Usefulness of Cardiac Resynchronization Therapy in Patients With Continuous Flow Left Ventricular Assist Devices

Vlad Cotarlan, MD[a,b,*], Frances Johnson, MD[b,c], Jennifer Goerbig-Campbell, MD[b,c], KellyAnn Light-McGroary, MD[b], Chakradhari Inampudi, MD[b], Jennifer Franzwa, RN[b], Kyle Jenn, RN[b], Carol Johnson, RN[b], Rudhir Tandon, MD[b], Rizwan Tahir, MD[b,d], Yassar Nabeel, MD[b,e], Uzodinma Emerenini, MD[b,f], and Michael Giudici, MD[b]

The benefit of cardiac resynchronization therapy in patients supported by a left ventricular assist device (LVAD) is unknown. There are currently no guidelines regarding the continuation, discontinuation or pacemaker (PM) settings post-LVAD implant. The aim of the study was to assess the hemodynamic benefit of biventricular (BiV) pacing in LVAD patients. We studied 22 patients supported by LVADs (age 62 ± 9, 21 males) who had received a BiV PM before LVAD implant. A total of 123 complete sets of hemodynamics were obtained during BiV pacing (n = 54), right ventricular (RV) pacing (n = 54), and intrinsic rhythm (n = 15).

There were no significant differences in right atrial (RA) pressure, mean pulmonary artery pressure (mPA), PCWP, cardiac output, PA saturation (PASat) and right ventricular stroke work index between BiV and RV pacing. Hemodynamics obtained during intrinsic rhythm in 15 non−PM-dependent patients were not significantly different compared with those obtained during BiV or RV pacing. Furthermore, hemodynamics were similar at different heart rates ranging 50 to 110 beats/min. Right ventricular stroke work index was significantly lower at the highest heart rate compared with baseline and lowest heart rates suggesting decreased RV performance at higher heart rate. In conclusion, BiV pacing does not have any acute hemodynamic benefit compared with RV pacing or intrinsic rhythm in LVAD patients. A lower heart rate may confer better RV performance. **(Am J Cardiol 2019;123:93−99)**

Cardiac resynchronization therapy (CRT) is a very effective treatment for patients with systolic left ventricular (LV) heart failure (HF) and a left bundle branch block (LBBB).[1] The role of CRT is to synchronize LV myocardial contraction and improve LV function which is usually accomplished through biventricular (BiV) pacing but triple or multisite pacing has been used successfully in selected patients.[2−4] It is widely accepted that approximately 2/3 of patients respond to CRT and 1/3 have no benefit or may have worsening or refractory HF. Continuous flow left ventricular assist devices (CF-LVAD) are implanted in carefully selected patients with end stage heart failure who have failed guideline directed medical treatment including CRT. Thus, many patients have CRT devices in place at the time of LVAD implant. At present there is no clear evidence base to guide physicians in the optimized use of pacemakers after LVAD implantation.[5] Available reports suggesting benefit or harm in continuing or initiating CRT post-CF-LVAD are conflicting and based on retrospective studies and case reports.[6−13] To our knowledge, a prospective trial to assess the role for CRT in LVAD patients has not been performed.

The primary objective of this study was to better understand the physiological effects of different pacing strategies in patients with CF-LVADs. We evaluated the acute hemodynamic effects of BiV pacing compared with right ventricular (RV) pacing and no pacing (when possible) in stable LVAD patients. The secondary aim was to assess the effect of BiV and RV pacing on hemodynamics at different heart rates (HR). We hypothesized no significant difference in hemodynamics between BiV and RV pacing. Based on the evidence and knowledge at the time the study was designed, we expected improved cardiac output (CO) with BiV and RV pacing at higher heart rates.

Methods

This was a cross-sectional nonrandomized trial conducted in the cardiac catheterization laboratory at the University of Iowa Hospital. Twenty-two patients with functioning BiV pacemaker (PM) supported by a Heart Mate II (HM2) or Heart Mate III (HM3) CF-LVAD as bridge to transplantation (BTT) or destination therapy (DT) were enrolled. Patients served as their own controls. The

[a]University of Cincinnati; [b]University of Iowa; [c]Iowa Heart Center; [d]Geisinger Medical Center; [e]MetroHealth System; and [f]Tulane University.
Manuscript received June 22, 2018; revised manuscript received and accepted September 17, 2018.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Study performed at the University of Iowa Hospitals and Clinics.

See page 99 for disclosure information.

*Corresponding author: Tel: (513)558-4721; fax: (513)558-8454.

E-mail address: vlad.cotarlan@uc.edu (V. Cotarlan).

0002-9149/
https://doi.org/10.1016/j.amjcard.2018.09.022

study protocol was approved by the University of Iowa Institutional Review Board.

