GLOBAL CARDIOLOGY SCIENCE & PRACTICE
A Qatar Foundation Academic Journal

OPEN ACCESS

Research article

Prospective study of tricuspid valve regurgitation associated with permanent leads in patients undergoing cardiac rhythm device implantation: Background, rationale, and design

Hisham Dokainish[1,*], Esam Elbarasi[1], Simona Masiero[2], Caroline Van de Heyning[3], Michela Brambatti[2], Sami Ghazal[1], Said AL-Maashani[1], Alessandro Capucci[2], Lisanne Buikema[1], Darryl Leong[1], Bharati Shivalkar[3], Johan Saenen[3], Hielko Miljoen[3], Carlos Morillo[1], Syam Divarakarmenon[1], Guy Amit[1], Sebastian Ribas[1], Aaron Brautigam[1], Erika Baiocco[2], Alessandro Maolo[2], Andrea Romandini[2], Simone Maffei[2], Stuart Connolly[1], Jeff Healey[1]

[1]McMaster University, Hamilton, ON, Canada
[2]Universita' Politacnica delle Marche, Ancona, Italy
[3]Antwerp University Hospital, Antwerp, Belgium
*Email: hisham.dokainish@phri.ca

ABSTRACT

Given the increasing numbers of cardiac device implantations worldwide, it is important to determine whether permanent endocardial leads across the tricuspid valve can promote tricuspid regurgitation (TR). Virtually all current data is retrospective, and indicates a signal of TR being increased after permanent lead implantation. However, the precise incidence of moderate or greater TR post-procedure, the exact mechanisms (mechanical, traumatic, functional), and the hemodynamic burden and clinical effects of this putative increase in TR, remain uncertain. We have therefore designed a multicenter, international, prospective study of 300 consecutive patients (recruitment completed, baseline data presented) who will undergo echocardiography and clinical assessment prior to, and at 1-year post device insertion. This prospective study will help determine whether cardiac device-associated TR is real, what are its potential mechanisms, and whether it has an important clinical impact on cardiac device patients.

http://dx.doi.org/10.5339/gcsp.2015.41

Submitted: 12 April 2015
Accepted: 30 June 2015

QSCIENCE.com
An Initiative of Qatar Foundation

Cite this article as: Dokainish H, Elbarasi E, Masiero S, Van de Heyning C, Brambatti M, Ghazal S, AL-Maashani S, Capucci A, Buikema L, Leong D, Shivalkar B, Saenen J, Miljoen H, Morillo C, Divarakarmenon S, Amit G, Ribas S, Brautigam A, Baiocco E, Maolo A, Romandini A, Maffei S, Connolly S, Healey J. Prospective study of tricuspid valve regurgitation associated with permanent leads in patients undergoing cardiac rhythm device implantation: Background, rationale, and design, *Global Cardiology Science and Practice* **2015:41** http://dx.doi.org/10.5339/gcsp.2015.41

BACKGROUND

Over the last decade there has been a significant increase in the number of cardiac device implantations worldwide—permanent pacemakers (PPM), implantable cardiac defibrillators (ICD), and biventricular pacemakers (BiV)—in patients with cardiac rhythm disorders.[1–3] This trend is likely to continue because of the increased life expectancy of the population, increasing prevalence of cardiac disease, improved treatments for coronary heart disease leading to increased survival of patients and increased prevalence of conduction disturbances, left ventricular (LV) dysfunction and heart failure (HF), and consequent increasing indications for the use of these devices.

Tricuspid regurgitation after implantation of permanent endocardial leads

One of the potential complications of rhythm device therapy is tricuspid valve regurgitation (TR), thought to be due to interference of tricuspid valve (TV) function by permanent endocardial leads. Small, retrospective studies have shown that lead-related TR may be present in between 25–29% of patients with PPM, compared to 12% to 13% in controls.[4,5] Other retrospective studies have also indicated an increase in the severity of TR from pre- to post-permanent lead implantation by 1 or 2 grades (for example, mild to moderate, or mild to severe, respectively) in 11% to 25% of patients over a period of 1 to 827 days after PPM or ICD placement.[6–8] In a recent study from our center, we retrospectively assessed the effects of PPM leads compared with temporary leads inserted during ablation procedures on TR, finding that in 11% of patients with PPM, there was an increase of TR (by one grade or more) after pacemaker implantation, but that there was no significant increase in TR in patients undergoing ablation.[9] Importantly, patients undergoing permanent device implantation demonstrated that cardiac resynchronization therapy (CRT) was not associated with an increase in post-procedure TR. A recent retrospective study of 1596 patients undergoing ICD or PPM insertion found that the prevalence of grade 3 or 4+ TR increased from 27% to 31% by 1 month and to 35% at 4 years.[10] By contrast, in a retrospective analysis of 61 patients referred for PPM or ICD, there was no change in TR severity at 6 months follow-up.[11] In another small prospective study of 35 patients undergoing echocardiography pre- and post-PPM or ICD, there also was no change seen in the degree of TR post-device implantation.[12]

