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IS CARDIAC VENOUS ANATOMY A CRUCIAL FACTOR IN MAXIMIZING THE RESPONSE TO CARDIAC RESYNCHRONISATION THERAPY?

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Abstract: Cardiac resynchronization therapy (CRT) restores the synchrony of the heart's contractions. The most critical issue in CRT implantation is the positioning of the coronary sinus (CS) lead because not every region can be accessed due to variations in coronary venous anatomy. The aim was to determine the correlation between different CS lead positions and hemodynamic changes and clinical outcome over time. Our study prospectively enrolled 51 patients with conventional indications for CRT which was divided into three groups according to the vein in which the left ventricle lead was placed during the procedure (posterior, lateral, and anterior). The groups were compared by baseline demographic characteristics, comorbidity, complications, new hospitalizations as well as by hemodynamic parameters before and six months after the procedure. After six months, all patients responded to CRT in the lateral group, 66.7% patients in the posterior group and 50% in the anterior group ($p<0.01$). Patients in the anterior group had a smaller decrease in NYHA functional class compared to the posterior and the lateral groups ($p<0.01$). The largest increase of preoperative ejection fraction value was in the posterior group (68.7%) compared to the lateral (42.2%) and anterior groups (19.8%) ($p<0.01$, A vs. P&L; P vs. A&L). In the anterior group there was a smaller decrease of QRS complex compared to the posterior and lateral groups ($p< 0.05$, A vs. P&L). Also there was a smaller decrease in the degree of mitral regurgitation in the anterior group compared to the lateral and posterior groups ($p<0.05$, A vs. P&L).

One of the main determinants of CRT response is the anatomy of CS tributaries, and therefore the position of the LV lead is crucial in maximizing the effect of CRT.

Key words: Cardiac resynchronization therapy, coronary sinus venography, lead position

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INTRODUCTION

During the last decade, an increasing number of patients suffer from congestive heart failure syndrome which is responsible for substantial morbidity and mortality (Hunt et al., 2001). The primary treatment mode for patients with this syndrome is a pharmacological approach consisting of antagonists to the sympathetic nervous system and renin-angiotensin-aldosterone axis activated to compensate for the failing cardiovascular system (Paker et al., 2001; Pitt et al., 1999).

Cardiac resynchronization therapy (CRT) restores the synchrony of atrioventricular, interventricular and intraventricular contractions. Significant clinical evidence endorses the use of CRT in patients with either ischemic or non ischemic cardiomyopathy (NYHA class III or IV, LVEF $\leq$ 30%) with QRS > 120 ms (Cazeau et al., 2001, Auricchio et al., 2002, Abraham et al., 2002). Numerous studies have shown that in these patients CRT significantly improves cardiac output, systolic pressure, the magnitude of myocardial wall contractions, mitral regurgitation and left atrial pressure (Nelson et al. (a), Nelson et al. (b), 2001).

However, 30-40% of patients fail to respond to CRT and show no clinical improvement (Bleeker et al., 2006). Possible reasons are non-optimal positioning of the left ventricle (LV) pacing lead, high myocardial scar burden, sub-optimal device programming and the lack of LV dissynchrony (Ypenburg et al., 2008). An optimal LV lead position may be defined by positioning the lead coincident to the latest activated areas of the LV, since that location maximizes the hemodynamic benefit and provides a better outcome (Gras et al., 2007). Furthermore, the most critical issue in CRT implantation is the positioning of the coronary sinus (CS) lead because not every region can be accessed due to variations in coronary venous anatomy (Gilard et al., 1998).

Therefore, exact and detailed information on coronary venous anatomy provided by cardiac imaging prior to CRT implantation is crucial in order to maximize the response to this type of treatment. The most commonly used branches of the CS for the CRT are the lateral, posterior and anterolateral cardiac veins depending on their accessibility and availability (Morgan et al., 2009).

Determining the correlation between different coronary sinus lead positions and hemodynamic changes and clinical outcome over time could be of great benefit for achieving the highest CRT response.

METHODS

We prospectively enrolled in our study 51 patients with conventional indications for CRT. Patients who had myocardial infarction 30 days prior to CRT implantation, indications for coronary artery bypass grafting or valve surgery were excluded from the study. Intraoperative cardiac venography during the procedure was done in order to determine the arborization (number, localisation and diameter) of CS tributaries. The LV lead was placed into the posterior or lateral cardiac veins as the first choice. If the posterior and lateral veins were not accessible (the absence of tributary, small vein diameter or unfavorable arborization angle) the LV lead was then placed in the anterior vein. Prior to the procedure, we registered the demographic parameters of the patients and the presence of the following comorbidities: hypertension, hyperlipidemia, type of cardiomyopathy, chronic obstructive pulmonary disease (COPD), chronic renal failure (CRF), atrial fibrillation, diabetes mellitus and cerebral vascular insult (CVI). The reduction of the QRS complex duration after the procedure was recorded as well as complications during the postoperative course.

