


Anatomical and histological assessment of left bundle branch area pacing in human heart with refractory heart failure

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Abstract

As an emerging pacing technique, left bundle branch area pacing (LBBAP) has served as a physiological pacing modality that overcomes the limitations of His bundle pacing (HBP) or right ventricular pacing. Three patients with terminal heart failure who were waiting for heart transplantation and met the indications of pacemaker implantations received LBBAP. Symptoms were relieved and stabilized and eventually received heart transplantation. Diseased hearts from the recipients were dissected post-transplantation, and the direct visual of pacing lead locations in the interventricular septum were evaluated, and the histopathological examination around the lead was conducted for the first time in human. As a result, we found that the locations of LBBAP leads were matched with fluoroscopic views during the procedure and Masson's staining showed extensive fibrosis occur around the lead but did not result in high thresholds.

Keywords Left bundle branch area pacing; Refractory heart failure; Anatomical assessment; Histopathological evaluation

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The authors attest they are in compliance with human studies committees of the authors' institutions, including patient consent where appropriate.

Introduction

His bundle pacing (HBP) is an effective modality for achieving physiological ventricular activation. Recently, a pacing technique called left bundle branch pacing (LBBP) or left bundle branch area pacing (LBBAP), which targets the more distal portion of the conduction system, has been introduced and may be an alternative to HBP and CRT to maintain the left ventricular electrical synchrony using a low and stable pacing output.^{1,2} However, efficient and unified LBBAP criteria remain incomplete while clinical studies supporting the long-term clinical outcomes are still limited. Recently, Huang, *et al.* summarized the general operating procedures and standards of LBBP,³ which applies to the majority of patients with pacemaker indications, and the success rate is satisfactory. However, for patients with heart failure and significantly enlarged heart, the success rate is affected significantly according to research reports.^{4–6} Most studies have shown that operators used imaging technique and electrical parameters to locate the position and depth of the pacing lead

model 3830 and to make sure the stability of the lead parameters through follow-up.^{3,7,8} For example, sheath angiography or nine-partition method⁹ was utilized to determine the initial lead tip location and test the pacing impedance, and capture threshold was used to check if there was a lead perforation. For patients with significantly enlarged heart in particular, achieving an ideal position of the pacing lead in the septum remains a challenge. To investigate the actual location and depth of the LBBAP lead and the tissue histopathological changes around the pacing lead, we performed the anatomical and histopathological evaluation of LBBAP in a human heart.

Case report

The first patient (P1) was a 53-year old male and had a history of myocardial infarction and ventricular aneurysm resection, reduced left ventricular ejection fraction (LVEF, 23%) and

prolonged QRS duration (156 ms). P1 received cardiac resynchronization therapy-cardioverter-defibrillator (CRTD) and LBBAP. After AV delay optimization, left bundle branch block (LBBB) was partially corrected (see *Figure S4*). The symptoms of heart failure were significantly relieved. The pacing parameters were stable during postoperative follow-up. Two years later, he received heart transplantation. During post-operation necropsy of the diseased heart, the free wall of the right ventricle was exposed to directly display the location of the pacing lead in relation to the ventricular septum *Figure 1*.

Patient 2 (P2), a 61-year-old female, with a history of valvular heart disease and bradycardia, LVEF 29%, aggravated heart failure symptoms, poor drug response and the battery depletion of her dual-chamber pacemaker, was upgraded to CRTD with LBBAP implantation. During the follow-up, the pacing parameters were stable and the symptoms were stabilized. One year later, she received heart transplantation. Dissection of the diseased heart found that the lead was located in the superior interventricular septum, the depth of the lead was 11 mm in this patient including the length of helix, and tissue reaction was observed around the tip-attached

area. Histopathologic examination showed obvious myocardial fibrosis in the ventricular septal area surrounding the lead compared with the septal myocardium far away from the lead. *Figure 2*.

