Image Guided Left Ventricular Lead-Implantation for Cardiac Resynchronization Therapy

Assessment of the Left Phrenic Nerve and Coronary Sinus



E.R. Nieuwenhuis, BSc. 8th of December 2016 Confidential until the 8th of June 2017

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Assessment of the Left Phrenic Nerve and Coronary Sinus

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ABSTRACT

Objective. Visualization and implementation of the left phrenic nerve (LPN) and the coronary sinus ostium in CARTBox3 to support left ventricular lead placement in cardiac resynchronization therapy.

Introduction. Cardiac resynchronization therapy can be used to resynchronize a dyssynchronous ventricle contraction in patients with heart failure. The response rate of the therapy needs to be improved, since 30% of treated patients do not benefit from the therapy. One of the factors that can improve the response rate is optimal left ventricular lead position. CARTBox3 software was developed to determine an optimal lead position and provides image guided placement of the left ventricular lead to the optimal position during cardiac resynchronization therapy. To complete the CARTBox3 functionality, a way to visualize and segment the LPN course and coronary sinus ostium is developed.

Method. A feasibility study of LPN visualization using MRI was performed. Based on the time planning and the availability of CT data it was chosen to develop and validate a method for LPN segmentation using contrast and non-contrast cardiac CTs. The LPN segmentation was implemented into CB3. Also from CT data, the ostium was determined by finding intersection points of segmented right atrium and coronary sinus volumes. Two segmentation methods were tested on contrast and non-contrast cardiac CTs.

Results. Current clinically available MRI technology was proven to be unsuitable to visualize the LPN. The LPN segmentation based on contrast CT data was in accordance to mapping data of patients who underwent epicardial ablation (n=7). The intraobserver variability study shows acceptable limits (<5mm), in 8/9 (89%) subjects and 6/7 (86%) subjects of contrast and non-contrast CTs respectively. In the interobserver variability study it shows 6/9 (67%) subjects and 5/7 (71%) subjects respectively. The LPNFuse software allowed incorporation of the LPN course in CARTBox3. For the segmentation of right atrium and coronary sinus, the fast growing cut edge method was found to be better than the robust statistic segmenter. Though these segmentations were made in scans with non-optimal contrast distribution.

Conclusion. In this study current clinical MRI technology was unsuitable to visualize the LPN. The developed segmentation method in CT is reproducible and had no preference for contrast or non-contrast CT images. Based on the same CTs, a method to define the coronary sinus ostium was developed. The next step is a proof-of-principle study to evaluate the clinical value of the implemented LPN and ostium in CB3 to guide the LV lead implantation during CRT.

TABLE OF ABBREVIATIONS

Abbreviation	Meaning
3D	Three Dimensional
Advise-CRT	Advanced Image Supported Left Ventricular Lead Placement in Cardiac
	Resynchronization Therapy
CB3	CARTBox3
СР	Center Point
CRT	Cardiac Resynchronization Therapy
CS	Coronary Sinus
CSV	Comma Separated Value
СТ	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
DWIBS	Diffusion Weighted Whole-Body Imaging with Background Body Signal Suppression
FGCE	Fast Growing Cut Edge
GIMP	GNU Image Manipulation Program
HF	Heart Failure
IP	Intersection Points
LPCB	Left Pericardiacophrenic Bundle
LPN	Left Phrenic Nerve
LV	Left Ventricle
MRI	Magnetic Resonance Imaging
NRRD	Nearly Raw Raster Data
PN	Phrenic Nerve
RA	Right Atrium
RSS	Robust Statistic Segmenter
STL	STerioLithography

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1 INTRODUCTION

Heart failure (HF) is recognized as a worldwide problem (1) and even in the Netherlands approximately 1% of the population suffers from HF (2). In a healthy heart the ventricles of the heart contract synchronously during the cardiac cycle. However, in some cases of HF and ventricular arrhythmias, the ventricular contraction becomes dyssynchronous. This results in a lower pump function of the heart and a reduced systemic blood supply. Treatment of HF depends on the cause and clinical symptoms.

Cardiac resynchronization therapy (CRT) can restore the ventricular synchronous contraction. And is recommended by the guideline, to treat patients with HF New York Heart Association (NYHA) class III-IV, despite optimal pharmacological treatment; a LVEF of < 35%, and QRS duration of \geq 120ms (3). The majority of patients who benefit of CRT have a left bundle branch block.

A patient who undergoes CRT receives a device with three leads, a right atrial lead, a right ventricular lead and a left ventricular (LV) lead, Figure 1. Via the ostium of the coronary sinus (CS) the LV lead is placed in one of the CS tributaries at the free wall and stimulates the LV myocardium, see Figure 2. The CRT controller senses the intrinsic cardiac activation via the right atrial lead, and stimulates the RV and the LV at specific atrioventricular and interventricular delays. Thereby restoring synchronous contraction.





RAO

Figure 1. Illustration of CRT device in chest. The left ventricular lead is placed in one of the tributaries of the coronary sinus (4).

Figure 2. Right anterior oblique (RAO) of the heart. CS=coronary sinus (5).

Unfortunately, around 30% of the patients that are treated with CRT do not respond to the therapy (6,7). To increase the response rate, many studies are done to find predictors and factors that determine the response rate (6). One of the factors that determines the response rate is the position of the left ventricular lead (8,9). An optimal LV lead position can be found when the following four factors are met(3,10):

- 1. The LV lead is placed in the latest contracting area,
- 2. The LV lead is placed outside infarcted/scar area,
- 3. The LV lead is placed at a position where stimulation does not cause phrenic nerve stimulation,
- 4. The LV lead is placed in a stable position with good electrical function,

Since the function of the phrenic nerve (PN) is the innervation of the diaphragm, a position of the LV lead close to the left PN (LPN) can cause hiccups at the rate of the pacing stimulus, which is intolerable for the patient (11).

