Permanent His Bundle Pacing: Electrophysiological and Echocardiographic Observations From Long-Term Follow-Up

Pugazhendhi Vijayaraman, MD, FHRS,* Gopi Dandamudi, MD, FHRS^ Daniel Lustgarten, MD, FHRS[#] and Kenneth A Ellenbogen, MD, FHRS[!]

*Geisinger Wyoming Valley Medical Center, Wilkes-Barre, PA;

^Indiana University, Indianapolis, Indiana

[#] University of Vermont Health System, Burlington, VT

[!]Virginia Commonwealth University Health System, Richmond, VA

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Address for Correspondence: Pugazhendhi Vijayaraman, M.D.

Director, Cardiac Electrophysiology

Geisinger Wyoming Valley Medical Center

MC 36-10

1000 E Mountain Blvd

Wilkes-Barre, PA 18711

Tel: 570 808 3137; Fax: 570 808 2306

Email: pvijayaraman1@geisinger.edu

pvijayaraman@gmail.com

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ABSTRACT

Background: Permanent His bundle pacing (HBP) is a physiological alternative to right ventricular pacing (RVP). It is not known whether HBP can cause His-Purkinje conduction (HPC) disease. The aim of our study is to assess His bundle capture and its effect on LV function in long-term follow-up and to determine HPC at the time of pulse generator change (GC) in patients with chronic HBP.

Methods: HB electrograms were recorded from the pacing lead at implant and GC. HBP QRS duration(d), HV intervals and HB pacing thresholds at GC were compared with implant measurements. HPC was assessed by pacing at cycle lengths of 700, 600 and 500ms at GC. LV internal diameters, EF and valve dysfunction at baseline were compared with echocardiography during follow-up.

Results: GC was performed in 20 patients (men 13; age 74±14yrs) with HBP at 70±24 months post implant. HV intervals remained unchanged from initial implant (44±4ms vs 45±4 ms). During HBP at 700, 600 and 500 ms (n=17), consistent 1:1 HPC was present. HBP QRSd remained unchanged during follow-up (117±20 vs 118±23 ms). HBP threshold at implant and GC was 1.9±1.1V and 2.5±1.2V @ 0.5 ms. Despite high pacing burden (77±13%), there was a no significant change in LVEF (50±14% at implant) during follow-up (55±6%, p=0.06).

Conclusions: HBP does not appear to cause new HPC abnormalities and is associated with stable HBP QRSd during long-term follow-up. Despite high pacing burden, HBP did not result in deterioration of left ventricular systolic function or cause new valve dysfunction.

Keywords: His bundle pacing; long-term follow-up; His-Purkinje conduction; LV function

INTRODUCTION

RV pacing has been associated with ventricular dyssynchrony, reduction in left ventricular ejection fraction and adverse clinical outcomes.[1,2,3] Permanent His bundle pacing (HBP) is a physiologic alternative to right ventricular (RV) pacing. Deshmukh et al,[4] first described successful permanent His-Bundle pacing (HBP) in a small series of patients with AF and dilated cardiomyopathy in 2000. Subsequently, there have been multiple reports on permanent HBP, which have demonstrated it is feasible and associated with an improvement in exercise capacity, myocardial perfusion, ventricular synchrony and left ventricular ejection fraction (LVEF) compared to RV pacing.[5,6,7,8,9] Despite these studies, permanent HBP has not gained widespread acceptance in clinical practice due to a variety of reasons: perceived difficulties associated with HBP lead implantation, lead dislodgement, and concern for progression in AV conduction system disease. Fibrosis is known to occur near the tip of the actively fixed RV leads. Concern that fibrosis will compromise reliable His bundle capture is one additional factor limiting broad adoption of permanent His bundle pacing. Long-term follow-up of permanent HBP has not been reported in the literature. The aim of our study is to assess His bundle capture and its effect on LV function in medium to long-term follow-up and to determine His-Purkinje conduction at the time of pulse generator change in patients with chronic HBP.

METHODS

Patients: Permanent HBP has been performed at Geisinger Wyoming Valley Medical Center since 2006. Our analysis involved patients who had undergone successful permanent HBP between the years 2006 to 2014 and presented subsequently for generator change due to routine battery depletion. All patients provided written informed consent prior to implantation. This was a retrospective study approved by the institutional review board.