Patient 3 (P3), a 52-year-old female, was diagnosed with dilated cardiomyopathy and had a single-chamber pacemaker implanted 10 years ago due to atrial fibrillation and bradycardia. Ventricular pacing percentage was 100%. Due to the progression of heart failure with reduced LVEF (31.3%), the patient's pacemaker was upgraded to CRTD with LBBAP implantation. Approximately 1 year later, she got a heart transplant. The dissection of the diseased heart showed the location of the lead in relation to the ventricular septum. The lead was located in the superior with a depth of 7 mm, which was consistent with the intraoperative DSA image and the findings of immediately postoperative cardiac ultrasound. Fibrotic tissue was seen around the tip of the lead. Histopathologic examination showed obvious myocardial fibrosis in the ventricular septum where the pacing lead was deployed while there was no obvious tissue fibrosis in the septal myocardium far away from the lead *Figure 3*.

Figure 1 Anatomical and histological assessment of LBBAP of P1. (A, B) Location of 3830 lead under digital subtraction angiography (DSA) image and ultrasound; (C, D) anatomical observation showed that the lead was located in the midventricular septum and was vertical to the septum, the depth of the lead including the helix length was 9 mm; (E) Masson staining showed no obvious fibrosis in the ventricular septum far from the lead; (F) Masson staining showed myocardial fibrosis in the ventricular septum surrounding the lead (stained blue), original magnification 10 ×.

