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Hemodynamic Doppler echocardiographic evaluation of permanent His bundle and biventricular pacing after AV nodal ablation☆

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ABSTRACT

placing after atrioventricular (AV) nodal ablation for permanent atrial fibrillation (AF) may include cardiac resynchronization therapy (CRT) with either His bundle pacing (HBP) or biventricular pacing (BVP), or conventional single site right ventricular apical pacing (RVAP). To determine the relationship between pacing method and hemodynamic outcome, we used Doppler echocardiographic methods to evaluate left ventricular (LV) hemodynamics after AV nodal ablation and either HBP, BVP, or RVAP.

Method: 20 patients were evaluated > 6 months after AV nodal ablation, 10 each with chronic HBP or BVP, and all with RVAP lead. Doppler echocardiography was used to measure 3 parameters indicative of CRT: 1) LV dP/dt, 2) the LV pre-ejection interval, and 3) myocardial performance index, relative to intra-patient RVAP.

Results: Primary endpoint of LV dP/dt on average improved by > 17% with both HBP and BVP, compared to RVAP. HBP but not BVP, had improvement across all three parameters.

Conclusion: HBP provides LV electromechanical synchrony across multiple echo Doppler parameters. Both HBP and BVP were hemodynamically superior to RVAP following AV nodal ablation.

1. Introduction

Background.

Atrioventricular (AV) nodal ablation in conjunction with permanent pacing provides definitive rate control of atrial fibrillation (AF) but can induce ventricular dyssynchrony [1–4]. Multiple pacing sites have been utilized post AV nodal ablation, including conventional single-site right ventricular apical pacing (RVAP), RV septal or outflow pacing, biventricular pacing (BVP), and His bundle pacing (HBP) [3–9]. In patients with uncontrolled AF, AV nodal ablation and BVP is superior to pharmacologic rate control [5]. In cardiac resynchronization therapy (CRT) for heart failure, HBP is at least a noninferior alternative to BVP [9–12].

AV nodal ablation patients can do well with RVAP, BVP, or HBP, yet it remains unproven which approach may provide a better hemodynamic outcome [3,7–11]. Since HBP replicates physiologic activation, we postulated it might provide more left ventricular (LV) intraventricular synchrony and hemodynamic benefit after AV nodal ablation. To evaluate this hypothesis in a pilot study, we utilized Doppler echocardiographic methods to compare permanent HBP or BVP, relative to intra-patient RVAP, in patients with 100% pacing after AV nodal ablation. Additional observations were made regarding single site LV only pacing, and selective vs. non-selective His bundle capture.

Methods.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki Protocol, and was approved by the Mercy Hospital Investigational Review and Ethics Board (Des Moines, IA), and all study subjects signed an informed consent. This included 8 females and 12 males aged 65.7+/-8.4 years with symptomatic permanent AF who underwent elective AV nodal ablation with pacemaker implantation > 6 months prior to enrollment. The decision to place biventricular or His bundle leads was not randomized but was made at the discretion and best practice of the individual implanter. Since patients were attended by multiple different physicians, the assignment to BVP or HBP was dependent on the preference and skill set of the implanting physician, with only 1 physician (RHH) performing HBP procedures at that time. Thus, a contemporaneous cohort was created of patients with either BVP or HBP.

All pacemaker/ablation procedures were completed prior to initiation of the study. As the patients with these procedures returned for pacemaker clinic, the study was conceived to evaluate the hemodynamic

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outcome, relative to standard RVAP with each patient as their own control. The pre-specified sample size was 20 patients, 10 with BVP and 10 with HBP in each group. Ambulatory patients were approached for enrollment as they presented for a routinely scheduled pacemaker clinic visit, and consecutive eligible patients were asked to participate in the study and sign the informed consent. Enrollment was closed after the

