Left ventricular four-dimensional rotational angiography with low radiation dose through interphase registration

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Aims
Ventricular tachycardia ablations could benefit from four-dimensional (4D) (dynamic 3D) visualization of the left ventricle (LV) as roadmap for anatomy-guided procedures. Our aim was to develop an algorithm that combines information of several cardiac phases to improve signal-to-noise ratio in low-dose, noisy rotational angiography [three-dimensional rotational angiography (3DRA)] image datasets, enabling semi-automatic segmentation and generation of 4D rotational angiography (4DRA) LV surface models.

Methods and results
We developed a novel slow pacing protocol for low-dose 4DRA imaging and applied interphase registration (IPR) to improve contrast-to-noise ratio (CNR) such that 4D LV segmentation could be achieved using a single iso-intensity value (ISO). The method was applied to construct four-phase dynamic LV models from five porcine experiments. Optimal choice of IPR and ISO parameters and resulting LV model accuracy were assessed by comparison with ‘ground-truth’ manual LV delineations using surface distance measures [root mean square distance (RMSD), Hausdorff distance (HD), fraction of surface distances ≤3 mm (d3 mm)]. Using IPR with optimized parameters, CNR improved by 88% ($P < 0.0001$) and increased segmentation accuracy was proven irrespective of ISO. Significant improvement was achieved in RMSD [mean at optimal ISO: $−28.3\%$ (95% confidence interval (CI) $−21.7$ to $−35.0$, $P < 0.0001$)], HD $[−21.4\%$ (95% CI $−18.6$ to $−24.1$, $P < 0.0001$)], and d3 mm $[+7.8\%$ (95% CI $+4.6$ to $+10.9$, $P < 0.0001$)]. An average d3 mm of $95.6 ± 2.8\%$ was reached at optimal ISO. Time to generate a 4D model was $+11.5$ min with IPR vs. $+22$ min without.

Conclusion
Interphase registration significantly improves 4DRA image quality and facilitates semi-automatic segmentation, resulting in clinically useful accuracy despite low-dose image acquisition protocols, while shortening 4D model generation time. This opens the prospect of 4D imaging in clinical settings.

Keywords
C-arm imaging • Rotational angiography • Image quality • Electroanatomical mapping • Semi-automatic segmentation • Radiation dose

Introduction
Three-dimensional rotational angiography (3DRA) has become a widespread modality for 3D imaging of the heart, particularly for use during catheter ablation procedures. With 3DRA, high-resolution X-ray projection images are acquired per-procedurally along a 200° C-arm rotation around the patient and reconstructed into a 3D tomographic image. Associated radiation dose has been greatly reduced without compromising image quality and currently compares favourably to state-of-the-art computed tomography imaging.¹

A 3D model of the heart can be segmented from the 3DRA image and subsequently be used in an electroanatomical mapping system or in overlay with live fluoroscopy during the procedure to offer online visual feedback of catheter positions supported by highly detailed 3D anatomy.²,³ This approach, using static 3D models acquired after...
What’s new?

- Perspective of clinical realization of four-dimensional (4D) surface model sequence for more accurate integration with electroanatomical mapping systems and per-procedural fluoroscopy or co-registration with scar visualization modalities, facilitating catheter ablation in locations with a high degree of motion like the left ventricle.
- Pre-clinical study on porcine experiments in a close to realistic clinical workflow.
- Development of a filtering framework, based solely on post-reconstruction image registration, for noise and artefact reduction in dynamic three-dimensional rotational angiography (4D rotational angiography) images, acquired through a novel low radiation dose image acquisition protocol at slow pacing rate. Subsequent facilitation of semi-automatic segmentation with clinically useful accuracy.
- Method optimization and validation with manual left ventricular segmentations of four cardiac phases as golden standard, based on generally accepted and clinically relevant similarity measures.