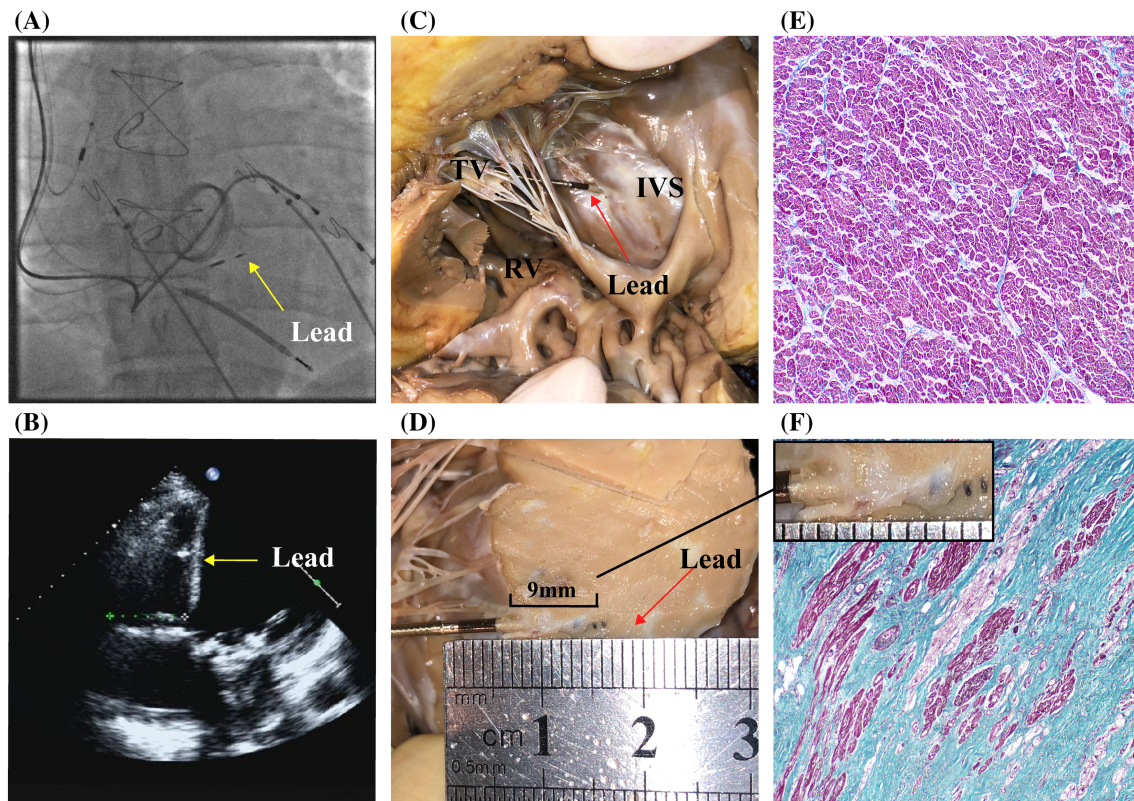


Figure 2 Anatomical and histological assessment of LBBAP of P2. (A, B) Location of 3830 lead under digital subtraction angiography (DSA) image and ultrasound; (C) The free wall of the right ventricle was exposed and the lead tip was found in the superior interventricular septum; (D) The depth of the lead including the helix length was 11 mm, obvious tissue reaction was observed in the tip-attached area; (E) Masson staining showed no obvious fibrosis in the ventricular septum far from the lead; (F) Masson staining showed myocardial fibrosis in the ventricular septum surrounding the lead (stained blue), original magnification 10 ×.

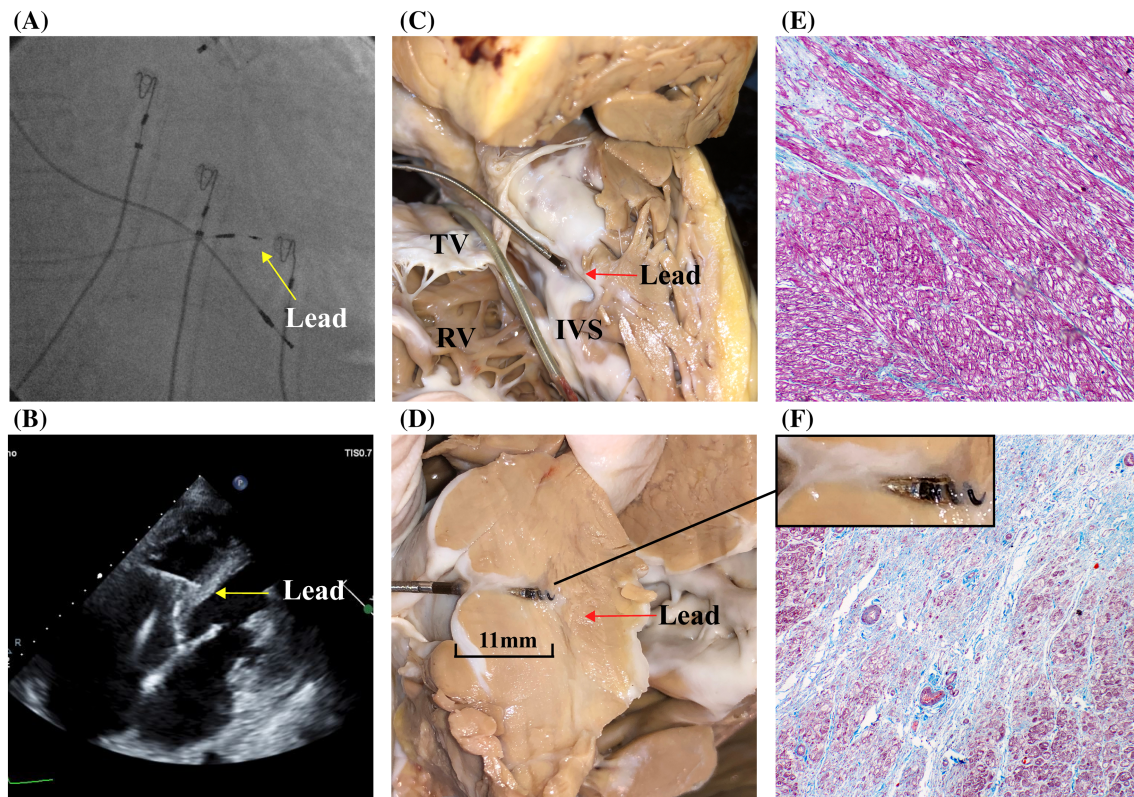


Table 1 displays an overview of the clinical data and pacing parameters of three reported patients (Table 1).