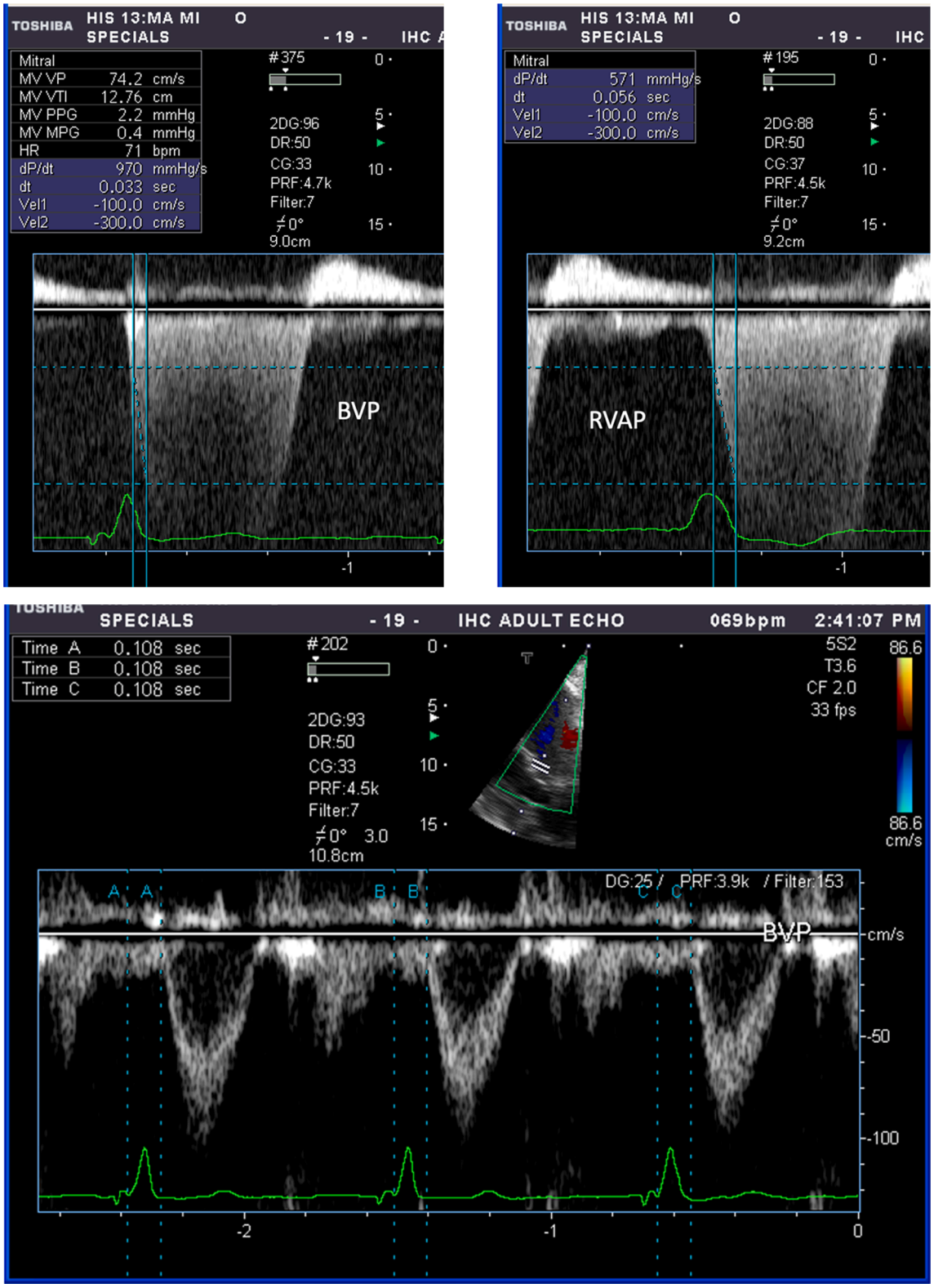

Fig. 1. a-c. Doppler hemodynamic parameters. Fig. 1a: Method of measuring dP/dt from the continuous wave (CW) doppler of mitral regurgitation. Trans-mitral CW Doppler tracing is shown from one of the study subjects. The time for mitral regurgitant velocity to increase from 1 to 3 m/s, reflecting a 32 mmHg increase in the left ventriculo-atrial systolic pressure gradient, was faster with biventricular pacing (BVP left panel) versus RV apical pacing (RVAP right panel) in the same patient. Fig. 1b: Measurement of the LV pre-ejection interval (LPEI) using pulse wave Doppler. Calipers indicate time (ms) from Q wave to onset of LV outflow. Fig. 1c: Method of calculating the myocardial performance index (MPI, see text for additional details).