Methods

Experimental setup, image acquisition, and image reconstruction

To obtain a dynamic 3DRA sequence, accurate reconstructed 3D images of a sufficient number of cardiac phases are needed. To this end, we recently developed a single 200° C-arm rotation 4DRA image acquisition protocol using slow pacing at a fixed heart rate in congruence with the fixed image acquisition rate of the 3DRA system. This way, every acquired projection image is prospectively accorded with a specific cardiac phase, avoiding unnecessary radiation exposure (Figure 1, left panel).

This protocol was applied in five porcine experiments. The pigs (20–30 kg) were pre-anesthetized with ketamine hydrochloride (20 mg/kg), (Anesketin, Eurovet), followed by continuous infusion of propofol (0.15 mg/kg/min) (Diprivan, AstraZeneca), intubated and ventilated with a 1:1 mixture of air and oxygen. Between 90 and 150 cc of undiluted iodine contrast agent (Iomeron 300, Bracco) was administered through the femoral vein.

Four-dimensional rotational angiography imaging was performed using an Artis System (Siemens Medical). During a 15 s C-arm rotation, 381 projections were acquired during right atrial pacing at 105 b.p.m., such that 15 distinct cardiac phases were imaged with 25 or 26 projections each. Similar detector entrance dose settings to static 3DRA imaging in clinical setting were used. Image reconstruction was done on a dedicated Siemens workstation, using an algorithm similar to the FDK algorithm. Voxel size of reconstructed images was limited to $1 \times 1 \times 1 \text{ mm}^3$ for computational efficiency. This is largely sufficient as ventricular ablation lesions easily amount to a depth of $\geq 3 \text{ mm}$ and a width of $\geq 4 \text{ mm}$.

For this protocol to be eventually applicable for patient use, radiation dose restriction is paramount. Acquiring 15 phases in clinical setting would imply an unacceptably high estimated radiation dose of $\geq 10 \text{ mSv}$, even with low-dose image acquisition protocols. We therefore performed this work on four phases only since they may suffice in covering most of the LV’s mechanical variation. Taking into account that hardware limitations impose image acquisition to be performed at equal time intervals, the following 4 phases out of the recorded 15 phases were retrospectively selected: the phase closest to end diastole (DD), the phase closest to end systole (SS), and two interposed phases: one halfway ventricular contraction (DS) and one halfway ventricular expansion (SD) (Figure 1, right panel). Time intervals between the four selected phases were therefore 0.12–0.16 s. Reconstruction with another image. In this particular case, we use intramodal registration methods to increase signal-to-noise ratio (SNR) in one cardiac phase by application of motion correction on the other phases and subsequent averaging. By combining the original and the warped versions of the same cardiac phase, relevant anatomical information is amplified, while noise and artefacts are attenuated. Optimal registration is obtained by maximization of the mutual information of the original and warped images. However, such image registration methods have many adjustable parameters that may have a strong impact on the efficacy of the method for a particular application. Therefore, application-specific method optimization is crucial.

In this paper, we optimized and quantitatively evaluated a non-rigid IPR-based filtering method for 4DRA images. This article focusses on the left ventricle (LV), as it is the cardiac chamber with the most prominent motion throughout the cardiac cycle, while accurate LV ablations often constitute life-saving procedures.

adenosine administration or during rapid ventricular pacing, proved highly functional for ablation of supraventricular arrhythmias and atrial fibrillation and is currently being used in many clinical settings. In the case of ventricular ablation, however, positional mismatch with the static 3D model becomes important due to the ventricles’ high degree of motion throughout the cardiac cycle.

Recently, efforts towards development of dynamic, multi-phase 3DRA [i.e. four-dimensional rotational angiography (4DRA)] have been made, to enable more accurate anatomical localization of catheters throughout the cardiac cycle while retaining high anatomical detail.