Therefore, since prior studies are retrospective, it remains unclear whether permanent endocardial leads do indeed result in a significant increase in TR, and if so, what is the clinical impact on patients, what are the potential mechanisms, and whether CRT may prevent (physiologic) TR.

Mechanisms of lead-related tricuspid regurgitation

TR after lead placement may occur by multiple mechanisms. It may be the result of mechanical causes such as scar formation or thrombus on the leads impairing closure of TV leaflets.[13,14] Neoendocardium formation can commence within 12 hours post-procedure, with development of fibrous sheaths around the electrode, resulting in multiple endocardial attachments, fibrosis, and adhesion that may affect TV function.[13] Thrombosis and edema of the valve tissue may also occur 4 to 5 days after implantation which may or may not lead to acute TR.[14] Perforation or laceration of the leaflets by leads is another potential cause of TR, and leaflet perforation or lacerations are most commonly noted at the posterior leaflet.[15] A recent 3D echocardiographic study showed a clear association between device lead position and TR, depending on whether the lead was impinging on the posterior, septal leaflet or not interfering with leaflet motion, suggesting that 3D echocardiographic guidance could be considered for PPM lead placement in order to minimize TR.[16] Another proposed mechanism for late TR in patients with PPM is active RV pacing causing valve malfunction by dyssynchronous RV pacing from apex to base.[17,18] Thus, the finding that CRT may prevent TR[9] suggests that minimization of ventricular dyssynchrony could mitigate functional (physiologic) TR in patients with CRT devices. All the above TR mechanisms may co-exist, but the magnitudes of their potential contributions to TV malfunction are not well defined. The time course for TR development and progression after endocardial lead insertion in the RV is also not fully defined.[4,19]

There are several proposed mechanisms of TR—which may not be mutually exclusive—in patients undergoing permanent lead insertion, including mechanical (lead insertion position), direct traumatic and functional mechanisms. The effect of CRT on severity of TR needs clarification, as it may mitigate against develop of functional TR.

Clinical impact of tricuspid regurgitation

Mild TR is a common echocardiographic finding which is usually devoid of clinical relevance; however, more advanced grades of TR (moderate or severe) can be associated with a poor prognosis.[20] Moderate to severe TR can be deleterious to the patient because it raises the central venous pressure by increasing the right sided preload, leading to right ventricle (RV) dilatation. Chronically, the increase in right sided blood volume can result in an increase in the right atrial pressure leading to a decrease in venous return and low cardiac output, ultimately leading to RV failure. The clinical impact of TR is likely under-recognized because many patients are asymptomatic even when hemodynamically significant TR is present. Incre asing TR severity has been shown to be associated with increased mortality, regardless of LV ejection fraction or pulmonary artery systolic pressure (PASP).[21,22] Indeed, a recent retrospective study of 239 patients undergoing cardiac device implantation revealed that significant lead-associated TR (moderate or greater) was associated with poor long-term survival.[23] The deleterious effects of hemodynamically significant TR may be avoided with echo-guided lead insertion,[16,24] as well as prompt diagnosis and management of valve dysfunction following device implantation. Possible treatment strategies for TR related to device implantation may include medical treatment with diuretics to reduce circulating volume, surgical/percutaneous lead extraction, or lead repositioning,[25,26] although further investigation of this area is needed.

While hemodynamically significant TR (moderate or greater) can portend a poor prognosis, it is unknown how long clinical sequelae may take to manifest. More prospective data is needed to define the true clinical impact—if it indeed exists—on device-associated TR, and its time course.

