An image fusion tool for echo-guided left ventricular lead placement in cardiac resynchronization therapy: performance and workflow integration analysis

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Abstract

Background: The response rate to cardiac resynchronization therapy (CRT) may be improved if echocardiographic-derived parameters are used to guide the left ventricular (LV) lead deployment. Tools to visually integrate deformation imaging and fluoroscopy to take advantage of the combined information are lacking.

Methods: An image fusion tool for echo-guided LV lead placement in CRT was developed. A personalized average 3D cardiac model aided visualization of patient-specific LV function in fluoroscopy. A set of coronary venography derived landmarks facilitated registration of the 3D model with fluoroscopy into a single multimodality image. The fusion was both performed and analyzed retrospectively in 30 cases. Baseline time-to-peak values from echocardiography speckle-tracking radial strain traces were color-coded onto the fused LV. LV segments with suspected scar tissue were excluded by cardiac magnetic resonance imaging. The postoperative augmented image was used to investigate: (1) registration accuracy and (2) agreement between LV pacing lead location, echo-defined target segments, and CRT response.

Results: Registration time (264 ± 25 s) and accuracy (4.3 ± 2.3 mm) were found clinically acceptable. A good agreement between pacing location and echo-suggested segments was found in 20 (out of 21) CRT responders. Perioperative integration of the proposed workflow was successfully tested in 2 patients. No additional radiation, compared to the existing workflow, was required.

Conclusions: The fusion tool facilitates understanding of the spatial relationship between the coronary veins and the LV function and may help targeted LV lead delivery.

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Keywords: cardiac resynchronization therapy, echocardiography, fluoroscopy, image fusion, image-guided intervention

Introduction

Cardiac resynchronization therapy (CRT) is an excellent treatment to improve cardiac function and quality of life for many patients with systolic heart failure (HF) and QRS prolongation [1]. However, studies [2] have shown that a significant proportion of patients (~30%) do not respond to CRT. The current guidelines [3] for biventricular pacing suggest that the left ventricular (LV) lead is positioned at the lateral or posterolateral branch of the coronary sinus [4]. A more individualized approach, where electrical and mechanical activation patterns could determine optimal LV lead placement, was investigated elsewhere [5], [6], [7], [8]. Several other authors reported that that resynchronization may be improved if the LV lead is placed at the site of latest mechanical activation and away from myocardial scar [9], [10], [11], [12], [13].

CRT implantation is performed under X-ray guidance which provides an excellent visualization of catheters and pacing leads but lacks detailed information on cardiac function and structure. Studies [8], [12], [14], [15], [16], [17], [18], [19], [20] have demonstrated that multimodality image fusion could be used to overcome these limitations. However, they rely on techniques and imaging modalities which are not part of the clinical routine for CRT candidates.

In contrast, we propose a more pragmatic approach using echocardiography and X-ray. Measurement of myocardial deformation, by echocardiography, gives information about sites with delayed contraction and regions of suspected tissue damage. A novel tool, which combines preoperative echocardiographic strain imaging, a 3D model of cardiac geometry and retrograde coronary sinus (CS) venography into a single multimodality image was developed and described in this paper. The proposed methods can be used even in the absence of patient-specific cardiac geometry. The current study addresses important topics not covered by our previous work [21]: the implications of integrating the guidance tool in an implantation lab, registration accuracy, interobserver variability, and concordance between implanted LV lead position (deployed using conventional approach) and echo-defined segment position.

Methods

[Study population](#)

In this paper, we analyzed CRT procedures from a recent single-center interventional study conducted at the Oslo University Hospital [22]. This earlier study included 30 heart failure candidates (age = 64 ± 9 years, males = 78%) eligible for CRT implantation with reduced ejection fraction (28 ± 6 %), wide QRS complex (172 ± 14 ms), New York Heart Association functional class II (40%) or III (60%) and optimal medical therapy. Patients with recent myocardial infarction, atrial fibrillation, severe aortic stenosis or severe renal failure were excluded from the study [22]. Coronary artery disease was found in 46% of the cases. All patients except one had left bundle branch block (LBBB) according to the Strauss criteria [23]. All patients gave written informed consent. The study protocol was registered at www.clinicaltrials.gov (identifier NCT01996397) and complied with the Declaration of Helsinki.

[Study design](#)

The image fusion tool was a non-commercial prototype that has not been cleared for clinical use. Therefore, the present study was designed to verify the tool's performance by investigating registration and application accuracy postoperatively (without using the fusion tool to guide implantation). Verification of performance was done by analyzing data from 30 CRT implantations retrospectively. The registration time and registration accuracy were measured and any differences between the anatomical approach that was originally used for placing the LV lead and the echo-defined target location suggested by the fusion tool were recorded. The corresponding steps and their relationship with the proposed workflow (**Figure 1(a)**) are illustrated in **Figure 1(b)**.

