A novel skeleton based quantification and 3D volumetric visualization of left atrium fibrosis using Late Gadolinium Enhancement Magnetic Resonance Imaging

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Aims and objectives

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice [1]. Radio-frequency catheter ablation (RFCA) has become the alternative procedure for those patients refractory to drug treatment [2]. Adequate patient selection is necessary to reduce the recurrence rates of RFCA; the outcome of RFCA can be strongly predicted from the fibrosis extent in left atrium (LA), as stated from previous studies [3-5]. At the present the clinical reference standard technique for the assessment of the LA substrate is the electro-anatomical mapping system (EAM), performed during electrophysiological study: the main limitations of this technique are the invasiveness and the suboptimal accuracy, with reported errors that can reach 10 mm in the localization [6,7]. Although these limitations, the clinical quantification of LA fibrosis extent from EAM is well admitted, as reported and recommended in guidelines for the management of AF [8].

In this context late gadolinium enhancement magnetic resonance imaging (LGE-MRI) appears to be a promising alternative for fibrosis assessment, as a non-invasive and potentially more accurate method, useful for selecting suitable candidates for RFCA [3]. Some studies have used LGE-MRI for the follow-up after RFCA procedure [9-11] and only a few have proposed it for selecting suitable candidates for RFCA [3, 12]. The thin myocardium of the LA, that leads a low signal to noise ratio, and the high anatomical variability of LA make it difficult to automate the whole analysis. In addition patients suffering from AF often have an irregular heartbeat and breathing, making hard to acquire cardiac-gated and respiratory-gated 3D images. As an overall result, the quality of LGE-MRI images of the LA is frequently poor.

The quantification of enhancement for the assessment of scar tissue has been made in previous study on intensity histogram of the manually segmented LA wall [13]. Recently a k-means classifier has been introduced for the quantification of healthy and damaged tissue from manual LA wall segmentation [14]. In other studies 3D visualization is done automatically, generating lesion visualization for expert user interpretation with the maximum intensity projection based technique [15, 16]. Manual segmentation of enhanced tissue and regions can be time consuming, tedious and error prone process. Often it requires substantial training and considering the time involved, it is not recommended for clinical practice. In addition, 2D LGE-MRI images are difficult to interpret and prone to inconsistencies even amongst experts. On the other hand automatic computational algorithms are unable to give correct results due to the poor quality of LGE-MRI images and presence of artifacts. In this e-poster we present a novel semi-automatic tool based on two types of image data: LGE-MRI images and magnetic resonance angiography (MRA) images. The fast 3D LA fibrosis quantification is achieved automatically using a skeleton based algorithm while accurate 3D views are obtained through a 3D volumetric approach. The user has the scope to manually edit the automatic results. An EAM system is used to assess the LA substrate as a reference technique. The aim is to develop a non-invasive, semi-automatic and robust 3D segmentation,
quantification and visualization of LA fibrosis tool, allowing fast availability and accuracy of results), for stratifying patients that are candidates for radiofrequency catheter ablation.
Methods and materials

Patients

Between June and December 2012 we enrolled 10 patients suffering AF, candidates for RFCA. According to the Utah score [3] patients were classified into four stages, based on the percentage of LA fibrosis extent (FE): Minimal (<5%), Mild (5%≤FE<20%), Moderate (20%≤FE<35%) and Severe (FE≥35%).

For the assessment of AF recurrence, all patients were seen in follow-up at 3 months following RFCA. Each patient received a 12 lead ECG and 8-day Holter monitor for detection of arrhythmia recurrence post blanking. Recurrence was defined as any atrial arrhythmia sustained for longer than 30 seconds.