The feasibility of acquiring and reconstructing one or more specific heart phases has been shown, but the challenge remains to find a compromise between quality and radiation dose. Often, retrospective electrocardiogram (ECG) gating is used, requiring multiple acquisition rotations around the patient. This leads to proportional increases in radiation dose with clinically unacceptable values.

Alternatively, the reconstruction of a dynamic image can be done with a similar total number of acquired projection images as for static 3D imaging to keep radiation dose at a comparable level, but this implies that only a limited amount of projections is available for the reconstruction of each phase. This leads to an important increase in noise and prominent undersampling effects, also accentuating other artefacts like streak artefacts from metal electrodes or iodine contrast in the heart cavities. Hence, image quality suffers and manual delineation is necessary to segment the cardiac chambers, precluding clinical usability.

To reduce these artefacts, and noise in general, we developed a filtering method using post-reconstruction interphase registration (IPR). Image registration is generally used for combining images from the same or different modalities that describe the same anatomy (intra- and intermodal registration, respectively). It is based on spatial warping of one image to be anatomically aligned
of all 15 phases was necessary for retrospective phase selection to be performed.

**Groundtruth**

Groundtruth segmentations for the four selected heart phases were created by manual delineation of the contrast volume (i.e. the luminal border of endocardium and papillary muscles) within a region of interest (ROI) spanning LV from apex to basis, proximal of both LV inflow and LV outflow tract. This was done slice-by-slice after resampling the image volume along 1 mm thick slices orthogonal to the LV long axis.

**Interphase registration**

Segmentation of the LV can be done for all four phases separately as described below (Figure 2A). Instead, our proposed method applies a filtering method based on non-rigid IPR prior to segmentation, aiming at reducing image noise and artifacts and improving segmentation quality (Figure 2B). The image of one phase (the anchor phase) is selected as reference and the images of the other three phases are warped to it through IPR. The four images are averaged and the LV model for the anchor phase is obtained by segmentation of the averaged image as described below. This model is then warped onto the other phases using the known IPR transformations, such that LV models for all phases are obtained.

**Registration procedure and optimization**

B-spline intensity-based non-rigid registration between the four phases was performed using Elastix, a publicly available toolbox enabling modification of various registration method parameters. Preliminary experiments resulted in the selection of six parameters relevant to this application, namely control point spacing, histogram binning, pyramid schedule, number of iterations, resolutions, and spatial samples. Different settings for these parameters were combined into parameter sets \( n = 78 \). Application-specific parameter optimization was done by registration of each phase to each other phase (i.e. 12 phase pairs per experiment) for each of the five experiments (i.e. 60 registrations per parameter set), using each parameter set (i.e. 78 \( \times \) 60 registrations in total). Each registration from Phase A to Phase B was evaluated by warping the groundtruth LV segmentation of Phase A onto Phase B using the computed transformation and comparing it with the groundtruth LV segmentation of Phase B. This comparison was performed using five different similarity measures:

1. Spatial overlap of two volumes, quantified by the dice similarity coefficient; \(^{19,20}\)
2. Root mean square deviation (RMSD) of the closest point distances (CPDs), i.e. the set of distances between all points on one surface to their closest point on the other surface;
3. Maximal CPD, i.e. the Hausdorff distance (HD); \(^{21}\)
4. Percentage of CPD values \( \leq 3 \text{ mm} \) (d3 mm) and \( \leq 4 \text{ mm} \) (d4 mm), respectively.

These two measures can be considered as application-specific cut-offs for tolerable errors, as ventricular ablation lesion size easily reaches a depth of 3 mm and a width of 4 mm, especially in the LV where irrigated catheters are commonly used. \(^{13–15}\)

To determine the most suitable set of registration parameters, principal component analysis was performed on the ensemble of the five similarity measures.
measures over all registration experiments. The first principal component, a linear combination of the five similarity measures, defines a new axis (composite score $Q$, theoretical range: 2 to 100) along which the variance between different observations is, per definition, maximized. The reference phase that on average resulted in the highest $Q$ values was selected as anchor phase for all experiments. The same criterion was used to select the optimal set of IPR parameters for each of the remaining three phases. Figure 2A (see Supplementary material online) illustrates the parameter set optimization.