All patients underwent a standard right heart catheterization (RHC). Vitals including HR, blood pressure, and arterial oxygenation were monitored according to catheterization laboratory protocol. An automatic high fidelity sphygmomanometer cuff was used to record blood pressure. In addition, a PM programmer and telemetry were used to continuously monitor the cardiac rhythm and rate and make PM adjustments. An electrophysiologist and a heart failure attending were present to make PM changes and obtain hemodynamic measurements and study-related data. A complete set of hemodynamic parameters was first obtained during BiV pacing at the presenting HR. Measurements were taken during end expiration and included right atrial (RA) pressure, systolic and diastolic RV pressures, systolic and diastolic pulmonary artery (PA) pressures, pulmonary capillary wedge pressure, PA oxygen saturation, CO measured by Fick and thermodilution methods. LVAD parameters (flow, power, and pulsatility index) and blood pressure were recorded with each set of hemodynamics. After baseline hemodynamics were obtained, the coronary sinus (CS) lead pacing was turned off and a second complete set of hemodynamics was obtained during RV pacing. One patient receiving RV pacing only (due to previous issues with ventricular tachycardia related to CS lead pacing) had hemodynamics during RV pacing first followed by BiV pacing. For patients who were not pacemaker (PM) dependent, a complete set of hemodynamics was also obtained during intrinsic rhythm.

To further assess the effect of HR and ventricular pacing on CO and RV performance, additional hemodynamics were measured at HRs ranging from 50 to 110 beats/min during both BiV and RV pacing. The pacing protocol was different in PM versus non−PM-dependent patients depending on the cardiac rhythm/rate and level of conduction abnormalities, as follows.

For non−PM-dependent patients (n = 15), after the initial hemodynamic measurements during BiV pacing, RV pacing and no pacing, additional hemodynamics were obtained at pacing rates higher than intrinsic heart rate ranging from intrinsic rate to as high as 110 beats/min. This was accomplished through atrioventricular (AV) sequential pacing for 9 patients in sinus rhythm (SR) and through ventricular pacing for 6 patients in atrial fibrillation (AF).

All PM-dependent patients (n = 7) had complete AV block, 6 with underlying AF and 1 in SR. For AF patients, after the initial hemodynamic measurements during BiV and RV pacing at the presenting HR, additional hemodynamics were obtained at pacing rates ranging from 50 to 110 beats/min through ventricular pacing (BiV and RV pacing). For 1 patient in SR, the additional BiV and RV hemodynamics were obtained at pacing rates higher than intrinsic atrial rate through AV sequential pacing. For PM-dependent patients, the protocol was initially designed to obtain hemodynamics at 70, 90, and 110 beats/min. Since no change was observed in the first 3 subjects in the 70 to 110 beats/min range, we decided to broaden the pacing range from 70 to 110 through 50 to 110 beats/min. Thus, 3 patients had hemodynamic measurements at 70, 90, and 110 beats/min and 3 patients had measurements at 50, 80, and 110 beats/min.

After changing each pacing mode, a period of 3 minutes was allowed for hemodynamic stabilization before obtaining the next set of hemodynamic measurements.

Data are presented as mean ± standard deviation (SD), median (range) or number (%). A paired Student's *t* test was used to compare continuous variables. Analysis of variance was used to compare the 3 groups in Table 3. A nominal 2-sided p value < 0.05 defined statistical significance.

Results

A total of 123 complete sets of hemodynamics were obtained in 22 patients (21 males, 1 female, mean age 62 ± 9 years) supported by either a HM2 (n = 20) or a HM3 (n = 2) CF-LVAD. Table 1 lists individual baseline clinical characteristics and hemodynamics during BiV pacing at presenting HR: 15 non−PM-dependent patients (1 to 15) and 7 PM dependent (16 to 22). Ten AF patients were post-atrioventricular node (AVN) ablation of whom 6 were PM dependent whereas 4 were not due to the presence of a junctional escape rhythm (9, 10, 13, and 14). Patient 18 was in SR but PM dependent due to AVN ablation before LVAD implant for uncontrolled AF. Past medical history was also significant for: hypertension in 45% of patients, diabetes (59%), ischemic CMP (50%). Severe RV systolic dysfunction requiring inotropic support was present in 4 patients (9, 16, 17, and 20). Patients were treated with common HF medications: ACE inhibitor in 73% of patients, beta blocker (50%), aldosterone-receptor blocker (36%), loop diuretic (77%), and sildenafil (41%).

The median time from BiV PM to LVAD implant was 1.2 years (range 0.1 to 6.3 years) and the median time from LVAD implant to enrollment was 0.5 years (range 0.1 to 5.4 years). Response to CRT before LVAD was determined based on the review of cardiology notes: 12 patients had been documented as nonresponders before LVAD implant and 2 as partial responders, whereas in 8 patients the CRT response could not be determined.

None of the 22 patients had a significant hemodynamic change when transitioned from BiV to RV pacing. We listed individual hemodynamics during BiV and RV pacing in Tables 1 and 2 as well as mean hemodynamic values with statistics in Table 3. Hemodynamics were also similar during intrinsic rhythm in 14 non−PM-dependent patients despite significantly lower HR (70 ± 17 vs 81 ± 9, p = 0.01). We did observe a mild decrease in CO and PA saturation during intrinsic rhythm in 1 non−PM-dependent patient who was tested during a slow junctional escape rhythm (patient 10). However, this particular non−PM-dependent patient had a previous AVN ablation for persistent AF and was tested during a slow junctional escape rhythm of around 40 beats/min.

