

Pacing Inter-lead Fluoroscopic RAO and LAO Distance and Cardiac Resynchronization Therapy Response

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Abstract

Objective: The Inter-lead Distance (ILD) between the Right and Left Ventricular (RV and LV) pacing leads may play a role in Cardiac Resynchronization Therapy (CRT) response. We sought to measure the ILD during the CRT procedure in the Left and Right Anterior Oblique (LAO and RAO) fluoroscopy projections and correlated these measurements with Trans-Thoracic Echocardiographic (TTE) reverse remodeling.

The ILD was measured in the LAO and RAO projections to obtain 2 direct (LAO ILD and RAO ILD) and 1 merged bi-dimensional (LAO ILD×RAO ILD Index) body surface-normalized indexes.

Methods and results: Between January and December 2010, 48 consecutive CRT patients were enrolled (15/48, 31.2% with upgrading indications). Forty-five patients (mean age 72.6 ± 9 years, 28 males) completed the TTE follow up at mean of 12.3 ± 7.8 months. They were divided into CRT “responders” and “non-responders” according to the combined endpoint of LV Ejection Fraction (LVEF) improvement and LV End-Systolic Volume (ESV) reduction. Twenty-five (55%) patients were classified as responders. No difference in the 3 ILD indexes was found between responders and non-responders. In the univariate analysis, non-responders patients were more frequently affected by an ischemic cardiomyopathy and by a previous anterior myocardial infarction (Table 2). In the further multivariate analysis, no variable characterized the study groups.

Conclusions: In our study, the mono and bi-dimensional ILD failed to predict a reverse remodeling in CRT patients.

Keywords: Cardiac resynchronization therapy; Pacing lead fluoroscopic distance

Introduction and Aim

CRT has beneficial effects, improving symptoms, exercise capacity, quality of life and also mortality in patients with drug-refractory congestive HF, as demonstrated by several randomized clinical trials. These studies have also assessed echocardiographic endpoints, such as reverse remodeling features of LV and mitral regurgitation. However, depending on the criteria used, 20% to 40% of patients may not respond to CRT [1-3]. The eligibility criteria for CRT include clinical, TTE and ECG parameters. A decrease of ≥ 10% in LV ESV has been shown to predict lower mortality over long-term follow-up [4,5]. Positioning the LV lead is often challenging, owing to Coronary Sinus (CS) anatomy or the unacceptable electrical parameter achieved, and often related to phrenic nerve stimulation. Recently, radiological ILD (right to left ventricular leads), which is related to the LV lead position, has been assessed in terms of its ability to predict the response to CRT. Measurements have been taken on chest X ray scans in anterior and lateral standard projections [1,6,7]. One of the best echocardiographic projections for detecting intraventricular mechanical delay in clinical practice is the parasternal short axis with M-mode scan, which resembles the plane of view of the LAO projection [8-10].

We therefore sought to measure the ILD between the RV and LV leads in the LAO and RAO standard fluoroscopy projections during the implantation procedure in CRT patients, and to correlate these findings with reverse remodeling

Methods

Study patients and inclusion criteria

The present study was observational, prospective and non-controlled in design.

Between January and December 2010, 48 consecutive patients with standard clinical indications for CRT were enrolled in our EP laboratory. Baseline assessment included medical history, physical examination, 12-lead electrocardiogram (focusing on QRS average duration in leads V1, V6 and D2), and TTE (this last within 3 months before the procedure). Candidates for CRT implantation were considered suitable for the study regardless of coexisting ICD indications; therefore, both CRT-P and CRT-D patients were enrolled. In 15/48 (31.2%) patients, the CRT procedure was part of an upgrade from an existing device. All these last patients were having a paced QRS at baseline. At the time of the procedure, all patients were in NYHA class 2 to 3 despite optimal medical therapy.

All patients successfully underwent LV lead implantation in lateral or postero-lateral CS branches; in all cases, acceptable pacing thresholds were achieved without phrenic nerve stimulation. An anterior CS venous branch was chosen in no patients for LV pacing. Five patients had previously undergone a CABG revascularization procedure, 3 had undergone aortic valve replacement (1 surgical and 2 by means of percutaneous implantation) and 2 had received a mitral

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valve prosthesis (1 bio-prosthesis and 1 mechanical). The TTE Follow-up was completed at 12.3 ± 7.8 months.