Besides the abovementioned factors, venous anatomy is also of importance during CRT. Recognized difficulties in intravenously LV lead placement regarding anatomy are (9):

- Finding and entering the ostium of the coronary sinus, especially for unexperienced physicians. The thebesian valve can (partially) cover the ostium and therefore complicate cannulation, or a prominent sub-eustachian hardens cannulation of the CS.
- There is no suitable vein to place the LV lead in the optimal pacing site.

Recent research has shown that pre- and periprocedural physiological and anatomical information supports the physician in decision making for optimal LV lead placement and also decreases procedure time (7,12,13). The location of the LPN is currently determined by LPN capture and diaphragm motion during the LV lead implantation. This procedure is accurate, but can be time consuming and can cost an extra LV lead in case another coronary vein is chosen as LV lead location. With pre-procedural knowledge of the individual LPN anatomy, estimation on LPN stimulation could be made for each vein. If pre-procedurally no suitable target vein can be found, a surgical epicardial approach for LV lead placement can be considered. Identification of a suitable target vein can save procedure time. In order to optimize the LV lead placement, image guided lead placement is currently being investigated by multiple research groups (14–18). However, the combination of visualization of the late contracting area, scar area, phrenic nerve and anatomy of the coronary veins in one navigation toolbox has not been done before.

CART-Tech (CART-Tech B.V., Utrecht, the Netherlands) has developed a software toolbox for treatment planning and image guided CRT, CARTBox3 (CB3). Currently a study, **Adv**anced Image **S**upported Left Ventricular Lead Placement in **C**ardiac **R**esynchronization Therapy (Advise-CRT) study is performed to investigate the feasibility of CB3. The infarcted area and late activated segment can be visualized with magnetic resonance imaging (MRI). To complete the CB3 functionality, a way to visualize and segment the LPN course needs to be developed.

The use of MRI for LPN visualization is desired, since MRI is already part of the standard workup of the CRT patients. To the best of our knowledge, no literature is published on the visualization of the LPN with MRI *in vivo*. Nevertheless, visualization of other nerves with MRI is described. Herein, possible usability of the sequences 'diffusion weighted whole-body imaging with background body signal suppression' (DWIBS) and Dixon are found. DWIBS could be useful in the physiological part of the LPN, via diffusion of water molecules within the nerve (19). Furthermore, it has advantages of free breathing during scan time and it suppresses fat- and background signal when compared to normal diffusion weighted imaging (20). A study of Börnert *et al.* showed the use of Dixon within whole heart coronary MR angiography (21). Within Dixon an in- and out-of-phase water and fat image is made and visualization of pericardial fat can be done. Herein, the hypothesis is to see flow voids in the pericardial fat e.g. caused by the blood flow in the pericardiacophrenic artery and vein. The left pericardiacophrenic artery and vein accompany the LPN throughout its course in the thoracic cavity. These structures are referred to as the left pericardiacophrenic bundle (LPCB).

In contrast to MRI, there is published about visualization of the right and left PN course using computed tomography (CT)(22–24). Some of these studies used visualization of the pericardiacophrenic artery and vein to describe the LPN course. All studies used contrast and a 64-multidetector CT scanner.

To summarize, CRT is a useful therapy to restore the synchronal contraction of the ventricles. Unfortunately, 30% of the patients do not respond to the therapy. To increase the response rate, an optimal position of the LV lead needs to be determined and visualized. Which can be done using image guided LV lead placement. CB3 includes the factors for optimal LV lead position: late activated area, ischemic area and the LPN. The first two factors are visualized using MRI. LPN is not implemented yet and the question arose if the LPN also could be visualized using MRI. Furthermore, visualization of the coronary sinus ostium is of interest to save time on cannulating the coronary sinus. Altogether, this resulted in the objective of this study:

Visualization and implementation of the left phrenic nerve and the coronary sinus ostium in CARTBox3 to support left ventricular lead placement in cardiac resynchronization therapy.

To obtain the objective, the following question will be answered in this thesis.

Which imaging modality is feasible to visualize the left phrenic nerve? How can the left phrenic nerve course be implemented in CARTBox3 and is the developed method reproducible? And how can the coronary sinus ostium anatomy be implemented into CARTBox3?

2 METHOD

The objective can be divided into two parts: 1) Feasibility of MRI to visualize the LPN and 2) Identification and segmentation of the LPN on CT and implementation of the LPN segmentation into CB3. For visualization of the CS and its first-order tributaries only CT images were used and will be described in the CT section.

2.1 MAGNETIC RESONANCE IMAGING

During the orientation phase a literature study was done, findings concerning anatomy of the LPN were confirmed by anatomical examinations in the mortuary. Furthermore, visualization methods were explored using *in*- and *ex-vivo* material to get an overview of the opportunities according to the objective, see Appendix A.

Phantom studies

With respect to MRI, DWIBS and Dixon sequences were found to be of interest. To test the effect of DWIBS, this sequence was performed on an *in-vivo* pig for visualization of its spinal cord. Thereafter it was tested on a phrenic nerve phantom (a chicken filet combined with a phrenic nerve of a pig), see Figure 3. The effect of DWIBS on a nerve bundle smaller in diameter than the spinal cord could then be seen *ex-vivo*. On the same phrenic nerve phantom Dixon was tested, to compare the effects between Dixon and DWIBS.

Dixon was furthermore tested on a pig heart that was excised including the pericardium and the phrenic nerve, Figure 4. The heart came available after the pig was euthanized after an animal study. To retain the shape of the ventricles during the process in formaldehyde, both ventricles were filled with gauze. Gauze was placed in the ventricles via one incision in the pericardium and one incision in each ventricle. The PN was sutured on the pericardium in order to keep a reference position. After two weeks in formaldehyde the heart was scanned.



Figure 3. Phantom: Chicken filet with on top a phrenic nerve of a pig.



Figure 4. Heart of a pig including pericardium and phrenic nerve. On the left side the fresh heart is shown on the right side the same heart after two weeks in formaldehyde.

Visualization phantom and in-vivo pig

Results of the DWIBS sequence on the phantom and *in-vivo* pig were loaded into RadiAnt DICOM Viewer (2.2.9.10728 (64-bit), Medixant) and visually evaluated. In the scans of the *in-vivo* pig the effect of different *b*-values¹ was tested in visualizing the spinal nerve. And PN was assessed in the phantom, with different *b*-values, T1 and T2 weighted images.

