic pressure (LVEDP), mean LV pressure, and the maximum/minimum rates of LV pressure change (LV dP/dT_{max} and LV dP/dT_{min} , respectively). No differences in LV hemodynamics were seen across pacing protocols.

The echocardiographic measurements for each pacing protocol are summarized in Table 3. LVEF was highest in atrial pacing ($62 \pm 11\%$), intermediate in AH-sequential pacing ($59 \pm 7\%$) and lowest in AV-sequential pacing ($57 \pm 12\%$), but this difference was not statistically significant (Figure 2). LV volumes, stroke volume, LA volume, isovolumetric contraction and relaxation times, and global

TABLE 1 Baseline characteristics

Demographics	
Age (years)	65 ± 9
Male	9 (69%)
Physical examination	
Weight (kg)	94 ± 15
Height (cm)	176 ± 7.7
BMI (kg/m ²)	30.5 ± 6.4
Systolic blood pressure (mmHg)	136 ± 17
Diastolic blood pressure (mmHg)	74 ± 12
Screening ECG	
Heart Rate (bpm)	65 ± 14
PR interval (ms)	221 ± 26
QRS duration (ms)	99 ± 12
QTc (ms)	439 ± 32
Past medical history	
Hypertension	10 (77%)
Diabetes	2 (15%)
Cerebrovascular accident	1 (8%)
Chronic lung disease	1 (8%)
Renal disease	0 (0%)
Cancer in past 5 years	1 (8%)
Obstructive sleep apnea	5 (39%)
Current alcohol use	0 (0%)
Tobacco (no/current/former)	7 (54%)/0 (0%)/6 (46%)
Medication	
Beta blocker	7 (54%)
Calcium channel blockers	3 (23%)
Anticoagulant	12 (92%)
Aspirin	4 (31%)
ACE	3 (23%)
ARB	3 (23%)
Digoxin	2 (15%)
Aldosterone	1 (8%)
Class I or III antiarrhythmic drugs	9 (69%)

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; bpm, beats per minute; BMI, body mass index.

longitudinal strain were similar across pacing groups. Intraventricular dyssynchrony was measured by the difference in electromechanical delay (time from QRS onset to local contraction) of the septal to lateral walls and was not different between atrial pacing and AH- or AV-sequential pacing ($p = .48$, $p = .14$, respectively).

4 | DISCUSSION

In patients with 1°AVB, there were no significant differences in measures of systolic function (LVEF, stroke volume, global longitudinal

strain) or chamber volumes (LVEDV, LVESV, LA volume) during atrial, AV-sequential, or AH-sequential pacing. Atrial pacing resulted in further prolongation of the PR interval, but no adverse hemodynamic or echocardiographic changes were identified. Correction of 1°AVB with A-His-bundle sequential pacing demonstrated no hemodynamic benefit compared to baseline or atrial pacing in patients with modest PR prolongation.

Almost one in five (17.5%) of the patients with atrial fibrillation and normal left ventricular function, screened for potential inclusion in the current study were found to have 1°AVB. Taking age, male predominance, and cardiac comorbidity into account, this proportion is congruent with estimates from earlier studies (Crisel et al., 2011; Magnani et al., 2013). Additionally, concurrent medication use may have increased the incidence of PR prolongation in this population. The vast majority of patients in our study were using drugs known to prolong AV nodal conduction time (Pryostovsky, 1988). The influence of these drugs on AV nodal conduction is further supported by the fact that two patients were excluded from the study because their PR normalized after holding their AV nodal agents prior to their procedure.

During exercise, the PR interval shortens with increasing heart rate, primarily via a withdrawal of parasympathetic tone (Atterhog & Loogna, 1977; Danter & Carruthers, 1990). However, when heart rate is artificially increased by atrial pacing in the absence of simultaneous withdrawal of the parasympathetic tone, the PR interval paradoxically increases (Josephson, 2015). In the present study, we found that atrial pacing significantly prolonged the PR interval in patients with baseline 1°AVB. Thus, although the PR prolongation was mild in several of the patients at baseline, all patients had more notable PR prolongation during atrial pacing.