Study endpoint

The present study aimed to assess only TTE parameters and their changes after CRT in accordance with the recent literature [11].

The following TTE cut off were adopted as indexes of reverse remodeling:

1. A 6% absolute increase in LVEF
2. A 10% reduction in LV ESV

Patients were divided into “responders” and “non-responders” study groups, according to both the above TTE parameters; a combined single endpoint (increase of LVEF+reduction of LV ESV) was used for the analysis and study groups were compared. No analysis of clinical or functional variables, quality of life indexes or mortality rates was planned; therefore, data on these outcomes were not collected. Written informed consent to undergo the CRT procedure was obtained from all the study patients. No study patient underwent a longer surgical procedure or greater fluoroscopic exposure than is required for a standard CRT procedure. The study protocol was notified to our Institutional Ethics Committee, in accordance with National AIFA (Agenzia Italiana del Farmaco) rules for observational studies.

Fluoroscopy imaging and definitions of study indexes

For all procedures, an SIAS Fluoroscopy Digital System (S.I.A.S. S.p.A via Minghetti, 40057 Cadriano di Granarolo Emilia-BO; Italy) was used. At the end of each procedure, a conclusive fluoroscopic check of lead positions was routinely performed, by using LAO $45^\circ (\pm 5^\circ)$ and RAO $30^\circ (\pm 5^\circ)$ projections.

The LAO and RAO ILD were then calculated as follows: a radiologic radiopaque ruler with a centimeter scale was placed above the patient's chest along the left parasternal line (for RAO projections) and along a virtual median left clavicular line (for LAO projections); this was used as an “in-patient” caliper to calculate the distance between the LV and RV lead tips and to minimize X-ray beam distortion. Care was taken to keep the same distance (<5 cm) from the chest wall and the surface

of the brilliance amplifier (Figure 1). Both the values of RAO-ILD and LAO-ILD were regarded as measurements related to the cardiac long axis (for the RAO projection) and cardiac short axis (for the LAO projection) and were normalized for the patient's body surface.

In order to obtain a single bi-dimensional ILD index, RAO-ILD and LAO-ILD were merged and body-surface normalized, with the rationale of exploring the role of leads separation in both main cardiac axes, by applying the following formula:

$$\text{ILD Index} = \text{RAO-ILD} \times \text{LAO-ILD} / \text{body surface}$$

The final LV lead positions have been analyzed in both short and long cardiac axis, but for the purposes of the study no classifications in segments in LAO (anterior to postero-lateral segments) and RAO (basal to apical segments) projections have been performed. When RAO ILD value was found as equal to zero it has been excluded from the index calculation.

Echocardiography equipment, settings and study definitions

Conventional two-dimensional pulsed Doppler TTE imaging was performed by means of a Philips Ie33 system (Koninklijke Philips Electronics N.V. Groenewoudseweg 15621 BA, Eindhoven, and the Netherlands). All echo examinations were performed by 3 echo cardiographers (N.F., M.M., A.Z) experienced in ultrasound imaging (all had >10 years of post-training experience), who were unaware of the fluoroscopic indexes measured for each patient. Mitral and tricuspid regurgitations were calculated and graded semi-quantitatively by means of color-flow Doppler imaging in the four-chamber apical view; the LVEF was determined by calculating the end-diastolic and end-systolic volumes according to Simpson's method, while LV end-systolic and end-diastolic diameters were calculated in the M-mode in the parasternal short- and long-axis views, in accordance with the guidelines of the American Society of Echocardiography. All the volumes data are body surface normalized [9,10].

Reverse remodeling was defined as a 6% absolute reduction in LVEF and a 10% reduction in ESV [11]. For the aim of the present study, the patients were considered “responders” or not, on the basis of TTE parameters of reverse remodeling and not considering the clinical and functional status achieved after the CRT.