Implantation technique: A detailed description of the permanent HBP has been described previously.[9] Briefly, a 4.1 Fr bipolar active fixation lead (SelectSecure, model 3830, Medtronic) was implanted in the His bundle region using a dedicated delivery sheath (deflectable C304 or C315His, Medtronic). Selective HBP (S-HBP) was defined as ventricular activation occurring solely over the His-Purkinje system: (1) His-Purkinje mediated cardiac activation and repolarization as evidenced by electrocardiographic (ECG) concordance of QRS and T wave complexes; (2) the paced-ventricular interval was almost identical to the His-ventricular interval (figure 1). Non-selective HBP was (NS-HBP) was defined based on capture of basal ventricular septum in addition to His bundle capture as: (1) no isoelectric interval between pacing stimulus and QRS; (2) the electrical axis of the paced QRS must be concordant with the electrical axis of the spontaneous QRS (if known); (3) narrowing of QRS with higher output or vice-versa (figure 2).[10,11,12] The HBP lead was connected to the RV port (no back-up lead) or the left ventricular port in a patient with CRT device (RV lead in RV port). Our definition of nonselective-HBP is different from the initial description of para-hisian pacing[4,13] to eliminate the confusion associated with using para-hisian capture[14] in reference to assessment of accessory pathway conduction.

Protocol: His bundle capture threshold, R wave amplitudes, pacing impedances and HV intervals were measured at implant. Twelve lead EKG at baseline and during HBP, along with baseline and paced QRS duration were also recorded for each patient. In patients with sinus node dysfunction, ventricular pacing avoidance algorithm was routinely used. Patients were followed in device clinic at 2 weeks, 2 months, 1 year and yearly thereafter. R wave amplitudes, pacing thresholds, and lead impedances were recorded at each visit. Patients were also followed by remote monitoring every 3 months. Any significant increases in pacing threshold, lead dislodgement or loss of capture were routinely tracked. Percentage right ventricular pacing (His bundle pacing) was recorded. At the time pulse generator change, His bundle capture threshold, R wave amplitudes, pacing impedances and HV intervals from the HBP lead were again measured. In addition, pacing from HBP lead was routinely performed at cycle lengths of 700, 600 and 500 ms to assess for 1:1 His bundle capture and conduction,[15] during generator change (figure 3).

Echocardiography: All patients underwent echocardiography prior to their initial permanent pacemaker implantation. Follow-up echocardiograms were obtained as clinically indicated and prior to pacemaker generator change. LVEF was measured using Simpson's biplane method. In situations of poor image quality, EF measurements were supplemented by visual assessment by the echocardiographer. Left ventricular internal diameters at systole and diastole were obtained. Mitral and tricuspid regurgitation if present were reported as mild, moderate or severe.

Follow-up: Urgent care visits or hospitalization for heart failure during follow-up were documented. Any new development of atrial fibrillation was recorded.

Statistical analysis

Continuous data are presented as mean ± standard deviation. Differences between continuous variables were assessed using paired Student's t test. The statistical significance was defined as a p value <0.05.

RESULTS

Patient Characteristics: Between the years 2006 to 2014, a total of 425 patients underwent HBP at our institution. Of these, twenty consecutive patients with previously successful permanent HBP presented for pulse generator change due to battery depletion and were included in our analysis. Baseline clinical characteristics along with findings at the time of generator change are summarized in Table 1. The primary indication for permanent pacing was AV nodal disease (second or third degree AV block) in 12, intra-Hisian block in 1 (HV), sinus node dysfunction in 5, failed LV lead placement in 1, and AV node ablation in 1. A dual chamber pacemaker was implanted in 15, single chamber in 1, CRT-P in 1 and CRT-D in 3 patients. Mean age 74±14 years; men 65%; hypertension 65%; diabetes 10%; coronary artery disease 40%, atrial fibrillation 65%; and cardiomyopathy 30%. The mean duration of permanent HBP at the time of generator change was 70±24 months (range: 36 – 102 months).