However, even this moderate degree of PR interval prolongation (mean of 275 ms), did not seem to negatively impact LV pressures or systolic function in this acute study. In patients with normal LVEF and short-term exaggeration of their pre-existing 1°AVB, treatment of asymptomatic 1°AVB does not appear to confer a hemodynamic benefit even when the PR prolongation is moderately severe.

The mean LVEF was normal in all pacing modes and not different across the pacing groups. The majority of patients (8/13) had higher LVEFs during atrial pacing compared to AH-sequential or AV-sequential pacing. These differences were more dramatic between atrial and AV-sequential pacing, though overall small and not statistically significant across the groups. It does not appear that restored AV synchrony via AH-sequential pacing provides a better acute hemodynamic profile than atrial pacing.

Unnecessary right ventricular pacing has been shown to be detrimental in patients with reduced LVEF and especially so in patients with 1°AVB (Kutalek et al., 2008; Wilkoff et al., 2002). Moreover, 1°AVB patients were shown to fare worse with atrial pacing when compared to ventricular backup pacing at a low rate (Sweeney et al., 2010). Also, in patients with preserved LVEF, both atrial pacing and PR prolongation have been associated with higher rates of atrial fibrillation (Nielsen et al., 2011, 2012). Given the potential adverse effects of atrial and RV pacing, CRT may be

TABLE 2 Electrocardiographic and hemodynamic parameters during pacing protocols

Parameter	Atrial	AH-sequential	p-value	AV-sequential	p-value
<i>Electrocardiographic data</i>					
PR/Stim to QRS (ms)	275 ± 73	177 ± 24	.0016*	159 ± 11	.0016*
QRS duration (ms)	95 ± 15	105 ± 22	.19	157 ± 20	<.0001
<i>Systemic & LA hemodynamic data</i>					
Systolic blood pressure (mmHg)	125 ± 14	127 ± 16	.48	122 ± 17	.56
Diastolic blood pressure (mmHg)	65 ± 11	68 ± 10	.03	66 ± 12	.75
Mean LA pressure (mmHg)	11 ± 6	13 ± 8	.18*	11 ± 7	.47*
LA V wave (mmHg)	18 ± 8	18 ± 8	.58	18 ± 9	.73
<i>Left ventricular pressure data (n = 4)</i>					
LVEDP (mmHg)	12 ± 2	11 ± 1	.46	12 ± 4	.75
Mean LV pressure (mmHg)	44 ± 17	46 ± 18	.99*	43 ± 21	.90
LV dP/dT _{max} (mmHg/s)	1224 ± 201	1201 ± 209	.23	1156 ± 192	.18
LV dP/dT _{min} (mmHg/s)	-1321 ± 113	-1261 ± 156	.16	-1246 ± 143	.45

Note: p-values reflect comparison of atrial pacing to AH-sequential and AV-sequential pacing by paired t-test or Wilcoxon's signed-rank test (*). Bold values refer to p-values <.0026 considered significant after Bonferroni's correction for multiple comparisons.

Abbreviations: LA, left atrial; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure.

TABLE 3 Echocardiographic evaluation at baseline and during pacing

Parameter	Atrial	AH-sequential	p-value	AV-sequential	p-value
LVEF (%)	62 ± 11	59 ± 7	.25	57 ± 12	.11
LVEDV (ml)	116 ± 25	119 ± 29	.25	116 ± 32	.53
LVESV (ml)	44 ± 13	48 ± 15	.22*	48 ± 13	.18
Stroke volume (ml)	64 ± 19	74 ± 19	.03	67 ± 22	.49
LA volume	65 ± 32	67 ± 34	.48	65 ± 31	.94
Isovolumetric contraction time (ms)	83 ± 18	89 ± 16	.37	130 ± 13	.29*
Isovolumetric relaxation time (ms)	97 ± 35	102 ± 29	.67*	136 ± 12	.31*
Global longitudinal strain	18 ± 3	18 ± 2	.79*	18 ± 2	.47
Septal to lateral electromechanical delay (ms)	4 ± 14	14 ± 45	.48	21 ± 33	.14

Note: p-values reflect comparison of atrial pacing to AH-sequential and AV-sequential pacing by paired t-test or Wilcoxon's signed-rank test (*). p-values <.003 considered significant after Bonferroni's correction for multiple comparisons.

