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Intensity and Distribution of Patchy Late Gadolinium Enhancement in Left Atrium in Patients With Atrial Fibrillation

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Abstract

Purpose: Late gadolinium enhancement (LGE) cardiac magnetic resonance imaging (MRI) studies were performed on healthy individuals to establish signal intensity thresholds for reproducible left atrial (LA) patchy LGE detection. Using established criteria, differences in LA patchy LGE between healthy volunteers (HV) and patients with atrial fibrillation (AF) or hypertension were analyzed.

Methods: Fifty-three patents with AF (mean age 56 years, 60% men), 25 patients with hypertension and no history of AF (mean age 54 years, 40% men), and 28 HV (mean age 50 years, 52% men) were enrolled in an observational, non-interventional, case-control prospective study. LA patchy LGE quantification was performed using LGE MRI (1.5 T scanner, voxel size 1.25x1.25x2.5 mm) and the custom-built software based on estimation of LA voxel image intensity ratio and comparison with threshold value obtained from HV data.

Results: Based on analysis of healthy individuals' data, the optimal threshold value for the left atrial patchy LGE quantification was determined at 1.38. Patients with AF had a higher extent of LA patchy LGE (9.1 [1.72; 18.58] %) than patients with hypertension (3.81 [0.57; 9.51] %) and HV (0.78 [0.05; 3.5] %). The predominant location of LA patchy LGE in AF was in the pulmonary vein ostia region, in hypertension – LA posterior wall, and in HV – lower part of LA posterior wall. In AF patients, the extent of LA patchy LGE correlated with LA end-diastolic volume (r=0.37) and LA ejection fraction (r=-0.4), in HV – with age (r=0.66) and LA end-diastolic volume (r=0.4).

Conclusions: AF and hypertension are associated with higher extent and different location of LA patchy LGE compared to changes caused by natural aging. The extent of LA patchy enhancement correlates with LA dilatation.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population [1]. Data from animal and human studies demonstrated that excessive myocardial fibrosis in the left atrium (LA) [2-4] can exacerbate electrical inhomogeneity of the myocardium and contribute to the progression of AF [5,6]. Due to an important clinical role of LA structural changes in AF, a robust noninvasive method for their assessment is needed for better comprehension and treatment of AF [6].

Late gadolinium enhancement (LGE) magnetic resonance imaging (MRI) identifies pathological changes in myocardium associated with cardiomyocyte necrosis and edema, scarring or fibrosis [7]. Recently, the ability of high resolution LGE MRI to quantify fibrotic changes in thin LA myocardium as patchy enhancement has been demonstrated [8,9]. Previous studies have revealed 10-40% incidence of LA patchy LGE/fibrosis in patients with AF and investigated its potential diagnostic and prognostic usefulness for interventional treatment of AF [10-12].

Because of the complex anatomy and histology of LA, the fibrosis quantification techniques based on LGE MRI threshold determination vary, and a preferable approach has not yet been established [9,13,14]. This insufficiency may be due to very limited data availability regarding the validation of LGE MRI findings at histopathological level [13-15]. This limitation sets a complex problem of establishing a type of "reference myocardium" for LA fibrosis quantification using LGE MRI.

The main hypothesis of the study was that HV, especially young, have minor changes in LA and their imaging results can be used as a ground-truth for LA patchy LGE quantification. It was also hypothesized that patients with cardiovascular disease with and without AF may have differences in the amount and distribution

Key Words

Left atrium, Structural remodeling, Atrial fibrillation, Hypertension, Aging, Hypertension, Late gadolinium magnetic resonance imaging.

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of LA patchy LGE. In the current study, the signal intensity (SI) characteristics of LGE in LA and patchy LGE myocardium were assessed quantitatively in HV, patients with AF, and patients with hypertension and with no history of AF.

Methods

Study design

This was an observational, non-interventional, case-control prospective study and its protocol was approved by the local ethics committee in compliance with Declaration of Helsinki. All patients gave written informed consent. The study was conducted during 2016-2017 at the National Medical Research Center of Cardiology of the Ministry of Healthcare of the Russian Federation.