¹ Degree of diffusion weighting

3D reconstruction pig heart

The images of the Dixon sequence were visualized within 3D slicer software (4.5.0-1 r24735) to assess the location of the LPN. The result of the 3D reconstruction was visually evaluated. MR images were loaded and a 3D reconstruction of the fat tissue was made.

2.2 COMPUTED TOMOGRAPHY

A retrospective study was done for visualization and identification of the PN using cardiac CT. Since cardiac CT is not part of the clinical workup of CRT patients yet, cardiac CTs of 9 patients who underwent an endo- or epicardial radiofrequency ablation were used instead. The cardiac CTs were performed according to the University Medical Centre Utrecht, ECG-gated via step-and-shoot on 256-slice CT-scanner (Brilliance iCT, Philips). In seven out of nine patients contrast and non-contrast cardiac CTs were acquired (6/7 epicardial ablation patients and 1/2 endocardial ablation patients). Visualization and segmentation of the right atrium (RA) and the CS including its tributaries, was done using the contrast and non-contrast images of 2/7 of the above mentioned patients.

2.2.1 Left phrenic nerve

Visualization of the left phrenic nerve

The cardiac CTs were loaded into 3D slicer. A 3D visualization of the dataset was made and the image brightness was adapted to visualize the LPN in the 2D slices.

Segmentation of the left phrenic nerve

The LPN was segmented in cardiac CTs that were made with and without the use of contrast. Segmentation was done using 3D slicer. The workflow is shown in Figure B. 1, Appendix B. To reduce time, segmentation of the LPN course was done coarsely in a limited number of axial slices, and does therefore not include the full LPN course. More than 5 markers were placed at positions evenly divided over the length of the LPN course and represent the LPN segmentation. Observers were trained before performing the segmentation.

LPNFuse

To complete the LPN segmentation LPNFuse was developed to perform a linear interpolation on the segmented LPN course. In LPNFuse, original CT data (Digital Imaging and Communications in Medicine, DICOM) and the STL (STereoLithography)-file of the segmented LPN are imported. After interpolation the data can be exported as: 1) a Comma Separated Value File (.csv) including all coordinates of the completed LPN course. Or 2) a new DICOM treatment file where the STL-file and original CT dataset are fused, the complete LPN course is marked in the DICOM treatment file. The DICOM treatment file will be fused with the interventional imaging system during the CRT implantation procedure in the Advise-CRT study.

Verification of the segmentation method

Since a golden standard for LPN segmentation is missing, verification of the LPN location was done by a retrospective comparison with mapping data of patients who underwent an epicardial VT ablation (n=7). During the mapping process of epicardial ablation, the left ventricle is mapped and stimuli of 10-15mA with a pulse duration of 2ms are given to check if there is any LPN capture. Upon LPN capture the 3D position of the mapping catheter is marked and stored in a 3D point set. Screenshots of left lateral and posterior anterior view of both, epicardial mapping and of the DICOM treatment file of a contrast CT, were fused using GIMP 2.8.14 (GNU Image Manipulation Program). Hereby the location of the completed LPN segmentation and the marked LPN capture points could be compared.

Validation of segmentation method

To investigate the reproducibility of the LPN segmentation method an intra- and interobserver variability study of the LPN segmentation was done for contrast and non-contrast CT data. Intraobserver variability was performed by one observer. And segmentation of the LPN was done twice per CT dataset (n=9). For the interobserver variability study three observers segmented the LPN in a contrast cardiac CT (n=9) and in a non-contrast cardiac CT (n=7). The 7 non-contrast cardiac CT datasets were made from the same patients of the contrast cardiac CTs. The three selected observers were a student technical medicine, a biomedical engineer experienced in navigation guided therapy and a thoracic radiologist in training. The order of the patients and the presence or absence of contrast in the intra- and interobserver studies was randomly chosen.

After LPN segmentations were completed with LPNFuse, the variability between observers was determined by calculating the distance between the completed LPN courses. The latter was done for each z-coordinate level in three dimensions and only for the overlapping area between the two compared LPN courses. For anatomical and image acquisition reasons, a distance of <5mm was considered as a comparable observation.

Comparison of LPN segmentation in cardiac CT made with and without contrast In order to define if the same structure was segmented in contrast and non-contrast cardiac CT, a comparison between these datasets was made. To compare the segmentations of the LPN in CT data with and without contrast, it was quantified whether the observers followed the same structure in the contrast scan and the non-contrast scan, 'yes' or 'no'. If the answer was 'yes', it was rated how many structures of the LPCB were identifiable, followed by the position which was marked as LPN. The amount of structures was given by 1, 2 or 3. The position of the segmented structure was classified as anterior, middle or posterior. If no structure of the LPCB was followed no classification was given. In case an observer did not followed the same structure in contrast and non-contrast CT scans, it was rated if another structure of the LPCB was followed (yes or no).

2.2.2 Coronary sinus, right atrium and ostium

Segmentation of coronary sinus and right atrium

The CS and RA were also segmented using 3D Slicer. To investigate the most optimal segmentation method we have compared two segmentation methods: *Robust Statistics Segmenter* (RSS)(25) and *Fast Grow Cut Effect* (FGCE)(26). RSS segmentation is based on an active contour algorithm, while FGCE makes use of a region growing algorithm. Both methods were applied to 2 patients on contrast and non-contrast CTs. Within RSS, the target object is initialized by a label. Seeds of this label are placed in axial, sagittal and coronal planes. Input parameters for CS and RA segmentation are shown in Table 1. The object boundary could then be extracted by evolvement of an active contour. For FGCE it was needed to apply multiple labels for CS and RA segmentation. In total 4 labels (vein for CS, RA, right ventricle and tissue) were marked in axial, sagittal and coronal planes, see Figure 5. In both methods, segmentation volumes or labels of CS and RA were saved as Nearly Raw Raster Data (NRRD)-files.