As hemodynamic parameters we registered the NYHA (New York Heart Association) functional class, left ventricle ejection fraction (LVEF), grade of mitral regurgitation, left ventricle end diastolic diameter (LVEDD) before the procedure and after the six month follow-up period. In addition to these hemodynamic parameters, the number of non-responders to CRT and hospitalizations due to cardiac insufficiency were also recorded after and during the six month follow up period, as well as complications after the surgery.

Patients who had a statistically significant enhancement of one or more hemodynamic parameters (NYHA class reduction by one grade or more, LVEF + $\geq$ 5%) after six months were designated as responders to CRT therapy. LVEF value was obtained according to the Simpson method using Doppler echocardiography. Conventional echocardiography parasternal M-mode was used to measure LVEDD and LVESD. The degree of mitral regurgitation was assessed in orthogonal echocardiographic projection using the color flow Doppler.

Patients were divided into three groups according to the vein in which the LV lead was placed during the CRT procedure (posterior, lateral, and anterior). These groups were compared on the basis of the preoperative and postoperative characteristics mentioned above.

Statistical analysis was performed using the SPSS software version 17.0 package. To assess the difference in the results between the groups we used Chi-Square test and variance analysis (ANOVA).

RESULTS

Patients

The LV lead was implanted in the posterior vein in 20 (40%) patients, in the lateral vein in 21 (42%) and in the anterior in 10 (18%) patients. The demographic characteristics of the patients are shown in Table 1. There was no statistically significant difference between the groups regarding baseline characteristics. Ischemic cardiomyopathy was found in 10 (50%) patients in the posterior group, 9 (42.8%) in the lateral group and 4 (40%) in the anterior group, also without statistically significant difference ($\chi 2$= 0,86, p>0,05).

Baseline hemodynamic characteristics are shown in Table 2. Patients in all three groups did not differ statistically; therefore these groups were homologous regarding baseline hemodynamics.

QRS complex duration and postoperative complications

After the surgery there was an expected decrease of QRS duration in all groups. There was a decrease compared to baseline values by 17.8 % in the posterior group, by 16.1 % in the lateral group and by 4.6 % in the anterior group which was statistically significant (F=3.43, p<0.05, A vs. P&L). The early postoperative course was complicated by one dissection of the coronary sinus, two lead displacements and three pacemaker pocket hematoma, however without statistical difference between the groups.

Six month follow-up

Changes between the baseline values and values after six months are shown in Table 3. After six months, 7 (33%) patients in the lateral group and 5 (50%) patients in the anterior group did not respond to CRT according to the previously mentioned criteria. All patients in the posterior group responded to the treatment. This difference is statistically highly significant ($\chi 2$= 11.7, p>0.01). Patients in the anterior group had a smaller decrease in NYHA functional class (by 11%) compared to the posterior (by 46%) and lateral (by 40%) groups (F=8.7, p<0.01). The largest increase of preoperative LVEF value was in the posterior group (68.7%) compared to the lateral (42.2%) and anterior group (19.8%) (F=5.8, p<0.01,A vs. P&L; P vs. A&L). Also there was a smaller decrease in the degree of mitral regurgitation in the anterior group (13.8%) compared to the lateral (38.6%) and posterior groups (41.7%) (F=3.4, p<0.05, A vs. P&L). There was an expected decrease in both LVEDD and LVESD but without statistical significance between the compared groups. Also, these groups did not differ in the number of new hospitalizations due to heart failure during the follow up period.

DISCUSSION

In order to maximize the effect of CRT, the LV lead should be placed in the latest activated areas of the heart. Possible reasons behind non-responsiveness to CRT are the position of the LV lead outside of the last activated areas of the left ventricle, presence of high-myocardial scar burden and suboptimal device programming (Ypenburg et al., 2008). Technically, the final position of the LV pacing lead depends primarily on the anatomy of the coronary venous system, as well as on the performance and stability of the pacing lead and the absence of phrenic nerve stimulation. Ignorance of the significant variations of coronary venous anatomy lead to the placement of the LV lead in sub-optimal localizations in the heart, which could be the reason of the large number of non-responders to CRT.