Abbreviations: LA, left atrium; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.

an attractive strategy in 1°AVB patients. Preliminary data indicate that CRT may be beneficial in patients with 1°AVB (Olshansky et al., 2012). AH-sequential pacing offers the most physiologic way of achieving cardiac resynchronization in patients with normal His-Purkinje activation (Deshmukh et al., 2000; Narula et al., 1970). Early data suggest that permanent HBP is feasible and safe and potentially improves patient outcomes (Kronborg et al., 2012; Vijayaraman et al., 2017; Zanon et al., 2011). In preliminary reports in patients with indications for CRT, HBP has been shown to improve LV function and dimensions (Ajijola et al., 2017). The largest outcomes study (>750 patients) comparing HBP to RV pacing showed that HBP was associated with reductions in death, heart failure hospitalization, or upgrade to CRT (Abdelrahman et al., 2018). On the other hand, in another study addressing the acute effects of pacing, HBP was shown to have an inferior impact on LV

hemodynamics compared to atrial or LV pacing and was not significantly better than RV apical pacing (Padeletti et al., 2007). AH-sequential pacing may indeed be superior to AV-sequential pacing in 1°AVB over the long term; however, the present study did not demonstrate any acute hemodynamic advantage of AH-sequential pacing over atrial pacing. It is possible that small differences in hemodynamics (not detected in the present study), accumulate over time to effect a larger impact on outcomes. Alternatively, the inter-ventricular dyssynchrony introduced by AV-sequential pacing may have hemodynamic consequences that are more pronounced as LV function declines, resulting in a non-linear impact on ventricular function and significant differences in longitudinal outcomes.

Patients with abnormal LVEF were excluded from participation in the present study. It is likely that diastolic function and AV synchrony

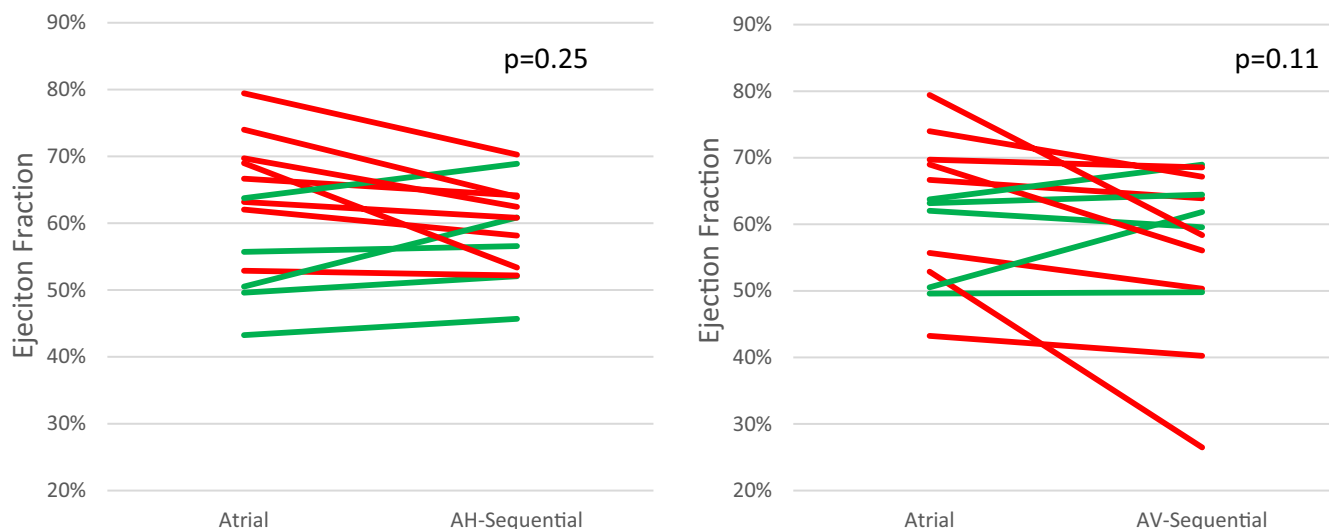


FIGURE 2 Change in PR interval between baseline and during atrial pacing. All patients except one (red line) demonstrated a significant increase in PR interval with atrial pacing

is more important in patients with low LVEF than in patients with normal LVEF. Whether or not the observed increase in AV dyssynchrony during atrial pacing would translate into adverse hemodynamic consequences in patients with low LVEF remains untested.