Tuble 1. Input parameters for coronary sinus and right athum in Kobust statistic segmenter.						
Target object	Coronary sinus	Right atrium				
approximate volume(mL)	4	60				
intensity homogeneity [0-1.0]	0.6	0.4				
boundary smoothness [0-1.0]	0.8	0.6				
output label value	1	2				
maximal running time(min.)	5	5				

Table 1. Input parameters for coronary sinus and right atrium in Robust Statistic Segmenter.



Figure 5. Labels as seeds in axial, sagittal and coronal planes of a non-contrast cardiac CT for fast growing cut edge segmentation. Labels and their colors: vein (coronary sinus) is blue, right atrium is pink, right ventricle is red and tissue (background) is green.

Definition & visualization ostium

The segmented volumes of CS and RA were used to define the ostium using MATLAB (R2015a, The MathWorks, Inc.). First, the boundary edges of the CS and RA volume were determined. Secondly, intersection points of the CS- and RA-boundary edges were obtained to mark the location of the ostium. Finally, the intersection points were projected on a plane and a simplified interpretation of the ostium in a 3D-space was defined by a best fitted circle through the intersection points. The best fitted circle can be processed by the LPNFuse tool, and implemented in CB3, as was done for the LPN. In Appendix C an overview of the steps taken in defining the ostium is represented.

3 RESULTS

3.1 MAGNETIC RESONANCE IMAGING

The results of the MRI studies to visualize the LPN are represented in Appendix D. Within the *in-vivo* pig, Figure D. 1, the pig's heart could be seen in the DWIBS image with a b-value of 0. But the heart is no longer visible in case of a b-value of 600 or 800. The pig's spinal cord is visible in each image. And the ribs are only visible in images made with a b-value of 800.

Regarding the phantom (Figure D. 2), no differences in the DWIBS images were observed for b-values 0 and 800. In both cases fluid and the PN were more enhanced than the chicken filet. Dixon showed a black spot at the location of the PN. Surroundings of the PN and the chicken filet itself have an equal distributed enhancement.

At last, fat segmentation was done on the *ex-vivo* heart, Figure D. 3. Thereby the PN was not individually recognized. Of note: the high resolution used for scanning the *ex-vivo* heart and PN is not applicable in humans.

3.2 COMPUTED TOMOGRAPHY

3.2.1 Left phrenic nerve

Visualization of the left phrenic nerve

In 3D reconstructions 1-3 structures of the LPCB were seen, see Figure 6. In the axial slices of the CT dataset the LPCB was recognized as small enhanced 'dots' Figure 7, of which the course continues along the pericardium.



Figure 6. An overview of a CT dataset loaded in 3D slicer. Top: A 3D reconstruction of a heart. The arrows point at the left pericardiacophrenic bundle (artery, vein and nerve). Bottom: left side an axial view; in the middle a sagittal view; and on the right a coronal view.



Figure 7. Examples of axial slices of a contrast cardiac CT at the left side and a non-contrast cardiac CT at the right side. The three arrows points at three structures of pericardiacophrenic bundle.





D. PA view, ablation mapping E. PA view, segmentation LPN F. Fusion of D & E Figure 8. The verification method of left phrenic nerve (LPN) segmentation with ablation mapping data. The heart is shown in left lateral (A-C) and posterior-anterior view (D-F). Yellow dots in A & D mark the LPN stimulation points during mapping of the left ventricle. The white arrows in B & E points to the segmented LPN course. LL, left lateral; PA, posterior anterior; LPN, left phrenic nerve.

Verification of segmentation method

In 6 out of 7 patients who underwent epicardial ablation, verification of the LPN segmentation with mapping data was done. Of one patient no mapping data was available and was therefore excluded. Figure 8, gives an example of the verification. The two different views are from the same patient. In all 6 patients an agreeable location of LPN segmentation and LPN capture points were found.

LPNFuse

In Figure 9, the interface of LPNFuse and the output of LPNFuse are shown. In Appendix E, observation in interpolation are shown.



Figure 9. Left: Segmented points of the left phrenic nerve (blue dots) and interpolated line (red line) in LPNFuse. Right: The left phrenic nerve (yellow arrow) is added to original CT data and visualized in 3D slicer.

Validation of segmentation method

Intraobserver

For the intraobserver variability study, 9 patients were included. A mean distance with standard deviation was calculated for each patient, see Figure 10. In patient no. 3 and patient no. 6, one of the scans let to an intraobserver variability >5mm.



Figure 10. Intraobserver variability per patient for LPN segmentation in contrast and non-contrast cardiac CTs.

Interobserver

The same patients as used for the intraobserver variability study could be used for the interobserver variability study, see Figure 11 for the results. In patient no. 2, for observer 2-3 in the contrast image, a difference bigger than >5mm was found. In patient no. 3 and 4 all LPN segmentations of different observers let to a difference >5mm. And in patient no. 7, observer 2 has a difference of >5mm with observer 1 & 3 for the contrast image. The accepted variability in contrast and non-contrast CT images was respectively (7/9) 67% and (5/7) 71% and thereby comparable.



Figure 11. Interobserver variability per patient for LPN segmentation in contrast and non-contrast cardiac.

Comparison of LPN segmentation in contrast and non-contrast cardiac CTs

Segmentation of the LPN by observer 1 is in agreement for the contrast and the non-contrast CT. Sometimes a switch between the LPCB structures appeared, and in 1 of 7 patients (patient no. 4) two different structures of the LPCB were segmented. For observer 2, segmentation of LPN was different for contrast CT and non-contrast CT in 3 of 7 patients (patient no. 3, 4 and 7). And at last, observer 3 segmented LPN differently in contrast and non-contrast CT images in 1 of 7 patients (patient no. 4) and in 2 of 7 patients (patient no. 2 and 6) LPN partly was different segmented.

3.2.2 Coronary sinus, right atrium and ostium

Segmentation of coronary sinus and right atrium

On the left side of Figure 12, one can see the segmentation results of a contrast CT using RSS. And on the right side the results of the FGCE are shown. Both are results of a cardiac CT where contrast was used.