[Implantation](#)

The CRT implantation was performed with access from the subclavian vein under local anesthesia and sedation with midazolam and morphine. The atrial lead was placed in the right atrial appendage. The right ventricular (RV) lead was placed in an apical position. Final LV lead position was determined by the implantation team using the conventional approach (targeting the LV posterolateral or lateral wall) [3],

[4]. The proposed fusion tool was integrated into an implantation lab equipped with a biplane Artis zeego (Siemens Healthcare, Erlangen, Germany) C-arm system. Verification of image fusion performance was investigated after implantation was completed (the tool was not used for actual guidance). Standard DICOM tags (embedded into fluoroscopy images) were used to assess the projection geometry of the C-arm imaging system, implement the 3D-2D registration procedure and render the augmented fluoroscopic images.

Imaging

Echocardiography was performed the day before implantation (step № 1, **Figure 1**) using a GE Vivid E9 (Horten, Norway) system and a transthoracic 2D echo probe (GE M5Sc-D, Horten, Norway). Off-line speckle tracking radial strain analysis was conducted using the GE EchoPAC BT13 (Horten, Norway) software package. LV regional function was estimated in accordance with the 17-Segment American Heart Association (AHA) model [24]. The apical segments (i.e. segments 13-17) and the septal segments (i.e. segments 2, 3, 8 and 9) were not considered as possible targets for lead placement [4], [25], and therefore, were not included in the model. Following the procedure outlined by the STARTER [11] trial, strain curves were analyzed for the remaining 8 free wall segments imaged using short-axis views at mitral valve and papillary muscle level. A single expert cardiologist, blinded for the final lead positions and clinical outcomes, retrospectively analyzed baseline strain curves and determined the segment with latest time-to-peak radial strain as the echo-defined target for LV lead implantation in each patient. The latest time-to-peak strain was estimated as maximal strain and not maximal systolic strain, as outlined in [11], [13]. Multiple targets were reported when more than one segment was identified with equivalent latest time-to-peak values. Segments bordering the echo-defined targets segments were defined as 'adjacent'. The remaining segments were defined as 'remote'.

In 19 (out of 30) patients with normal renal function, late gadolinium enhancement (LGE) Cardiac Magnetic Resonance (CMR) imaging was acquired preoperatively (step № 4, **Figure 1**) according to a standard acquisition protocol [26] on any of three MRI scanners: 3.0T Skyra, 1.5T Avanto or 1.5T Aera

(Siemens, Erlangen, Germany) using phased array body coil 10-20 min after intravenous injection of 0.2 mmol/kg of gadoterat meglumine (Guerbet, Villepinte, France). Three long axes and a complete set of short axis images of 7 mm thickness were made with a 2D segmented inversion recovery steady state free precession sequence. Short axis LGE images were evaluated for scar localization by a single, expert radiologist, blinded from the final lead positions and clinical outcomes. Volumes were aligned to the 17-Segment Model without including the apical cap. Scar borders were identified and contours were manually drawn at a PACS workstation (Sectra Medical Systems AB, Linköping, Sweden). Maximum segmental transmural scar was evaluated manually after scar delineation and characterized on a 5-point quartile scale (0: no infarct, 4: 76-100% wall thickness affection). These findings were used only to exclude scar segments with transmural scar > 25% from being considered as potential targets in our analysis.

Both the echo-derived and the LGE CMR findings were utilized only in the postoperative analysis and not to guide actual implantations.

Patient follow-up

In line with the protocol described by [11], reverse remodeling was assessed no earlier than 6 months post-implantation. The time to follow-up distribution (rounded at an integer number of months) was: 15 patients at 6, 5 patients at 7, 5 patients at 8, 2 patients at 9, 1 patient at 11 and 1 patient at 12 months. Follow-up echocardiography examinations (performed in the outpatient clinic) were used to determine the change in LV volumes and change in left-ventricular ejection fraction (LVEF). Response to CRT was predefined as > 15% relative reduction in left ventricular end-systolic volume (LVESV) [13]. Volumes were determined using the 2D Auto EF quantification tool in EchoPAC.

Cardiac anatomical model and coronary venous landmarks

The proposed fusion technique utilizes 3D cardiac geometry to (1) implement registration (step № 6, **Figure 1**) and (2) visualize patient specific LV regional function in augmented images (steps № 7 and № 8, **Figure 1**). A 3D cardiac model, based on an average model and individualized to each patient, was

used. This is described in more detail in an earlier study [21]. In this previous study, two mean anatomical models (each containing LV epi-, LV endo- and RV endocardial surfaces) were constructed from a database of 33 HF patients. The average models differ in the LV sphericity index (SI) value ($SI_{LO}=0.49$ and $SI_{HI}=0.81$) to account for the shape variability observed in the database. Prior to fusion, in the current study, the mean model was personalized (steps № 1 and № 2, **Figure 1**) to fit echocardiographic measurements for the test subject: (1) selected to match the patient's LV SI and (2) scaled to match the patient's LV LAX length.