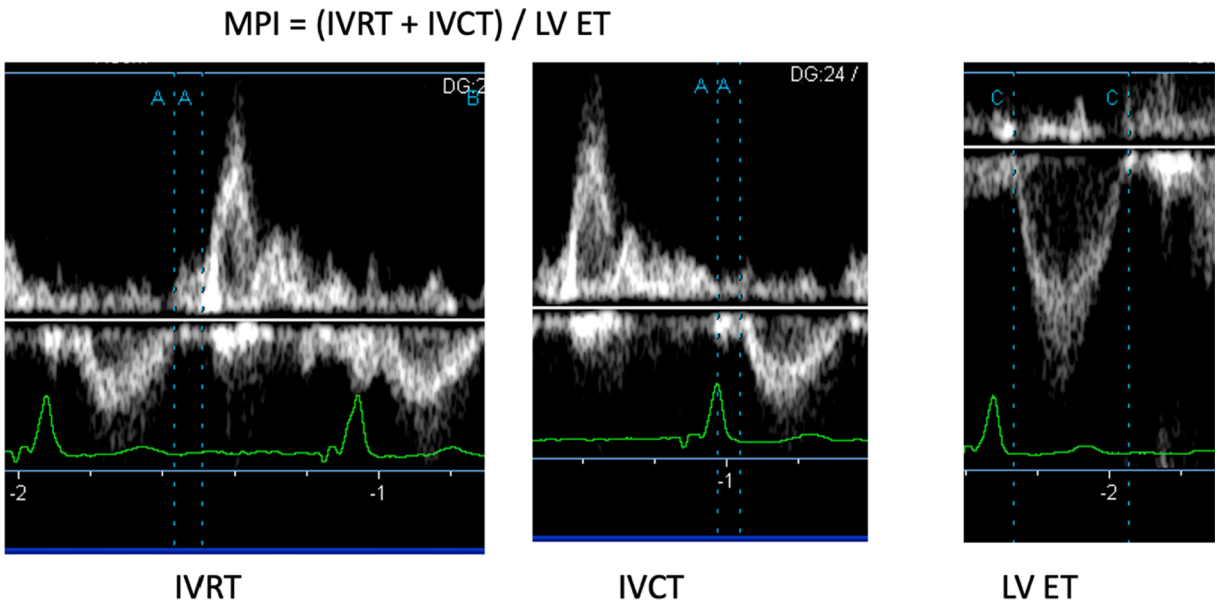

Fig. 1. (*continued*).

20th patient consented.

All patients had baseline narrow and normal morphology QRS, and no pacing indication other than planned AV nodal ablation, which was performed with radiofrequency energy at the time of pacemaker implantation in all cases. At transthoracic echo done < 3 months prior to the AV nodal ablation, the left ventricular ejection fraction (LVEF) in the BVP group was 43.7+/-13.4, and in the HBP group was 43.3+/-14.8. Simpson's biplane method was used to estimate LVEF. Medical therapy in both groups was comparable in that all patients had extensive and failed attempts at both rhythm and rate control of their AF, as well as guideline appropriate beta-blocker and vasodilator therapy for LV dysfunction. For BVP we implanted 2 transvenous bipolar leads (Medtronic, Minneapolis, MN), one positioned at the RV apex and the second in a lateral or posterolateral LV epicardial branch. The LV lead was configured in the atrial port of a dual chamber pacemaker and the AV delay was programmed to its minimum setting of 30 msec, resulting in sequential biventricular pacing with LV first by 30 msec. For HBP a Medtronic Model 3830 lead was utilized. His bundle capture at implant and during follow-up was documented according to established criteria [13–15]. A bipolar lead for "back-up" was placed in the RV apex. The His bundle lead was connected to the atrial port of a dual chamber pacemaker programmed to the DDIR mode with AV interval (typically 80–100 msec), causing an "atrial" (actually His bundle) paced event followed by ventricular sense. The study procedure consisted of a pacemaker programming session with transthoracic echocardiographic data acquisition that was specific for the study and not otherwise clinically indicated. Over a time of 1–2 h needed to complete the echocardiographic measurements, a fixed pacing rate (70 bpm) was maintained, and patients remained at rest with no fluid administration or sedation, so that cardiac loading conditions would remain constant. All patients were normotensive before starting the echo procedure. Doppler and two-dimensional echocardiographic data were acquired with a Toshiba Model Aplio ultrasound machine and a 2.25 MHZ transducer. Doppler echocardiographic data were applied to estimation of derived hemodynamic parameters that reflect LV intraventricular synchrony.

