CHAPTER 8

Noninvasive imaging of cardiac venous anatomy with 64-slice computed tomography and noninvasive assessment of LV dyssynchrony by 3D tissue synchronization imaging in patients with heart failure scheduled for CRT

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ABSTRACT

Objectives: Objectives of this study were to perform a prospective head-to-head comparison between multi-slice computed tomography (MSCT) venography and invasive venography in cardiac resynchronization therapy (CRT) candidates as well as to evaluate the relation between left ventricular (LV) lead position and effect on LV dyssynchrony and immediate response to CRT.

Methods: Twenty-one consecutive heart failure patients scheduled for CRT implantation were prospectively enrolled to undergo 64-slice MSCT to visualize the venous system, invasive venography during device implantation, and tri-plane tissue synchronization imaging (TSI) before and after implantation.

Results: Excellent agreement between MSCT and invasive venography was noted. No significant differences were observed between both techniques regarding vessel diameters. In 12 patients, a match was observed between the area of latest mechanical activation (on TSI) and LV lead position. These patients showed a significant decrease in LV dyssynchrony (43±7 ms to 11±9 ms, p <0.001) with acute reduction in LV end-systolic volume (188±54 ml to 162±48 ml, p <0.01) and improvement in LV ejection fraction (22%±9% to 34%±9%, p <0.01). Patients with a mismatch between area of latest activation and LV lead position remained dyssynchronous without improvement in LV function.

Conclusions: Visualization of major tributaries of the coronary sinus was comparable between invasive venography and MSCT venography. Optimal LV lead positioning in a vein draining the area of latest mechanical activation (determined from tri-plane TSI) resulted in acute improvement of LV dyssynchrony and systolic function after CRT implantation.
INTRODUCTION

Cardiac resynchronization therapy (CRT) is an attractive treatment for highly symptomatic heart failure patients with wide QRS complex and depressed left ventricular (LV) systolic function. In large randomized clinical trials, up to 30% of patients do not respond favourably to CRT. Two major issues need to be addressed during the selection process of potential candidates to improve the success rate. First, LV dyssynchrony appears an important predictor of response to CRT. The amount of intraventricular dyssynchrony can be reliably assessed noninvasively with tissue Doppler echocardiography. Second, attention to venous anatomy ensures the area of latest activation can be reached through a suitable vein. Particularly in patients with ischemic cardiomyopathy, lack of a suitable branch of the coronary sinus may hamper successful endovascular LV lead implantation. In 2005, preliminary data suggested that the cardiac venous system could be depicted noninvasively using 16-slice multi-slice computed tomography (MSCT). Recently, the feasibility of 64-slice MSCT to evaluate the cardiac veins was confirmed in a retrospective analysis of 100 patients. However, prospective comparisons between MSCT and invasive venography for assessment of venous anatomy are lacking. Moreover, information on location of LV dyssynchrony and venous anatomy should be integrated to determine whether a transvenous or a surgical approach should be selected for LV lead positioning. In the present study, 21 consecutive patients with heart failure scheduled for CRT underwent 64-slice CT of the cardiac venous system, invasive venography during device implantation, and 3-dimensional tissue synchronization imaging (TSI) echocardiography before CRT to assess location and extent of LV dyssynchrony. Study aims were (1) to perform a head-to-head comparison between MSCT venography and invasive venography in CRT candidates (to further validate the use of MSCT for assessing venous anatomy), and (2) to evaluate the effect of CRT when the LV lead is positioned inside or outside a vein draining the area of latest mechanical activation.

METHODS

A total of 21 consecutive patients with heart failure scheduled for CRT, underwent 64-slice MSCT before, and invasive venography during CRT implantation. Exclusion criteria were atrial fibrillation, documented contrast allergy, and reduced renal function (serum creatinine >140 μmol/L).

Imaging was performed with a 64-detector row Toshiba Multislice Aquilion 64 system (Toshiba Medical Systems, Otawara, Japan) with a collimation of 64 x 0.5 mm and a rotation time of 0.4 seconds. Between 95 and 140 ml (mean 108±11 ml) of contrast material (Iomeron 400, Bracco Altana Pharma GmbH, Konstanz, Germany) at an injection rate of 5 ml/min was used with an automatic bolus triggering technique. To optimize the scan for
venous visualization, an additional 2-second delay was applied after the contrast bolus reached the descending aorta before triggering the scan. For optimal filling of the cardiac venous system, the use of saline chasing was omitted. Tube voltage was 120 kV at 300 mA. A segmental reconstruction algorithm allowed inclusion of patients with a range of heart rates. The majority of the patients were already taking low-dose β-blockers; additional β blockade was considered contra-indicated because of the presence of heart failure. During the MSCT examination, electro-cardiography was performed simultaneously for retrospective gating of the data. An initial data set was reconstructed at 75% of the RR interval, with a slice thickness of 0.5 mm and a reconstruction interval of 0.3 mm. Data reconstruction was performed on a Vitrea post-processing workstation (Vital Images, Plymouth, Minnesota).