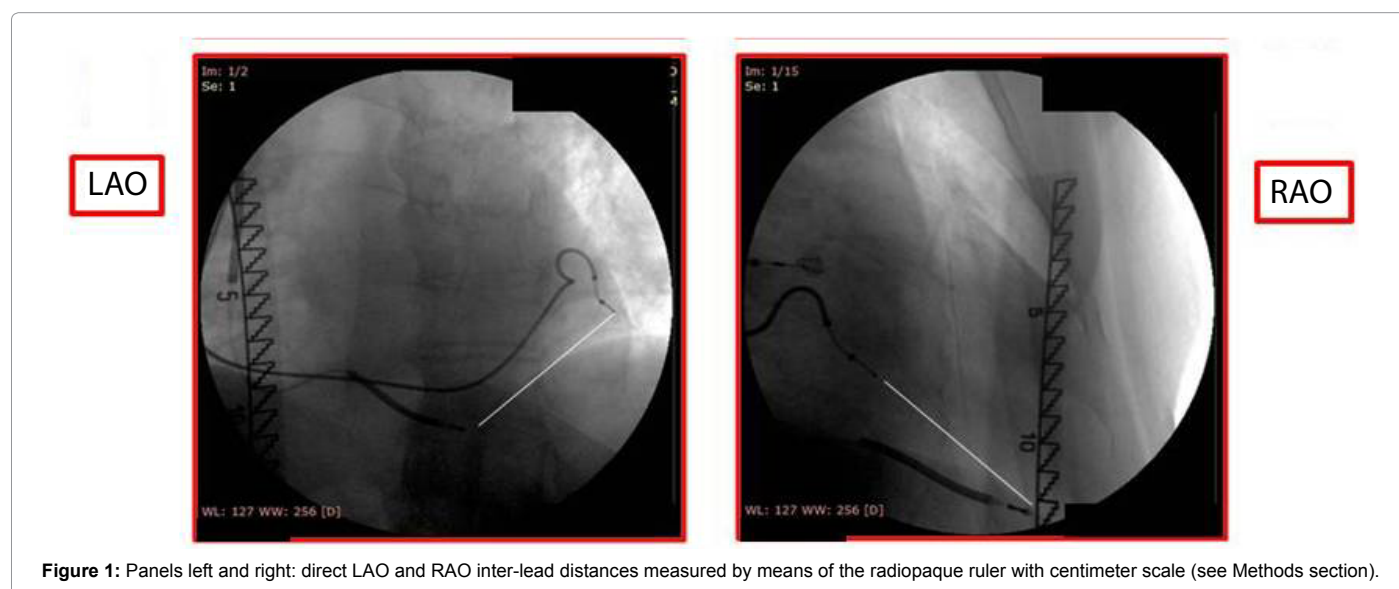


Figure 1: Panels left and right: direct LAO and RAO inter-lead distances measured by means of the radiopaque ruler with centimeter scale (see Methods section).

Data storage and informatics

All echocardiographic frames, loops and quantitative data were recorded in separate digital folders provided with a specific patient-related code (patient name and birth date) and subsequently stored on DVD supports, systematically archived in our echocardiography department laboratory. All patient-related clinical and demographic data and all the interventional procedures and echocardiographic reports were recorded in a dedicated, daily updated, database (DIGISTAT® United Medical Software, Florence Italy; CE certification as Medical Device and quality management system, under ISO 9001:2000 and ISO 13485:2004) with data export capabilities to Excel and SPSS formats, software versions for Windows; this system is routinely used in our department and has been described previously [12].

Statistics

Continuous variables are expressed as mean \pm standard deviation.

Discrete variables are presented as percentages. Univariate comparisons between variables were made by means of χ^2 test for categorical variables, and unpaired two-tailed Student's t-test for continuous variables with normal distribution. Fisher's exact test was used when required. A p value <0.05 was considered statistically significant.

Variables with p values between 0.05 and 0.1 on the univariate analysis were then assessed in the multivariate analysis which was performed by means of a logistic regression model. A variable was regarded as a predictor if the 95% confidence interval was below or exceeded 1 and the p value of the Wald test was <0.05 . Commercially available computer software (SPSS version 17.0) was used for all analyses.

Results

Of the first 48 study patients, 3 were excluded from the analysis for the following reasons: 1 did not complete the follow-up visits, 1 died of progressive HF and, in the third patient, loss of LV catheter performance prompted withdrawal of CRT pacing. The remaining 45 patients (mean age 72.6 ± 9 years, 28 males) completed the follow-up (mean 12.3 ± 7.8 months) and were considered suitable for the study analysis.