Finally, we measured hemodynamics during BiV and RV pacing at different HRs ranging from 50 to 110 beats/min according to the pacing protocol described in the method section. Thus, 11 patients were tested at 3 different HRs and 10 patients at 2 different HRs. One patient with baseline sinus tachycardia of around 106 beats/min (patient 2) was only tested at the presenting rate (BiV, RV, and intrinsic rhythm). We did not

Table 1
Baseline characteristics and hemodynamics during BiV pacing at baseline heart rate

	Baseline characteristics						Hemodynamics during BiV pacing at baseline HR						
Pt	PM Dep	Age	AVN	Rhythm	LBBB	Speed	HR	CVP	mPA	PCWP	CO	CI	PA Sat
1	No	36	No	SR	Yes	8800	75	16	31	28	5.4	2.1	65
2	No	53	No	SR	Yes	8800	106	17	35	15	5.8	3.0	52
3	No	53	No	AF	Yes	9200	70	8	19	8	4.3	1.9	64
4	No	56	No	SR	Yes	8800	80	15	26	20	4.9	2.5	66
5	No	56	No	SR	Yes	9200	75	7	20	6	5.4	2.5	66
6	No	58	No	SR	Yes	9400	82	13	36	26	6.7	3.4	59
7	No	59	No	SR	No	8800	90	4	18	5	3.8	1.8	56
8	No	59	No	AF	Yes	9000	72	22	42	27	5.7	2.5	57
9	No	61	yes	AF*	Yes	5400	80	16	32	22	5.0	2.5	56
10	No	61	yes	AF*	No	9000	80	14	31	16	6.3	3.0	61
11	No	64	No	SR	Yes	9000	90	9	26	11	6.6	3.3	44
12	No	69	No	AF	Yes	9000	68	23	43	20	5.0	2.3	51
13	No	70	yes	AF*	Yes	9600	80	5	19	13	5.3	2.5	73
14	No	76	yes	AF*	No	9000	90	13	23	14	4.5	2.4	48
15	No	77	No	SR	Yes	8800	76	15	23	18	3.7	1.7	60
16	Yes	51	yes	AF	Yes	5400	80	26	35	20	4.4	2.1	48
17	Yes	59	yes	AF	No	9200	80	16	27	13	4.4	2.2	64
18	Yes	62	yes	SR	No	9000	70	9	21	18	6.7	2.9	58
19	Yes	65	yes	AF	Yes	8800	72	9	23	12	7.7	3.5	73
20	Yes	68	yes	AF	No	9800	70	25	34	26	5.8	3.1	57
21	Yes	72	yes	AF	No	9200	70	8	18	10	4.7	2.2	59
22	Yes	74	yes	AF	No	9600	80	11	18	9	5.0	2.4	54

Pt = patient; PM = pacemaker; AVN = atrioventricular node; LBBB = left bundle branch block; HR = heart rate (bpm); CVP = central venous pressure; mPA = mean pulmonary artery pressure; PCWP = pulmonary capillary artery pressure; CO = cardiac output (L/min); CI = cardiac index (L/min/m^2); PASat = pulmonary artery oxygen saturation (%). All pressures measured in mm Hg, SR = sinus rhythm; AF = atrial fibrillation, *AF with complete AVB and junctional escape rhythm.

Table 2
Individual hemodynamics during RV pacing (presenting HR) and intrinsic rhythm

	RV pacing at presenting HR							Intrinsic rhythm						
Pt	HR	CVP	mPA	PCWP	CO	CI	PASat	HR	CVP	mPA	PCWP	CO	CI	PA Sat
1	75	14	32	24	4.7	1.9	66	75	14	33	26	5.2	2.0	69
2	106	17	34	15	5.4	2.8	55	106	17	37	14	5.7	2.9	57
3	70	8	19	10	4.3	1.9	61	48	9	21	9	4.2	1.8	56
4	80	16	26	21	5.3	2.7	67	80	15	25	20	5.3	2.7	65
5	75	7	19	7	5.5	2.6	64	75	8	20	7	5.3	2.5	66
6	82	12	36	27	6.9	3.5	59	82	13	36	27	7.3	3.7	61
7	90	2	13	8	3.8	1.8	57	87	1	12	2	3.5	1.7	53
8	72	23	40	26	5.0	2.2	60	72	20	36	20	5.8	2.6	60
9	80	16	32	17	4.8	2.4	61	53	15	34	23	4.5	2.2	56
10	80	15	30	18	5.5	2.6	61	40	17	25	16	3.6	1.7	50
11	90	9	27	11	6.5	3.2	49	85	8	27	13	6.7	3.3	43
12	70	22	42	20	4.5	2.1	52	68	22	38	18	4.6	2.1	49
13	80	6	16	14	5.3	2.5	73	50	4	16	16	5.3	2.5	73
14	90	13	23	15	3.8	2.1	45	55	14	19	11	4.0	2.2	39
15	76	16	20	19	3.9	1.8	59	74	14	22	17	3.8	1.8	58
16	80	27	35	20	5.1	2.4	49							
17	80	16	26	12	4.6	2.3	64							
18	70	9	29	19	6.0	2.6	58							
19	70	12	24	12	7.3	3.3	70							
20	70	24	35	28	6.2	3.3	58							
21	70	7	17	9	3.8	1.8	59							
22	80	11	21	12	5.0	2.4	54							