To be included in the study patients must have been diagnosed with AF documented by electrocardiogram (ECG) and have sinus rhythm at the time of inclusion in the study. AF was categorized as either paroxysmal (lasts less than 7 days) or persistent (lasts more than 7 days and converted to sinus rhythm). In patients who had no hypertension as well as no signs of cardiovascular disease or other disease included in the list of exclusion criteria, AF was stratified as "lone AF". Patients with previously diagnosed hypertension (three blood pressure measurements ≥ 140/90mmHg on three different days in a 3-month period, or 1 measurement of ≥ 180/110mmHg) and without history of arrhythmia were also enrolled in the study.

Patients were excluded from the study cohort if they had claustrophobia, pregnancy, clinical instability, metallic implants, implanted pacemakers or defibrillators, rheumatic heart disease, acute and chronic inflammatory diseases, diabetes, heart failure, ischemic heart disease, cardiomyopathies, valvular and congenital heart disease, chronic kidney and hepatic diseases, and hyperthyroidism.

Sixty patients with AF and 30 patents with hypertension and no history of AF underwent clinical examination by cardiologist and met criteria for inclusion in the study. The examination included blood count test, biochemical blood test, thyroid stimulating hormone test, urine analysis, 12-ECG, echocardiography, 24-hour ECG monitoring, stress-testing, coronary angiography, if indicated, and cardiac MRI including LGE MRI. Because of inferior quality of LGE images, seven patients with AF and five patients with hypertension were later excluded from the study.

Twenty eight HV (HV group) (11 women, 17 men), who were not known to suffer from any significant illnesses relevant to the proposed study, whose body composition measurements, such as weight, were within normal ranges and whose mental state was such that they were able to understand and give valid consent to the study, were also enrolled in the study. All HV gave an informed consent and underwent the same examination and MRI protocol as patients in other groups.

Cardiac magnetic resonance protocol

Cardiac MR was performed on a 1.5-Tesla scanner (Magnetom Avanto, Siemens Medical Solutions, Germany) using a five-channel phased-array surface coil. Preliminary, patients with persistent AF were converted to sinus rhythm. Cine-MRI was performed using standard steady state free precession (SSFP) sequences in short breath-hold. Image acquisition was performed in four- and two-chamber view and a stack of short-axis slices was obtained to cover the whole LV and LA. The scan parameters were as follows: repetition time (TR) = 3.4 ms, echo time (TE) = 1.5 ms, flip angle = 73°, slice thickness = 6 mm, maximum field of view (FOV) = 400 mm, matrix 256×256 mm.

LGE MRI was performed 15-20 min after contrast agent intravenous injection (gadoversetamide (OptiMark, Libel-Flarsheim Company, USA), at a dose of 0.15 mmol per kg of body weight). For image acquisition, 3D IR GRE MR-pulse sequence with isotropic voxel and fat saturation was used. Imaging protocol was described earlier by Oakes et al. [9]. The parameters for image acquisition were: TR = 610-1100 ms, TE = 2.44 ms, flip angle = 22°, slice thickness = 2.5 mm, maximum field of view (FOV) = 400 mm with voxel size of 1.25×1.25×2.5 mm (reconstructed to 0.625×0.625×2.5 mm), inversion time (TI) of 270 to 380 ms and parallel imaging with GRAPPA technique with R 2. Study was performed during free breathing using breath synchronization. ECG-gating was used for image acquisition during LA diastole phase. Acquisition time of LGE MRI was from 5 to 15 minutes. All subjects tolerated the study well.

Cine-MRI analysis

LA volumes and ejection fraction (EF) were determined from 2-chamber view across the LA short axis cine-MRI images using Circle/cvi42 (2013 Circle Cardiovascular Imaging Inc.). An experienced operator manually defined endocardial contours of LA excluding the LA appendage. Phase systole and phase diastole were marked manually. Based on these data the software calculated LA end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF).

LGE image analysis

Only validated images were considered for further quantitative analysis. Validation of successful high resolution LGE images was the following: feasible visualization of heart chambers and vessels, esophagus, absence of blurring, absence/minimal artifacts, correct fat suppression, correct TI, high SI of aorta or mitral valve [Figure 1 A, B].