**Image quality**

Objective indices of image quality were obtained by calculating SNR and contrast-to-noise ratio (CNR) in the 3D images. Signal intensity (SI) was defined as the mean voxel intensity value (VIV) inside of three large ROIs for the LV cavity (at basal, mid, and apical level) and of six ROIs for the LV wall (baso-, mid-, apico-septal and baso-, mid-, apico-lateral region). Identical ROIs were used in the corresponding images before and after IPR-based filtering. The VIV was expressed in grey value on a 14-bit scale proper to the Siemens reconstruction workstation. Image noise was derived from averaged standard deviations (s.d.) of the VIV in the same ROIs. Signal-to-noise ratio was defined as cavity SI divided by image noise and CNR as the difference between cavity SI and wall SI, divided by image noise.

**Segmentation**

Segmentation was performed with an in-house developed semi-automatic segmentation (SAS) tool (EPSegmenter) based on VIV as previously reported in De Buck et al., i.e. the tool we use clinically for creating static 3D models from 3DRA images. Different LV models were obtained for each reconstructed image by selecting different VIV thresholds (iso-intensity value, ISO) within a pre-specified range, followed by manual trimming of the segmented 3D surface for further improvement of the LV model where necessary. A suitable ISO range was defined for each experiment separately such that all resulting models were deemed clinically usable as judged visually by a clinical cardiologist. To facilitate the analysis of segmentation accuracy between different experiments, the ISO values for each experiment are expressed as offsets $\Delta$ISO relative to the optimal ISO value without the use of IPR, i.e. $\Delta$ISO = 0 corresponds to the ISO value for which SAS of the original phase images resulted on average in the highest composite score $Q$.

**Timing**

All IPR and SAS operations were performed on a desktop PC (Dual Intel Xeon 6-core 2.30 GHz 64-bit processors, 32 GB RAM, Dell) and timed. The time required for image acquisition and reconstruction was also recorded. The time needed for routine overhead actions like placement and adjustment of the C-arm and operating table was disregarded, as was the time needed to find optimal ISO values for SAS ($\sim$1–2 min each).

**Statistical analysis**

All data were analysed using SPSS (IBM). Descriptive data for continuous variables are presented as mean ± s.d. Normality was checked by the Shapiro–Wilk test. Results for relative differences were opposed to the zero-mean hypothesis using a single-sample t-test. The level of
significance was set at 0.05. In addition, two-way repeated-measure factorial analysis of variance was used for comparison between IPR and non-IPR SAS accuracy measures.

**Results**

**Selection of optimal interphase registration anchor phase and registration parameters**

The optimal anchor phase and the optimal set of IPR parameters for all other phases were determined by assessing the similarity between the groundtruth LV delineations after warping, using the composite score Q. Both interposed phases SD and DS resulted in the highest Q values. However, SD was selected as best anchor phase as the optimal set of IPR parameters was the same for all three other phases in case of SD, but not for DS. The LV models of the four phases as obtained without and with the use of IPR are shown for one experiment in **Figure 3** and in the Supplementary video (see Supplementary material online).

**Image quality**

**Table 1** shows the quantitative image quality data for the 3D images in the four phases and five experiments before and after application of the IPR-based filtering method. The use of IPR resulted in a noise reduction of 46.4% ($P < 0.0001$), while SI in both LV cavity and LV wall remained approximately unchanged. This led to SNR and CNR increasing significantly ($P < 0.0001$) by 86.5 and 88.0%, respectively. **Figure 3B** (see Supplementary material online) illustrates the quality gain for all four phases in one experiment.