Figure 12. Top: results of coronary sinus segmentation with the use of Robust Statistic Segmenter applied on a contrast cardiac CT. Right: segmentation results of 4 labels are shown with the use of Fast Grow Cut Effect. Blue, coronary sinus; pink, right atrium; red, right ventricle and green background tissue. Left: axial view. Right: 3D view.

Definition ostium

In Figure 13, the defined ostium is represented in a translated and rotated state (center point = (0,0), z=0). Different shapes of the outer ostium boundary are derived from the different segmentation algorithms.





Contrast CT, RSS





Contrast CT, FGCE



Non-contrast CT, RSS

Non-contrast CT, FGCE

Figure 13. Coronary sinus ostium contours based on right atrium and coronary sinus segmentation volumes are shown in a translated and rotated form. Ostium was defined for contrast and non-contrast cardiac CT data. On both CT datasets two segmentation methods were applied Robust Statistic Segmenter (RSS) and Fast Grow Cut Edge (FGCE). The datasets are from the same patient. CP: center point, MP: midpoint.

Figure 14 shows the segmented volumes of the RA (red) and CS (blue) and the defined ostium (projected intersection points & simplified interpretation, green & yellow respectively). The RA volumes of the dataset made with contrast seems thinner than the volumes segmented from CT made without contrast. Orientation of the ostium was different in each possible combination of segmentation method and the use of contrast in CT. Furthermore, z-ranges differ in contrast and non-contrast CT.





Contrast CT, RSS

Contrast CT, FGCE



Non-contrast CT, RSS

Non-contrast CT, FGCE

Figure 14. Visualization of the right atrium (red), coronary sinus (blue) and the defined ostium (yellow) for contrast and non-contrast cardiac CT data. On both CT datasets two segmentation methods were applied Robust Statistic Segmenter (RSS) and Fast Grow Cut Edge (FGCE). The datasets are from the same patient.

4 DISCUSSION

As mentioned before, optimal LV lead position is known as a factor which increases the responserate of CRT (8,9,12). CB3 software was developed to support the physician in optimal LV lead placement using image guidance. The CB3 software uses MRI images to determine the late contracting areas and the scar area, and since MRI is part of the standard workup of a patient for CRT it was preferred that MRI was also used to visualize the LPN and the CS ostium. Results on the feasibility of MRI and the developed method for LPN segmentation and CS ostium definition will be discussed in this section.

4.1 FEASIBILITY OF MRI IN VISUALIZATION OF LEFT PHRENIC NERVE

Ideas for visualization of LPN, showed in Appendix A, were mostly based on the anatomical and physiological characteristics of the LPN and surroundings tissues. Finally, DWIBS and Dixon sequences were considered most useful for imaging of the LPN.

The spinal cord was clearly visible in the DWIBS images of the *in-vivo* pig. Though it should be considered that the spinal cord is bigger in diameter than the phrenic nerve. Therefore, the results of the phantom are more eligible than the *in-vivo* pig. A higher b-value should represent a stronger diffusion effect. However, this is not observed in the phantom. A possible explanation for no difference between b-value of 0 and 800 in the DWIBS sequence could be caused by the fact that the created phantom is *ex-vivo*. So, the nerve does not diffuse water molecules as it does *in-vivo*. Nevertheless, the PN, pericardium and fluid can be distinguished from the chicken filet. This could be explained by the fact that water molecules still are available. Regarding the use of diffusion imaging for visualization of the PN, one should acknowledge that the PN is a thin structure and moves a little *in-vivo*, due to beating of the heart and movement of the diaphragm. It is therefore uncertain whether diffusion through the LPN actually can be detected.

Dixon makes use of an T1 and T2 weighted and an in- and out-of-phase image. The out-of-phase image of the phantom is as expected. The PN does contain myelin on the outside, which in its turn contains fat. Therefore, the black hole in the phantom should represent the nerve fibers and is enclosed by myelin. From the tested sequences on the phantom, we found Dixon to be most useful. Therefore, it was chosen to explore the PN visualization by Dixon on an *ex-vivo* pig heart. It thereby was possible to segment the fat part as a volume and add it to a 3D reconstruction of the heart. Herein the location of the PN was recognized. However, at some overlapping areas with epicardial fat it was not possible to distinguish the PN. For this last experiment we scanned with high resolutions, since the LPN has a thickness of 1-2mm. To retrieve enough signal for a high resolution, one should increase scanning time. Nevertheless, *in-vivo* movement of the LPN due to heart beating and movement of the diaphragm should be considered. This makes it impossible to scan for needed time to retrieve a proper resolution and it will therefore not be applicable in human.

4.2 THE USE OF CT IN LEFT PHRENIC NERVE AND OSTIUM VISUALIZATION

CT is not part of the standard care in CRT device implantation. Therefore, research and development of the LPN and ostium was done using the CT data of patients who underwent endo- or epicardial ablation. Some of these patients already had a device and artefacts were seen as a result of the device leads. Patients which will be included for the Advise-CRT study do not have a device yet. In case artefacts of device leads led to a wrong segmentation of LPN, this will not be of influence during Advise-CRT study. The study included a small number of study objects, thus statistics could not be applied. Furthermore, it was not possible during this study to verify LPN segmentation with LPN stimulation during CRT and to check whether ostium visualization made cannulation of the coronary sinus more easy, since approval by the medical ethical committee for the Advise-CRT was retrieved last June.

4.2.1 Left phrenic nerve

During the 3D reconstruction process in 3D Slicer, it was mentioned that brightness setting does play role in LPN visualization. Since, the LPN is such a small structure a wrong brightness level could make the LPN invisible. Unfortunately, it was not possible to set the brightness on a fixed level, and for each 3D reconstruction the correct brightness level needs to be found. Expertise on the anatomy of the LPN course is therefore of extra importance, otherwise the LPN was missed on 3D reconstruction. The three possible LPN courses at the free LV wall described by Sánchez-Quintana *et al.*, could help in the orientation of LPN location (27). In addition, experience in observing axial slices of CT data might be of influence in LPN segmentation. Therefore, the 3D reconstruction could therefore be of help in less experienced observers.