Their clinical and TTE features are displayed in Table 1.

During follow-up, 4 patients died of progressive HF: 1 patient (the above-mentioned) died before completing the follow-up visits and was therefore excluded from the analysis; 3 other patients died of progressive HF after the 1st year of follow up; these had completed the follow-up visits and were therefore included in the study analysis (1 was classified as a responder and 2 as non-responders; see below). Twenty-five (55%) patients were classified as responders.

Comparison of study groups based on reverse remodeling

In accordance with the study combined endpoint, patients were divided into CRT "responders" or "non-responders" with regard to the LVEF improvement+LV ESV reduction. No statistical difference was found in terms of age, sex, and the presence of permanent atrial fibrillation or the use of standard medical therapy for HF, for the comparison between "responders" and "non-responders". Moreover, no difference in ILD indexes (RAO ILD, LAO ILD and ILD Index) was found between those study groups. The "non-responders" were significantly characterized by an ischemic etiology of HF; they were also more affected by a previous anterior myocardial infarction.

All the above data are shown in the Table 2. On multivariate analysis, no variable characterized the study groups (Table 3).

Discussion

Main findings

To our knowledge, this is the first study that has analyzed the predictive role for reverse remodeling of RV to LV pacing leads distance, measured in the short and long cardiac axes by means of LAO and RAO fluoroscopic projections, in CRT patients.

Our data failed to show a positive predictive role of Inter-lead distance, as assessed by body surface-normalized RAO and LAO ILD (mono-dimensional) and ILD Index (bi-dimensional).

Recent literature and discussion of study outcome

Our hypothesis was that the distance between the LV and RV pacing leads could predict TTE reverse remodeling. We therefore measured the Inter-lead distance intra-operatively, using the standard fluoroscopic RAO and LAO projections, with the intention to determine the best geometrical views for assessing the position of the LV lead and its best separation from the RV lead tip, in the short and long cardiac axes, i.e. posteriorly (RAO) and left lateral (LAO), Three recent studies have addressed the same topic.

Heist and co-workers measured the Inter-lead distance on post-operative chest X-ray scans in 51 consecutive patients and found a positive correlation with acute (within 24 hours) hemodynamic changes. They found that the horizontal component in the lateral projection of this distance (i.e. posterior to anterior) better correlated with an acute response to CRT; none of the other Inter-lead distances measured in the lateral or postero-anterior projections were correlated with positive acute hemodynamic changes [7].

From the same group, Merchant and co-workers measured the Inter-lead distance (also on chest X-ray scans) in search of a correlation with TTE improvements. They found a correlation with the electrical

Clinical, echo features and fluoroscopic indexes	Total N 45
Age years \pm SD	72.6 \pm 9
Sex male n (%)	28 (62.2)
PM n (%)	27 (60)
ICDn (%)	18 (40)
Baseline Paced QRS n (%)	15 (31.2)
Permanent AFn (%)	13 (28.9)
ACE or ARBn (%)	45 (100)
BBn (%)	43 (95.6)
DIURn (%)	44 (97.8)
CADn (%)	17 (37.8)
Prev Ant MIn (%)	6 (13.3)
QRS durations \pm SD	188.3 \pm 19
LBBB typicaln (%)	22(48.9)
NYHA n \pm SD	2.5 \pm 0.6
RV apex leadn (%)	42 (93.3)
EDV pre ml/m ² \pm SD	115.5 \pm 40.3
EDD premm \pm SD	66.2 \pm 7.8
LVEF pre % \pm SD	32.3 \pm 7.4
ESV preml/m ² \pm SD	79.3 \pm 32
MR /4 n \pm SD	1.6 \pm 1
TR /4n \pm SD	1.1 \pm 1
Follow up months \pm SD	12.3 \pm 7.8

Table 1: Clinical and echocardiographic features of the study patients.