Pt = patient; HR = heart rate (bpm); CVP = central venous pressure; mPA = mean pulmonary artery pressure; PCWP = pulmonary capillary artery pressure; CO = cardiac output (L/min); CI = cardiac index (L/min/m^2); PASat = pulmonary artery oxygen saturation (%). All pressures measured in mm Hg.

Table 3
Hemodynamics during BiV and RV pacing at baseline (presenting HR) in all patients and during intrinsic rhythm compared with BiV and RV Pacing in 15 non-PM-dependent patients

Parameter	Hemodynamics at presenting HR in all enrolled patients (n = 22)		Hemodynamics during intrinsic rhythm compared with BiV and RV pacing at presenting HR (n = 15)			
	BiV (n = 22)	RV (n = 22)	BiV (n = 15)	RV (n = 15)	Intrinsic (n-15)	p
HR, bpm	79±8	79±8	81±9	81±9	70±17	0.01*
CVP (mm Hg)	14±6	14±6	13±5	13±6	13±6	ns
Mean PA (mm Hg)	27±8	27±7	28±8	27±9	27±8	ns
PCWP, (mm Hg)	16±7	17±6	17±7	17±6	16±7	ns
CO(TD), L/min	5.3±1	5.1±1	5.2±0.9	5.0±0.9	5.0±1.1	ns
CI(TD), L/min/m^2	2.5±0.5	2.4±0.5	2.5±0.5	2.4±0.5	2.4±0.6	ns
PA Sat (%)	58.5±8	59.2±7	58.6±7.7	59.4±7.2	56.9±9.2	ns
RVSWI	449±200	429±207	485±207	436±221	495±239	ns

BiV = biventricular; RV = right ventricular; HR = heart rate; RA = right atrium; PA = pulmonary artery; PCWP = pulmonary capillary artery pressure; CO = cardiac output; CI = cardiac index; TD = thermodilution; RVSWI = right ventricular stroke work index in (mm Hg × mL/min × m^2 × bpm).
* P value significance between intrinsic rhythm compared to BiV and RV pacing.

observe clinically significant differences in hemodynamics when the pacing rate was increased or decreased in any of the 21 patients tested at 2 or 3 HRs. Hemodynamics during BiV and RV pacing at the presenting HR, lowest tested HR (intrinsic or paced) and highest tested HR, are shown in Figures 1 and 2.

We calculated the right ventricular stroke work index (RVSWI) = (mPA − CVP) × CI/HR as a measure of RV performance and found that RVSWI was significantly lower at the highest HR (110 beats/min) compared with the presenting HR (78 beats/min) during both BiV pacing (354 ± 146 vs 450 ± 205, p = 0.001) and RV pacing (363 ± 146 vs 430 ± 208, p = 0.01). RVSWI at the lowest HR was higher than the RVSWI at the highest HR and not significantly different compared with baseline (presenting) HR (Figure 3).

LVAD parameters (flow, power, and pulsatility index) have not significantly changed during the study for either HM2 or HM3 patients.

Discussion

In this prospective study, we found no difference in hemodynamics between BiV and RV pacing in CF-LVAD supported