Three-dimensional volume-rendered reconstructions were used to obtain general information on the anatomy of the cardiac veins. Thereafter, the course of the veins was evaluated in three orthogonal planes using multi-planar reformatting. The tributaries of the coronary sinus evaluated include posterior interventricular vein, posterior vein of the LV, and left marginal vein. First-degree side branches were also noted, if present. The diameter of the coronary sinus ostium was measured in 2 directions (anteroposterior and superoinferior), and the diameters of the tributaries were measured close to their origin.

Retrograde venography was performed after implantation of the right atrial and right ventricular leads in all 21 patients. The coronary sinus was cannulated from a subclavian entry site by an 8F guiding catheter. A balloon occlusion catheter (Arrow model 6714; Arrow International Inc., Reading, Pennsylvania, or Medtronic model 6215, Medtronic Inc., Minneapolis, Minnesota) was advanced to the proximal part of the coronary sinus. Three venograms (right anterior oblique 30°, anteroposterior and left anterior oblique 30° views) were then obtained with an acceptable occlusion balloon position. A non-ionic contrast agent with low osmolarity (Iomeron 350; Bracco Altana Pharma GmbH) was used. Next, the balloon occlusion catheter was withdrawn and the LV pacing lead was positioned, preferably in the (postero)lateral vein. The choice of LV lead position was made independently by the implanting cardiologist, who was blinded to the MSCT and dyssynchrony data. At implantation, both the sensing and pacing thresholds (at pulse duration of 0.5 ms) of the LV pacing lead were measured. The final position of the LV pacing lead was assessed by fluoroscopy.

The different image series were stored digitally and analyzed by an experienced observer without knowledge of the MSCT data, at a separate workstation using commercially available software (QCA-CMS version 6.0; Medis, Leiden, The Netherlands). Images were first analyzed to identify the tributaries of the coronary sinus and presence of 1st degree side branches. The proximal vein diameters of the coronary sinus, posterior interventricular vein, posterior vein of the left ventricle, and left marginal vein were measured after catheter-based image calibration.

All patients underwent a transthoracic echocardiogram before and within 72 hours after CRT implantation. Studies were performed with a commercially available echocardiographic platform (VIVID 7; GE Vingmed Ultrasound, Horten, Norway), equipped with a 3V-probe for
3-dimensional acquisition. Patients were scanned in left lateral decubitus position, from the apical window in tri-plane modus. Care was taken to visualize the true LV apex, allowing simultaneous acquisition of the apical 4-, 2-, and 3-chamber views. Color-coded TSI was applied to the tri-plane view to assess longitudinal myocardial regional function. Gain settings, filters, and pulse repetition frequency were adjusted to optimize color saturation. Sector size and depth were optimized for the highest possible frame rate. At least 2 consecutive beats were recorded from each view, and the images were digitally stored for offline analysis (EchoPac; GE Vingmed Ultrasound). During post-processing, the tri-plane data set was frozen in end-diastole, and the endocardial border was manually traced in the apical 4-, 2- and 3-chamber views, respectively. Then, using the same heartbeat, the tri-plane data set was frozen in end-systole, and again the endocardial border was manually traced in the apical 4-, 2-, and 3-chamber views. Three-dimensional LV end-diastolic and end-systolic volumes were generated automatically by the software (Echopac), and LV ejection fraction was reported accordingly.