Furthermore, in the current study, the average LV epicardial surface model was augmented with markers identifying average locations for the CS ostium (**CS_{model}**), the middle cardiac vein bifurcation (**MCV_{model}**) and the anterior interventricular vein bifurcation (**AIV_{model}**) [27]. The purpose of the markers was to provide additional anatomical cues and facilitate registration of the cardiac model with the images of the coronary venography. As the dataset in the current study did not provide images suitable for coronary venous segmentation, the average landmarks were computed from a set of 15 HF patients from the study from Auricchio et al. [28]. The locations of these landmarks (expressed as angles with regards to the LV bullseye plot) were aligned in a common frame of reference, combined and averaged (**Figure 2(a)**). The landmarks were embedded onto the average 3D LV surface using the approach described earlier [21], [29].

Figure 3 illustrates an example of a 2D X-ray image fused with the augmented LV model. Three items were mapped onto the epicardial surface: the 17-Segment Model (AHA) layout [24], the locations of the average coronary venous landmarks (**CS_{model}** – red line, **MCV_{model}** – blue line and **AIV_{model}** – cyan line) and marker depicting the course of the atrioventricular plane (**AV_{plane}** – green line). The septal- and the anterolateral wall of the fused LV model (seen from X-ray detector point-of-view) are shown in

Figure 3(a) and

Figure 3(b) respectively.

Figure 3(c) illustrates the LV posterior wall (seen from inside the LV) in RAO projection. Similarly,

Figure 3(d) illustrates LV base (seen from inside the LV) in LAO projection. The AV_{plane} marker was visible when the LV base or LV posterior wall were viewed from inside the LV.

3D-2D registration

Intraprocedural occlusion contrast venography of the coronary sinus was acquired (step № 5, **Figure 1**) in two different projections (RAO and LAO) and a set of patient-specific coronary venous anatomical landmarks ($CS_{venogram}$, $MCV_{venogram}$, $AIV_{venogram}$) was selected (

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190 **Figure 4(a)**). The 3D coordinates of the selected landmarks were automatically computed.

191 Manual registration of the 3D model was performed by first translating the model to align its contour with

192 the patient's outer border in the acquired images. The registration was refined by rotating the model to

193 match its base with the patient's coronary sinus in the RAO projection (

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196 **Figure 4(b)).** Further refinement was achieved by rotating the model to align its basal ring with the

197 patient's coronary sinus ring in the LAO projection (

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200 **Figure 4(c)**). The model was then rotated around its LV long-axis to line-up the model's coronary venous

201 landmarks (**CS_{model}**, **MCV_{model}**, **AIV_{model}**) with the patient's coronary landmarks identified by the

202 contrast venography (**CS_{venogram}**, **MCV_{venogram}**, **AIV_{venogram}**), as shown in

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205 **Figure 4(d).**

206 The overall alignment between the contour of the projected personalized cardiac model and the patient's
207 heart silhouette in the acquired venography was used as a quality check for the registration (

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209 **Figure 3).** The coronary veins are typically characterized by their epicardial course that represents the
210 outer boundaries of the ventricles. Therefore, the overall alignment between the contour of the projected
211 model and the outline of the patient's coronary venous tree was also utilized as a quality assurance of the
212 registration.

213 The RV pacing lead (

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216 **Figure 4(e))** was identified in the fluoroscopic images to visually verify that the RV lead was contained
217 within the RV of the projected cardiac model. The RV pacing lead was visible both in the venogram (step
218 № 5, **Figure 1**) and in the control X-ray images acquired after the LV lead deployment (step № 12,
219 **Figure 1**). The 3D location of the RV pacing lead tip was used to compensate for respiratory and
220 cardiovascular motion. The tool was designed to track any change in pose of the X-ray imaging system
221 and to correspondingly maintain the achieved registration, assuming the patient did not move.
222 Registration time was recorded from the beginning to the end of this registration procedure.

223 Registration accuracy and reproducibility assessment

224 *Diagram in **Figure 1(b)** illustrates the steps used to investigate registration accuracy and reproducibility.*
225 *Two expert electrophysiologists (**Obs1** and **Obs2**), blinded from the implanted lead positions and clinical*
226 *outcomes, followed the previously outlined 3D-2D registration procedure. For each patient, the average*
227 *model was personalized (selected and scaled in accordance with the patient's LV SI and LV LAX length*
228 *echocardiography measurements) and the image fusion was performed postoperatively by both observers*
229 *(dashed rectangle in **Figure 1(b)**) utilizing baseline fluoroscopic cine loops. A pair of control X-ray cine*
230 *loops (acquired under biventricular pacing) were used to identify the implanted quadripolar leads (*

231

232 **Figure 5)** and to compute the 3D locations of each electrode in the end-diastolic frame.