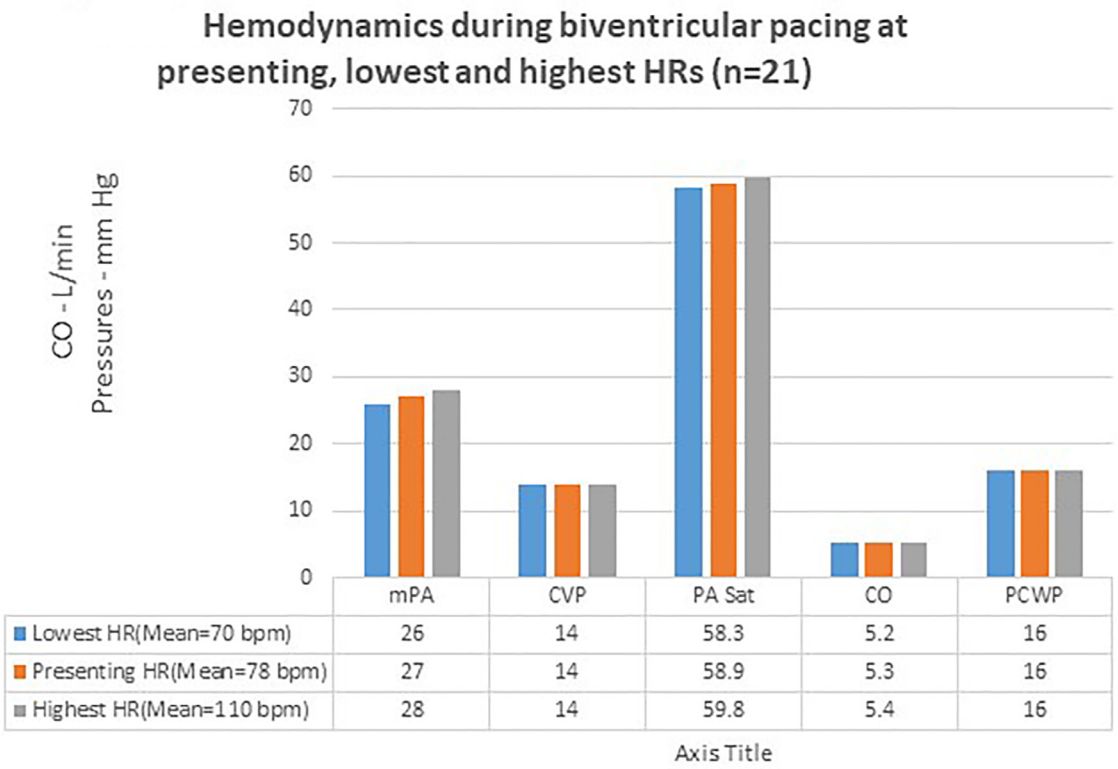

Figure 1. Hemodynamics during biventricular pacing at presenting, lowest, and highest HRs (n = 1). (HR = heart rate (beats/min); PASat = pulmonary artery oxygen saturation (%); mPA = mean pulmonary artery pressure; CVP = central venous pressure; CO = cardiac output; PCWP = pulmonary capillary artery pressure. All pressures measured in mm Hg.)

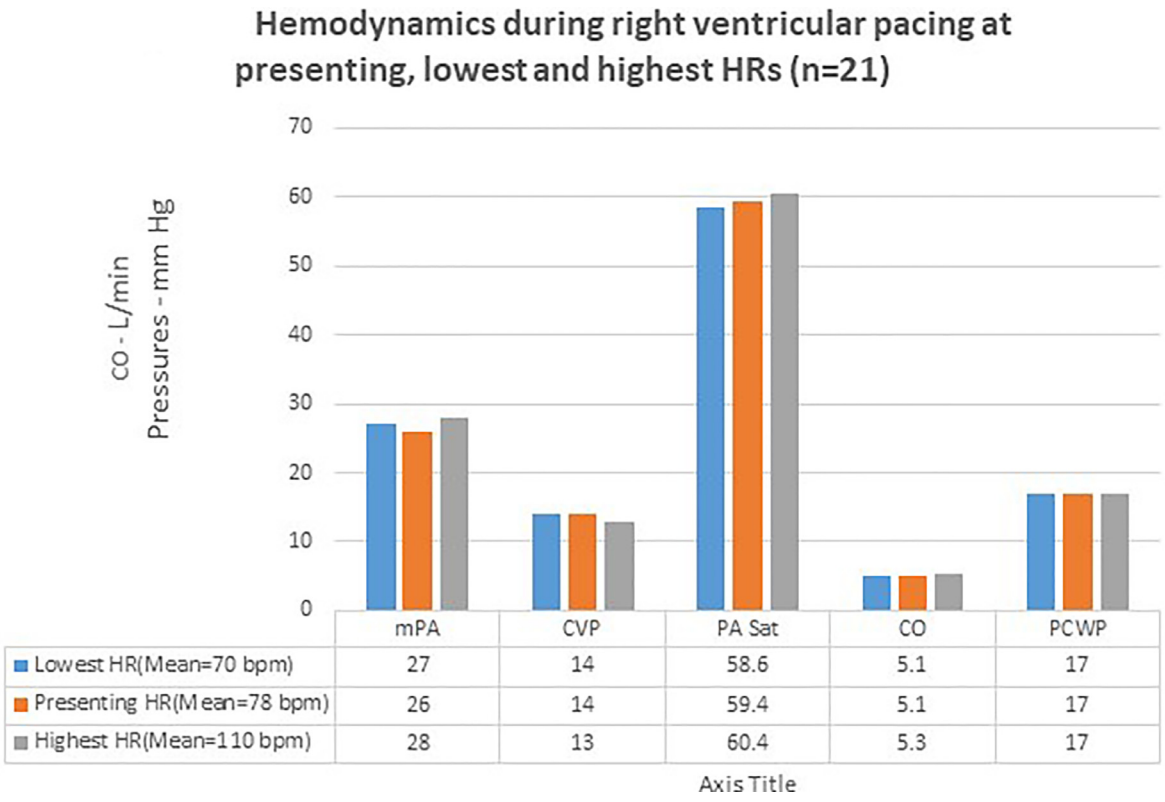

Figure 2. Hemodynamics during right ventricular pacing at presenting, lowest and highest HRs (n = 21). (HR = heart rate (beats/min); PASat = pulmonary artery oxygen saturation (%); mPA = mean pulmonary artery pressure; CVP = central venous pressure; CO = cardiac output; PCWP = pulmonary capillary artery pressure. All pressures measured in mm Hg.)