During post-processing, the tri-plane TSI data set was used to analyze myocardial velocity curves as previously described. TSI automatically calculates the time from the beginning of the QRS complex to peak systolic velocity in every position in the image with reference to the QRS interval. The TSI algorithm detects positive velocity peaks within a specified time interval, and the color coding ranges from green (earliest), over yellow-orange to red (latest) within this interval. By using surface mapping and manual tracing of the endocardial borders, a 3-dimensional rendered volume was automatically generated, allowing for a spatial representation of electromechanical activation times. Sample volumes were placed in the basal and mid segments of the septal, lateral, inferior, anterior, posterior, and anteroseptal LV walls to measure the time between onset of QRS complex and peak systolic myocardial velocity. From these 12 measurements, the LV dyssynchrony parameters calculated include delay between septum and lateral wall and standard deviation of all 12 LV segments. The severity of mitral regurgitation was graded semiquantitatively from color-flow Doppler in the conventional parasternal long-axis and apical 2- and 4-chamber images. Mitral regurgitation was characterized as mild, 1+ (jet area/left atrial area <10%); moderate, 2+ (jet area/left atrial area 10% to 20%); moderately severe, 3+ (jet area/left atrial area 20% to 45%); and severe, 4+ (jet area/left atrial area >45%).

All analyses were performed with the statistical software program SPSS 12.0.1 (SPSS, Inc., Chicago, Illinois). Continuous data are presented as mean±SD. Categorical data are presented as absolute numbers or percentages. Comparisons between MSCT and invasive venography were performed using the independent samples t test and Pearson’s correlation analysis; comparisons between characteristics before and after implantation were performed using the paired samples t test. Comparisons between categorical variables were performed with Chi-Square testing. A p-value <0.05 was considered significant.
RESULTS

There were 13 (62%) men and 8 (38%) women with a mean age of 67±11 years; all were in New York Heart Association (NYHA) class III despite optimized medical therapy (86% used diuretics, 95% angiotensin-converting enzyme inhibitors, 71% β-blockers, 48% spironolactone). Patients with ischemic (12, 57%) and those with nonischemic cardiomyopathy (9, 43%) were both included; 6 (29%) had a history of percutaneous coronary intervention, and 6 (29%) had a history of coronary artery bypass grafting (combined with mitral valve annuloplasty in 2 patients). MSCT was successfully performed in all included patients. Average heart rate during scanning was 65±14 beats/min, scan time 21±11 seconds, helical pitch 14.3±0.7. On average, 108±11 ml of contrast was used. CRT device and transvenous LV lead implantation were successful in all but 1 patient (absence of suitable veins on venography, and this patient was referred for surgical LV lead implantation), without major complications. All remaining 20 patients received a combined CRT-implantable cardioverter defibrillator device (Contak Renewal 4 CRT-D, Guidant, and Insync Marquis or Sentry CRT-D, Medtronic Inc.). Two types of LV leads were used, Easytrack 4517-90 (Guidant) or Attain OTW bipolar 4194 (Medtronic Inc.). Five patients underwent upgrading of a previously implanted implantable cardioverter defibrillator to a CRT-debrillator device. During implantation, invasive balloon occlusion venography was performed in all 21 patients.

Table 1. Prevalence of the major cardiac veins and number of side branches using multi-slice computed tomography (MSCT) and invasive venography.