Pacing Characteristics: Selective HBP was achieved in 7 (35%) patients and nonselective HBP in 13 (65%). Baseline QRS duration was 102±27 ms and the paced (HBP) QRS duration prolonged to 117±20 ms at implant (p=0.04). At the time of generator change, the paced QRS duration and morphology did not differ significantly when compared to at implant (118±23 ms, p=0.5). His bundle capture threshold at implant was 1.95±1.1V @ 0.5 ms. At the time of generator change, the HBP threshold was higher at 2.5±1.2V @ 0.5 ms (p=0.02). His bundle capture thresholds in patients with selective and nonselective HBP were not significantly different at implant (1.6±0.5 vs 2.1±1.3V, p=0.2) or at generator change (2.4±1.0 vs 2.5±1.3V, p=0.7). In one patient (18), HBP threshold increased significantly from 1.2V at

implant to 4.5V at the time of generator change, 36 months post implant (CRT-D). The HBP lead was removed by manual traction without difficulty and a new HBP lead was successfully implanted in this patient (HBP threshold 1V). There were no significant differences in the sensing amplitude (5.9±5.1 mV, range 1-10.1mV vs 6.1±3.9 mV, range 1.1-14 mV; p=0.43) or pacing impedance (516±98 vs 484±112 Ohms; p=0.06) at the time of generator change compared to implantation in the entire group. Overall ventricular pacing (HBP) burden during last follow-up was 77±13%. In the 5 patients with primary sinus node dysfunction, overall HBP burden was low at 14±19% with the use of minimal ventricular pacing^{Tm} algorithm (range: 1-47%). In five patients with pacemaker model EnRhythm^{Tm} (Medtronic Inc, Minneapolis, MN), there was premature battery depletion (advisory) despite low ventricular pacing burden in 4 patients (patient 9,15,17 and 20).

His-Purkinje conduction: HV intervals at the time of implant were 44±4 ms and did not change significantly at the time of generator change (45±4 ms, n =19, p=0.5). At the time of generator change HBP was performed at 700,600 and 500 ms in 17 patients to assess distal His-Purkinje conduction. In all 17 patients tested, 1:1 His capture and conduction was present during pacing at 500 ms (figure 4).

Echocardiographic data: Baseline and follow-up echocardiograms were available in all patients. Baseline LV ejection fraction (EF) was 50±14% and during last follow-up the EF was 55±6% (p=0.06) (figure 5). In the six patients with LV dysfunction at baseline, the ejection fraction improved from 36±12% to 50±7% during last follow-up (p=0.03). Left ventricular end-diastolic diameter improved from 51±8 mm at baseline to 47±7 mm at last follow-up (p=0.06). Mitral regurgitation was present in 11 patients (mild 10, moderate 1) and tricuspid regurgitation (mild 7, moderate 1) in 8 patients at baseline. Only one patient with underlying chronic obstructive pulmonary disease and pulmonary hypertension, showed

evidence of worsening tricuspid regurgitation (patient 1) from mild at baseline to moderate during follow-up in spite of improved LVEF from 35% at implant to 54%. No patient showed worsening mitral regurgitation.

Clinical Outcome: Two patients (2 and 16) had a heart failure hospitalization (HFH) during follow-up. In patient 2, HFH was secondary to worsening renal function from diabetic nephropathy (serum Cr 2.4 mg/dl). Patient 2 also developed new persistent atrial fibrillation during follow-up. Diastolic dysfunction and dietary indiscretion was attributed to the heart failure admission 2 years after AV node ablation and HBP in patient 16, whose baseline LVEF had improved from 25 to 45%. Patient 6 had developed an inferior wall myocardial infarction with subsequent decline in his LVEF from 58 to 44%.

DISCUSSION

In this study, we present medium to long-term follow-up on 20 patients with permanent HBP who presented for generator change. This allowed us a unique opportunity to assess the effects of long term HBP on pacing characteristics and His-Purkinje conduction. During a mean follow-up of 70±24 months, His bundle capture thresholds remained relatively stable with only a modest increase in pacing output (0.6V). One of the concerns of permanent HBP had been historically high pacing thresholds and early battery depletion. Despite the average pacing thresholds similar to those reported by other investigators,[16,17] the device longevity was longer in this series. Most investigators used a back-up RV pacing lead, thus requiring a biventricular or dual chamber device leading to additional battery depletion. We did not routinely place a back-up RV lead thus *limiting* current drain. Early in our experience, we programmed a pacing output twice the safety margin. Subsequently we changed our approach to program a pacing output at 1V above chronic His bundle capture (3 month) threshold at 1

ms pulse duration. In seven of these patients we had used the largest battery available from the manufacturer (Adapta L and EnRhythm^{Tm}, Medtronic Inc, Minneapolis, MN) to combat early battery depletion. Unfortunately, five of these devices had an advisory for premature battery depletion, despite minimal ventricular pacing in 4. Midway through this series, we learned to use the C315His sheath for implanting the His bundle pacing lead, which generally provides better pacing thresholds than those obtained using the C304 sheath.[9] Currently we are able to obtain lower His bundle capture thresholds in >50% of the patients by demonstrating acute His bundle injury current at implant.[18] In addition, our current practice is to primarily use the larger battery device.