**Segmentation accuracy**

The accuracy of the LV models in all four phases as obtained by SAS without and with the use of IPR over the selected ISO range for each experiment was evaluated by comparison with the manual ground-truth delineations. The use of IPR with optimized parameters resulted in average $d_3$ mm and $d_4$ mm values of 95.6 ± 2.8 and 97.1 ± 2.0%, respectively, with a mean segmentation error over the whole surface (RMSD) of 1.5 ± 0.3 mm at $\Delta$ISO = 0.
Figure 4 shows the values of d3 mm and the composite score Q (mean ± s.d.) averaged over all phases and all experiments for the IPR and non-IPR results over the range of ISO values considered, expressed relative to optimal non-IPR ISO (ΔISO = 0).

P < 0.0001) for d3 mm, RMSD, and HD, respectively, while fractional increase in Q was +7.6% (95% CI 4.7–10.5, P < 0.0001).

Timing

The average time required for the different steps in our workflow using our current implementation is depicted in Figure 5. The cumulative processing time for generating a static 3D model, as performed in routine clinical practice in our lab, is about 4 min. Generating a four-phase dynamic 3D model (i.e. a 4D model) required on average 22.0 min without IPR and only 11.5 min with use of IPR (P = 0.001).

Acquisition time was ±1 min, followed by a reconstruction time of ±5 min for 4DRA (381 projections) and ±0.5 min for 3DRA (67 projections). Interphase registration of the anchor phase to each of the three other phases is computed in parallel and requires only 2 min. After IPR, segmentation of the anchor phase at ΔISO = 0 and propagation to the other phases requires 3.3 ± 0.9 and ±0.2 min, respectively, thus about 3.5 min for SAS of all four phases with IPR. Segmenting a single phase without IPR at ΔISO = 0 took 4.0 ± 1.0 min on average, thus about 16 min for SAS of all four phases without IPR.

The time required for SAS of a single image without use of IPR doubled at non-optimal ISO values, due to the progressive deterioration of segmentation quality at ΔISO ≠ 0 and hence a larger need for manual trimming. This ISO-dependent deterioration due to noise and artefacts is much less important after IPR as shown in Figure 4. Here, SAS time increases by maximum 50% and only at the extremes of the ISO range. SAS of a static 3D model in clinical setting only takes up to 3 min, attributable to less prominent noise because of the higher amount of images (≥67) used.

Discussion

Image quality implications

Applying IPR to pre-process the very noisy reconstructed phase images before semi-automatic segmentation leads to a better
differentiation between high and low intensity voxels, thus defining the contrast-filled LV cavity more clearly against the surrounding non-contrast enhanced myocardium. This is quantitatively expressed by SNR and CNR being almost doubled. This way, more accurate models can be obtained, with a distance to the groundtruth delineations of \(<3\) mm for \(>95\%\) of the model surface and \(<4\) mm for \(>97\%\), while also the mean and maximum error decrease significantly (\(-28\%\) and \(-21\%\) on average, respectively). Such errors would certainly fall within the tolerability window for clinical ablation procedures. In addition, using IPR results in a broader range of ISO values yielding high d3 mm- and Q values than when IPR is not applied prior to SAS. Hence, more robust SAS conditions are created and the operator dependence on selecting a suitable ISO value for SAS is reduced.

The remaining fraction of intersurface distances that are \(\geq 3\) mm is attributable to residual noise, in particular due to metal streak artefacts not being filtered sufficiently. However, recent advances in iterative reconstruction methods show the possibility of further metal artefact correction, while motion compensation incorporated at the reconstruction stage also shows promising results.

### Timing implications

Applying the IPR-based filtering method to the reconstructed 3D images also facilitates their SAS as shown by the reduced SAS time needed. Moreover, using IPR offers the advantage that only a single phase (the anchor phase) needs to be explicitly segmented, because of the spatial relationship that is established by warping all phases. This drastically reduces the time required to generate a 4D model sequence. This decrease in time would be even more important when more than four phases would be used to generate the 4D model.