patients who had previously failed CRT. Hemodynamics was also similar during intrinsic rhythm in 14 of 15 non−PM-dependent patients. Only 1 patient had a mild decrease in CO during intrinsic rhythm but this patient was post-AVN ablation for persistent AF and was tested during a slow unreliable junctional escape rhythm around 40 beats/min.

BiV pacing was found to be superior to conventional RV pacing in non-LVAD patients with atrioventricular block (AVB) and LV systolic dysfunction.[14] We did not see any acute hemodynamic benefit for BiV over RV pacing in our cfLVAD patients with complete AVB (50% of our patients). We have further showed that patients supported by a CF-LVAD have no significant change in CO, PA saturation, and filling pressures at HRs ranging from 50 to 110 beats/min.

We can confidently conclude from our data that there is no acute hemodynamic benefit for BiV pacing over RV pacing. There was also no hemodynamic advantage for ventricular pacing (whether BiV or RV) over intrinsic rhythm if the intrinsic rate was in the physiologic range (50 to 110 beats/min). Contrary to our expectation, CO and filling pressures measured by invasive hemodynamics did not significantly change across a wide range of HRs (50 to 110 beats/min). A previous noninvasive study reported that body position and activity but not HR affected estimated pump flows in patients supported by a different centrifugal CF-LVAD (HeartWare).[15] Our data support in a more rigorous way, through invasive hemodynamics, that HR does not significantly influence the CO in patients supported by either axial flow (HM2) or centrifugal (HM3) CF-LVADs.

RV function has a major impact on LVAD flow and is the main factor in maintaining cardiac output in LVAD patients. It has been shown that CRT improves not only LV function but also RV function although whether this is a direct effect or a result of improved LV function is a matter of debate.[16,17] In our study, BiV and RV pacing had no impact on right RVSWI. This remained true even in 4 patients with severe RV failure who were in stable condition but on inotropic support at the time of the study. Given similar CO and filling pressures across all HRs, RVSWI was significantly lower at the highest tested HR (110 beats/min) compared with the baseline and lowest HRs suggesting decreased RV performance at high HRs. BB are frequently discontinued in LVAD patients with severe RV dysfunction. However, a lower HR has better energetic efficiency and might be beneficial for RV performance. In LVAD patients with RV Failure intolerant to BB, Ivabradine is a potential attractive alternative to lower HR especially in those with RV failure and sinus tachycardia.

We believe that our data is sufficient to prove that BiV pacing has no acute hemodynamic benefit compared with RV pacing or intrinsic rhythm in LVAD patients who failed CRT before implant. However, the situation is possibly different in LVAD patients who have not failed CRT. A few case reports showed improvement in LV function when CRT was added to LVAD patients who had indications for BiV pacing with successful weaning and removal of the LVAD in all cases.[9−13] It is important to note that in most