Role and importance of echocardiography in the assessment of tricuspid regurgitation

Echocardiography is an imaging technique using ultrasound that can readily assess the presence, severity and mechanism of TR. Advantages to echocardiography in the assessment of TR include that it is non-invasive, does not involve ionizing radiation, is ubiquitous in clinical settings, and when performed comprehensively, can result in accurate determinations of TR severity and mechanism, as well as potential impacts of TR on RV size, function and cardiac output.[16,24,27,28] On physical examination, typical findings in patients with TR include a respirophasic systolic murmur at the left sternal border that increases with inspiration; however, in many patients the murmur is subtle (or absent) and may be difficult to detect.[24] Therefore, evaluation with two-dimensional (2D) echocardiography and color Doppler flow mapping is essential in diagnosing TR, and can accurately assess the morphology of the TV and evaluate the degree of regurgitation, and can evaluate the impact of the volume overload on right-sided cardiac structures and PASP.[16,24,27–32] In addition, calcifications, tethering, flail motion or vegetations can be identified by echocardiography. The simplest approach to evaluate TR severity is color flow Doppler imaging in several views to establish the characteristics, direction and size of the TR jet.[27] Since the RV is situated in the anterior chest, transthoracic images are usually diagnostic. TR jet area, TR vena contracta width, and TR proximal isovelocity surface area (PISA) are assessed to accurately quantify TR severity.[27–32]

Echocardiography with Doppler is a safe, readily-available, non-invasive method to detect TR, can accurately grade its severity and delineate potential TR mechanisms, as well as effects on cardiac chambers and intracardiac pressures.

NEED FOR A PROSPECTIVE STUDY

Given that the current data suggesting PPM leads may lead to TR is based on retrospective studies, and that the exact mechanisms and clinical impact of TR associated with cardiac devices remain unclear, there is a clear need for an adequately-powered, prospective study to fill in these knowledge gaps. We have therefore designed a prospective, multicenter study of patients undergoing PPM, ICD, BIV, and BIV/ICD implantation at McMaster University, Hamilton, Canada, University of Antwerp, Belgium, and Universita' Politecnica delle Marche, Ancona, Italy. We hypothesize that, in patients undergoing permanent lead insertion via cardiac device implantation, there will be a significant increase in the incidence of clinically important TR (moderate or severe regurgitation), as detected by comprehensive echocardiography with Doppler. We further hypothesize that CRT will prevent increases in (physiologic) TR.

METHODS

Consecutive patients ≥ 18 years of age referred to the recruiting centres with a clinical indication for device implantation will be eligible. Patients with previous endocardial leads will be excluded in this study. Patients with congenital heart disease will also be excluded, as they could have developed TR due to the underlying heart anomalies. Consenting patients will have an echocardiogram performed </= 30 days prior to device implantation, with clinical follow-up and echocardiography at 1 year post-procedure. Baseline clinical and echocardiographic characteristics will collected and include: sex, age, hypertension, diabetes mellitus, smoking status, dyslipidemia, significant coronary artery disease, New York Heart Association (NYHA) class, chronic kidney disease, and medication use. To examine whether active RV pacing by itself has an impact on TR grade, we will document the percentage of time in which our patients are actually being paced (these data will be extracted from pacemaker interrogation at 12 months post-pacemaker insertion), lead position, and whether patients were actually being paced during the echocardiographic acquisition. All echocardiographic studies will be sent to the core echocardiography laboratory at the Population Health Research Institute at McMaster University in Hamilton, Ontario Canada for centralized analysis by 2 experience echocardiographers blinded to all clinical data.

Statistical analysis

The primary endpoint of the study will be the absolute difference in prevalence of moderate or severe TR post-device, compared to pre-device insertion, as measured by echocardiography. Secondary endpoints will include the absolute difference in RV size and function and RA size post-device insertion and the incidence of new heart failure, new hospitalization or death. Clinical and echocardiographic data will be compared pre- and at 1 year post-device insertion.

Assuming the baseline proportion of patients receiving RV leads who have moderate to severe TR is 17%[20], a sample size of 300 patients will have 90% power to detect a 50% relative (8.5% absolute) increase in the proportion of patients with moderate/severe TR following implantation of a RV lead, assuming a conservative 20% loss-to-follow-up rate.