Table 1. Baseline characteristics of the compared patients

	Posterior N= 20	Lateral N=21	Anterior N=10	p
Male	17 (85%)	17 (80%)	8 (80%)	0,92
Age (mean ± SD)	61,8 ± 13,4	64,7 ± 7,6	59,5 ± 10,3	0,43
Hypertension	8 (40%)	8 (38%)	3 (30%)	0,86
Ischemic cardiomyo-pathy	11 (55%)	9 (42,8%)	4 (40%)	0,65
COPD	1 (5 %)	1 (4,7 %)	0 (0 %)	0,77
CRI	2 (10 %)	1 (4,7 %)	1 (1 %)	0,79
Atrial fibrilation	5 (25 %)	7 (33,3 %)	30(%)	0,84
Diabetes mellitus	6 (30,3 %)	6 (28,6 %)	2 (20 %)	0,83
CVI	0 (0%)	2 (9,5 %)	2 (20 %)	0,14

Table 2. Baseline hemodynamic characteristics of the compared patients

	Posterior N= 20	Lateral N=21	Anterior N=10	p
NYHA functional class	3,1 ± 0,6	2,85 ± 0,6	2,7 ± 0,5	0,18
QRS duration (ms)	164,2 ± 24,9	160,6 ± 24,8	144,67 ± 28,6	0,14
LVEF (%)	22,5 ± 5,1	26,3 ± 7,9	22,7 ± 5,6	0,15
Mitral regurgitation (grade)	2,1 ± 1,2	2,4 ± 0,8	2,4 ± 0,82	0,82
LVEDD (cm)	6,93 ± 0,7	6,95 ± 0,8	7,17 ± 0,7	0,75
LVESD (cm)	5,8 ± 0,7	5,9 ± 0,9	6,3 ± 0,9	0,25

Table 3. Hemodynamic parameters, nonresponders to CRT, rehospitalizations after six months

	Posterior N= 20	Lateral N=21	Anterior N=10	p
Nonresponder	0 (0%)	7 (33,3%)	5 (50%)	**<0,01**
NYHA functional class	-46,1 %	-40 %	-11 %	<0,01 (A vs P&L)
QRS duration	-17,8%	-16,1 %	-4,6 %	**< 0,05 (A vs P&L)**
LVEF (%)	38,8± 10,2 (+69,8 %)	37,4±9,6 (+42,2 %)	27,2 ±6,1 (+19,8 %)	**<0,01 (A vs P&L) <0,01 (P vs A&L)**
Mitral regurgitation	-41,7 %	-38,6 %	-13,8 %	**<0,05 (A vs P&L)**
LVEDD	-8,5 %	-6,5 %	-6,9 %	0,92
LVESD	-11,1 %	-9,9 %	-9,5 %	0,97
Complications during postoperative recovery	2 (10%)	1 (23,8%)	3 (30%)	0,15
Rehospitalizations	1 (5%)	2 (4,7%)	1 (10%)	0,79

Therefore the presence of an adequate CS tributary in the latest activated area of the heart is mandatory because the final LV position depends on the anatomy of cardiac veins (Gras et al., 2007, Gilard et al., 1998). In broad clinical practice, the LV lead is positioned as far as possible from the right ventricle pacing lead, commonly in the lateral and posterior veins (first choice), therefore avoiding the anterior vein (second choice). Detailed assessment of the coronary venous anatomy can be obtained by coronary venography. Although this is an invasive procedure it gives perfect insight into the venous anatomy with minimal complications.

Duray et al. (2008) report in their study that the LV lead was implanted in the first choice veins in 71% of patients. This is in agreement with our study where the LV lead is placed in first choice veins in 82% of patients. Veire et al. (2008) suggest that the inadequate tributaries are in correlation with the presence of ischemic cardiomyopathy. On the contrary, in our study the LV lead is placed in the vein of first choice in 83.3% of patients with ischemic cardiomyopathy. A possible explanation could be the use of CT venography by Veire et al. (2008) in their study while we used intraoperative coronary venography which gives better insight into CS anatomy.

A larger reduction of the QRS complex was recorded in patients with the LV lead placed in the first choice veins. This restoration of heart electrophysiology could implicate greater hemodynamic benefit in long term follow-up within this group. Our study showed that the greatest chronic hemodynamic benefit of CRT is achieved when the LV lead is placed in the posterior and lateral veins, while a diminished effect is found in the anterior vein. Butter et al. (2001) also confirmed this in their hemodynamic study.

The improvement in the clinical outcome and hemodynamics via myoepicardial pacing performed through a toracotomy have been pointed out by De Rose et al. (2003) and Fernandez et al. (2004). This indicates that myoepicardial pacing could provide a better alternative than second choice veins when first choice veins are not available.

The position of the LV lead is crucial in maximizing the effect of CRT. Therefore, one of the main determinants of CRT response is the anatomy of CS tributaries which can be identified by coronary venography. However, further studies on a larger scale with a longer follow-up period are needed to assess the real clinical benefit with a special emphasis on CS anatomy.