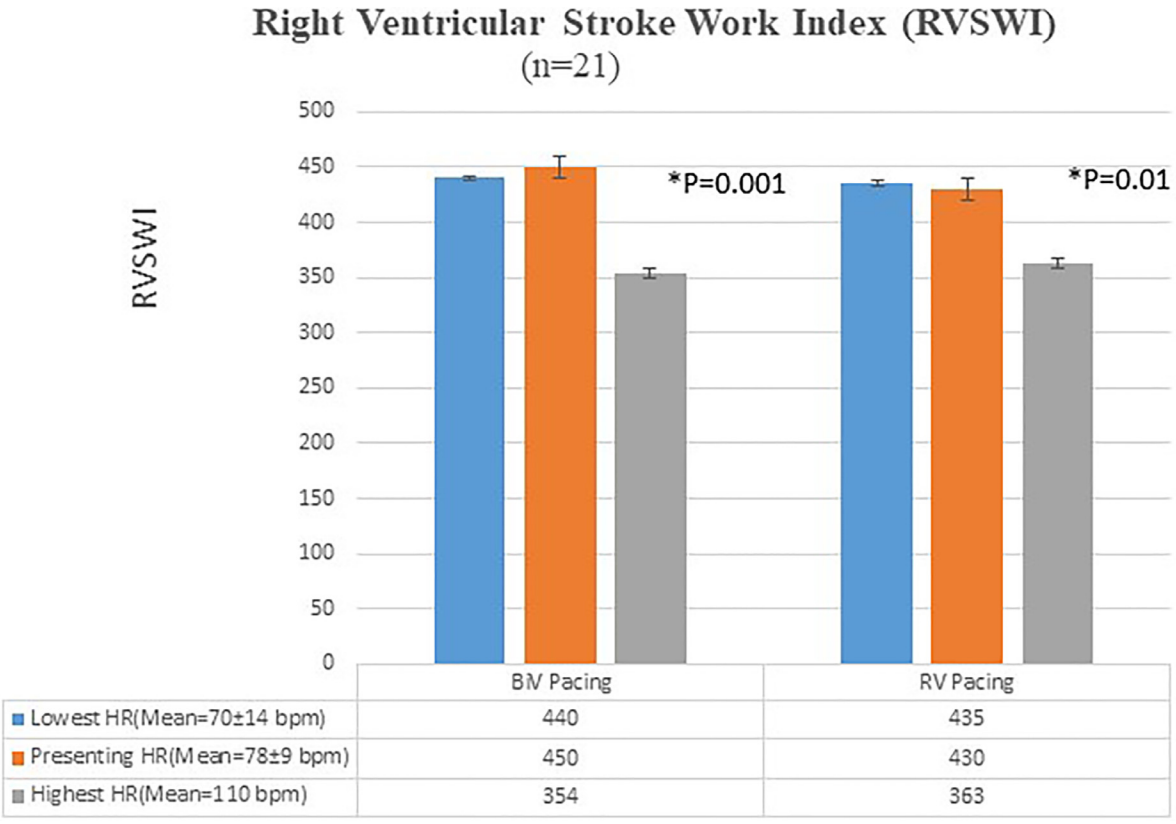

Figure 3. Right ventricular stroke work index. (RVSWI measured mm Hg × ml/min × m^2 × beats/min, *p values between highest and baseline [presenting] HR).

published case reports, CRT was implemented after LVAD implant or, in one case, within previous days. Thus, it is possible that mechanical circulatory support could have been avoided if CRT had been initiated before LVAD implant or early enough to allow improvement in LV function.

In the absence of any guidelines, management of BiV PM post-LVAD remains challenging among HF and electrophysiology (EP) physicians. Our practice had been in the past to continue BiV pacing post-LVAD implant despite uncertain benefit or harm. However, we have started to analyze each patient individually and make decisions on a case-by-case basis since there are potential advantages and disadvantages for maintaining CRT post-LVAD implant. CRT discontinuation could extend battery life and delay device replacement. A potential advantage for CRT continuation includes the possibility for LV recovery, especially in those not previously exposed to CRT. Partial or minimal improvement that might be derived from CRT could be beneficial to maintain AV opening and improve aortic insufficiency which is common in LVAD patients.

In summary, in patients who have failed CRT, discontinuation is reasonable post-LVAD if needed to preserve battery life, avoid device replacement or for other reasons such as VT or infection. Reduction from BiV to RV to pacing rates as low as 50 beats/min is reasonable in PM-dependent patients whereas back up pacing as low as 50 beats/min is also reasonable in non−PM-dependent patients. In contrast, BiV pacing post-LVAD is reasonable in patients who have not clearly failed CRT, for those who derived benefit before implant, and for those who might derive benefit post-LVAD implant either because of recent BiV PM placement or expected LV recovery. Last but not least, we believe that CRT should be attempted in all eligible patients before durable LVAD implant and should also be considered post-LVAD in patients with wide LBBB not exposed to such therapy.

This was a relatively small nonrandomized study that included mostly men. However, the rigorous EP and hemodynamic protocols with multiple measurements during different PM setting as well as intrinsic rhythm (when possible) makes our hemodynamic data fairly robust. The role of CRT in patients with AFib is less clear than in those with sinus rhythm. However, most AFib patients had AVN ablation which allowed ideal control of HR during BiV and RV pacing. We did not perform LV pacing alone which was shown to be superior to BiV pacing during long-term follow-up in a substudy of adaptive CRT (aCRT) trial.[18] This was an acute study and it is well documented that some patients are slow responders to CRT. Adaptive CRT was beyond the scope of this study and showed potential benefit during long-term follow-up.[18,19] A similar study with a crossover design using each patient as their own control including use of aCRT could be performed to confirm or refute our acute data.

In conclusion, BiV pacing does not have any acute hemodynamic benefit compared with RV pacing or intrinsic rhythm in CF-LVAD patients. Decision to continue or discontinue CRT post-LVAD should be individualized after careful review of HF and EP history. Studies to assess the

long-term clinical benefits of cardiac resynchronization therapy in LVAD patients are warranted.

Disclosures

Authors have no disclosure.