ENROLLMENT TO DATE AND BASELINE DATA

So far, 300 patients have been recruited: 126 at McMaster University, 90 at Universita' Politecnica delle Marche, and 84 at University of Antwerp. Of the 300 patients, 154 (52%) underwent PPM, 102 (34%) underwent ICD, and 44 (15%) underwent BIV. The indication for PPM insertion in the 154 patients recruited thusfar are AV-node disease (65%), and sick sinus syndrome (30%) and other (5%).

Table 1. Baseline Clinical Variables

Variable	N = 300
Age (years) (mean ± SD)	70 (± 16)
Female (N,%)	115 (38%)
Body mass index (kg/m^2) (mean ± SD)	28 (± 6)
Hypertension (N,%)	209 (70%)
Diabetes (N,%)	76 (26%)
Smoking (past or current) (N,%)	107 (36%)
Dyslipidemia (N,%)	168 (56%)
History of prior myocardial infarction (N,%)	90 (30%)
Prior revascularization (percutaneous or surgical) (N,%)	87 (29%)
Prior valve surgery (N,%)	23 (8%)
New York Heart Association Class (N,%)	
1	131 (44%)
2	107 (35%)
3	56 (19%)
4	6 (2%)
Heart rate (bpm) (mean ± SD)	63 (± 18)
Systolic blood pressure (mmHg) (mean ± SD)	132 (± 24)
Diastolic blood pressure (mmHg) (mean ± SD)	72 (± 11)
Pre-procedure electrocardiogram	
Sinus rhythm	208 (69%)
AF or flutter	48 (16%)
Complete heart block	42 (15%)

Table 2. Baseline Echocardiographic Variables

Variable	N = 262
Left ventricular diastolic diameter (cm) (mean ± SD)	5.2 (± 0.9)
Left ventricular systolic diameter (cm) (mean ± SD)	3.9 (± 1.2)
Intraventricular septal diameter (cm) (mean ± SD)	1.0 (± 0.3)
Left ventricular mass (g) (mean ± SD)	188 (± 74)
Left ventricular stroke volume (ml) (mean ± SD)	71 (± 25)
Left ventricular ejection fraction (%) (mean ± SD)	49.3% (± 17)
Left atrial volume index (ml/m^2) (mean ± SD)	41 (± 19)
Right ventricular diastolic diameter (cm) (mean ± SD)	3.7 (± 0.6)
Right ventricular size: Normal or mildly dilated (N,%)	285 (95%)
Moderate or severely dilated (N,%)	14 (5%)
Right ventricular function: Normal (N,%)	253 (84%)
Mildly depressed (N,%)	34 (11%)
Moderately or severely depressed (N,%)	13 (5%)
Tricuspid annular systolic excursion (cm) (mean ± SD)	1.9 (0.4)
Tricuspid regurgitation: None/trivial (N,%)	195 (65%)
Mild (N,%)	86 (28.7%)
Moderate (N,%)	15 (5%)
Severe (N,%)	4 (1.3%)
Right ventricular systolic pressure (mmHg) (mean ± SD)	35 (± 13)

The indication for implantation in the 102 ICD patients were primary prevention (55%) and secondary prevention (45%). The baseline clinical and echocardiographic characteristics of the patients recruited thusfar are shown in Tables 1 and 2, respectively.

SUMMARY

Based on current data, it is unclear: whether permanent cardiac device implantation is indeed associated with increases in TR; what are the potential mechanisms of any increase in TR; what is—if any—the clinical impact of device-associated TR; and whether CRT can prevent (functional) increases in TR. This prospective study will help answer these clinically important questions. If clinically significant TR is indeed found to be associated with device implantation, this could have an impact on device patient morbidity and mortality, and could be used to influence how these procedures are performed in the future—possible echocardiographically-guided lead insertion—and also could provide rationale and support for the development of subcutaneous ICDs and leadless pacing strategies for patients with cardiac rhythm disorders.[33,34]