The prospective primary endpoint for the study was LV dP/dt derived using the early portion of the mitral regurgitant continuous wave spectral Doppler velocity: dP/dt (mmHg/s) = 32/T where T is the time for mitral regurgitant velocity to increase from 1 to 3 m/s, reflecting a 32 mmHg increase in the left ventriculo-atrial systolic pressure gradient (16, Fig. 1a). Secondary echocardiographic endpoints included the LV pre-ejection interval (LPEI) measured from Q wave to onset of LV outflow (Fig. 1b), and the LV myocardial performance index (MPI or Tei index), determined from spectral pulsed-Doppler tracings of LV inflow and transaortic flow as MPI = IVCT + IVRT/LVET where IVCT is isovolumic contraction time, IVRT is isovolumic relaxation time and LVET is LV ejection time (Fig. 1c). Both dP/dt and LPEI reflect synergy in early systole, whereas MPI is a function of synergy during early systole and protodiastole [17].

In each patient with biventricular leads, 3 pacing configurations were tested in random order: 1) RVAP, 2) BVP and 3) single site LV (dP/dt only). In each patient with a His bundle lead, random-order testing was with His bundle vs. RVAP, then with additional non-selective His bundle capture if present (see below). The His bundle capture threshold was re-verified at the start of the session. At baseline, selective His bundle capture was present in 6/10 and non-selective capture (His bundle along with adjacent septum) in 4/10 patient. In 4/6 patients with selective HBP, we were able to observe additional non-selective capture at a higher pacing output, and dP/dt was repeated in those cases to compare selective vs. non-selective capture (in those 4 cases, only selective His bundle capture is included in the primary end-point data). Neither septal-only nor simultaneous RVAP and HBP were evaluated. Data were analyzed by paired t tests for intragroup comparisons (RVAP vs. either BVP or HBP). In this analysis each patient serves as his/her own control, which partially accounts for any intrinsic baseline differences between the groups and is sensitive to small changes in the echocardiographic parameters. An unpaired analysis was also performed. This assumes the groups are intrinsically similar at baseline, allowing for inter-group comparison of the parameters. Although patient enrollment was not randomized, baseline characteristics of the 2 groups were similar with respect to pre-and post-intervention LV ejection fraction, medical therapy, and ambulatory status. All results are shown as mean +/-SD, and p values are based on a 95% confidence interval.

2. Results

At time of enrollment (>6 months post ablation) LVEF was 51.3+/-9.8 in the BVP group and 56.8+/-11.2% in the HBP group. Intragroup analysis (each patient as his/her own control) found dP/dt increased significantly with both BVP and HBP compared to RVAP (Table 1, and Fig. 2). The average magnitude of improvement was similar for the 2

Table 1
Intragroup Doppler Echocardiographic Measurements.

	LV dP/dt (mmHg/s)	LPEI (ms)	MPI
RVAP	965 +/- 265	159 +/- 57	0.59 +/- 0.15
HBP	1165 +/- 265	142 +/- 67	0.52 +/- 0.13
p value	0.003	0.05	0.03
RVAP	879 +/- 152	142 +/- 23	0.60 +/- 0.14
BVP	1069 +/- 174	129 +/- 18	0.56 +/- 0.13
p value	0.01	0.16	0.18
LV only pacing	956 +/- 216		
p value	0.34 (vs. RV apical pacing in BVP group)		

Paired intragroup analysis (each patient as own control). LV dP/dt was improved (absolute 17% increase for each vs. paired control) with both HBP and BVP. HBP trended to significant improvement across all three of the measured parameters of resynchronization. There was no advantage to single site LV vs. RV apical pacing. LV = left ventricular, LPEI = LV pre-ejection interval, MPI = myocardial performance index, RVAP = right ventricular apical pacing, HBP = His bundle pacing, BVP = biventricular pacing.