4.1 | Limitations

Selective His-capture was achieved in slightly more than half of included patients with non-selective His-capture achieved in the remainder. Although, non-selective His pacing has been suggested to be comparable to selective His pacing (Upadhyay & Tung, 2017; Zhang et al., 2017), the beneficial effects of AH-sequential pacing may have been attenuated by this high percentage of non-selective His-capture. All but one of the patients studied had a baseline PR interval ≤ 230 ms. In the MVP trial, the negative effects of atrial pacing were primarily seen in patients with a PR interval exceeding 230 ms (Sweeney et al., 2010). It is plausible that the observed results would have been different, had patients with more pronounced PR prolongation been recruited. The study is small, moreover, and the numerical trends in measures such as LVEF could have been significant with a larger sample (Table 3). With $\alpha = 0.05$ and $\beta = 0.8$, the current study was powered to detect differences in LVEF of 8%–10%, LVEDV 23–24 ml, in LVESV 11–12 ml, in IVCT 14–80 ms and IVRT of 26–70 ms. In the subset of patients with LV pressure data, there was adequate power to detect a 5–6 mmHg difference in LVEDP and 34–39 mmHg difference in mean LV pressure. While these effect sizes represent clinically significant changes, the present study does not have adequate power to detect smaller differences, which may also be clinically relevant. Echocardiographic evaluation of the right ventricular function and/or timing was not assessed in the present study. Therefore, any inferences about inter-ventricular dyssynchrony due to pacing mode cannot be drawn. The present study

only addresses acute effects of pacing in patients with 1°AVB and any inferences about long-term effects based on our data must be drawn with great caution. A fixed paced AV interval of 150 ms was used for AV- and AH-sequential pacing protocols. This resulted in a slightly different effective AV interval in those with selective vs non-selective HB capture (Table 2). A more individualized approach to AV timing using mitral inflow curves may have resulted in a more favorable response to restoration of AV synchrony. Each pacing protocol was instituted for at least one minute prior to obtaining measurements. It is possible, this was an insufficient amount of pacing to elicit significant hemodynamic changes that may have been detected with more prolonged exposure to each pacing protocol. The CD Leycom pressure sensor catheter was only used in a small subset of the patients due to cost restraints. This part of the study is, thus, underpowered for any definitive conclusions regarding the impact of pacing strategy on left ventricular hemodynamics to be drawn.

4.2 | Conclusion

The acute effects of AH-sequential or AV-sequential pacing are not superior to atrial pacing in patients with asymptomatic 1°AVB. In spite of relatively pronounced PR prolongation during atrial pacing, LVEF and LVEDV were not significantly perturbed. Normalizing atrioventricular and/or inter-ventricular dyssynchrony did not result in acute improvements in cardiac output or loading conditions.

CONFLICT OF INTEREST

ZL received support from NIH T32 training grant #5T32HL069749, receives grant support from Boston Scientific and serves as a consultant for Huxley Medical and Boston Scientific. FH reports support from the Crafoord Foundation, Eva and Carl-Eric Larsson Foundation,

Bundy Academy and Skåne University Hospital Research Foundation. ES reports no disclosures. FA reports no disclosures. KC reports no disclosures. JIK reports research support from Abbott. EJV reports grants and personal fees from Novartis, during the conduct of the study; grants and personal fees from Amgen, grants from Pfizer, personal fees from Philips, grants from NHLBI, outside the submitted work, BDA reports significant research support from Abbott Medical, and modest Honoraria from Abbott Medical, Biosense Webster, Medtronic, and Biotronik. TDB reports grants from the National Heart, Lung, and Blood Institute (National Institutes of Health) and the Mayo Clinic; has received grants from Boston Scientific, St. Jude Medical Corporation, Biosense Webster, and Medtronic; and has received compensation for consulting from Cardiofocus and Ventrix during the conduct of the study but outside of the submitted work, JPD reports honoraria for advisory boards, events committees, and lectures from Medtronic, Boston Scientific, Abbott, MicroPort, Biotronik, Biosense Webster, Farrapulse, and VytronUS.