The interpolation of the segmented LPN in LPNFuse is another factor which could influence the observer variability outcome. In situations of interpolation were too few points were segmented or in case an outlier was made could lead to differences between observers, Figure E. 1 B&C in Appendix E. The effect of interpolation on interobserver variability will probably depend on the amount of marked points on the LPN course.

For the intraobserver variability good results were found. In 8/9 and 6/7 in contrast and non-contrast CT datasets respectively the observed difference was <5mm (Figure 10). By a randomly picked order of patients and contrast and non-contrast CT datasets, the chance on recognition of the LPN course by the observer based in anatomical references was aimed to minimize. Also a couple of weeks passed before the second segmentation was done in each dataset. To conclude, the segmentation method can be considered as a reproducible method which is independent on the use of contrast.

The results of the interobserver variability study (Figure 11) showed a mean distance >5mm between all observers in patients no. 3 and 4, for the contrast and non-contrast CT. In patient no. 7, a mean distance >5mm was seen for LPN segmentation of observer 2 compared to the other two observers. Leading to an accepted variation in LPN segmentation in 6/9 (67%) and 5/7 (71%) cases of respectively the contrast and non-contrast cardiac CTs. Assuming an accepted variation equals the identification of the LPN, our results are somewhat lower than was found in literature where 75-85% of the LPN were identified (24,28). The studies both used a 64-slice CT scanner, had a bigger study population and only used contrast CT. Matsumoto *et al.* (28) found that the LPN was not reliably detected in more likely female and older subjects. Moreover, they did not found a significant difference in body mass index and heart rate between the groups where the LPN could be, and could not be segmented. On the other hand, Yamashita *et al.* did found that older subjects and that presence of epicardial fat over the LV free wall were more likely to detect the LPN (29). We compared subject factors as age, gender, body mass index, body surface area and the presence of device leads, but did not find discriminatory criteria values for accepted (<5mm difference) and non-accepted (>5mm difference) outcomes.

Above mentioned subject factors could not explain the difference >5mm in this small study population for the patients no. 3, 4 and 7. Nevertheless, it was seen that observer 2 followed for patient no. 3,4, and 7 in contrast and non-contrast CT data different structures that sometimes were outside the LPCB. Which can explain differences, between observer 2 and the other two observers. Following structures outside the LPCB when observer 1 and 3 have a low variability (<5mm), makes

experience in observing anatomical structures in CT data, likely to be of influence. Another point which can explain a higher variability, is when another structure of the LPCB was followed, this resulted already in a difference around 4mm. This was seen between observers 1 and 3 in patient no. 3. Switching between LPCB structures was also seen and resulted in differences between the LPN segmentation.

To prevent switching between structures in the LPCB it would be better to segment all structures which are visible in the LPCB. By only segmenting one structure, switching between structures can take place and therefore lead to differences in observer variability. Besides, it is not known which of the three structures is the LPN. Segmentation of all structures is not only expected to reduce the interobserver variability, but it might also give a better presentation of possible LPN locations and therefore indication for LV lead placement. On the other hand, if only one structure is enough to give an impression on the phrenic nerve location, this is less time consuming than segmenting 2 or 3 structures.

During the third and last phase of the Advise-CRT study different pacing levels will be tested for LPN stimulation. With the data of pacing levels on LPN stimulation a relation between the segmented LPN course and pacing stimuli could be found. And will give more insight in which of the structures is the LPN and if one structure is enough for planning.

Intra- and interobserver variability is only calculated on the overlapping z-range of the segmented LPN courses. The segmented LPN course outside the z-range could therefore not be evaluated. Other studies have investigated the location of most LV leads, and in which area PN stimulation appears most. The MADIT-CRT study showed that LV leads placed apically were unfavorable for CRT (30). LPN segmentation in the apical area is therefore of inferior interest. They also showed that LV lead was mostly placed along the lateral wall (59%) compared to posterior (22%) and anterior (19%) wall. In addition, a pooled study of Biffi *et al.* showed that PN stimulation appears mostly when LV lead is placed in the mid lateral, mid posterior and apical area of the heart (31). Whereas mid lateral and mid posterior includes most LV lead placements, which makes the lateral and posterior area of superior interest for LPN visualization.

Identification of the LPN is expected to provide the most clinical benefit when it is visualized before the procedure starts. Than the physician can plan the procedure and choose the LV lead based on the imaging information. In the current clinical practice sometimes LPN capture is evoked in all positions. It must be investigated whether these situations are caused by the presence of thin side branch of the LPN, which courses to the ventral side of the pericardium. The side branch is smaller than the LPN itself and might therefore not be detectable on CT. Despite this, the main course of the LPN can be visualized and will most likely be supportive to choose a target vein.

4.2.2 Coronary sinus, right atrium and ostium

Homogeneity can explain the differences seen in the sizes of the RA and CS volumes determined by the RSS and FGCE based segmentations. Especially in case of the RSS method homogeneity can be the restricted factor for volume segmentation. The contrast images were made for other purposes, namely, visualization of the pulmonary veins. Therefore, inhomogeneity of contrast was found in the RA and CS, which led to a smaller volume in the contrast CT images compared to the non-contrast CT images. The parameter which restricted the growth in non-contrast images is the approximate volume, since areas are homogeneous and less contrast between structures was seen. However, this is also not optimal since it could lead to overestimation of the real target area. By using a scan protocol for visualization of the RA and CS, a contrast CT is expected to give better segmentation results of the RA and CS than the non-contrast CT when RSS is chosen as segmentation method.

Homogeneity played an inferior role in the use of FGCE, since this method based on region growing and will stop the seed will stop with growing when it reaches another seeds region. This lead to more equal volumes for RA in contrast and non-contrast CT images. And is less contrast dependent. Though the boundary edge is less smoothed than the RSS method.