Variables	EF+ESV Non-Responders 20 pts	EF+ESV Responders 25 pts	p
Age years ± SD	73 ± 7.1	72.3 ± 10.4	0.8
Sex male n (%)	13(65)	15(60)	0.7
PM n (%)	10(50)	17(68)	0.2
ICDn (%)	10(509)	8(32)	0.2
Baseline Paced QRS n (%)	7(35)	8(32)	0.8
Permanent AFn (%)	7(35)	6(24)	0.4
ACE or ARBn (%)	20(100)	25(100)	-
Betablockersn (%)	20(100)	23(92)	0.2
Diureticsn (%)	20(100)	24(96)	0.4
CADn (%)	12(60)	5(20)	0.006
Prev Ant MI n (%)	6(30)	0	0.003
QRS durationms ± SD	186 ± 18.4	190 ± 20	0.5
LBBB typicaln (%)	9(45)	13(52)	0.6
NYHA n ± SD	2.6 ± 0.6	2.4 ± 0.6	0.4
RV apex leadn (%)	19(95)	23(92)	0.7
IV septum mm ± SD	11.6 ± 3.2	11.9 ± 2	0.7
Post wallmm ± SD	11 ± 2.6	11.4 ± 1.9	0.5
EDV pre ml/m ² ± SD	109.5 ± 45	120.3 ± 36	0.4
EDD premm ± SD	67.3 ± 7.6	65.3 ± 8	0.4
ESV preml/m ² ± SD	75.4 ± 36	82.4 ± 29	0.5
LVEF pre % ± SD	32.1 ± 6.3	32.5 ± 8.3	0.9
MR /4 n ± SD	1.9 ± 1.2	1.5 ± 0.9	0.2
TR /4n ± SD	1.3 ± 1	1 ± 0.8	0.3
Follow up months ± SD	10 ± 6.8	14 ± 8.3	0.09
LAO ILDCm/m ² ± SD	4.4 ± 1.8	4.3 ± 1.2	0.9
RAO ILDCm/m ² ± SD	3.9 ± 1.6	3.6 ± 1.5	0.5
RAO-LAO index cm/m ² ± SD	37.1 ± 17.1	34.8 ± 18	0.6

Table 2: Univariate Comparison between 2 study groups according with the study endpoint.

ACE: Angiotensin Converting Enzyme; ARB: Angiotensin Receptor Blockers; CAD: Coronary Artery Disease Etiology; MR: Mitral Regurgitation; TR: Tricuspid Regurgitation; RV: Right Ventricle; EDV: Left Ventricular End-Diastolic Volume; EDD: Left Ventricular End-Diastolic Diameter; LBBB: Left Bundle Branch Block; ESV: Left Ventricular End-Systolic Volume; ESD: Left Ventricular End-Systolic Diameter; ILD: Body Surface-Normalized Inter-Lead Distance; BSA: Body Surface Area; LBBB: Left Bundle Branch Block; Paced QRS: Baseline QRS Paced Complex In Patients With A Preexisting Device; RAO-LAO Index: Body Surface-Normalized Inter-Lead Distance In RAO X LAO (See Methods Section); EF + ESV Responders/ NON Responders: According To The Study Endpoint (See Text); OR: Odds Ratio; C.I.: Confidence Intervals

Variables	OR	95 % C.I.	P
CAD	0.32	0.07-1.4	0.1

Table 3: Covariate included in the multivariate logistic regression: odd ratios and related confidence intervals.

delay and with the horizontal distance, but not with the vertical distance [6]. In a study by Buck and co-workers, the same methods were used to measure Inter-lead distance: the study outcomes were assessed by means of 6-month echocardiographic follow-up examination, to determine the persistence of inter-ventricular and intra-ventricular mechanical delay. They found that a more posterior positioning of the LV lead correlated with a reduction in intra-ventricular dissynchrony [1]. The method of measuring the Inter-lead distance used in all the above studies allowed the authors to conclude that an antero-posterior separation (i.e. a basal LV lead position) was important for acute hemodynamic improvement or echocardiographic response to CRT. The antero-posterior (horizontal) distance on the lateral chest X-ray projection identified positive outcomes better than the distance in other geometrical planes. However, while measuring the horizontal distance may be a reliable approach in the case of RV apical lead

positioning, which can allow greater postero-anterior separation; it may be less appropriate in the case of RV lead placement in the RV septum or RVOT.