ETHICS APPROVAL

All patients gave written informed consent; the study was approved by the Duke University Institutional Review Board and complied with the Declaration of Helsinki.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Zak Loring, Frerick Homqvist, Edward Sze, Fawaz Alenezi, Kristen Campbell, Jason Koontz, Eric Velazquez, Brett Atwater, Tristram Bahnsen, and James Daubert. The first draft of the manuscript was written by Zak Loring and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, ZL, upon reasonable request.

ORCID

Zak Loring  <https://orcid.org/0000-0002-4613-582X>

Fredrik Holmqvist  <https://orcid.org/0000-0001-5369-1296>

James P. Daubert  <https://orcid.org/0000-0002-9616-9219>

REFERENCES

- Abdelrahman, M., Subzposh, F. A., Beer, D., Durr, B., Naperkowski, A., Sun, H., Oren, J. W., Dandamudi, G., & Vijayaraman, P. (2018). Clinical outcomes of his bundle pacing compared to right ventricular pacing. *Journal of the American College of Cardiology*, 71(20), 2319–2330. <https://doi.org/10.1016/j.jacc.2018.02.048>
- Ajjola, O. A., Upadhyay, G. A., Macias, C., Shivkumar, K., & Tung, R. (2017). Permanent His-bundle pacing for cardiac resynchronization therapy: Initial feasibility study in lieu of left ventricular lead. *Heart Rhythm: The Official Journal of the Heart Rhythm Society*, 14(9), 1353–1361. <https://doi.org/10.1016/j.hrthm.2017.04.003>
- Atterhog, J. H., & Loogna, E. (1977). P-R interval in relation to heart rate during exercise and the influence of posture and autonomic tone. *Journal of Electrocardiology*, 10(4), 331–336. [https://doi.org/10.1016/S0022-0736\(77\)80005-8](https://doi.org/10.1016/S0022-0736(77)80005-8)
- Bader, H., Garrigue, S., Lafitte, S., Reuter, S., Jaïs, P., Haïssaguerre, M., Bonnet, J., Clementy, J., & Roudaut, R. (2004). Intra-left ventricular electromechanical asynchrony: A new independent predictor of severe cardiac events in heart failure patients. *Journal of the American College of Cardiology*, 43(2), 248–256. <https://doi.org/10.1016/j.jacc.2003.08.038>
- Bax, J. J., Marwick, T. H., Molhoek, S. G., Bleeker, G. B., van Erven, L., Boersma, E., Steendijk, P., van der Wall, E. E., & Schalij, M. J. (2003). Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation. *American Journal of Cardiology*, 92(10), 1238–1240. <https://doi.org/10.1016/j.amjcard.2003.06.016>
- Burri, H., Jastrzebski, M., & Vijayaraman, P. (2020). Electrocardiographic analysis for his bundle pacing at implantation and follow-up. *JACC: Clinical Electrophysiology*, 6(7), 883–900. <https://doi.org/10.1016/j.jacep.2020.03.005>
- Crisel, R. K., Farzaneh-Far, R., Na, B., & Whooley, M. A. (2011). First-degree atrioventricular block is associated with heart failure and death in persons with stable coronary artery disease: Data from the Heart and Soul Study. *European Heart Journal*, 32(15), 1875–1880. <https://doi.org/10.1093/eurheartj/ehr139>