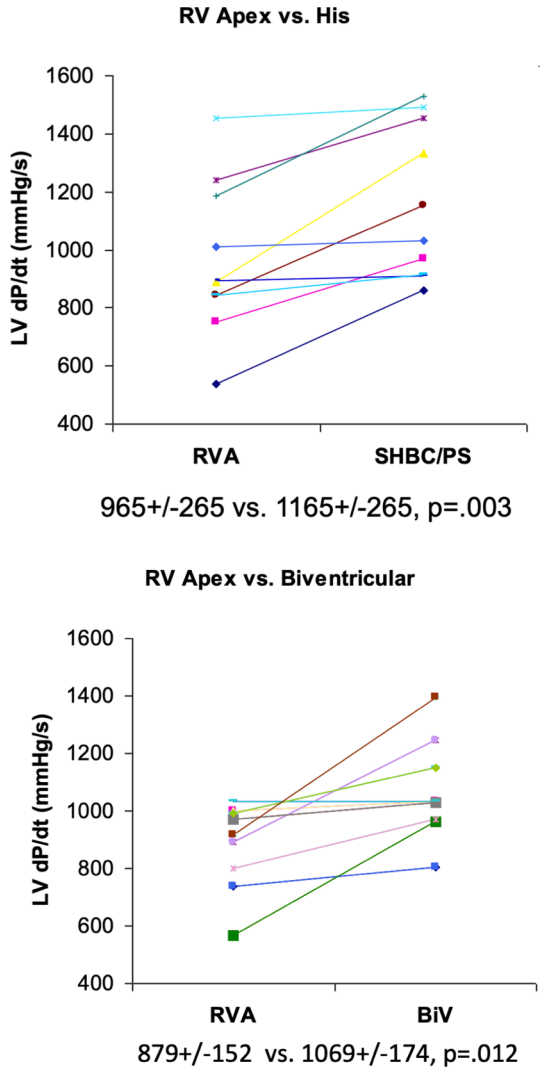

Fig. 2. Upper panel: Primary endpoint of LV dP/dt with RV apical and His bundle capture. RVA = RV apical pacing site, SHBC /PS = selective His bundle capture, plus non-selective His bundle pacing with *para*-Hisian septal capture. Lower panel: LV dP/dt with RV apical and biventricular pacing. RVA = RV apical pacing site, BiV = biventricular pacing.

groups (17.8% for BVP, 17.2% for HBP). Intragroup improvement (decrease) in LPEI and MPI were observed with HBP but not with BVP (Table 1). Single site LV only pacing was no better than RVAP with respect to dP/dt (Table 1). There was no difference in dP/dt between selective vs. non-selective HBP, although the sample size was inconclusive (dP/dt 1003+/-123 in selective vs. 929+/-269 in non-selective, n = 4, p = 0.47). In the unpaired analysis (all RVP vs. BVP and HBP) the only significant difference was a higher dP/dt in the HBP group vs. RVAP control (Table 2). Unpaired comparison of the absolute dP/dt for BiV vs. HBP was 1069+/-174 vs. 1165+/-265 respectively (p = 0.37) a 9% difference which was not statistically different.