Imaging protocol

All patients underwent MRI exam pre-RFCA, to obtain MRA images for the anatomical reconstruction of anatomical complex left atrium-pulmonary veins (LA-PVs) and LGE-MRI images for the detection and visualization of LA fibrosis. MRI exams were performed by a 1.5 Tesla MR scanner (Magnetom Avanto, Siemens Medical System, Erlangen, Germany), with intensity-gradients of 45 mT/m, slew rate of 200 T/m/s, using a 12-element phased-array receiver coil. The anatomical images of LA and PVs were obtained using the contrast-enhanced 3D FLASH sequence during a first pass of gadobenate dimeglumine (Multihance, Bracco, Milan, Italy) intravenous injection of a dose of 0.1 mmol/kg (2 ml/s injection rate), followed by a 40 ml saline flush. For the identification of fibrosis (LGE or area of hyperintensity of signal) was used a 3D inversion recovery prepared, respiration navigated, ECG-gated gradient echo pulse sequence, acquired 15 minutes after the contrast agent injection. Typical acquisition parameters were as follows: transverse imaging volume with voxel size 1.2x1.2x1.5 mm (reconstructed to 0.625x0.625x1.5 mm), slices for slab 60-80, TR/TE=6.3/2.3 ms, inversion time TI>310 ms, flip angle 22° with fat saturation, bandwidth (BW) 220 Hz/pixel and GRAPPA with R=2 and 62 reference lines. The TE of the scan (2.3 ms) was chosen so that fat and water were out of phase and the signal intensity of partial volume fat-tissue voxels was reduced, in order to improve delineation of the LA wall boundary. Typical scan time for the LGE-MRI study was between 15 and 20 minutes depending on subject respiration and heart rate [17].

Electrophysiological Study protocol

Before RFCA a detailed 3D bipolar voltage map of LA was registered using EAM system Carto3 (Biosense Webster, Diamond Bar, CA, USA) recording more than 200 points in the LA, and potentials maps were registered onto anatomical reconstructions of LA based on MR images. Normal endocardial voltage values were in the range 0.5-0.9 mV, whereas values below 0.5 mV were considered as abnormal areas. For this reason 3D surface
maps were classified as fibrosis using a threshold based approach in order to obtain a 3D surface mask of atrial fibrosis. The bipolar voltage value used as threshold was 0.50 mV and allowed to discriminate the illness from healthy myocardial tissue. Regarding the 3D visualization of the bipolar voltage maps, a color bar was chosen with a window into the range of 0.05-0.50 mV with red related to more fibrotic areas and violet to healthy myocardium.

**Semi-automatic image processing**

3D segmentation and visualization of LA fibrosis required integration of the MRA and LGE-MRI data. From MRA images a 3D cardiac surface anatomy of LA and PVs was obtained, whereas 3D fibrotic areas were detected using LGE-MRI images. Image processing was made with MeVisLab software (MeVisLab medical image processing and visualization software, http://www.mevislab.de, MeVis Medical Solutions AG, Bremen, Germany). The image processing was carried out as follows:

- Starting from MRA images, manually segmentation of LA and PVs in 3D views, avoiding 2D slice by slice segmentation and removing the structures surrounding LA and PVs that presented partial volume effect with them.
- Removing noise from LGE-MRI images: a median filter was applied to remove the high noise of LGE-MRI images, maintaining fibrosis signal. This filter prevents the detection of small isolated fibrosis areas that are generated only from noise and not of clinical interest.
- Non rigid fusion process: the fusion of MRA and LGE-MRI images is challenging, because MRA images were acquired without breath navigator and ECG-triggering. For this reason, after a first 3D affine registration, the user can manually correct the 3D LA and PVs mask. In addition a 6 mm wall thickness mask was used to account for all possible fusion errors.
- Quantification of LA fibrosis and EAM system comparison: the EAM system is considered the reference standard in quantification of extent of LA fibrosis, obtaining it as percentage of 3D surface areas instead of 3D volumetric measurements. A 2D skeleton based algorithm is introduced to model EAM system LA fibrosis quantification and to correct for the introduction of a not real 6 mm wall thickness.

To quantify the localization accuracy, the LA was divided into seven segments of clinical interest: right inferior pulmonary vein (RIPV), right superior pulmonary vein (RSPV), left inferior pulmonary vein (LIPV), left superior pulmonary vein (LSPV), anterior wall (AW), posterior wall and roof (PW-R) and floor (F). Each segment was then assessed on 3D visualization of LA fibrosis for the presence of fibrosis by two radiologist of experience in cardiac MRI imaging who were blinded to any 3D bipolar voltage map of EAM system. The same analysis was made on 3D bipolar voltage map of EAM system by two cardiologists of experience in electrophysiology who were blinded to any 3D visualization of LA fibrosis. It was possible to quantify the local agreement between the two methods, assuming the EAM system as the ground truth as reported in [11]. For each segment the, true positive (TP), true negative (TN), false positive (FP), and false negative (FN) numbers
were estimated and used to obtain the values of sensibility, specificity, positive predictive value and negative predictive value of the developed method.
Results

The patients were classified using the EAM system. Regarding the clinical objective, all patients classified as Minimal and Mild have shown no AF recurrence over a follow-up period of 3 months after RFCA, whereas for Moderate and Severe patients a sustained AF was registered. The discrepancies between results of fibrosis quantification, based on LGE-MRI images or estimated from the EAM system, are shown in Table 1.

