To the Editor: A 20-year-old unmarried young male was hospitalized for 1 week due to an unexpected finding of heart enlargement at his regular physical examination. His parents and two sisters presented no abnormal findings in electrocardiogram (ECG) and echocardiography (Echo) examinations. He had an uncle with unexplained sudden death at the age of 47 years. The patient had no history of drug abuse, smoking, heavy alcohol consumption, or illicit drug use. Blood tests showed elevated pro-brain natriuretic peptide (2292 pg/ml, normal range: <125 pg/ml), creatine kinase-muscle/brain mass (10.3 ng/ml, normal range: 0.3–4.0 ng/ml), alanine transaminase (194 U/L, normal range: 9–50 U/L), and aspartate aminotransferase (271 U/L, normal range: 15–40 U/L), while other blood test results were within normal range. The 12-lead surface ECG revealed atrial rhythm with 2:1 atrial ventricular block (AVB) and Type B Wolff-Parkinson-White syndrome (WPW), ventricular rate of 43 beats/min left ventricular (LV) hypotrophy with strain, and interventricular block. A previous ECG had been taken at another hospital about 1 week ago and also showed atrial rhythm and Type B WPW, but the ventricular rate was 72 beats/min (A:V = 1:1) at that time. The Echo indicated heart enlargement (left atrium [LA] 47 mm, right atrium [RA] 43 mm, LV 61 mm × 68 mm × 86 mm, and right ventricular [RV] 33 mm), diffused thickening of interventricular septum and LV walls up to 18 mm and decreased movement, low LV ejection fraction (LVEF; 40%), and mild mitral and tricuspid regurgitation. X-ray showed LV enlargement with a cardiothoracic ratio of 0.64.

Then, the patient underwent an electrophysiological study (EPS) to verify the arrhythmia. Before the programmed stimulation examination, the intracardiac electrogram showed alternate II° I and II° II AVB. During the coronary sinus (CSs) stimulation with a parameter of S1 = 600/500/450 ms, artroventricular (AV) was maintained at 2:1 conduction, HV was stable for 28 ms, but AH became increasingly longer. With a parameter of S1 = 400 ms, AV conduction rate was changed at 2:1–4:1; however, HV was maintained at 28 ms. When RV was stimulated with 600 ms, VA retrograde blocked. The patient’s EPS showed evidence of preexcitation and AVB, exhibited an unusual pattern of high-grade (2:1–4:1) AVB when stimulated CS with S1 = 400 ms. The highly unusual pattern of high-grade AVB with an accessory pathway may be simply explained by a block that has occurred in the proximal AV node because these accessory pathways lie directly and distally to the AV node. The EPS results indicated that AV conduction over the bypass was partly impaired because when potential H occurred, potential V was always present. Otherwise, even if complete AV nodal block was present, routine AV bypass conduction would become fully manifest and support 1:1 AV conduction. Radiofrequency catheter ablation of the bypass was not attempted because it failed to induce sustained tachycardia arrhythmia.

The patient had strong indications for a ventricular pacing therapy because of existence of II° II AVB and with the addition of his heart dysfunction, cardiac resynchronization therapy (CRT) was the best option for him. Because the risk of sudden cardiac death (SCD) at 5 years was 3.18%, 2014 European Society of Cardiology (ESC) recommendation[1] of implantable cardiac defibrillation (ICD) was generally not indicated. To further optimize the procedure and ensure optimal treatment results, we performed the CRT with a guidance by three-dimensional (3D) electroanatomic mapping (EAM) and anchored the LV lead to the latest activated region. The outer straight sheath was anchored to the CS by means of decapolar CS electrode (Johnson, USA). CS angiography results showed that the anterolateral vein (ALV), lateral vein, and posterolateral vein (PLV), and the latter was thicker than the first two [Figure 1a]. Then, we conducted a CS vein mapping procedure with the LV lead 4296 (Medtronic, USA), which was connected to Ensite Navx (Abbott, USA) via a crossover clamp. We placed the lead in the great vein, ALV, lateral vein, and PLV along with a Runthrough NS wire (Terumo, Japan). The reference line was set as the summit
of QRS for the surface ECG, and electrical delay was measured in milliseconds between the reference line on the surface ECG and the onset on the bipolar intracardiac electrogram. We collected the activation potential (reflected by the activation time) point by point when pulling back the lead and determined that the purple area was the latest activated region while the white one was the earliest. At the end, it is easy to detect the latest activated region where the lead could actually be reached [Figure 1b]. Candidate pacing sites were tested for phrenic nerve stimulation (PNS) by 10 V unipolar pacing on the tip of the lead. Finally, the lead was located at the end of the PLV, where the parameters were good, and no PNS [Figure 1c]. Post-ECG showed atrial rhythm, VAT pacing mode.