REFERENCES

[1] Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009–a World Society of Arrhythmia's project. *Pacing Clin Electrophysiol*. 2011;34:1013–1027.
[2] Kurtz SM, Ochoa JA, Lau E, Shkolnikov Y, Pavri BB, Frisch D, Greenspon AJ. Implantation trends and patient profiles for pacemakers and implantable cardioverter defibrillators in the United States:1993–2006. *Pacing Clin Electrophysiol*. 2010;33:705–711.
[3] Kremers MS, Hammill SC, Berul CI, Koutras C, Curtis JS, Wang Y, Beachy J, Blum Meisnere L, Conyers del M, Reynolds MR, Heidenreich PA, Al-Khatib SM, Pina IL, Blake K, Norine Walsh M, Wilkoff BL, Shalaby A, Masoudi FA, Rumsfeld J. The National ICD Registry Report: version 2.1 including leads and pediatrics for years 2010 and 2011. *Heart Rhythm*. 2013;10:e59–e65.
[4] Paniagua D, Aldrich HR, Lieberman EH, Lamas GA, Agatston AS. Increased prevalence of significant tricuspid regurgitation in patients with transvenous pacemakers leads. *Am J Cardiol*. 1991;82, 1130-2, A9.
[5] De Cock CC, Vinkers N, van Campe LC, Verhorst PM, Visser CA. Long-term outcome of patients with multiple (>3) noninfected transvenous leads: a clinical and echographic study. *Pacing Clin Electrophysiolog*. 2000;23:423–426.
[6] Klutstein M, Balkin J, Butnaru A, Ilan M, Lahad A, Rosenmann D. Tricuspid incompetence following permanent pacemaker implantation. *Pacing Clin Electrophysiol*. 2009;32(Suppl 1):S135–S137.
[7] Webster G, Margossian R, Alexander ME, Cecchin F, Triedman JK, Walsh EP, Berul CI. Impact of transvenous ventricular pacing leads on tricuspid regurgitation in pediatric and congenital heart disease patients. *J Interv Card Electrophysiology*. 2008;21:65–68.
[8] Kim JB, Spevack DM, Tunick PA, Bullinga JR, Kronzon I, Chinitz LA, Reynolds HR. The effect of transvenous pacemaker and implantable cardioverter defibrillator lead placement on tricuspid valve function: an observational study. *J Am Soc Echocardiogr*. 2008;21:284–287.
[9] Sadreddini M, Haroun M, Buikema L, Morillo C, Ribas S, Divarakaramenon S, Connolly SJ, Nieuwlaat R, Lonn EM, Healey JS, Dokainish H. Tricuspid valve regurgitation induced by temporary or permanent endocardial lead insertion, and the impact of cardiac resynchronization therapy. *Open Cardiovasc Med Journal*. 2014;8:83–87.