Discussion

At present time, an implanter deploys the LBBAP lead inside the interventricular septum based on his/her experience and lead deployment becomes more difficulty in an enlarged heart. In these three cases, we applied LBBAP that stabilized the further deterioration of cardiac function until patients received heart transplantation. For the first time, we observed the lead location under direct vision of the ventricular septum of the human diseased heart post-heart transplantation. The results in all three patients showed that the depth of the lead distal part inside the septum was not sufficient to capture LBB that was beneath the LV endocardium although the lead was almost vertical to the septum. We speculate that due to the length of sheath His 315 and the weak supporting force, the lead could not be screwed further to the far left side of the septum. However, paced QRS duration is significantly shortened in all three patients compared with

that during the non-LBBAP rhythm, suggesting left ventricular septal pacing (LVSP). These cases also found that intraoperative and postoperative imaging methods for assessment of the pacing lead location were basically consistent with the actual lead location found in heart necropsy, suggesting that these methods can be applied as a reliable method for lead location in difficult LBBAP cases. In addition, myocardial tissue fibrosis occurred around the pacing lead tip after lead implantation. For the first time, the relationship between LBBAP leads and septal anatomy and local tissue histopathological changes in the human heart were directly revealed.

Recent studies have proposed the concept of LBBAP or deep septal pacing (DSP),^{5,8,10} which may have longer LVAT and wider QRS duration than LBBP. LBBP is defined as pacing the proximal LBB or its branches with or without capture of LV septal myocardium. If pacing only captures LV septal myocardium, it is called LVSP or DSP in which the lead tip is not deep enough for the pacing current to reach the LBB or is directed away from the LBB region. LVSP demonstrates an atypical paced electrocardiogram (ECG) right bundle branch (RBB) block and relatively narrow QRS duration.⁵ In patients with significantly enlarged hearts and severe heart failure,

Figure 3 Anatomical and histological assessment of LBBAP of P3. (A, B) Location of 3830 lead under DSA image and ultrasound; (C, D) The lead was located in the midventricular septum, the depth of the lead including the helix length was 7 mm, and fibrotic tissue is seen around the tip of the lead. (E) Masson staining showed no obvious fibrosis in the ventricular septum far from the lead; (F) Masson staining showed myocardial fibrosis in the ventricular septum surrounding the lead (stained blue), original magnification 10 \times .