233 [Epicardium-to-electrode distance](#)

234 *To evaluate the registration accuracy, the absolute distance between the registered LV epicardial surface*

235 *and the 3D location of the LV electrodes was computed. The epicardium-to-electrode distance was*

236 *calculated for each electrode in all registrations.*

Figure 5(b) depicts a 3D LV model with an implanted quadripolar lead. The schematic illustrates the epicardium-to-electrode distance for an electrode outside and an electrode inside the surface.

Interobserver agreement using epicardium-to-electrode distance

The epicardium-to-electrode distances were matched (same patient and same electrode) and an interobserver difference was calculated for all pairs to evaluate interobserver agreement.

Interobserver agreement using LVOT long-axis direction

In each LV model, an aorta-LVOT centerline was constructed to define the LVOT long-axis [30]. The direction of the LVOT long-axis was estimated in all registrations. The direction vectors were matched (same patient) and interobserver difference (expressed as the angle between the corresponding LVOT long-axes) was computed for all pairs. The angles were used to estimate the interobserver registration agreement with respect to rotation around the LV long-axis. **Figure 2(b)** illustrates LVOT long-axis direction difference in an implantation case.

Concordance analysis

A 3rd observer (**Obs3**, an expert cardiologist), retrospectively determined the LV segments with the latest time-to-peak radial strain in each patient (step № 3, **Figure 1**). When available, LGE CMR imaging findings were used only to exclude segments as potential targets when having scar transmural > 25% (step № 4, **Figure 1**). The segment-to-electrode distance was defined as a distance measured along the LV surface from the center of an LV segment to the location of an LV pacing electrode, as illustrated in

Figure 5(c). In each fused image, the segment-to-electrode distances were computed for all (segment, electrode) pairs and the distances were compared to facilitate concordance analysis. Exact concordance was recorded when the pacing electrode was closest to the echo-suggested segment. Adjacent concordance was recorded when the pacing electrode was closest to the center of a segment bordering the echo-suggested segment. No concordance was recorded in all other cases. The distance from the echo-defined segment to the pacing electrode for both patient subgroups (CRT responders and CRT non-responders) were analyzed and compared. Furthermore, a color-coded texture was rendered onto the surface of the fused LV model to visualize the time-to-peak radial strain values and highlight eventual scar segments. This allowed **Obs1** and **Obs2** to qualitatively assess the concordance. The QRS width for CRT responders and non-responders was also analyzed.

[Statistical analysis](#)

Continuous variables were expressed as *mean* $\pm$ *SD*. A 95% confidence interval was used throughout the analysis. The Kolmogorov-Smirnov test was used to test sample probability distribution. The *t*-test (at 5% significance level) was used to determine if there was a significant difference in scores for two groups. The chi-square test (at 5% significance level) was used to determine if there was a significant difference between two groups of categorical variables.

Results

Image fusion was not possible for 3 (out of 30) patients due to incomplete fluoroscopy (2 patients) or echocardiography (1 patient) data. These patients were excluded both from the registration accuracy assessment and the concordance analysis. Another 2 (out of 30) patients were excluded only from the concordance analysis due to incompleteness of the follow-up data. Patient baseline characteristics and corresponding follow-up measurements are summarized in **Table II**. Follow-up characteristics for all available reports, CRT responder and CRT non-responder subgroups.

	All (n=28)	Responders (n=20)	Non-responders (n=5)	P-value
LVESV (mL)	130 $\pm$ 79	109 $\pm$ 55	209 $\pm$ 111	0.01
Δ LVESV (%)	31 $\pm$ 22	38 $\pm$ 16	0 $\pm$ 12	< 0.01
LVEF (%)	39 $\pm$ 6	40 $\pm$ 6	31 $\pm$ 7	0.02

LVDd (mm)	60 ± 11	58 ± 8	68 ± 14	0.04
Δ LVDd (%)	10 ± 9	13 ± 6	1 ± 3	< 0.01
Target LV segment to LV pacing electrode distance (mm)	41.0 ± 31.0	27.8 ± 22.2	88.4 ± 29.8	< 0.01

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and Error! Reference source not found. respectively. The average model with low LV SI ($SI_{LO}=0.49$) was used in 12 cases ($EDV=207\pm66$ ml, $SI=0.55\pm0.2$). The model with high LV SI ($SI_{HI} = 0.81$) was used in the remaining 16 cases ($EDV = 361\pm72$ ml, $SI = 0.84\pm0.2$).

Average coronary venous landmarks

The average coronary venous landmarks, expressed as angles measured counterclockwise from a common reference in the LV bullseye plot (**Figure 2(a)**), were located at $76.8\pm5.7^\circ$ (**CS_{model}**), $96.2\pm5.5^\circ$ (**MCV_{model}**), and $296.5\pm8.4^\circ$ (**AIV_{model}**).