LGE MRI image analysis included LA myocardium semiautomatic segmentation, characterization of LA myocardium SI, and LA patchy LGE quantification. LA myocardium segmentation was performed by a specially trained operator using ImageJ 1.46r (NIH, USA). LA endocardial border was defined manually. LA epicardial border was reconstructed automatically parallel to endocardial border based on specified individual LA wall thickness (1.5-3 mm). In order to reflect the individual anatomy of LA wall epicardial border was corrected manually. Regions of mitral annulus, descending aorta, esophagus and artifacts were thoroughly excluded from the segmentation [Figure 1 F-H]. The blood pool located in the LA cavity was segmented as a region surrounded by the LA endocardial border [Figure 1B]. Additional specially trained operator verified and corrected the obtained LA borders (Supplement).

The evaluation of LA wall SI comprised automatic estimation of the histogram representing the SI of the entire LA wall myocardium voxels [Figure 1B]. The typical shape of the histogram curve was close to Gaussian curve. Thus, mean LA SI and maximum LA SI was estimated on the histogram using Gaussian tools. The histogram of blood voxel SI was reconstructed automatically, and mean blood SI was estimated automatically.

To overcome disadvantages of manual operator-based calculations of the extent of LA patchy LGE, a LGE Heart Analyzer software package was developed and written in MATLAB (Mathworks Inc., USA). This software requires the layers of both segmented LA myocardium and blood to be uploaded in DICOM format. Then it automatically estimates voxel intensity histogram, MIR and voxels with IIR above a manually set threshold value and calculates the extent of LA patchy LGE. Using CardioViz 3D v. 1.4.0 platform (Asclepios Research Project, Inria Sophia Antipoli) LGE Heart Analyzer also reconstructs a three-dimensional model of LA with mapped patchy LGE.

Statistical analysis

Continuous data are expressed as median (25th percentile – 75th percentile), and categorical variables are presented as absolute numbers (percentage). For intergroup comparison, a Mann-Whitney rank sum test and/or Kruskal-Wallis test followed by Dunn's test were used. The associations of LA patchy LGE with quantitative indicators were assessed using Spearman correlation. By Bland-Altman plots, inter- and intra-observer agreements in LA segmentation were represented as mean difference and corresponding 95% confidence interval (1.96 SD). Receiver operating characteristic (ROC) analysis was performed to differentiate between HV and patients with AF based on quantitative assessment of LGE in LA (MIR values) by calculating areas under the curve (AUC) and optimal cutoff values from the ROC curves, using the Youden index. The DeLong method was used to compare different AUCs. For all tests, the significance level was set to p≤0.05. All statistical analyses were conducted using SigmaPlot v.10 (Systat Software Inc.).

Results

A total of 78 patients and 28 HV were enrolled the observational, non-interventional, case-control prospective study. 53 patients (21 women, 32 men) had AF and 25 patients had hypertension (15 women, 20 men) without a history of arrhythmias. Their baseline characteristics are presented in [Table 1].

AF was accompanied by hypertension in 25 patients. The other 28 patients had "lone AF". Forty-five AF patients received antiarrhythmic drugs, and 28 oral anticoagulants if indicated according to individual CHA2DS2Vasc score. Patients who had hypertension (45) took effective antihypertensive medications for at least 6 months and achieved 0 grade of hypertension.

The were no significant differences between the groups in age, gender, smoking, left ventricle ejection fraction and indexed mass.