Early HBP implanters used an additional RV pacing lead in most patients because of low R wave sensing, high His pacing thresholds and concern for "what if they develop conduction disease distal to the AV node in the His –Purkinje system". To our knowledge there is no documented literature on the natural history of progression of conduction disease in AV nodal block. An important observation in our study was the stability of His-Purkinje conduction and the His bundle paced QRS duration in this series. The HV interval remained unchanged from baseline. None of these patients developed new His-Purkinje conduction disease during follow-up. The paced QRS duration and the morphology at the time of GC were similar to the paced QRS at implant. When paced at 500 ms, 1:1 His capture and conduction remained unchanged. Even in the one patient (13) with intra-Hisian AV block, distal His capture was persistent. Recent reports suggest stable distal His-Purkinje conduction in patients with intra-Hisian block during medium term follow-up.[19,20] It is not known whether patients with AV nodal block develop disease in the His-Purkinje fibers in the future. In this small series we did not find any discernible evidence to suggest development of new His-Purkinje disease in patients with AV nodal block. Historical concerns regarding local

fibrosis and development of new His-Purkinje conduction disease should not be a deterrent for broad adoption of permanent HBP in clinical practice.

It is well established that chronic right ventricular pacing is detrimental to left ventricular function and is associated with heart failure and increased mortality.[1,2,3] While biventricular pacing is beneficial compared to RV pacing in patients with heart failure,[21] it has not been proven to prevent HFH or improve mortality in patients without LV dysfunction or heart failure.[22,23] However, in patients with systolic heart failure and QRS duration <130-150 msec, HFH or mortality do not improve with biventricular pacing and even show worsening of their condition.[24,25]. In these cases, His bundle pacing may be effective in ameliorating heart failure.

In our series, there was a non-significant increase in left ventricular ejection fraction during long-term follow-up despite high HBP burden (77%). This was primarily due to a significant increase in EF in the 6 patients with underlying LV dysfunction ($p = 0.02$). The improvement in LVEF could be attributed to HBP in 4 pts (LBBB 1, pacing induced cardiomyopathy 1, AF related in 2). In the 16 patients with normal LV function, EF remained unchanged ($p = 0.96$). Previous studies have shown that permanent HBP maintains LV synchrony, left ventricular performance, myocardial perfusion and prevent heart failure during short and medium term follow-up compared to right ventricular pacing.[4,5,6,7,17] Several small series have shown improvement in LV function with permanent HBP in patients with traditional indication for cardiac resynchronization therapy (CRT).[26,27] It is possible that HBP may provide alternative option for patients requiring CRT. In addition, our study shows that there is no significant worsening of valve regurgitation. The HBP lead is primarily located in the right atrium with minimal or no interference to the tricuspid valve.[28,29,30] Right ventricular pacing has been associated with new tricuspid regurgitation and valve abnormalities due to

fibrous lesions between the lead and the tricuspid valve in addition to pulmonary hypertension resulting from LV dysfunction.[31] A recent study showed reduced incidence of tricuspid valve abnormalities and venous stenosis with the Medtronic 3830 pacing lead compared to traditional RV pacing leads attributed to the smaller lead diameter (4.1 Fr).[32] During the entire follow-up period there were only two heart failure hospitalizations in our series despite high HBP burden. In a study of 304 patients with normal LV function and AV block, Zhang et al,[33] showed that 26% of patients developed new onset heart failure during a median follow-up of 7.8 years of right ventricular pacing. Both of our patients with HFH (patient 2 and 16) had selective HBP and improved LV function at the time of their hospitalization. It is unlikely that HBP contributed to the heart failure hospitalization in these patients. It is likely that permanent HBP may provide an excellent option for the majority of patients requiring ventricular pacing in the future.