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REFERENCES

Abraham, W.T., Fisher, W.G., Smith, A.L., Delurgio, D.B., Leon, A.R., Loh, E., Kocovic, D.Z., Packer, M., Clavell, A.L., Hayes, D.L., Ellestad, M., Trupp, R.J., Underwood, J., Pickering, F., Truex, C., McAtee, P., and *J. Messenger*; MIRACLE Study Group. Multicenter In Sync Randomized Clinical Evaluation (2002). Cardiac resynchronization in chronic heart failure. *N Engl J Med*. **346**,1845–1853.

Auricchio, A., Stellbrink, C., Sack, S., Block, M., Vogt, J., Bakker, P., Huth, C., Schondube, F., Wolfhard, U., Bocker, D., Krahnefeld, O., and *H. Kirkels* (2002) Pacing Therapies in Congestive Heart Failure (PATH-CHF) Study Group. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol*. **39**, 2026-2033.

Bleeker, G.B., Bax, J.J., Fung, J.W., van der Wall, E.E., Zhang, Q., and *M.J. Schalij* (2006). Clinical versus echocardiographic parameters to assess response to cardiac resynchronization therapy. *Am J Cardiol* **97**, 260–263.

Butter C, Auricchio A, Stellbrink C, Fleck E, Ding J, Yu Y, Huvelle E, and *J Spinelli* (2001). Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation* 104 , 3026–3029.

Cazeau, S., Leclercq, C., Lavergne, T., Walker, S., Varma, C., Linde, C., Garrigue, S., Kappenberger, L., Haywood, G.A., Santini, M., Bailleul, C., and *J.C. Daubert* (2001). Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med*. **44** , 873– 880.

DeRose, J.J., Ashton, R.C., Belsley, S., Swistel, D.G., Vloka, M., and *F. Ehlert* (2003). Robotically assisted left ventricular epicardial lead implantation for biventricular pacing. *J Am Coll Cardiol*. **41**, 1414–1419.

Duray, G.Z., Hohnloser, S.F., and *C.W. Israel* (2008). Coronary sinus side branches for cardiac resynchronization therapy: Prospective evaluation of availability, implant success, and procedural determinants. *J Cardiovasc Electrophysiol*. **19**, 489-494.

Fernandez, A.L., Garcia-Bengochea, J.B., Ledo, R., Vega, M., Amaro, A., and *J. Alvarez* (2004) Minimally invasive surgical implantation of left ventricular epicardial leads for ventricular resynchronization using video-assisted thoracoscopy. *Rev Esp Cardiol.* **57**, 313–319.

Gilard, M., Mansourati, J., and *Y. Etienne* (1998) Angiographic anatomy of the coronary sinus and its tributaries. *Pacing Clin Electrophysiol* **21**(Pt II), 2280–2284.

Gras, D., Bocker, D., Lunati, M., Wellens, H.J., Calvert, M., and *N. Freemantle* (2007) Implantation of cardiac resynchronization therapy systems in the CARE-HF trial: procedural success rate and safety. *Europace* **9**, 516–522.

Hunt, S.A., Baker, D.W., and *M.H. Chin* (2001).ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the International Society for Heart and Lung Transplantation: endorsed by the Heart Failure Society of America. *Circulation*. **104**, 2996-3007.

Morgan, M., and *V. Delgado* (2009). Lead positioning for cardiac resynchronization therapy: techniques and priorities. *Europace* **11**, 22–28.

Nelson, G.S., Curry, C.W., Wyman, B.T., Kramer, A., Declerck, J., Talbot, M., Douglas, M.R., Berger, R.D., McVeigh, E.R., and *D.A. Kass* (2000). Predictors of systolic augmentation from left ventricular preexcitation in patients with dilated cardiomyopathy and intraventricular conduction delay. *Circulation*. **101**, 2703–2709.

Nelson, G.S., Berger, R.D., Fetics, B.J., Talbot, M., Spinelli, J.C., Hare, J.M., and *D.A. Kass* (2000). Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation*. **102**, 3053–3059.

Packer, M., Coats, A.J.S., and *M.B. Fowler* (2001). Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. **344**, 1651-1658.

Pitt, B., Zannad, F., and *W.J. Remme* (1999). The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. **341**, 709 -717.

van de Veire, N., Marsan, N.A., Schuijf, J.D., Bleeker, G.B., Wijffels, M.C., and *L. van Erven* (2008). Noninvasive imaging of cardiac venous anatomy with 64-slice multi-slice computed tomography and noninvasive assessment of left ventricular dyssynchrony by 3-dimensional tissue synchronization imaging in patients with heart failure scheduled for cardiac resynchronization therapy. *Am J Cardiol*. **101**, 1023–1029.

Ypenburg, C., van de Veire, N., Westenberg, J.J., Bleeker, G.B., Marsan, N.A., and *M.M. Henneman* (2008) Noninvasive imaging in cardiac resynchronization therapy—Part 2: follow-up and optimization of settings. *Pacing Clin Electrophysiol.* **31**, 1628–1639.