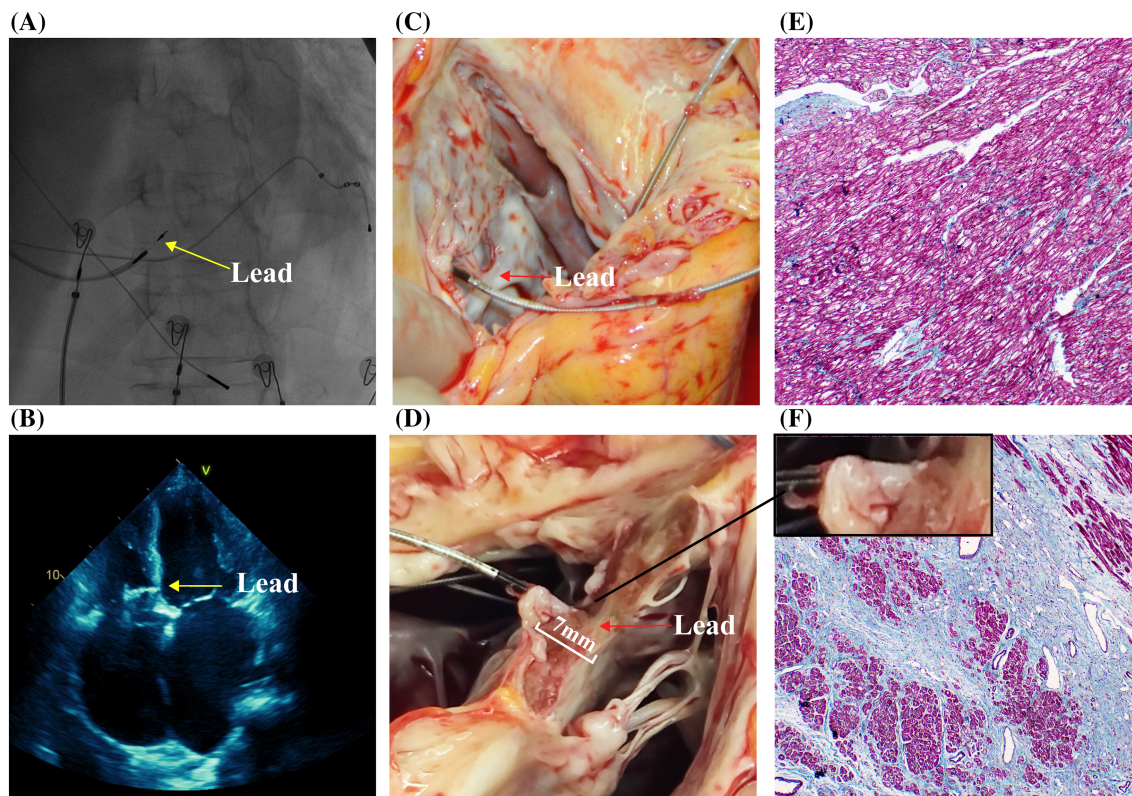


Table 1 Patient characteristics

Characteristic	Patient 1	Patient 2	Patient 3
Age (years)	53	61	52
Sex	Male	Female	Female
Height (cm)	179	155	161
Weight (kg)	86	45	46
Diabetes	No	No	No
Hypertension	No	Yes	No
Coronary heart disease	Yes	No	No
Cardiomyopathy	Yes	No	Yes
Valvular heart disease	No	Yes	No
Persistent atrial fibrillation	Yes	Yes	Yes
Baseline echo characteristics			
Pre-DSP and post-DSP LVEF (%)	18/31	43/60	33/42
Pre-DSP and post-DSP LVEDD (mm)	94/85	62/57	54/47
Septal thickness (mm)	18	16	10
Pre-DSP right atrium diameter (mm)	56*54	90*79	74*53
Pacing and ECG characteristics			
Pre-DSP QRSd (ms)	188	213	220
Post-DSP QRSd (ms)	152	112	145
Intraventricular conduction delay (IVCD)	Yes	No	Yes
Threshold (unipolar)	1.3	0.75	1.5
R wave (mV)	8	10.5	15
Impedance (Ohms)	980	430	530

DSP, deep septal pacing; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.

especially in patients with obvious enlargement of the right atrium, the support force of the sheath needs to be higher; otherwise, it is difficult to screw the lead tip deep into the septum for capturing LBB, leading to a low success rate of LBBP implantation. In the results from the International LBBAP Collaborative Study Group, permanent LBBAP (including DSPs that meet electrical standards) was achieved in 277 of 325 patients (85%) and was unsuccessful in 48 patients because of inability to penetrate the septum (21 patients) and inadequate electric resynchronization (27 patients, including DSPs that do not meet electrical standards).⁶ In another LBBAP study of feasibility assessment, permanent LBBAP was successful in 93 (93%) out of 100 patients while in five patients, the lead tip could not be placed in the LV septum and in the other two patients with cardiomyopathy, LBBAP failed to achieve significant narrowing of QRS width.⁴ Whereas there have been some cases of LVSP or DSP with encouraging clinical outcomes.^{11–13} In a study in 27 patients undergoing CRT implantation, LVSP provided short-term haemodynamic improvement and electrical resynchronisation that was at least as good as during BVP and HBP.¹⁴ Heckman discussed the different novel pacing strategies and proposed that there seems to be a significant overlap between LVSP and LBBP and whether clinical outcomes differ between deep LVSP with and without direct capture of the left bundle

remains to be determined.¹⁵ Our cases also showed the improvement of LVEF and heart failure symptoms after 1-year follow-up. As a conclusion, we demonstrate that direct visual of pacing lead locations, which were matched with fluoroscopic views during the LBBAP procedure, describe the histopathological changes that may occur around the lead in three diseased human hearts, and the results are encouraging. Nevertheless, large randomized multicentre studies with longer follow-up duration in patients with severe heart failure are warranted to confirm the potential benefits of LBBAP approach.