Registration time

The cardiac model to venogram registration process took 264 ± 25 seconds. There was no significant difference (P-value = 0.11) in registration times between the two observers; **Obs1** spent 255 ± 32 s, and **Obs2** spent 274 ± 14 s. Registration accuracy

The epicardium-to-electrode absolute distance was 4.4 ± 2.3 mm. No significant difference (P-value = 0.22) in individual (**Obs1** vs **Obs2**) values was found; for **Obs1** distance was 4.6 ± 2.7 , and for **Obs2** was 4.3 ± 2.0 . For each matching epicardium-to-electrode distance (same patient), an interobserver distance difference was calculated; the distance difference was 1.5 ± 1.1 mm.

The interobserver LVOT long-axis direction difference, used to measure the interobserver registration agreement concerning variation in rotation around the LV long-axis, was $9.5\pm4.0^\circ$.

Concordance analysis

Exact concordance was found in 11 (44%), adjacent in 9 (36%) and no concordance in the remaining 5 (20%) patients. The concordance distribution for CRT responders was: 11 exact, 8 adjacent and 1 remote. The concordance distribution for CRT non-responders was: 0 exact, 1 adjacent and 4 remotes. The distributions were identical for both observers. LGE CMR imaging was available in 19 (out of 30) patients. Segments with scar transmuralities $> 25\%$ were found in 9 (out of 19) patients. Seven patients had multiple segments (3 on average) with scar transmuralities above the threshold. In 4 implantation cases,

knowledge on scarred tissue led to change in the target segment as suggested only by echocardiography. It was possible to suggest adjacent segments which, coincidentally, had the same late activation as the excluded scarred segments.

There was a significant difference ($p < 0.01$) in the echo-suggested segment to the LV pacing electrode distance between CRT responders (27.8 ± 22.2 mm) and CRT non-responders (88.8 ± 29.8 mm). Variance in echo-suggested segment to pacing electrode distance for 5 CRT non-responders included in the study is depicted in **Figure 6**. A significant difference in QRS width between these 2 subgroups was also observed (**Table I**).

Discussion

An image fusion tool which allows for targeted LV lead placement in CRT by combining LV functional information from echocardiography with X-ray fluoroscopy into a single multimodality image was investigated. In contrast to our earlier implementation [21], the new tool was designed to be a vendor-independent platform, to provide a simultaneous view of two fluoroscopic projections and allow more degrees of freedom when manipulating 3D models. Multimodality image fusion for CRT application has already been investigated earlier [8], [12], [14], [15], [16], [17], [18], [19], [20]. However, these earlier methods rely on imaging modalities, proprietary echocardiographic or fluoroscopic systems, advanced sensor-based navigation interfaces and complex pre-procedural steps (e.g., whole-heart segmentation) which are not part of the clinical routine for CRT candidates. In contrast, our solution builds on imaging modalities and techniques routinely used in CRT candidates (echocardiography, fluoroscopy and optionally CMR). The tool was integrated into an implantation lab equipped with a biplane Artis zeego (Siemens Healthcare, Erlangen, Germany) C-arm system. A set of DICOM tags (embedded into the acquired fluoro images) was used to reconstruct corresponding C-arm imaging geometry, implement 3D-2D registration and project the cardiac models onto 2D fluoroscopy. This reliance on standardized information may simplify integration in other potential facilities.

The tool utilizes 3D cardiac geometry to implement the 3D-2D registration and to visualize patient specific LV function in fluoroscopy (

Figure 3). In this study, LGE CMR imaging was available for 19 and could not be performed in the remaining 13 patients (due to renal failure). CMR, CT or 3D ultrasound could provide input for a patient-specific 3D cardiac model. However, as volumetric imaging data is typically not available for patients undergoing CRT implantation, we demonstrated the feasibility of the suggested fusion technique by not relying on 3D imaging but rather on an average cardiac model developed in our earlier work [21]. In this previous study, the leave-one-out cross-validation technique was used to (1) evaluate the test-to-mean surface distance and (2) estimate the coronary branch selection accuracy when the average surface was used instead of the test surface. The results from this earlier study demonstrated that use of the average cardiac geometry has no practical drawbacks for the application of echo-guided LV lead deployment in CRT; the patient-specific to average surface distance error was -0.35 ± 4.5 mm and correct coronary veins were selected in $\sim 95\%$ of the cases when basing the selection on the mean model instead of the patient-specific model [21], [29]. Furthermore, the average 3D LV epicardial surface was extended to include a set of average coronary venous landmarks to facilitate 2D/3D image fusion. The average landmarks were not utilized in our earlier work [21]. As the dataset in our current study did not have 3D segmentation of corresponding coronaries, the average landmarks were derived from a set of 15 HF patients from the study from Auricchio et al. [28]. Patient-specific coronary venous landmarks (CS_{venogram} , MCV_{venogram} , AIV_{venogram}) could consistently be identified by regular 2D coronary venography and matched to the corresponding average landmarks (CS_{model} , MCV_{model} , AIV_{model}) embedded on the average model (