Limitations

This was a small, single center, retrospective, observational series of selected patients with successful permanent His bundle pacing without comparisons of clinical outcomes with RV pacing. The small sample size also limits the statistical analysis. However this is the first study to report on long-term follow-up and clinical outcomes of permanent HBP. A randomized, multicenter evaluation of HBP compared to RV pacing with long-term follow-up is necessary to prove the superiority of permanent HBP. Because capture thresholds with permanent HBP are still higher than a standard RV lead, improvement in lead designs, (longer helix), delivery sheaths, and new devices with longer battery life would be necessary.

CONCLUSIONS

Permanent HBP does not appear to cause new His-Purkinje conduction abnormalities during long-term follow-up. HV intervals, His bundle paced QRS duration, 1:1 His capture and

conduction remained stable during long-term follow-up. Despite high pacing burden, HBP did not result in deterioration of left ventricular systolic function or cause new valve dysfunction.

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FIGURE LEGENDS

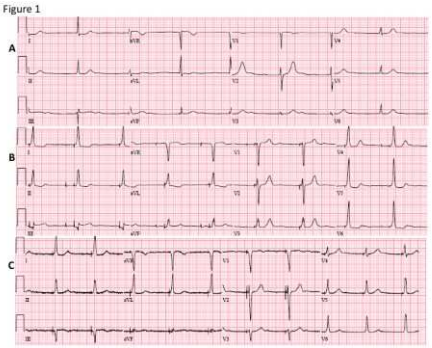

Figure 1: A. Twelve lead ECG of patient 2 at baseline shows sinus bradycardia and long first degree AV block. **B.** AV sequential pacing with selective His bundle capture at implant with paced QRS duration and morphology identical to baseline. **C.** Eight years later following generator change, ECG demonstrating persistent selective HBP with underlying atrial fibrillation. The stimulus to QRS interval is unchanged from implant. Note the significant morphology changes in aVF and V3 during HBP, which may be indicative of a latent His Purkinje conduction abnormality brought out by pacing, i.e. intraventricular conduction delay, despite maintenance of a narrow QRS throughout.

Figure 2

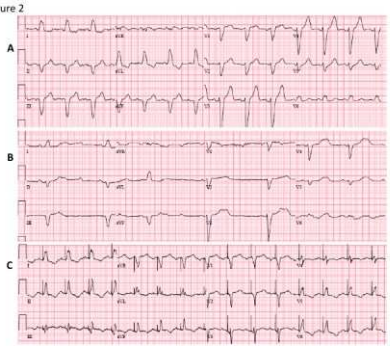

Figure 2: A. Twelve lead ECG of patient 13 with longstanding LBBB of 8-year duration with QRS duration of 160 ms. **B.** High-grade 3:1 AV block with underlying LBBB. **C.** Nonselective HBP with QRS duration of 126 ms at 4 years following generator change.

Figure 3

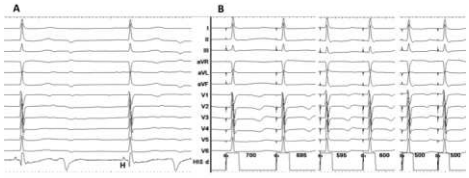

Figure 3: Twelve lead ECG and intracardiac electrogram from the HBP lead at the time of generator change in patient 6. **A.** Complete AV block and narrow complex escape rhythm with HV interval of 45 ms, unchanged from baseline after 5 years. **B.** Selective His bundle capture with QRS duration identical to the escape rhythm with 1:1 His capture and conduction during pacing at cycle lengths of 700, 600 and 500 ms.

Figure 4

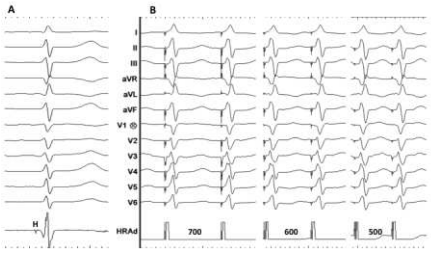

Figure 4: Twelve lead ECG and intracardiac electrogram from the HBP lead at the time of generator change in patient 1. **A.** Atrial fibrillation with slow ventricular response. HV interval was unchanged from baseline after more than 8 years of HBP. **B.** Nonselective His bundle capture with minimal QRS fusion and 1:1 His bundle capture during pacing at cycle lengths of 700, 600 and 500 ms.