<table>
<thead>
<tr>
<th></th>
<th>MSCT</th>
<th>Invasive Venography</th>
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<tbody>
<tr>
<td>Coronary sinus</td>
<td>21/21 (100%)</td>
<td>21/21 (100%)</td>
</tr>
<tr>
<td>Posterior interventricular</td>
<td>21/21 (100%)</td>
<td>18/21 (86%)</td>
</tr>
<tr>
<td>vein</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 side branches</td>
<td>14/21 (67%)</td>
<td>12/18 (66%)</td>
</tr>
<tr>
<td>1 side branch</td>
<td>2/21 (9%)</td>
<td>3/18 (17%)</td>
</tr>
<tr>
<td>2 side branches</td>
<td>4/21 (19%)</td>
<td>3/18 (17%)</td>
</tr>
<tr>
<td>3 side branches</td>
<td>0/21 (0%)</td>
<td>0/18 (0%)</td>
</tr>
<tr>
<td>4 side branches</td>
<td>1/21 (5%)</td>
<td>0/18 (0%)</td>
</tr>
<tr>
<td>Posterior vein of LV</td>
<td>20/21 (95%)</td>
<td>20/21 (95%)</td>
</tr>
<tr>
<td>0 side branches</td>
<td>15/20 (75%)</td>
<td>12/20 (60%)</td>
</tr>
<tr>
<td>1 side branch</td>
<td>2/20 (10%)</td>
<td>1/20 (5%)</td>
</tr>
<tr>
<td>2 side branches</td>
<td>3/20 (15%)</td>
<td>6/20 (30%)</td>
</tr>
<tr>
<td>3 side branches</td>
<td>0/20 (0%)</td>
<td>0/20 (0%)</td>
</tr>
<tr>
<td>4 side branches</td>
<td>0/20 (0%)</td>
<td>1/20 (5%)</td>
</tr>
<tr>
<td>Left marginal vein</td>
<td>12/21 (57%)</td>
<td>13/21 (62%)</td>
</tr>
<tr>
<td>0 side branches</td>
<td>6/12 (50%)</td>
<td>5/13 (38%)</td>
</tr>
<tr>
<td>1 side branch</td>
<td>2/12 (17%)</td>
<td>3/13 (23%)</td>
</tr>
<tr>
<td>2 side branches</td>
<td>3/12 (25%)</td>
<td>4/13 (31%)</td>
</tr>
<tr>
<td>3 side branches</td>
<td>0/12 (0%)</td>
<td>0/13 (0%)</td>
</tr>
<tr>
<td>4 side branches</td>
<td>1/12 (8%)</td>
<td>1/13 (8%)</td>
</tr>
</tbody>
</table>
Identification of the coronary sinus and its major tributaries on MSCT and invasive venography in the entire study population is reported in Table 1. The posterior interventricular vein was not observed with invasive venography in 3 patients (14%), whereas on MSCT this vein was observed in all patients. The left marginal vein was observed in 12 patients (57%) on MSCT and in 13 patients (62%) with invasive venography. The number of visible side branches of the major tributaries is reported in Table 1. Figure 1 illustrates the excellent agreement between MSCT and invasive venography in a patient with heart failure with a history of coronary artery bypass grafting. The diameters of the coronary sinus and tributaries, measured with MSCT and invasive venography are depicted in Figure 2. No significant differences in measured diameters were observed between MSCT and invasive venography, and excellent correlations were observed between noninvasively and invasively measured diameters (Figure 2).

At baseline, all patients had severe LV dilatation with depressed LV function, accompanied by functional mitral regurgitation (Table 2); also, a significant extent of LV dyssynchrony was observed. Immediately after implantation, LV end-diastolic volume remained unchanged, whereas LV endsystolic volume decreased significantly with an improvement in LV ejection fraction and mitral regurgitation. The extent of LV dyssynchrony was significantly reduced after CRT implantation.
with heart failure. A large left marginal vein is identified and used for LV lead implantation.

Figure 4 shows pre-implantation venograms and MSCT images of an 85-year-old patient. Fraction and reduction in LV end-systolic volume were not observed in these patients (Figure 3).

Standard deviation 12 LV segments (ms) 43±8 26±21 0.001

Using a 12-segment LV model with 3-dimensional TSI imaging, the area of latest mechanical activation was lateral in 8 patients (38%), anterolateral in 9 (43%), posterolateral in 2 (9.5%), and inferolateral in 2 (9.5%). From the fluoroscopic images obtained during CRT implantation, the precise LV lead position was determined. If the LV lead was positioned in a cardiac vein draining the area of latest mechanical activation, this was considered a match between LV lead position and area of latest activation. In 12 patients (57%), a match was noted between the area of latest mechanical activation on tri-plane TSI and the final LV lead position. In these patients, a significant decrease in LV dyssynchrony was observed (Figure 3). Moreover, positioning the LV lead in a vein draining the area of latest mechanical activation (match) resulted in an acute decrease in LV end-systolic volume (average reduction of 26 ml or 13.3%) with an increase in LV ejection fraction (average increase of 12%) after CRT implantation. In contrast, LV dyssynchrony persisted in the 8 patients (38%) with a mismatch between the LV lead position and the area of latest mechanical activation, and improvement in LV ejection fraction and reduction in LV end-systolic volume were not observed in these patients (Figure 3). Figure 4 shows pre-implantation venograms and MSCT images of an 85-year-old patient with heart failure. A large left marginal vein is identified and used for LV lead implantation.
This LV lead position matched the area of latest mechanical activation (identified with 3-dimensional TSI), and synchrony was restored acutely after CRT (septal-to-lateral delay 90 ms at baseline, 10 ms after implantation, standard deviation of 12 LV segments 45 ms at baseline, 5 ms after implantation). In addition, a reduction of LV end-systolic volume from 191 to 153 ml was observed with an increase in LV ejection fraction from 13% to 28%.