3. Discussion

Implementation of His bundle pacing on a commercial scale will likely require significant new investment to design specialized leads and pulse generators, whereas BVP is already an established technology. Thus, data regarding the relative merit of these pacing techniques is essential. Prior echocardiographic studies in CRT have focused on patients with moderate to severe LV dysfunction, left bundle branch block (LBBB), and heart failure. Echocardiographic indicators of response have included remodeling indices such as LVEF and LV end systolic volume, as well as multiple Doppler echocardiographic markers of improved left ventricular synchrony [18–26]. In this study, we focused on an AV nodal ablation indication for CRT, and directly measured Doppler echocardiographic parameters of LV intraventricular synchrony to evaluate hemodynamics of BVP and HBP in ambulatory patients. This patient cohort is distinctive, in that irrespective of CRT, the benefit of AV nodal ablation involves resolution of tachy-cardiomyopathy, which is mechanistically different from correction of electromechanical delay in pre-existing LBBB. Our patients were studied at a time interval (>6 months post-ablation) that allowed for LV remodeling and normalization of LVEF, so that the singular hemodynamic effect of pacing could be evaluated under stable therapeutic conditions. Both BVP and HBP provided a similar intragroup increment in LV dP/dt of>17%. Thus, it appears BVP and HBP yield roughly comparable hemodynamic effect vs. RVAP in this type of patient. Deshmukh demonstrated the feasibility of permanent HBP combined with either pharmacologic rate control of AF, or AV nodal ablation, but did not separate out the treatment effect of rate control only versus HBP [6]. Prior studies have compared BVP, HBP, and single site RV pacing (RVAP or RV septal pacing sites) in patients with heart failure [10–12,27,28]. In an acute study using temporary pacing catheters, Arnold et al found an increment of systolic blood pressure with HBP compared with BVP [27]. Using similar methodology, Sohaib et al reported an almost identical mean instantaneous systolic BP increase with both HBP and BVP vs. RVAP but there was more outlier responses in the BVP group [28]. With transvenous BVP, the position of the LV lead is limited by the epicardial venous anatomy, phrenic nerve, and underlying LV substrate potentially leading to inconsistency of resynchronization. Moreover, even with a well-positioned LV lead, BVP is essentially an attempt to coordinate two non-physiologic activation wavefronts, subject to variations in LV lead

Table 2
Intergroup Doppler Echocardiographic Measurements.

	LV dP/dt (mmHg/s)	LPEI (ms)	MPI
All RVAP	924 +/- 171	151 +/- 43	0.59 +/- 0.14
HBP	1165 +/- 265	142 +/- 67	0.52 +/- 0.13
p value	0.01	0.66	0.18
BVP	1069 +/- 174	129 +/- 18	0.56 +/- 0.13
p value	0.09	0.15	0.18

Unpaired intergroup analysis. RVAP control data is aggregated. HBP shows significant improvement for dP/dt vs. control, with no other significant differences. LPEI = LV pre-ejection interval, MPI = myocardial performance index, RVAP = right ventricular apical pacing, HBP = His bundle pacing, BVP = biventricular pacing.

position and exit conduction. Although HBP does reproduce "physiologic" activation, it was notable that BiV pacing performed almost as well, and the absolute benefit of HBP over BiV seemed marginal in the paired and unpaired comparisons.

Multiple studies in both echocardiography and catheterization laboratories, confirm Doppler echocardiographic parameters are sensitive and reproducible markers of dyssynergic LV contraction [16,29]. Among the available echocardiographic indices of LV performance and synchrony, we pre-specified the LV dP/dt as the primary endpoint. The dP/dt determined using the slope of the early portion of the mitral regurgitant continuous wave spectral Doppler velocity has been validated at cardiac catheterization [16,30]. Left bundle branch block (LBBB), and RVAP with LBBB pattern, both prolong LV activation time [31]. Ventricular dyssynergy with pacing is ameliorated in some cases by biventricular "upgrade" [32,33]. LBBB delays both opening of the aortic valve at the end of isovolumic contraction period and opening of the mitral valve at the end of the isovolumic relaxation period, effectively shortening the left ventricular filling period [34–36]. These abnormal mechanics that result from dyssynergic activation of left ventricular contraction and relaxation cause reductions in LVEF, cardiac output, and dP/dt [35–38]. Accordingly, the instantaneous increase of dP/dt that was observed with both His bundle and biventricular stimulation in this study can be attributed to improved ventricular synergy in both cases.