As reported into the Fig. 1 the bias, i.e. the mean difference between the two method measurements, has value of 0.2 with 95% CI (-1.27%, 1.67%) that include the null value, confirming that there is no substantial bias of the LGE-MRI based fibrosis quantification. All measurements are in the 95% limits of agreement (-3.8%, 4.2%). In addition a non-parametric Wilcoxon Mann Withney paired test was made to find possible difference between the two methods results into fibrosis quantification. The test suggests that there is no difference (p=0.969) although it is understandable that this is on a smaller patient sample. Fig. 2 shows instead the 3D LA wall in white with segmented fibrosis in red for the antero-posterior and postero-anterior views, in comparison with 3D bipolar voltage maps of the EAM system for all the four fibrosis classes. Very good agreement in the localization of fibrosis areas is achieved. Table 2 summarize the agreement of the proposed algorithm in the localization accuracy of LA fibrosis. Starting from 3D visualization of LA fibrosis of all patients, for each segment of clinical interest the TP, TN, FP and FN numbers are estimated and reported, considering 3D bipolar voltage maps as reference standard. From this values the overall sensitivity and positive predictive value in indentifying areas of LA fibrosis of the proposed tool, based on LGE-MRI images and semi-automatic approach, are 0.95 with 95% CI (0.84, 0.99) and 0.93 with 95% CI (0.82, 0.99) respectively. The specificity and negative predictive value of absence of LA fibrosis areas are instead 0.88 with 95% CI (0.70, 0.97) and 0.92 with 95% CI (0.74, 0.99) respectively.
### Table 1: Atrial Fibrosis Extent estimated with the EAM system (FEEAM) and with LGE-MRI (FEMRI) and difference |#| for all 10 patient of different atrial fibrosis stage. Last column reports the AF recurrence over the different stages.

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**Fig. 1:** Bland-Altman plot of the measurements of fibrosis extent based on the EAM system (FEEAM) and on LGE-MRI (FEMRI). Mean difference (0.2%) is reported as blue solid line and 95% agreement limits as blue dashed lines (-3.8%, 4.2%), calculated as Mean difference ± 1.96 × standard deviation (SD).

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Table 2: True Positive (TP), True Negative (TN), False Positive (FP), and False Negative (FN) numbers of each segment of clinical interest: right inferior pulmonary vein (RIPV), right superior pulmonary vein (RSPV), left inferior pulmonary vein (LIPV), left superior pulmonary vein (LSPV), anterior wall (AW), posterior wall and roof (PW-R) and floor (F). The analysis is made for all patients considered, based on 3D LA fibrosis visualization and using 3D bipolar voltage maps of EAM system as reference standard.

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**Fig. 2:** Comparison of 3D results between LGE-MRI based methods and 3D bipolar voltage maps of EAM system relative to patients classified as Minimal, Mild, Moderate and Severe. 3D postero-anterior (PA) (first row) and antero-posterior (AP) (third row) views of segmented LA fibrosis, obtained from LGE-MRI images, as red areas on the white healthy cardiac 3D LA wall. 3D PA (second row) and 3D AP (fourth row) views of bipolar voltage maps, measured with EAM system and with a color bar that is violet for potentials upper 0.5 mV (healthy myocardium) and reaches red for potentials lower 0.05 (fibrosis); white points are the 3D locations of the registered potentials onto the 3D LA cardiac surface.

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Conclusion

Despite the small number of patients studied, the 10 consecutive patients with different grading of fibrosis areas allow to evaluate the developed algorithm in all possible scenarios. The more frequent classes are Minimal and Mild, whereas there is only one patient for Moderate and Severe classes. Fibrosis extent in LA, estimated from LGE-MRI images or EAM, strongly predicts the outcome of RFCA. There is no AF recurrence among Minimal and Mild stages, whereas patients classified as Moderate and Severe experience a sustained AF, confirming an atrial arrhythmic recurrence. The small number of patients is not a key feature since 3D segmentation, visualization and quantification, once obtained and validated, can easily be extended to all patients that will be treated with RFCA. Automatic segmentation of fibrosis areas from LGE-MRI images is hard to achieve due to the relatively poor contrast of LA, compared to surrounding anatomy. LGE-MRI presents long time of acquisition, resulting in a not well defined 3D LA shape, not suitable for a direct segmentation. MRA images instead present high contrast of blood-pool with respect of surrounding structures and the background, but cannot localize fibrosis areas. The approach of this study has been to use MRA images, that allow a segmentation of LA and PVs, and then to transfer knowledge of the shape of LA and PVs into the LGE-MRI images in order to isolate the LA volume. The main idea is that fibrosis areas must be located on the LA wall and the integration of these two types of images can overcome single limits of each type of images.