The patient underwent CRT-pacemaker (CRT-P) implantation without complications, was also prescribed a standardised β-blocker/angiotensin receptor blocker (ARB)/spironolactone, and was advised to avoid high-intensity physical activity. To determine the potential genetic source of the patient’s clinical presentation, one month after the treatment, we performed gene analysis of blood. The exons of hypertrophic cardiomyopathy (HCM)-related genes were amplified and sequenced by targeted exome capture on an Illumina/SolexaHiSeq 2000 sequencer. It was revealed that the patient has a heterozygous lysosome-associated membrane protein 2 (LAMP2) gene mutation caused by a G>A transition in base 928 of exon 7, and a mutation in the MYBPC3 gene caused by G>A transition in base 122 of exon 2, supporting the diagnosis of Danon disease. Gastrocnemius muscle biopsy showed myocyte vacuolization, and periodic acid–Schiff staining (Wuhan Servicebio Technology CO., LTD) revealed diffuse glycogen deposition. Genotyping results of family members (his parents and two sisters) were also negative for LAMP2 mutations, indicating that the patient has a de novo LAMP2 mutation. Three months after the procedure, an Echo examination showed that his heart had become smaller (LA 43 mm, RA 38 mm, LV 61 mm × 65 mm × 87 mm, and RV 28 mm), and LVEF increased slightly to 41%. After another 3 months (6 months post-procedure), the LVEF was still maintained at 40%. The programmed results showed that all parameters from the three leads were good, and no malignant events, except several preatrial contractions. Based on the poor progression of Danon disease, CRT is the only bridge treatment to prevent worsening of LV dysfunction, so CRT was suggested. The risk of SCD at 5 years was 3.18%; ESC recommendation was that ICD is generally not indicated. On the other hand, SCD is the most common ultimate clinical cause in such patients if left untreated. Unfortunately, ICD therapy does not always prevent SCD or terminate lethal ventricular tachyarrhythmias in Danon disease. Therefore, no matter which type of cardiomyopathy or the severity of heart failure, timely evaluation for a heart transplant is strongly recommended. In view of the need to maintain LV function, the ineffectiveness of defibrillation, the financial load of ICD, and parental support, the patient received CRT-P to preserve cardiac function and as a short-run bridge therapy for heart transplantation. Long-term pharmacologic therapy is only experimental due to the lack of clinical trials on β-blockers, angiotensin-converting enzyme inhibitor/ARB, and spironolactone.

Superior CRT outcome occurs when the LV lead position coincides with the region of latest mechanical contraction. Studies have revealed that a greater delay in time from the onset of the QRS complex to the local sensed LV lead EGM (Q-LV) is associated with a greater possibility of benefit from CRT.[16] The conventional anatomical LV lead placement strategy does not verify vein targeting with maximal electrical delay in many CRT patients, resulted in CRT nonresponse influencing long-term survival rate and quality of life. Rad et al.[17] reported that conducting CS 3D electrical mapping with a guidewire for LV lead placement in the latest activated region and avoidance of PNS improves the outcome of CRT, particularly in patients with multiple selectable target veins. It is suggested that CS 3D mapping can be used at the time of CRT implantation to assess LV electrical activation pattern and guide LV lead placement to the latest activated region lack PNS.
We mapped directly the activation time of CS point by point with the LV lead, which was anchored to the latest activated region free of PNS. This method is more accurate and practical since the region guidewire, but not the LV lead, could reach. The patient was pacing dependent because of the presence of II° II AVB, so CRT was vital to maintain LV function. Since the ALV and lateral vein were thinner and there were three branches in PLV, we made an attempt to affirm whether the LV lead could anchor in ALV or lateral vein, but the lead failed to go forward sufficiently because of narrowness and early activation mapping. We then made sure which branch of PLV was the latest activated region with no PNS. At last, we located the lead 4296 in the outer branch of PLV. Six months later, his heart function was preserved with no serious adverse events. As a result, early detection and treatment in addition to family screening are necessary components in the management of the disease. This case report validates the importance of genetic testing and muscular biopsy in the assessment of patients with undiagnosed hypertrophic cardiomyopathy and conduction disorders. Furthermore, for those with an indication of ventricular pacing combined with LV dysfunction, CS EAM guidance for CRT may be a better choice to anchor the LV lead to the latest activation target vein and lack of PNS easily.

There are some limitations of this procedure. First, we had only a standard bipolar LV lead available instead of a quadrupolar LV lead, or MPP, which could further optimize the pacing polarity. Second, the available target veins were limited for this patient, but may provide a new method to guide optimization of CRT implantation in the future. Third is the lack of cardiomyocyte biopsy due to parental decision. Fourth, failure to CRT with defibrillator implantation versus palliative CRT was partly ascribed to economic reasons. The last constraints were short visits and long intervals between follow-up visits.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014; 35:2733‑79. doi: 10.1093/eurheartj/ehu284.
2. Danon MJ, Oh SJ, DiMauro S, Manaligod JR, Eastwood A, Naidu S, et al. Lysosomal glycogen storage disease with normal acid maltase. Neurology 1981;31:51‑7. doi: 10.1212/WNL.31.1.51.
3. Boucek D, Jirikovic J, Taylor M. Natural history of danon disease. Genet Med 2011;13:563‑8. doi: 10.1097/GIM.0b013e31820ad795.
4. Martin S, Ingles J, Hunyor I, Bagnall RD, Puranik R, Semsarian C, et al. LAMP2 shines a light on cardiomyopathy in an athlete. Heart Rhythm Case Rep 2017;3:172‑6. doi: 10.1016/j.hrscr.2016.11.005.
5. Singh JP, Fan D, Heist EK, Alahbad CR, Taub C, Reddy V, et al. Left ventricular lead electrical delay predicts response to cardiac resynchronization therapy. Heart Rhythm 2006;3:1285‑92. doi: 10.1016/j.hrthm.2006.07.034.
6. van Gelder BM, Meijer A, Bracke FA. Timing of the left ventricular electrogram and acute hemodynamic changes during implant of cardiac resynchronization therapy devices. Pacing Clin Electrophysiol 2009;32 Suppl 1:S94‑7. doi: 10.1111/j.1540‑8159.2008.02262.x.
7. Rad MM, Blauw Y, Dinh T, Pison L, Crijns HJ, Prinzen FW, et al. Left ventricular lead placement in the latest activated region guided by coronary venous electroanatomic mapping. Europace 2015;17:84‑93. doi: 10.1093/europace/euu221.