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Evaluation MSGMIRC. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845–1853.
2. Anselme F, Bordachar P, Pasquié JL, Klug D, Leclercq C, Milhem A, Alonso C, Deharo JC, Gras D, Probst V, Piot O, Savouré A. Safety, feasibility, and outcome results of cardiac resynchronization with triple-site ventricular stimulation compared to conventional cardiac resynchronization. *Heart Rhythm* 2016;13:183–189.
3. Zanon F, Marcantoni L, Baracca E, Pastore G, Lanza D, Fraccaro C, Picariello C, Conte L, Aggio S, Roncon L, Pacetta D, Badie N, Noventa F, Prinzen FW. Optimization of left ventricular pacing site plus multipoint pacing improves remodeling and clinical response to cardiac resynchronization therapy at 1 year. *Heart Rhythm* 2016;13:1644–1651.
4. Thibault B, Dubuc M, Khairy P, Guerra PG, Macle L, Rivard L, Roy D, Talajic M, Karst E, Ryu K, Paiement P, Farazi TG. Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead. *Europace* 2013;15:984–991.
5. Parikh V, Sauer A, Friedman PA, Sheldon SH. Management of cardiac implantable electronic devices in the presence of left ventricular assist devices. *Heart Rhythm* 2018;15:1089–1096.
6. Gopinathannair R, Birks EJ, Trivedi JR, McCants KC, Sutton BS, Deam AG, Slaughter MS, Hottigoudar RU. Impact of cardiac resynchronization therapy on clinical outcomes in patients with continuous-flow left ventricular assist devices. *J Card Fail* 2015;21:226–232.
7. Andrew D Choi A.F., Anelechi A., Sean P., Eric A. Biventricular pacing in patients with left ventricular assist devices—Is left ventricular pacing Proarrhythmic? JACC March 9, 2010, Vol 55, Issue 10A: ACC Poster, 2010.
8. Schleifer JW, Mookadam F, Kransdorf EP, Nanda U, Adams JC, Cha S, Pajaro OE, Steidley DE, Scott RL, Carvajal T, Saadiq RA, Srivathsan K. Effect of continued cardiac resynchronization therapy on ventricular arrhythmias after left ventricular assist device implantation. *Am J Cardiol* 2016;118:556–559.
9. Nishimura M, Ogiwara M, Ishikawa M, Imanaka K, Okamura N, Kato M, Asano H, Katogi T, Kohmoto O, Matsumoto K, Nishimura S, Kyo S. Successful bridge to resynchronization therapy with a left ventricular assist system in a patient with idiopathic dilated cardiomyopathy. *J Artif Organs* 2005;8:210–213.
10. Nishimura T, Kyo S. Triple-site pacing: a new supported therapy approach for bridge to recovery with a left ventricular assist system in a patient with idiopathic dilated cardiomyopathy. *J Artif Organs* 2010;13:54–57.
11. Keilegavlen H, Nordrehaug JE, Faerestrand S, Fanebust R, Pettersen R, Haaverstad R, Tuseth V. Treatment of cardiogenic shock with left ventricular assist device combined with cardiac resynchronization therapy: a case report. *J Cardiothorac Surg* 2010;5:54.
12. Muratsu J, Hara M, Mizote I, Asano Y, Sakata Y, Saito S, Matsumiya G, Sawa Y, Komuro I. The impact of cardiac resynchronization therapy in an end-stage heart failure patient with a left ventricular assist device as a bridge to recovery. A case report. *Int Heart J* 2011;52:246–247.
13. Verreault-Julien L, Philippon F, Charbonneau É, Kalavrouziotis D, LeRoux É, Sarrazin JF, Dubois M, Voisine P, Sénéchal M. Usefulness of cardiac resynchronization therapy in the recovery of patients with left ventricular assist devices. *Int J Cardiol* 2016;223:297–298.
14. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T, Sutton MS. Investigators BvRVPiHFPwABBHT. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013;368:1585–1593.
15. Muthiah K, Gupta S, Otton J, Robson D, Walker R, Tay A, Macdonald P, Keogh A, Kotlyar E, Granger E, Dhital K, Spratt P, Jansz P, Hayward CS. Body position and activity, but not heart rate, affect pump flows in patients with continuous-flow left ventricular assist devices. *JACC Heart Fail* 2014;2:323–330.
16. Gebska MA, Giudici MC, Rossen J, Wilson JS, Sigurdsson G, London B, Chatterjee K. Isolated right ventricular failure and abnormal hemodynamics caused by right ventricular pacing are reversed with cardiac resynchronization therapy. *HeartRhythm Case Rep* 2015;1:182–185.
17. Sharma A, Lavie CJ, Vallakati A, Garg A, Goel S, Lazar J, Fonarow GC. Changes in parameters of right ventricular function with cardiac resynchronization therapy. *Clin Cardiol* 2017;40:1033–1043.
18. Starling RC, Krum H, Bril S, Tsintzos SI, Rogers T, Hudnall JH, Martin DO. Impact of a novel adaptive optimization algorithm on 30-day readmissions: evidence from the adaptive CRT trial. *JACC Heart Fail* 2015;3:565–572.
19. Martin DO, Lemke B, Birnie D, Krum H, Lee KL, Aonuma K, Gasparini M, Starling RC, Milasinovic G, Rogers T, Sambelashvili A, Gorcsan J, Houmsse M. Investigators ACS. Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: results of the adaptive CRT trial. *Heart Rhythm* 2012;9:1807–1814.