Despite the fact that segmentation methods were only tested on two patients for contrast and noncontrast cardiac CTs, FGCE has the preference above RSS. Preference was mainly based on less dependence of homogeneity in the image. However, when contrast images are optimized for RA and CS visualization RSS should be reconsidered. The use of contrast images in both methods have the benefit to easily distinguish cardiac veins from cardiac arteries.

Different orientation of the ostium is related to the intersection points. Which is related to the segmentation of the RA and CS ostium. For now, it is not possible to see which of the orientations is correct and feedback obtained from the Advise-CRT study is needed, before improvements can be made on LPN and ostium visualization.

5 CONCLUSION

In this thesis research and was done on a method for visualizing and identifying the LPN and the CS ostium in order to improve the image guided LV lead placement in CRT that is enabled by the CB3 software. It can be concluded that clinically available MRI techniques were not feasible for LPN visualization, though promising results were observed in CT visualization and segmentation of the LPN. CT was therefore chosen as most suitable imaging modality in the upcoming Advise-CRT study.

A LPN segmentation was developed using CT-data made by a 256-slice CT scanner. The completion of segmented LPN courses was comparable to the mapping data of patients who underwent an epicardial ablation. A final comparison between a completed LPN course and the capture locations of the LPN, will be examined during phase 3 of the Advise-CRT study. Regarding the reproducibility of the segmentation method, acceptable intraobserver variability was found in contrast CTs (89%) and non-contrast CTs (86%). For the interobserver variability study these numbers were 67% and 71%, respectively. Based on these results we decided that the developed method for LPN segmentation is reproducible enough to be used in the Advise-CRT study. The outcomes for LPN segmentation in contrast CT images were comparable and outcomes for contrast CT were in accordance to other studies.

The CS ostium was defined by a best fitted circle, based on the intersection points of the segmented CS and RA volumes. Segmentation of the CS and RA was tested on contrast and non-contrast images with two methods, RSS & FGCE. Herein FGCE showed most promising results based on available CT datasets.

The Advise-CRT study will show the value of LPN and ostium visualization in image guided LV lead placement during CRT.

6 RECOMMENDATIONS & FUTURE PERSPECTIVES

Regarding the visualization of LPN using MRI, research is still ongoing. When it does become possible to visualize the LPN, it is most likely that the method used in this study could also be applied to the MRI data too.

Development of in house software for segmentation, makes the use of 3D slicer redundant. 3D slicer is universal applicable software, though it is not very user friendly. Moreover, by reducing the amount of different software, less mistakes in exportation or loss of data is expected.

Improvements could be made in the way interpolation in the LPNFuse tool was done. It would be better if interpolation was not only based on the segmented LPN points, but also includes a prediction model. The prediction model should be based on the trajectory of the LPN course, since the course has a smooth gradient and acute turns in the course are therefore not expected. If interpolation is based on a predictor-estimation model, mistakes in LPN segmentation or when too few points were marked could be of less influence or resolved.

Visual comparison of contrast and non-contrast images was performed. However, it would be better to register both datasets, to calculate differences between segmentation in both datasets. In this way distance is measured between segmented structures in the different type of datasets instead of observed.

Pacing stimuli which lead to LPN stimulation during CRT LV lead implementation should be saved. So, a relation in distance between the LPN capture points and the LPN position can be found. Factors as for example pericardial fat could be taken into account to check their influence on the LPN stimulation. Findings hereof can be of help in determining the response rate of subjects to CRT. In case the pacing findings confirm a correct segmentation of the LPN course, variability in the course could be studied further. The question "In which part of the LPN course shows the most variation?" arises. The implemented LPN model in CB3 can then be complemented with new findings and give a better support to CRT LV lead implementation.

In order to improve the ostium visualization, it is needed to check if the circle shape gives a proper presentation of ostium. It might be the case that the ostium is better visualized as an ellipse or another shape. Furthermore, evaluation on which segmentation method performs best for ostium visualization is recommended. In the model presented in this study the thebesian valve was not included. If ostium visualization proves to be beneficial, one could think on how to implement the thebesian valve.

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APPENDIX A – IDEAS ON MR SEQUENCE, LEFT PHRENIC NERVE VISUALIZATION

The first exploration on phrenic nerve visualization was to check the usability of MR. So an overview of considerations which should be taken into account was created, Figure A. 1.



Figure A. 1. Ideas and aspects to take into consideration while visualizing the course of the left phrenic nerve.

Anatomical features of the LPN

- The phrenic nerve rises from C3-C5. The LPN reaches the heart at the left atrial appendage and descends in between the pericardium and parietal pleura, on lateral side of the ventricle, to the left hemi diaphragm.
- The phrenic nerve is accompanied by the pericardiacophrenic artery and –vein when it courses along the left ventricle.
- The LPN is myelinated.
- The LPN has a diameter of 1-2mm.

Physiologic features of the LPN

- Diffusion of water-molecules in direction of the nerve
- Motoric- and sensory nerve fibres

Visualisation

- To visualise the course of the LPN, one can visualise/ *enhance* the *nerve* or structures which are related to its course (*background*) or *suppress* this background.
- Use of protocols for other nerves to visualise the phrenic nerve.
- The LPCB, includes the LPN and the pericardiacophrenic artery and –vein. If the nerve itself could not be visualised maybe the artery or vein is an option for LPN course visualisation.
- Since the phrenic nerve is surrounded by pericardial fat and the before mentioned artery and vein, suppression of these structures should outline the phrenic nerve.
- Another idea is to enhance fat. Pericardial fat and fat from myelin will be enhanced and 'holes' will be seen. These 'holes' are "flow-voids" and refers to the low signal in arteries and veins, due to the flow of blood (32). Identification of the pericardiacophrenic artery and –vein may lead to the identification of the course of the LPN. A possible option to identify these artery and vein is to create a 3D visualisation by segmentation of all these flow voids with an 'active contour'.

Tracer binding

- To nerve or pericardacophrenic artery

Artefacts

- Air artefacts. Since the phrenic nerve lays in between the parietal pleura and the pericardium, air artefacts can
 make it difficult to visualise the LPN course with MR imaging.
- Motion artefacts
 - Pulsation of pericardiacophrenic artery
 - o Breathing
 - Beating of the heart. Small movement of the pericard during the heartbeat is expected, however this might be too much to enable MR imaging of the course of the LPN.