Figure 4). These average landmarks may not precisely represent the variability of coronary venous anatomy among patients and could contribute to unfavorable 3D-2D registration. However, the variability ($\pm 2SD$) in the data set used to derive the average landmarks was less than one-third of the LV segment width (**Figure 2(a)**) and was considered acceptable for the clinical application of CRT where LV function was reported on a regional resolution. The presence of aberrant anatomies should be considered a contraindication for the use of the average anatomy.

Registration accuracy assessment is challenging to evaluate in-vivo. The 3D-2D registration accuracy was assessed by calculating the epicardium-to-electrode distance (the measure of fitness not utilized previously [21]). As the electrode leads are located inside the coronary veins laying on the epicardial surface, the distance values should ideally be close to 0. This metric, however, cannot capture potential rotational errors around the LV long axis. In the current setup, the rotational errors were assessed indirectly by analyzing the interobserver LVOT long-axis direction difference. Ideally, this indicator should also be close to 0. However, the LV lead placement is often limited by the coronary venous anatomy, and hence small rotational errors in registering the cardiac model may not directly lead to the selection of the wrong vein. The accuracy results suggest that the proposed tool can be used to accurately and reliably register personalized cardiac geometry (and hence deformation imaging) with X-ray imaging within an acceptable timeframe.

Viability information is important to exclude areas of a transmural scar as potential targets for lead placement [14], [31]. When available, LGE CMR imaging findings were combined with echocardiography analysis to identify segments with both late mechanical contraction and absence of the transmural scar. Segments with scar transmurality $> 25\%$ were excluded from further analysis. In 4 implantation cases, knowledge on scarred tissue affected target segment selection as suggested only by echocardiography (other segments with late activation were considered). Therefore, not having CMR imaging may lead to non-optimal target vein selection and result with the pacing of the non-viable myocardium. However, this would not significantly impact the mechanics of the proposed image fusion.

Echocardiographic strain analysis may also be considered when identifying potentially ischemic segments, as reported by [32]. The impact of using echocardiography speckle tracking to define the LV target segment has been studied by others [10], [11], [13], [19], [33]. In consistence with these studies, we found high combined exact and adjacent concordance in CRT responders. In contrast to our earlier implementation [21], the new tool provided means to assess the distance between the target segment and the pacing electrode. A significant difference in the echo-defined target segment to the pacing electrode distance was found between the CRT responders (27.8 ± 22.2 mm) and non-responders (88.8 ± 29.8 mm) (**Table II**Error! Reference source not found.). QRS duration was also significantly different between the two groups (**Table I**).

The presented tool was designed to aid intraoperative echo-guided LV lead placement but was validated retrospectively (after implantation). This provided valuable insight into the accuracy and potential usefulness of the tool before testing it in the clinic. The spatial relationships between the coronary venous tree, the regional LV function, the LV pacing electrodes and the cardiac surfaces (

Figure 3,

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398 **Figure 4**, and

Figure 5) was visualized in a single multimodal image.

Figure 7(a) shows a fused image for a CRT responder; the pacing electrode was concordant with the echo-defined target segment.

Figure 7(b) illustrates a CRT non-responder; the pacing electrode was not concordant with the echo-defined target segment. The tool may also have applications as an instrument for the education of trainees in CRT.

The presented guidance tool may also be extended to allow for visualization and testing of alternative echocardiography-derived LV parameters (e.g., strain-rate). Reliable radial strain analysis, especially for segments distal from the echo probe, can be challenging for typical CRT candidates with dilated ventricles. The longitudinal strain could be a solution, as it is more robust, and has more pronounced regional differences compared to radial strain [34]. Real-time 3D echocardiography (RT3DE), assessing the entire LV in a single recording, could be used to quantify LV function and facilitate LV lead placement in CRT. Furthermore, RT3DE could provide the patient-specific anatomy needed for the image fusion. However, the robustness of speckle-tracking strain from 3D echo remains inferior to 2D echo [35]. The study is limited by being performed in a single center environment with a modest number of selected patients. A clinical trial using the tool as primary guidance for LV implantation remains future work, as neither echocardiographic nor CMR findings were used to guide the implantation. It was therefore not possible to test if relocation of the LV lead would improve response. The amount of delay in time-to-peak-strain values relative to adjacent segments was not assessed and hence was not possible to determine a cut-off delay that could serve as a zone to define a potential “sweet spot” for lead placement.