- Danter, W. R., & Carruthers, S. G. (1990). The heart rate-PR interval relationship: A model for evaluating drug actions on SA and AV nodal function. *British Journal of Clinical Pharmacology*, 30(3), 490–492. <https://doi.org/10.1111/j.1365-2125.1990.tb03803.x>
- Deshmukh, P., Casavant, D. A., Romanyshyn, M., & Anderson, K. (2000). Permanent, direct His-bundle pacing: A novel approach to cardiac pacing in patients with normal His-Purkinje activation. *Circulation*, 101(8), 869–877. <https://doi.org/10.1161/01.CIR.101.8.869>
- Friedman, D. J., Bao, H., Spatz, E. S., Curtis, J. P., Daubert, J. P., & Al-Khatib, S. M. (2016). Association between a prolonged PR interval and outcomes of cardiac resynchronization therapy: A report from the national cardiovascular data registry. *Circulation*, 134(21), 1617–1628. <https://doi.org/10.1161/CIRCULATIONAHA.116.022913>
- Holmqvist, F., & Daubert, J. P. (2013). First-degree AV block—an entirely benign finding or a potentially curable cause of cardiac disease? *Annals of Noninvasive Electrocardiology*, 18(3), 215–224. <https://doi.org/10.1111/anec.12062>
- Josephson, M. E. (2015). Atrioventricular conduction. In *Josephson's clinical cardiac electrophysiology* (5th ed., pp. 93–112): Lippincott Williams & Wilkins.
- Kosowsky, B. D., Scherlag, B. J., & Damato, A. N. (1968). Re-evaluation of the atrial contribution to ventricular function: Study using His bundle pacing. *American Journal of Cardiology*, 21(4), 518–524. [https://doi.org/10.1016/0002-9149\(68\)90284-1](https://doi.org/10.1016/0002-9149(68)90284-1)
- Kronborg, M. B., Nielsen, J. C., & Mortensen, P. T. (2010). Electrocardiographic patterns and long-term clinical outcome in cardiac resynchronization therapy. *Europace*, 12(2), 216–222. <https://doi.org/10.1093/europace/eup364>
- Kronborg, M. B., Poulsen, S. H., Mortensen, P. T., & Nielsen, J. C. (2012). Left ventricular performance during para-His pacing in patients with high-grade atrioventricular block: An acute study. *Europace*, 14(6), 841–846. <https://doi.org/10.1093/europace/eur368>
- Kutalek, S. P., Sharma, A. D., McWilliams, M. J., Wilkoff, B. L., Leonen, A., Hallstrom, A. P., & Investigators, D. (2008). Effect of pacing for soft indications on mortality and heart failure in the dual chamber and VVI implantable defibrillator (DAVID) trial. *Pacing and Clinical Electrophysiology*, 31(7), 828–837. <https://doi.org/10.1111/j.1540-8159.2008.01106.x>
- Magnani, J. W., Wang, N. A., Nelson, K. P., Connelly, S., Deo, R., Rodondi, N., Schelbert, E. B., Garcia, M. E., Phillips, C. L., Shlipak, M. G., Harris,