[10] Al-Bawardy R, Krishnaswamy A, Rajeswaran J, Bhargava M, Wazni O, Wilkoff B, Tuzcu EM, Martin D, Thomas J, Blackstone E, Kapadia S. Tricuspid regurgitation and implantable devices. *Pacing Clin Electrophysiol*. 2015;38:259–266.
[11] Kucukarslan N, Kirilmaz A, Ulusoy E, Yokusoglu M, Gramatnikovski N, Ozal E, Tatar H. Tricuspid insufficiency does not increase early after permanent implantation of pacemaker leads. *J Card Surg*. 2006;21:391–394.
[12] Leibowitz DW, Rosenheck S, Pollak A, Geist M, Gilon D. Transvenous pacemaker leads do not worsen tricuspid regurgitation: a prospective echocardiographic study. *Cardiology*. 2000;93:74–77.
[13] Huang TY, Baba N. Cardiac pathology of transvenous pacemakers. *Am Heart Journal*. 1972;83:469–474.
[14] Chen TE, Wang CC, Chern MS, Chu JJ. Entrapment of permanent pacemaker lead as the cause of tricuspid regurgitation. *Circ J*. 2007;71:1169–1171.
[15] Wen-Zong L, Liang M. Severe tricuspid valve regurgitation due to perforation by permanent pacemaker lead. *J Card Surg*. 2011;26:555–556.
[16] Mediratta A, Addetia K, Yamat M, Moss JD, Nayak HM, Burke MC, Weinert L, Maffessanti F, Jeevanandam V, Mor-Avi V, Lang RM. 3D echocardiographic location of implantable device leads and mechanism of associated tricuspid regurgitation. *JACC Cardiovasc Imaging*. 2014;7:337–347.
[17] Alizadeh A, Sanati HR, Haji-Karimi M, Yazdi AH, Rad MA, Haghjoo M, Emkanjoo Z. Induction and aggravation of atrioventricular valve regurgitation in the course of chronic right ventricular apical pacing. *Europace*. 2011;13:1587–1590.
[18] Vaturi M, Kusniec J, Shapira Y, Nevzorov R, Yedidya I, Weisenberg D, Monakier D, Strasberg B, Sagie A. Right ventricular pacing increases tricuspid regurgitation grade regardless of the mechanical interference to the valve by the electrode. *Eur J Echocardiogr*. 2010;11:550–553.
[19] Iskandar SB, Jackson A, Fahrig S, Mechleb BK, Garcia ID. Tricuspid valve malfunction and ventricular pacemaker lead: Case report and review of the literature. *Echocardiography*. 2006;23:692–697.
[20] Nath J, Foster E, Heidenreich PA. Impact of Tricuspid regurgitation on long-term survival. *J Am Coll Cardiology*. 2004;43:405–409.
[21] Al-Mohaissen MA, Chan KL. Prevalence and mechanism of tricuspid regurgitation following implantation of endocardial leads for pacemaker or cardioverter-defibrillator. *J Am Soc Echocardiogr*. 2012;25:245–252.
[22] Fazio S, Carlomagno G. The importance of tricuspid regurgitation and right ventricular overload in ICD/CRT recipients: beside the left, beyond the left. *Pacing Clin Electrophysiol*. 2011;34:1181–1184.
[23] Höke U, Auger D, Thijssen J, Wolterbeek R, van der Velde ET, Holman ER, Schalij MJ, Bax JJ, Delgado V, Marsan NA. Significant lead-induced tricuspid regurgitation is associated with poor prognosis at long-term follow-up. *Heart*. 2014;100:960–968.
[24] Seo Y, Ishizu T, Nakajima H, Sekiguchi Y, Watanabe S, Aonuma K. Clinical utility of 3-dimensional echocardiography in the evaluation of tricuspid regurgitation caused by pacemaker leads. *Circ J*. 2008;72:1465–1470.
[25] Nazmul MN, Cha YM, Lin G, Asirvatham SJ, Powell BD. Percutaneous pacemaker or implantable cardioverter-defibrillator lead removal in an attempt to improve symptomatic tricuspid regurgitation. *Europace*. 2013;15:409–413.
[26] Pfannmueller B, Hirnle G, Seeburger J, Davierwala P, Schroeter T, Borger MA, Mohr FW. Tricuspid valve repair in the presence of a permanent ventricular pacemaker lead. *Eur J Cardiothorac Surg*. 2011;39:657–661.
[27] Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ. Recommendations for Evaluating of the Severity of Native Valvular Regurgitation with Two-Dimensional and Doppler Echocardiography. *J Am Soc of Echocardiography*. 2003;16:777–802.
[28] Rahko PS. Prevalence of regurgitant murmurs in patients with valvular regurgitation detected by Doppler echocardiography. *Ann Internal medicine*. 1989;111:466–472.
[29] Grossman G, Stein M, Kochs M, Hoher M, Koenig W, Hombach V, Giesler M. Comparison of the proximal flow convergence method and the jet area method for the assessment of the severity of tricuspid regurgitation. *Eur Heart J*. 1998;19:652–659.
[30] Shapira Y, Porter A, Wurzel M, Vaturi Sagie A. Evaluation of tricuspid regurgitation severity: echocardiographic and clinical correlation. *J Am Soc Echocardiogr*. 1998;11:652–659.
[31] Rivera JM, Vandervoort P, Mele D, Weyman A, Thomas JD. Value of proximal regurgitant jet size in tricuspid regurgitation. *Am Heart J*. 1996;131:742–747.
[32] Tribouilloy CM, Enriquiez-Sarano M, Bailey KR, Tajik AJ, Seward JB. Quantification of tricuspid regurgitation by measuring the width of the vena contracta with Doppler color flow imaging: a clinical study. *J Am Cardiol*. 2000;36:472–478.
[33] Weiss R, Knight BP, Gold MR, Leon AR, Herre JM, Hood M, Rashtian M, Kremers M, Crozier I, Lee KL, Smith W, Burke MC. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. *Circulation*. 2013;128:944–953.
[34] Auricchio A, Delnoy PP, Regoli F, Seifert M, Markou T, Butter C, collaborative study group. First-in-man implantation of leadless ultrasound-based cardiac stimulation pacing system: novel endocardial left ventricular resynchronization therapy in heart failure patients. *Europace*. 2013;15:1191–1197.