In our study, the LAO ILD in the short cardiac axis (RV to left lateral LV wall) and the RAO ILD in the long cardiac axis (postero-anterior tip separation) did not predict positive reverse remodeling. Moreover, we also failed to demonstrate that a bi-dimensional ILD index assessing both components was related with better outcomes. There may be some reasons for these results. First, the small number of study patients did not allow sufficient statistical power, though the studies cited mainly involved similar numbers of patients. Second, in none of our study patients was an anterior CS branch targeted for LV lead placement, a position which could display narrower right-to-left tip separation in the LAO view. Thus, the right-to-left lead separation was “maximized” in all our patients and, in this setting; some other variables could become more important in predicting positive remodeling (such as the presence of ischemic HF etiology, which was related to reverse remodeling in our study).

When assessing the Inter-lead distance in patients with ischemic HF, especially in those with previous lateral scars, a larger distance may lose importance if no wall contractility can be recruited in the “farthest” regions; thus, a narrower lead separation in “recruitable” regions may offer a better outcome.

For all these reasons, the RV-LV leads distance could represent a predictive parameter, probably not in all cases.

Limitations

The present study, though prospectively designed, included a limited number of patients. The fluoroscopic measurements of Inter-lead distance were taken manually; this method was validated by positioning an intracardiac pig-tail catheter with a radiopaque centimeter scale but no off-line digitally corrected measurements were used. The overall average QRS duration was roughly >180 msec in all the study patients and paced rhythms were included; thus the QRS duration, used as one of the variables in the echo groups comparisons, may not have been given the importance it deserved. Indeed, in patients with no paced rhythms, QRS duration is currently considered one of the features most predictive of CRT response.

No assessment of clinical, functional or quality of life parameters was scheduled in the study; moreover, as underlined in the methods, for the aim of the present analysis, the study patients were classified as “responders” or not with regard to TTE parameters and not considering the clinical response and the functional status after CRT.

Data about the final positions achieved for the CS leads placement were not collected.

Conclusions

In our study, both the mono-dimensional ILD in RAO and LAO fluoroscopic projections and the merged bi-dimensional ILD Index failed to predict a reverse remodeling in CRT patients.

References

- Buck S, Maass AH, Nieuwland W, Anthonio RL, Van Veldhuisen DJ, et al. (2008) Impact of interventricular lead distance and the decrease in septal-to-lateral delay on response to cardiac resynchronization therapy. *Europace* 10: 1313-1319.
- Manolis AS (2004) Cardiac resynchronization therapy in congestive heart failure: Ready for prime time? *Heart Rhythm* 1: 355-363.

3. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, et al. (2001) Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 344: 873-880.
4. Bax JJ, Abraham T, Barold SS, Breithardt OA, Fung JW, et al. (2005) Cardiac resynchronization therapy: Part 1--issues before device implantation. *J Am Coll Cardiol* 46: 2153-2167.
5. Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, et al. (2005) Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation* 112: 1580-1586.
6. Merchant FM, Heist EK, Nandigam KV, Mulligan LJ, Blendea D, et al. (2010) Interlead distance and left ventricular lead electrical delay predict reverse remodeling during cardiac resynchronization therapy. *Pacing Clin Electrophysiol* 33: 575-582.
7. Heist EK, Fan D, Mela T, Arzola-Castaner D, Reddy VY, et al. (2005) Radiographic left ventricular-right ventricular interlead distance predicts the acute hemodynamic response to cardiac resynchronization therapy. *Am J Cardiol* 96: 685-690.
8. Pitzalis MV, Iacoviello M, Romito R, Massari F, Rizzon B, et al. (2002) Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. *J Am Coll Cardiol* 40: 1615-1622.
9. Sahn DJ, DeMaria A, Kisslo J, Weyman A (1978) Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 58: 1072-1083.
10. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, et al. (1989) Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 2: 358-367.
11. Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, et al. (2010) 2010 focused update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC Guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. *Eur J Heart Fail* 12: 1143-1153.
12. Zoppo F, Zerbo F, Brandolino G, Bacchiega E, Lupo A, et al. (2011) Straight screw-in atrial leads „J-post shaped“ in right appendage versus J-shaped systems for permanent atrial pacing: a safety comparison. *Pacing Clin Electrophysiol* 34: 325-330.