Our secondary Doppler echocardiographic endpoints were LPEI and MPI. The delay in opening of the aortic valve at the end of the isovolumic contraction period that occurs with LBBB results in prolongation of LPEI. In our study LPEI trended lower (improved) with HBP ($p = 0.05$) but not with BVP ($p = 0.16$). MPI improves when the sum of isovolumic contraction and relaxation times decreases, and/or ejection time increases, and thus reflects both systolic and diastolic function [17]. In our study, HBP was associated with decrease (improvement) in MPI relative to RVAP, whereas BVP was not. In a comparable protocol, no change in MPI was found between HBP and RVAP [22]. However, MPI improvement is more evident when the baseline (pre-CRT) value is severely impaired, suggesting it is a less sensitive index when LVEF is relatively well preserved [32].

Temporary LV free wall pacing has been reported to improve stroke volume and stroke work when compared to RV pacing [39]. However, we found no advantage of LV free wall pacing compared to RVAP with respect to dP/dt. There was no adverse trend from non-selective vs. selective His bundle pacing, among the 4 patients in whom this was examined, consistent with findings of Catanzarati et al [40]. The His bundle lead implant procedure is limited by existing leads and implant tools, and acute implant success with verifiable His bundle capture is in the range of 65–90% [6,14,41]. In pacemaker dependent patients, there is concern about long-term pacing threshold stability with the His bundle lead, and uncertain potential for development of disease in the distal His-Purkinje system, which is why we utilized the RVAP back-up lead. Although the compact AV node is proximal to the His bundle, there is a small risk of damage to the HBP site during AV nodal ablation. Of course, BVP is not always attainable or effective either, with a non-responder rate exceeding 30% [42–44].

4. Limitations

The patient population traditionally assigned to CRT (advanced LV dysfunction, LBBB, sinus rhythm) has less potential for normalization of LV function than the ablate and pace patients described in this study [45]. Our results should therefore not be extrapolated to this broader CRT population without constraint. Our study specifically focuses on the AV nodal ablation subset with relatively well-preserved LVEF and 100% ventricular paced rhythm, so may be more comparable to cohorts in which biventricular pacing was used to prevent, rather than reverse, adverse ventricular remodeling [7,46]. This study was conceived as a hypothesis-generating pilot study, hence there were a limited number of enrollments in each arm. In practice, we have a choice to implant either biventricular or His bundle leads in the AV nodal ablation setting. Since our study indicates near hemodynamic equivalence, future randomized studies of BVP vs. HBP in the AV nodal ablation group may consider other issues such as procedure time and complications, battery longevity, tricuspid regurgitation, pacing threshold stability, and importantly the clinical response rate, which are all beyond the scope of the present study.

We did not attempt to obtain segmental tissue Doppler time-to-peak contraction velocity, since in our laboratory and others, reproducibility of tissue Doppler data used for CRT applications have been suboptimal [21,47]. Moreover, there is no consensus on which specific tissue Doppler or strain-rate imaging parameters are predictive of reverse remodeling in CRT [20,21,24–26,47]. Accordingly, recent emphasis has shifted to CRT optimization by measurement of ventricular activation times derived from intracardiac, electrocardiographic, or body surface potentials [48–50]. Activation time with His bundle pacing depends solely on integrity of His-Purkinje function distal to the pacing site, whereas activation time in BVP is subject to manipulation based on lead position or timing. For this reason, Doppler-derived hemodynamic parameters rather than activation time were used in our study to compare HBP and BVP. While tissue Doppler has been used to titrate sequential biventricular stimulation, the potential effect of this variable was not within the scope of our study [52,53]. We did not evaluate patients with pre-existing conduction abnormalities, in whom HBP can be utilized in conjunction with LV pacing to optimize CRT effect [54].

In summary, our results show improvement of dP/dt with both BVP and HBP in the setting of uncontrolled AF, nominally narrow QRS, and AV nodal ablation. In the intragroup analysis, HBP seemed to provide a favorable profile across multiple echo Doppler parameters of ventricular synchrony. The implications of this finding for long-term ventricular remodeling are unknown. Our experience suggests HBP is a hemodynamically effective initial approach to pacing with AV nodal ablation or could be utilized as an alternative in cases of unsatisfactory BVP, such as phrenic nerve stimulation, difficult coronary sinus venous anatomy, or non-responder.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101102.

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