Conflict of interest

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting information

References

- Zhang AS, Xz B, Mrg C. Left bundle branch pacing. *J Am Coll Cardiol* 2019; **74**: 3039–3049.
- Li X, Qiu C, Xie R, Ma W, Wang Z, Li H, et al. Left bundle branch area pacing delivery of cardiac resynchronization therapy and comparison with biventricular pacing. *ESC. Heart Fail* 2020; **7**: 1711–1722.
- Huang W, Chen X, Su L, Wu S, Xia X, Vijayaraman P. A beginner's guide to permanent left bundle branch pacing. *Heart Rhythm* 2019; **16**: 1791–1796.
- Vijayaraman P, Subzposh FA, Naperkowski A, Panikkath R, John K, Mascarenhas V, et al. Prospective evaluation of feasibility, Electrophysiologic and echocardiographic characteristics of left bundle branch area pacing. *Heart Rhythm* 2019; **16**: 1774–1782.
- Wu S, Chen X, Wang S, Xu L, Xiao F, Huang Z, et al. Evaluation of the criteria to distinguish left bundle branch pacing from left ventricular septal pacing. *JACC Clinical Electrophysiology* 2021; **7**: 1166–1177.
- Vijayaraman P, Ponnusamy SS, Cano S, Sharma PS, Naperkowski A, Subzposh FA, et al. Left bundle branch area pacing for cardiac resynchronization therapy. *JACC Clin Electrophysiol* 2020; **7**: 135–147.
- Chen K, Li Y. How to implant left bundle branch pacing lead in routine clinical practice. *J Cardiovasc Electrophysiol* 2019; **30**: 2569–2577.
- Zhang J, Sheng X, Pan Y, Wang M, Fu G. Electrophysiological insights into three modalities of left bundle branch area pacing in patients indicated for pacing therapy. *Int Heart J* 2021; **62**: 78–86.
- Jiang H, Hou X, Qian Z, Wang Y, Tang L, Qiu Y, et al. A novel 9-partition method using fluoroscopic images for guiding left bundle branch pacing—ScienceDirect. *Heart Rhythm* 2020; **17**: 1759–1767.
- Huang W, Zhou X, Ellenbogen KA. Pursue physiological pacing therapy—a better understanding of left bundle branch pacing and left ventricular septal myocardial pacing. *Heart Rhythm* 2021; **18**: 1290–1291.
- Gu M, Li H, Hu YR, Niu HX, Hua W. Cardiac resynchronization therapy using left ventricular septal pacing: an alternative to biventricular pacing? *HeartRhythm Case Rep* 2019; **5**: 426–429.
- Das A, Islam SS, Pathak SK, Majumdar I, Sharwar SA, Saha R, et al. Left bundle branch area. A new site for physiological pacing: a pilot study. *Heart Vessels* 2020; **35**: 1–10.
- Li Y, Chen K, Dai Y, Li C, Sun Q, Chen R, et al. Recovery of complete left bundle branch block following heart failure improvement by left bundle branch pacing in a patient. *J Cardiovasc Electrophysiol* 2019; **30**: 1714–1717.
- Salden FCWM, Luermans JGLM, Westra SW, Weijs B, Engels EB, Heckman LIB, et al. Short-term hemodynamic and electrophysiological effects of cardiac resynchronization by left ventricular septal pacing. *J Am Coll Cardiol* 2020; **75**: 347–359.
- Heckman L, Vijayaraman P, Luermans J, Stipdonk AMW, Salden F, Maass AH, et al. Novel bradycardia pacing strategies. *Heart* 2020; **106**: 1883–1889.