APPENDIX B - WORKFLOW SEGMENTATION LEFT PHRENIC NERVE





Import

Cardiac CT data (DICOM format) is loaded into the 3D slicer an axial, sagittal and coronal view are shown.

3D reconstruction heart

Within 3D slicer a reconstruction of the heart is made. Using the preset 'cardiac-ct' and a manual change of the brightness, the 3D reconstruction is optimized and the LPN can be seen (Figure 6). With the use of this 3D reconstruction one can orient on the location of the LPN course in the 3D reconstruction and on the axial slices.

Segmentation

In the axial slices of the cardiac CT the LPCB can be recognized by one, two or three brighter spots in between the pericardium and pleura (Figure 7). In case one structure is seen, that structure is followed and marked as phrenic nerve. In case 2 structures are seen, the most posterior structure was marked as LPN. When three structures are present, the middle structure is segmented. Segmentation is done by marking the LPN with a marker (of 2-3 pixels in diameter) in more than 5 axial slices.

Create LPN model

If one passed the axial slices and the course of the LPN is marked at several points, a model of these points is created.

Confirm model

The LPN model is applied to the 3D reconstruction of the heart. If the LPN model and beforehand thought LPN course on 3D reconstruction do agree, one went to the export step. If not, it is possible to make adjustments to the LPN model until it is found to agree to the 3D reconstruction.

Export

The LPN model is exported as VTK- and STL-file.



Figure C. 1. Workflow defining and visualizing the ostium, CS and RA within MATLAB. CS: Coronary sinus, RA: right atrium, IP: intersection points, IPt: translated IP, IPt_rot: translated and rotated IP, IPt_rot_p: projection of the translated & rotated IP, IPt_p: translated projection IP, IP_p: projected IP.

Import

Coronary sinus (CS) and right atrium (RA) volumes (.nrrd), created in 3D slicer, are loaded into MATLAB.

Define ostium

Edges are determined of the CS and RA volumes. Intersection points (IP) of these edges form a first definition of the CS ostium. The center point of the IP is calculated.

Translation

All IP are translated by the x-, y- and z-coordinate of the calculated center point (CP).

Determine rotation matrix

The rotation matrix is calculated from the translated IP. A normal vector (**N**) is determined from the translated IP. With N and CP, a d-factor is calculated, needed for plane description.

Define plane

A plane is defined according to the formula: a * x + b * y + c * z + d = 0. In this formula x, y and z, represents coordinates and a, b and c corresponding factors of **N**. With minimum and maximum xand z- value of IP, a 2D plane is defined. By rewriting the formula for plane description, y-coordinates can be found for corresponding x- and z-coordinates, and the 2D plane becomes a 3D plane.

$$y = \frac{a * x + c * z + d}{-b} = \frac{N(1) * x + N(3) * z + d}{-N(2)}$$

Rotation

Rotation of the translated IP is by multiplication of the translated IP with the rotation matrix.

Define positive and negative part IPt_rot

Before projection of the IP on the defined plane is possible, definition of a positive and negative part

is needed. After translation and rotation each point with a z-coordinate <0 is stored in the negative part. And if z-coordinate ≥ 0 it was stored as positive part.

Projection on XY-plane

The projection (x_0', y_0', z_0') of point (x_0, y_0, z_0) is calculated by the following formulas depending on positive or negative part of the rotated points:

Negative part IPt_rot		
$x_0' = x_0 + ta$		
$y_0' = y_0 + tb$		
$z_0' = z_0 + tc$		

were parameter *t* is calculated by:

$$t = \frac{N \cdot v}{N^2}$$

With **N** as normal vector in this case [0,0,1] since points are already rotated, and **v** as displacement vector of a translated and rotated intersection point to a point on the plane, the center point.

Reorder IPt_rot_p

Order the translated, rotated and projected IP at appearance of degrees within a circle (360°). Here steps of 5° were chosen. After ordering the IPt_rot_p in steps of 5°, the point with biggest distance to the origin (0,0,0) in each step was kept in the reordered vector. By doing this, an outer boundary can be drawn between the points. The boundary forms the CS ostium in rotated and translated form. Points used for defining the outer boundary were also used to define a best fitted circle for the boundary points, which represents a simplified ostium definition.

Inverse rotation

Inverse rotation on the points was applied to put them in original orientation.

Inverse translation

After inverse rotation, the points also underwent an inverse translation to place them in original position.

Check visualization

The inverse rotated and inverse translated projection points should lay on the plane defined before.

Visualize ostium

The ostium is visualized in the 3D space together with the RA and CS volume.

APPENDIX D - MRI RESULTS

DWIBS, in-vivo pig



Figure D. 1. Magnetic resonance images of an in-vivo pig made with the DWIBS sequence and different b-values. On the left side the b-value is 800, in the middle 600 and on the right the b-value is 0

Different sequences on phantom





DWIBS, b=0

STIR longTE

T2W TS

Figure D. 2. At the top the phantom is shown. The black horizontal line represents the slice which is seen in the lower 6 images. And the blue arrow represents the scan direction. The lower 6 images show different sequences at the same slice

3D reconstruction pig heart



Figure D. 3. On the left side the posterior part of the pig heart is shown. The black arrows point to the phrenic nerve. At the right side, 3D visualization of the fat-tissue is visualized on the 3D reconstruction of the heart.

APPENDIX E - OPTIONS FOR INTERPOLATION

It was seen in LPNFuse that interpolation can lead to the following three situations:

- 1. Enough points were marked to interpolate the LPN course, Figure E. 1 A.
- 2. Too few points were marked, interpolation makes a blunt shape, Figure E. 1 B.
- 3. An outlier was made, interpolation includes the outlier in LPN course, Figure E. 1 C.



Figure E. 1 Different options as a result of interpolation of marked points on left phrenic nerve course. The blue dots represent the marked points. The red line represents the interpolation as it occurs now. The blue line represents the expected LPN course