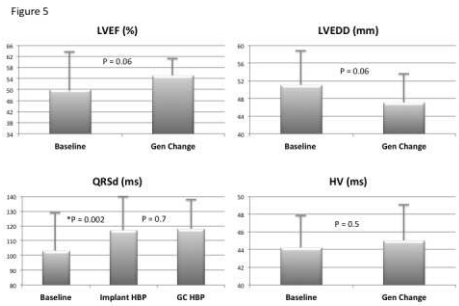

Figure 5: Left ventricular ejection fraction (LVEF), LV end diastolic diameter, QRS duration and HV intervals at baseline compared to at the time of generator change. There was no statistical difference between the two groups. *The HBP QRS duration was significantly longer at implant and generator change (GC) when compared to baseline.

Table 1: Patient Characteristics

Pt #	Age	Sex	Co-morbidities	Indication	At Implant						Time to Generator Change (m)	HBP pacing %	At Generator Change			
					HV (ms)	QRSd (ms)	HBP QRSd (ms)	HBP type	HBP threshold @0.5 ms	EF (%)			HV (ms)	HBP QRSd (ms)	HBP threshold @0.5 ms	EF (%)
1	78	M	HTN, HF, CAD, AF	AVB, AF	45	92	120	NS	2.75	35	102	99.6	45	124	3	54
2	70	M	HTN, CAD, AF	AVB, SSS	45	90	100	S	1.6	50	101	98	45	102	2.2	60
3	87	M	HTN	AVB	50	92	92	S	1.2	65	79	96	50	96	1.5	64

4	34	M	CAD, ICM	LBBB, CHF	50	142	100	S	1.6	25	41	85	50	102	2.2	41
5	87	M	HTN, CAD, ICM, AF	AVB, CHF, RVP	45	180	130	NS	1.25	20	38	99.2	45	136	2	44
6	93	M	HTN, CAD, ICM	AVB	45	86	92	S	1.2	58	67	100	45	86	2	44
7	51	M	AF	AVB, SSS	40	92	92	S	1.7	55	84	99	40	94	1.75	55
8	83	F	HTN, AF	AVB, AF	40	92	132	NS	1.5	65	91	98.9	40	136	2	63
9	76	F	AF	SSS	40	120	160	NS	3.6	57	60	18.3	40	150	2	60
10	84	M	HTN	AVB	50	90	130	NS	3.4	55	99	99.8	50	132	3.5	55
11	89	F	HTN, AF	SSS	40	100	130	NS	0.5	55	99	47	40	134	1.5	55
12	79	M	CAD, CABG, AF	AVB, SSS, AF	45	92	126	NS	0.6	60	55	95.9	45	130	0.8	60
13	81	F	HTN	HVB	HVB	160	126	NS	1.4	55	43	100	HVB	126	2.1	60
14	71	M	CAD, CABG, MVR, AF	AVB, SSS	50	86	86	S	2.6	60	49	92.8	50	88	2.5	59
15	79	F	HTN, AF	SSS, AF	45	86	126	NS	2.5	60	100	3	45	126	4	55
16	63	F	HTN, AF, NICM, DM	AVN abl, AF	45	90	130	NS	1	25	54	100	45	134	2	55
17	63	M	HTN, AF, DM	SSS	50	96	136	NS	4	55	54	1	50	136	4.5	54
18	69	F	CAD, CABG, MVR, ICM	AVB	45	86	86	S	1.2	40	36	100	45	90	4.5	50
19	85	M	HTN	AVB	40	102	132	NS	4.3	55	96	100	40	132	5	60
20	68	M	AF, NICM	SSS, AF	45	80	120	NS	1.2	45	57	3	45	124	0.8	55
Mean	**74.5**				**44**	**102.7**	**117.3**		**1.95**	**49.7**	**70.3**	**76.8**	**45**	**118.2**	**2.49**	**55.1**

AF – atrial fibrillation; AVB – AV nodal block; AVN – AV node; CABG – coronary artery bypass graft; CHF – congestive heat failure; DM – diabetes mellitus; EF: ejection fraction; HV – His-ventricular; HVB – HV block; HBP – His bundle pacing; HTN – hypertension, ICM – ischemic cardiomyopathy, LBBB – left bundle branch block; m – months; NICM – non-ischemic cardiomyopathy; QRSd – QRS duration; RVP – right ventricular pacing; SSS – sick sinus syndrome.