Conclusions

The presented guidance tool provides insight in the spatial relationship between an echo-defined target segment and the venous anatomy by fusion of 3D cardiac geometry with 2D fluoroscopy, and hence allows for positioning of the pacing electrode within or next to the echo-defined target segment. The presented registration methods demonstrated low interobserver variability and should allow for accurate alignment of a 3D cardiac model with 2D fluoroscopy. This method may help to improve the responder rate to CRT by allowing reassurance of LV lead positioning close to the latest contracting segment and away from a suspected myocardial scar.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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439 **Author Contributions**

440 Aleksandar Babić: Concept, SW implementation, Data analysis, Statistics, Drafting article

441 Hans Henrik Odland: Concept/design, Critical revision of article

442 Erik Lyseggen: Image fusion, implantation

443 Torbjørn Holm: Image fusion, implantation

444 Stian Ross: Data analysis/interpretation, Statistics

445 Einar Hopp: Data analysis/interpretation

446 Kristina H. Haugaa: Data analysis/interpretation, Critical revision of article

447 Erik Kongsgård: Critical revision of article

448 Thor Edvardsen: Concept/design, Critical revision of article

449 Olivier Gérard: Critical revision of article

450 Eigil Samset: Concept/Design, Secured funding, Critical revision of article

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457 **Supplementary material**

458 The following supplementary material is available online – Movie Clips:

459 Figure1.mp4 (codec: H.264): The video illustrates main steps of the envisioned full workflow.

460 Figure4.mp4 (codec: H.264): The video illustrates main 2D-3D registration steps. Furthermore, it
 461 depicts how echo-derived parameters (for a randomly selected case) are visualized both when
 462 selecting target vein and later when performing qualitative check against control X-ray images.

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Tables

Table 1 Baseline characteristics for all available reports, CRT¹ responder and CRT non-responder subgroups.

	All (n=30)	Responders (n=20)	Non-responders (n=5)	P-value ²
Age (years)	64 ± 9	64 ± 8	67 ± 9	0.25
Gender (male, %)	78	70	60	0.66
Ischemic heart disease (%)	46	82	60	0.55
NYHA ³ class II /III (%)	40/60	45/55	20/80	0.31
Scar burden (percentage of LV volume comprised of scar) (%)	5.2 ± 6.5	4.5 ± 6.2	7.7 ± 7.9	0.41
Intrinsic AV ⁴ delay (ms)	279 ± 47	284 ± 46	290 ± 39	0.8
Paced AV delay (ms)	126 ± 24	125 ± 16	130 ± 19	0.6
Aldosterone antagonist (Yes/No) (%)	60/40	60/40	60/40	1.0
Loop diuretics (Yes/No) (%)	68/32	60/40	100/0	0.08
LBBB ⁵ (%)	96 / 4	95 / 5	100 / 0	0.61
ICVD ⁶ / non-ICVD	4 / 96	5 / 95	0 / 100	0.61
LVESV ⁷ (mL)	199 ± 103	183 ± 97	213 ± 115	0.58
LVEF ⁸ (%)	28 ± 6	29 ± 6	30 ± 5	0.72
LVDd ⁹ (mm)	68 ± 9	66 ± 8	69 ± 14	0.60
QRS width (ms)	172 ± 14	174 ± 17	154 ± 15	0.03

¹ CRT = Cardiac resynchronization Therapy

² P-values are reported for inter-group (responders vs. non-responders) difference at 5% significance level

³ NYHA = New York Heart Association

⁴ AV = Atrioventricular

⁵ LBBB = Left Bundle Branch Block

⁶ ICVD = Interventricular Conduction Delay

⁷ LVESV = Left Ventricular End-Systolic Volume

⁸ LVEF = Left ventricular Ejection Fraction

⁹ LVDd = Left Ventricular Diastolic Dimension

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471 *Table II Follow-up characteristics for all available reports, CRT¹⁰ responder and CRT non-responder*472 *subgroups.*

	All (n=28)	Responders (n=20)	Non-responders (n=5)	P-value ¹¹
LVESV ¹² (mL)	130 ± 79	109 ± 55	209 ± 111	0.01
Δ LVESV (%)	31 ± 22	38 ± 16	0 ± 12	< 0.01
LVEF ¹³ (%)	39 ± 6	40 ± 6	31 ± 7	0.02
LVDd ¹⁴ (mm)	60 ± 11	58 ± 8	68 ± 14	0.04
Δ LVDd (%)	10 ± 9	13 ± 6	1 ± 3	< 0.01
Target LV ¹⁵ segment to LV pacing electrode distance (mm)	41.0 ± 31.0	27.8 ± 22.2	88.4 ± 29.8	< 0.01

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¹⁰ CRT = Cardiac Resynchronization Therapy

¹¹ P-values are reported for inter-group (responders vs. non-responders) difference at 5% significance level

¹² LVESV = Left Ventricular End-Systolic Volume

¹³ LVEF = Left Ventricular Ejection Fraction

¹⁴ LVDd = Left Ventricular Diastolic Dimension

¹⁵ LV = Left Ventricle

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Figures

Figure 1 Overview of the proposed workflow for the echo-guided LV lead placement. (a) Full envisioned workflow in the implantation lab. (b) Postoperative verification of registration performance workflow steps. Numbers placed in red circles correspond to the steps in the full envisioned workflow. CMR = Cardiac Magnetic Resonance, Long-Axis = Left Ventricular Long-Axis and LV = Left Ventricle.