As our results show that a 4-phase 4D sequence with clinically useful accuracy can be conceived departing from \(\pm 25\) images per phase, a reduced reconstruction time can also be expected. As mentioned above, all 15 phases had to be reconstructed for phase selection purposes, using 381 images. However, future development with ECG-triggered acquisition for prospective phase selection would enable reconstruction involving a total of only \(\pm 100\) images.

### Clinical applicability and radiation dose implications

So far, 4DRA imaging could not be considered in clinical practice due to the complexity of the imaging protocol and the associated radiation dose. The presented method could however offer a solution for both limitations.

On the one hand, slow pacing is done at a physiologically acceptable rate. Therefore, the risk of inducing unwanted arrhythmias like ventricular fibrillation is much lower compared with the rapid ventricular pacing approach in static 3D imaging. The use of IPR increases image CNR and speeds up 4D surface segmentation by reducing operator-dependent SAS to only one segmentation, in more robust conditions.

On the other hand, total radiation dose can presumably be kept at clinically acceptable levels.

As recently reported in De Buck et al., reducing the number of projection images for a 3D reconstruction of the left atrium to 67 does not compromise static 3D model accuracy significantly and involves an effective radiation dose of \(\pm 2.6\) mSv. When applying a dynamic protocol similar to our 4DRA protocol with four phases and 100 projection images, the number of projection images per cardiac phase and, consequently, image quality would be further reduced. However, this reduction can be compensated by exploiting the correspondence between subsequent cardiac phases, which is practically realized by the proposed IPR-based filtering method. Hence, four-phase 4DRA imaging becomes realistic at the cost of increasing the radiation burden by no more than 50%.

### Limitations

- This pre-clinical study was performed in porcine experiments to prove the performance of the proposed methodology in terms of image quality gain prior to optimizing it for human use. Effective radiation doses could therefore not be calculated. Moreover, computational efficiency of the used prototype methods needs improvement prior to per-procedural use.
- The proposed methodology requires a higher iodine contrast dose than static 3D imaging, mainly due to a non-zero LV ejection fraction at slow pacing rates. Attention must be drawn to optimal timing of contrast agent injection to obtain sufficiently high and uniform contrast agent concentration during C-arm rotation, while minimizing the total amount of iodine contrast.
- Four cardiac phases might be insufficient to fully capture the LV motion, especially during rapid LV geometry changes. Moreover, including end-diastole and end-systole necessitates triggered acquisition, a technical feature that is not available on 3DRA systems to date.
- Ventricular pacing might be necessary in case of certain tachyarrhythmias.

### Conclusion

Generating dynamic 3DRA (4DRA) models of the LV is feasible and accurate through the use of a novel acquisition protocol and application of a post-reconstruction non-rigid IPR methodology, reducing image noise and speeding up 4D surface model generation.

We demonstrated a significant impact of the IPR-based method on image quality. Due to the use of low-dose acquisition protocols, radiation dose can be kept at a clinically acceptable low level. Also, by using slow pacing, the risk of inducing unwanted ventricular tachyarrhythmias is minimized. These findings open the perspective of realizing a 4D image sequence for more accurate integration with electroanatomical mapping systems and per-procedural fluoroscopy or co-registration with scar visualization modalities, to facilitate catheter ablation in locations with a high degree of motion, like the LV.

### Supplementary material

Supplementary material is available at Europace online.

### Conflict of interest: H.H. is Coordinating Clinical Investigator for the Biotronik-sponsored EuroEco study on health economics of remote device monitoring. H.H. is a member of the scientific advisory...
board of General Electric, Siemens Medical Solutions, Boehringer-Ingelheim, Bayer, Daiichi-Sankyo, BMS/Pfizer, and Sanofi-Aventis, and receives unconditional research grants through the University of Leuven from St Jude Medical, Medtronic, Biotronik, and Boston Scientific Inc.

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