In clinical practice LGE-MRI images have the advantage of not requiring a second contrast agent injection as the contrast used for obtaining MRA images can be utilized; also MRA images are routinely acquired for the magnetic resonance catheter navigation of RFCA and 3D visualization of bipolar voltage maps. This means that there is no additional risk for patients and also no additional cost for this new acquisition, except the time involved in its acquisition. In contrast to the MRA images, LGE-MRI images are acquired with ECG-triggering and respiratory navigator with the possibility of a not perfect fusion between two data sets. Fusion of 3D LA and PVs mask with LGE-MRI images is made through DICOM header files and to correct possible errors a 3D manual rigid and affine registration module is implemented, as fast and easy to use for the user.

3D views allow a direct and immediate visualization of fibrosis areas compared to the 2D images visualization. This type of visualization gives an overall definition of fibrotic tissue present in LA and is not time consuming as viewing 2D LGE-MRI images slice by slice. The low signal to noise ratio of LA wall can lead to error if evaluated only into 2D images whereas 3D visualization allows a better understanding of the spatial distribution of the disease [15-17]. Another reason to obtain 3D visualizations is their usage before and during the RFCA procedure. These views can help Electrophysiologists to choice the procedural approach to treat AF. This can be done only with 3D views that can resume the overall distribution of fibrosis.
The application of this novel skeleton algorithm on the LGE-MRI images has led to a quantification of LA fibrosis for each subject. For all fibrosis classes a discrepancy between LGE-MRI and the EAM system results of less than 4% has been shown. Considering the classification interval of each fibrosis stage and the possible errors presented in the EAM system based fibrosis quantification, a discrepancy of less than 4% is well accepted. Bland-Altman analysis has shown that there is no presence of bias between the method based on LGE-MRI images and technique based on the EAM system, as the 95% of CI of the mean difference covers null value. Since all points of the difference of results between the two techniques are inside the limits of agreement, two methods can be considered as equivalent. From a statistical point of view the Wilcoxon-Mann-Whitney test, although applied to a small patient sample, has revealed that there is no significant difference between the two atrial fibrosis quantification systems.

The agreement of the proposed algorithm in the localization accuracy of LA fibrosis has been assessed. The subdivision of LA into seven segments of clinical interest and the related comparison show good agreement between the developed 3D volumetric visualization of fibrosis and the 3D bipolar voltage map of EAM system. Only 7% of analyzed segments have shown a non perfect localization of fibrosis, confirming a good localization of LA fibrosis areas. The overall assessment of LA fibrosis association reveals a sensitivity and positive predictive value in indentifying areas of LA fibrosis of 0.95 and 0.93 respectively. The specificity and negative predictive value of absence of LA fibrosis areas are instead 0.88 and 0.92 respectively. These values confirm that proposed tool can be considered reliable, although it has to be underline that these values are estimations based on a very small number of patients studied. The EAM system based method is the clinical reference standard for left atrial substrate characterisation through electrical mapping, but can present limitations and errors. There are only few studies [11,13] evidencing that low bipolar voltages areas of LA correlate to fibrosis areas detected from LGE-MRI images. For this reason comparison between results of the EAM system and LGE-MRI based method is necessary, since there is the need to demonstrate that LGE-MRI based method could be used as a surrogate to voltage endocardial mapping and to assess the effective reproducibility of its results and their reliability in clinical practice, as noted in the recent Expert Consensus Statement of the Hearth Rhythm Society [8].

A semiautomatic 3D segmentation and volumetric visualization of LA fibrosis areas based on integration of LGE-MRI and MRA images has been developed. LGE-MRI images coupled with advanced 3D image analysis technique have shown to be an effective and accurate tool in the quantification and localization of LA fibrosis, compared to the EAM system. It has also the advantage to be a non-invasive method and the achieved 3D views can be used by Electrophysiologists before and during RFCA to localize fibrotic tissue in a very fast and accurate way. The correct selection of patients that are candidates for RFCA can reduce also the considerable recurrence rate, the high cost, the procedure risk and avoid an invasive procedure, especially to patients who will not benefit from RFCA.
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References