- T. B., Ellinor, P. T., & Benjamin, E. J. (2013). Electrocardiographic PR interval and adverse outcomes in older adults: The health, aging, and body composition study. *Circ Arrhythm Electrophysiol*, 6(1), 84–90. <https://doi.org/10.1161/CIRCEP.112.975342>
- Narula, O. S., Scherlag, B. J., & Samet, P. (1970). Pervenous pacing of the specialized conducting system in man. His bundle and A-V nodal stimulation. *Circulation*, 41(1), 77–87. <https://doi.org/10.1161/01.CIR.41.1.77>
- Nielsen, J. C., Thomsen, P. E. B., Hojberg, S., Moller, M., Riahi, S., Dalsgaard, D., Mortensen, L. S., Nielsen, T., Asklund, M., Friis, E. V., Christensen, P. D., Simonsen, E. H., Eriksen, U. H., Jensen, G. V. H., Svendsen, J. H., Toff, W. D., Healey, J. S., & Andersen, H. R. (2012). Atrial fibrillation in patients with sick sinus syndrome: The association with PQ-interval and percentage of ventricular pacing. *Europace*, 14(5), 682–689. <https://doi.org/10.1093/europace/eur365>
- Nielsen, J. C., Thomsen, P. E. B., Hojberg, S., Moller, M., Vesterlund, T., Dalsgaard, D., Mortensen, L. S., Nielsen, T., Asklund, M., Friis, E. V., Christensen, P. D., Simonsen, E. H., Eriksen, U. H., Jensen, G. V. H., Svendsen, J. H., Toff, W. D., Healey, J. S., & Andersen, H. R. (2011). A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. *European Heart Journal*, 32(6), 686–696. <https://doi.org/10.1093/eurheartj/ehr022>
- Olshansky, B., Day, J. D., Sullivan, R. M., Yong, P., Galle, E., & Steinberg, J. S. (2012). Does cardiac resynchronization therapy provide unrecognized benefit in patients with prolonged PR intervals? The impact of restoring atrioventricular synchrony: An analysis from the COMPANION Trial. *Heart Rhythm: The Official Journal of the Heart Rhythm Society*, 9(1), 34–39. <https://doi.org/10.1016/j.hrthm.2011.07.038>
- Padeletti, L., Lieberman, R., Schreuder, J., Michelucci, A., Collella, A., Pieragnoli, P., Ricciardi, G., Eastman, W., Valsecchi, S., & Hettrick, D. A. (2007). Acute effects of His bundle pacing versus left ventricular and right ventricular pacing on left ventricular function. *American Journal of Cardiology*, 100(10), 1556–1560. <https://doi.org/10.1016/j.amjcard.2007.06.055>
- Prystowsky, E. N. (1988). The effects of slow channel blockers and beta blockers on atrioventricular nodal conduction. *Journal of Clinical Pharmacology*, 28(1), 6–21. <https://doi.org/10.1002/j.1552-4604.1988.tb03095.x>
- Sweeney, M. O., Ellenbogen, K. A., Tang, A. S., Johnson, J., Belk, P., & Sheldon, T. (2008). Severe atrioventricular decoupling, uncoupling, and ventriculoatrial coupling during enhanced atrial pacing: Incidence, mechanisms, and implications for minimizing right ventricular pacing in ICD patients. *Journal of Cardiovascular Electrophysiology*, 19(11), 1175–1180. <https://doi.org/10.1111/j.1540-8167.2008.01226.x>
- Sweeney, M. O., Ellenbogen, K. A., Tang, A. S. L., Whellan, D., Mortensen, P. T., Gibaldi, F., Sandler, D. A., Sherfese, L., & Sheldon, T. (2010). Atrial pacing or ventricular backup-only pacing in implantable cardioverter-defibrillator patients. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, 7(11), 1552–1560. <https://doi.org/10.1016/j.hrthm.2010.05.038>
- Upadhyay, G. A., & Tung, R. (2017). Selective versus non-selective his bundle pacing for cardiac resynchronization therapy. *Journal of Electrocardiology*, 50(2), 191–194. <https://doi.org/10.1016/j.jelecard.2016.10.003>
- Vijayaraman, P., Naperkowski, A., Subzposh, F. A., Abdelrahman, M., Sharma, P. S., Oren, J. W., Dandamudi, G., & Ellenbogen, K. A. (2017). Permanent His-bundle pacing: Long-term lead performance and clinical outcomes. *Heart Rhythm: The Official Journal of the Heart Rhythm Society*, <https://doi.org/10.1016/j.hrthm.2017.12.022>
- Wilkoff, B. L., Cook, J. R., Epstein, A. E., Greene, H. L., Hallstrom, A. P., Hsia, H., & Investigators, V. V. I. I. D. T. (2002). Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA*, 288(24), 3115–3123. <https://doi.org/10.1001/jama.288.24.3115>
- Zanon, F., & Barold, S. S. (2012). Direct His bundle and paraHisian cardiac pacing. *Annals of Noninvasive Electrocardiology*, 17(2), 70–78. <https://doi.org/10.1111/j.1542-474X.2012.00488.x>
- Zanon, F., Svetlich, C., Occhetta, E., Catanzariti, D., Cantù, F., Padeletti, L., Santini, M., Senatore, G., Comisso, J., Varbaro, A., Denaro, A., & Sagone, A. (2011). Safety and performance of a system specifically designed for selective site pacing. *Pacing and Clinical Electrophysiology*, 34(3), 339–347. <https://doi.org/10.1111/j.1540-8159.2010.02951.x>
- Zhang, J., Guo, J., Hou, X., Wang, Y., Qian, Z., Li, K., Ge, P., & Zou, J. (2017). Comparison of the effects of selective and non-selective His bundle pacing on cardiac electrical and mechanical synchrony. *Europace*, <https://doi.org/10.1093/europace/eux120>

How to cite this article: Loring, Z., Holmqvist, F., Sze, E., Alenezi, F., Campbell, K., Koontz, J. I., Velazquez, E. J., Atwater, B. D., Bahnson, T. D., & Daubert, J. P. (2022). Acute echocardiographic and hemodynamic response to his-bundle pacing in patients with first-degree atrioventricular block. *Annals of Noninvasive Electrocardiology*, 27, e12954. <https://doi.org/10.1111/anec.12954>