Figure 2 (a) Coronary venous landmark distribution (locations expressed as angles measured counterclockwise from a common reference – green dashed line) for data set (15 heart failure patients) used to compute average landmark model. The **CS_{model}** was located at 76.8° ($SD = 5.7^\circ$), the **MCV_{model}** was located at 96.2° ($SD = 5.5^\circ$), and the **AIV_{model}** was located at 296.5° ($SD = 8.4^\circ$). Sectors (marked with pattern fill) visualize variability within the corresponding landmarks. The variability was smaller than one-third of the LV segment width. (b) LVOT long-axis directions superimposed with LV bullseye plot for an implantation case. Green line depicts LVOT long-axis direction for registration performed by the Obs1. Blue line depicts LVOT long-axis direction for registration performed by the Obs2. Red arc depicts interobserver LVOT direction angular difference. AIV = Antero Interventricular Vein, CS = Coronary Sinus, LVOT = Left Ventricular Outflow Tract, MCV = Middle Cardiac Vein, Obs1 = Observer 1 and Obs2 = Observer 2.

Figure 3 An example of LV epicardium to fluoroscopy fusion (registration frame, coronary venography). The 17-Segment AHA layout and the markers identifying average locations of the coronary venous landmarks (**CS_{model}** with red-, **MCV_{model}** with blue- and **AIV_{model}** with magenta line) were automatically mapped onto the surface of the registered personalized cardiac model. A green line, located at the base of the LV free wall, depicts the atrioventricular plane (**AV_{plane}**). (a) RAO projection visualizing LV septal wall. (b) LAO projection visualizing LV anterolateral wall. (c) LV posterior wall (as seen from inside the LV) visualized in RAO projection. (d) LV posterior wall (as seen from inside the LV) visualized in LAO projection. AIV = Antero Interventricular Vein, AHA = American Heart Society, AV = Atrioventricular, CS = Coronary Sinus and MCV = Middle Cardiac Vein.

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513 **Figure 4** Image registration workflow steps. (a) Coronary vein landmarks selection and reconstruction. (b)
 514 Up/Down rotation. (c) Left/Right model rotation to align the basal ring of its projection with the coronary sinus
 515 ring. (d) Long-axis rotation to match embedded average coronary venous landmarks (CS_{model} , MCV_{model} ,
 516 AIV_{model}) with patient-specific landmarks ($CS_{venogram}$, $MCV_{venogram}$, $AIV_{venogram}$). (e) RV pacing lead
 517 landmarks were utilized to check if the lead was contained within the RV. AIV = Antero Interventricular Vein, CS =
 518 Coronary Sinus, MCV = Middle Cardiac Vein and RV = Right Ventricle.

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Figure 5 Registration accuracy measurements: **(a)** LV pacing electrodes identified and reconstructed from a control X-ray image pair (RAO and LAO projections). **(b)** Epicardium-to-electrode distance measurement method for a 3D LV model and an implanted LV pacing lead (red ellipses represent individual electrodes). **(c)** Segment-to-electrode surface paths (green curves) connecting segment centers (blue points) with an electrode on an implanted LV lead (red point). LAO = Left Anterior Oblique, LV = Left Ventricle and RAO = Right Anterior Oblique.

Figure 6 Echo-defined target segment to pacing electrode distance distribution (88.8 ± 29.8 mm) for 5 CRT non-responders. CRT = Cardiac Resynchronization Therapy.

Figure 7 Examples of an augmented X-ray images. Time-to-peak radial strain values were mapped to the LV epicardium. Sites of latest mechanical contraction were colored in red. Color marker at the LV base was used to hint if the LV anatomy was showing either its posterior wall (green marker) or its septal- and anterolateral wall (yellow marker). Pacing electrode was encircled in white. **(a)** LV posterior wall (seen from inside the LV), fortuitously implanted LV lead and location of the pacing electrode (concordant with the site of latest activation) in a CRT responder (RAO projection). **(b)** LV septal/anterolateral wall and implanted LV lead (non-concordant with the site of latest contraction) in a CRT non-responder (LAO projection). **(c)** An example illustrating presence of non-viable myocardium (marked with line patterns). CRT = Cardiac Resynchronization Therapy, LAO = Left Anterior Oblique, LV = Left Ventricle and RAO = Right Anterior Oblique.