Figure 3. (A) The favorable effects of positioning the left ventricular lead within the area of latest mechanical activation (match). (B) Absence of these effects in patients showing a mismatch between lead position and area of latest mechanical activation. The upper graphs depict dyssynchrony parameters calculated from tri plane TSI data, specifically, septal-to-lateral delay (SL delay) and standard deviation of time to peak myocardial systolic velocity in 12 LV segments (SD12). The lower graphs depict LV-end systolic volume (LVESV) and LV end-diastolic volume (LVEDV) before and after CRT implantation.
DISCUSSION

Until recently, invasive venography was the only technique enabling clinicians to evaluate the coronary sinus and its major tributaries. In several preliminary studies, 16-slice MSCT was proposed as a valid non-invasive alternative. These findings were recently confirmed in a retrospective analysis of 100 patients using 64 slice MSCT technology. All studies report a significant variability in the cardiac venous system, particularly in patients with a history of myocardial infarction. These results may have important implications for the decision of transvenous or surgical LV lead positioning. In contrast to previous reports on MSCT venography, the present study included exclusively patients with heart failure who were actually scheduled for CRT implantation, allowing for a direct comparison between MSCT venography and invasive venography during CRT implantation. In agreement with previously published series, the left marginal vein was not observed in a large percentage of patients. Moreover, all tributaries of the coronary sinus that were eventually used for LV lead insertion during CRT implantation were visualized on MSCT. Furthermore, no significant differences were observed between invasive venography and 64-slice MSCT venography regarding diameters of the different vessels, in line with a preliminary comparison between 16-slice MSCT and invasive venography.

In selected patients, CRT reduced symptoms, improved exercise capacity, and reduced morbidity and mortality. In these large randomized trials, CRT is successful in approximately 70% of patients. Positioning the LV lead in a vein draining the area of latest mechanical activation may be a valuable strategy to further improve the success rate. Tissue Doppler techniques have proven their efficacy to identify the area of latest mechanical activation. In the present study, tri-plane TSI was used to locate the area of latest mechanical activation. This approach may be particularly useful because it provides a true 3-dimensional representation of the left ventricle with a 3-dimensional dyssynchrony map obtained during a single heartbeat. Moreover, automated dyssynchrony calculations are possible that may potentially reduce observer variability. In 57% of patients, a match between area of latest mechanical activation and final LV lead position was noted, and CRT resulted in acute resynchronization with acute reduction in LV end-systolic volume and improvement in LV ejection fraction. These favourable effects were not observed in patients with a mismatch between area of latest mechanical activation and LV lead position. These observations agree with recent studies highlighting the importance of matching the LV lead position with the site of latest activation. This relation between the response to CRT and the match between area of latest mechanical activation and LV lead position underscores the important role of non invasive imaging to determine LV lead implantation strategy. With tri-plane TSI, the precise area of latest mechanical activation can be derived, whereas MSCT depicts the cardiac venous system on a 3-dimensional LV volume set. Transvenous LV lead implantation is preferred if a suitable tributary of the coronary sinus matches the area of latest mechanical activation.
Venous anatomy and LV dyssynchrony assessment in CRT

Figure 4. Case example of an 85-year-old patient with idiopathic dilated cardiomyopathy, NYHA class III heart failure and wide QRS complex (157 ms, LBBB-configuration). MSCT shows a large left marginal vein with prominent side branches (A, B, C). These findings are confirmed by invasive venography (D, E, F). In the 3-dimensional LV dyssynchrony assessment with TSI (I), the late mechanical activation (yellow) is located in the lateral wall. The LV lead is positioned in the left marginal vein (G, H), resulting in synchronous activation of the LV, represented (green) on TSI, obtained immediately after CRT (J). In addition, a reduction of LV end-systolic volume from 191 to 153 ml was observed, with an increase in LV ejection fraction from 13% to 28%.
the absence of a suitable coronary sinus tributary in the area of latest mechanical activation, a surgical approach may be preferred. In the present study, the LV lead was positioned without taking the LV dyssynchrony information into account. Accordingly, only 57% of patients exhibited a match between LV lead position and area of latest mechanical activation. These patients had substantial benefit from CRT. The remaining 43% of patients, however, had a mismatch between LV lead position and area of latest activation and did not benefit from CRT. Potentially, superior results could have been obtained if the pre-implantation information provided by tri-plane TSI and MSCT had influenced the implantation strategy in these patients. At present, CT venography is still associated with substantial radiation, but further technological development will most likely result in reduction of radiation burden.
REFERENCES