Table 1: Baseline characteristics of patients and healthy volunteers

	Atrial fibrillation n=53		Hypertension n=25	Healthy volunteers n=28	Kruskal-Wallis test (p)
	AF_{lone} n=28	$AF_{+hypertension}$ n=25			
Age, years	52 [41; 57]	57 [51; 62]	54 [50.5; 56]	48 [34; 53.5]	0.053
	56 [44.5; 60.5]				0.07
Men, n (%)	32 (60.4)		10 (40)	17 (60,7)	0.1
	18 (64.3)	13 (52)			0.055
Women, n (%)	21 (39.6)		15 (60)	11 (39,3)	0.1
	10 (35.7)	12 (48)			0.09
Smoking, n (%)	12 (22.6)		5 (25)	11 (39,3)	0.06
Body mass index, (kg/m²)	28 [25.6; 32.3]		28.9 [25; 31,9]	24.5 [22,3; 26]	0.01
Left ventricle ejection fraction, %	61.3 [58.4; 76.4]		62.8 [60; 73.1]	60.5 [60.3; 78.1]	0.8
Left ventricle indexed mass, g/m²	58.3 [48; 66.2]		61 [52.3; 66.7]	58 [51.6; 65.9]	0.4
Hypertension					
- grade 1, n (%)	-	1 (4)	2 (8)	-	0.06
- grade 2, n (%)	-	10 (40)	10 (40)	-	0.2
- grade 3, n (%)	-	14 (56)	13 (52)	-	0.06

AF – Atrial fibrillation

Table 2: Values of maximum intensity ratio in study groups

	HV	AF	P (vs HV)	Hypertension	P (vs HV)
MIR 2 SD	1.43 [1.24; 1.59]	1.69 [1.5; 1.92]	<0.001	1.54 [1.47; 1.89]	<0.001
MIR 3 SD	1.63 [1.5; 1.74]	1.93 [1.71; 2.24]	<0.001	1.85 [1.68; 2.12]	0.003
MIR 4 SD	1.87 [1.65; 2.08]	2.17 [1.93; 2.54]	<0.001	2.07 [1.83; 2.23]	0.02

AF - atrial fibrillation, HV - healthy volunteers, MIR - maximum intensity ratio, SD – standard deviation

Group of healthy volunteers had significantly lower body mass index.

Introduction of maximum intensity ratio indicator

Quantitative characterization of LGE in LA myocardium was performed based on image intensity ratio indicator (IIR was calculated for each voxel of LA wall as myocardial voxel SI divided by blood SI) [16]. Maximum intensity ratio (MIR) indicator was introduced in order to quantitatively assess the SI of the most enhanced regions in LA wall that represent a patchy LGE. MIR was calculated using Gaussian tools as maximum LA wall SI (at 2 standard deviations (SD), 3 SD and 4 SD) divided by mean blood SI [Figure 2].

The values of MIR at 2 SD, 3 SD and 4 SD were significantly lower in HV than in AF or hypertension without AF groups [Table 2].

Table 3: Age-related differences in left atrium in healthy volunteers

	HV, age < 40 n=11	HV, age >40 n=17	P (vs HV age < 40)
Left atrial end-diastolic volume, ml	45 [37; 46]	70 [50; 80]	0.04*
Left atrial indexed volume, ml/m²	30.5 [19.1; 30.5]	37 [29.6; 41.8]	0.05*
MIR 2 SD	1.22 [1.2; 1.28]	1.45 [1.4; 1.6]	0.01*
MIR 3 SD	1.39 [1.35; 1.54]	1.66 [1.58; 1.75]	0.013*
MIR 4 SD	1.55 [1.5; 1.71]	1.88 [1.82; 2.13]	0.05*

HV – healthy volunteers, MIR - maximum intensity ratio, SD – standard deviation
*Statistically significant difference
The values of MIR indicator also correlated with LA EDV (r=0.5, r=0.4, r=0.45, 2 SD, 3 SD and 4 SD, respectively).

Age-related differences in the intensity of LGE of the left atrial myocardium in healthy volunteers

Positive correlation between the age of HV and MIR indicator values (r=0.66; r=0.54; r=0.6, 2 SD, 3 SD and 4 SD, respectively) was observed in this study. Quantitative analysis of this relationship demonstrated that MIR values among the subgroup of HV over the age of 40 were significantly higher than the same indicators in the subgroup under the age of 40 [Table 3].

Estimation of the threshold for left atrial patchy LGE quantification

In order to assess capability of MIR for distinguishing between HV and patients with AF the ROC-analysis was performed [Figure 3]. It was determined that MIR calculated at 2 SD gives the best differentiation between HV and patients with AF (AUC=0.847)

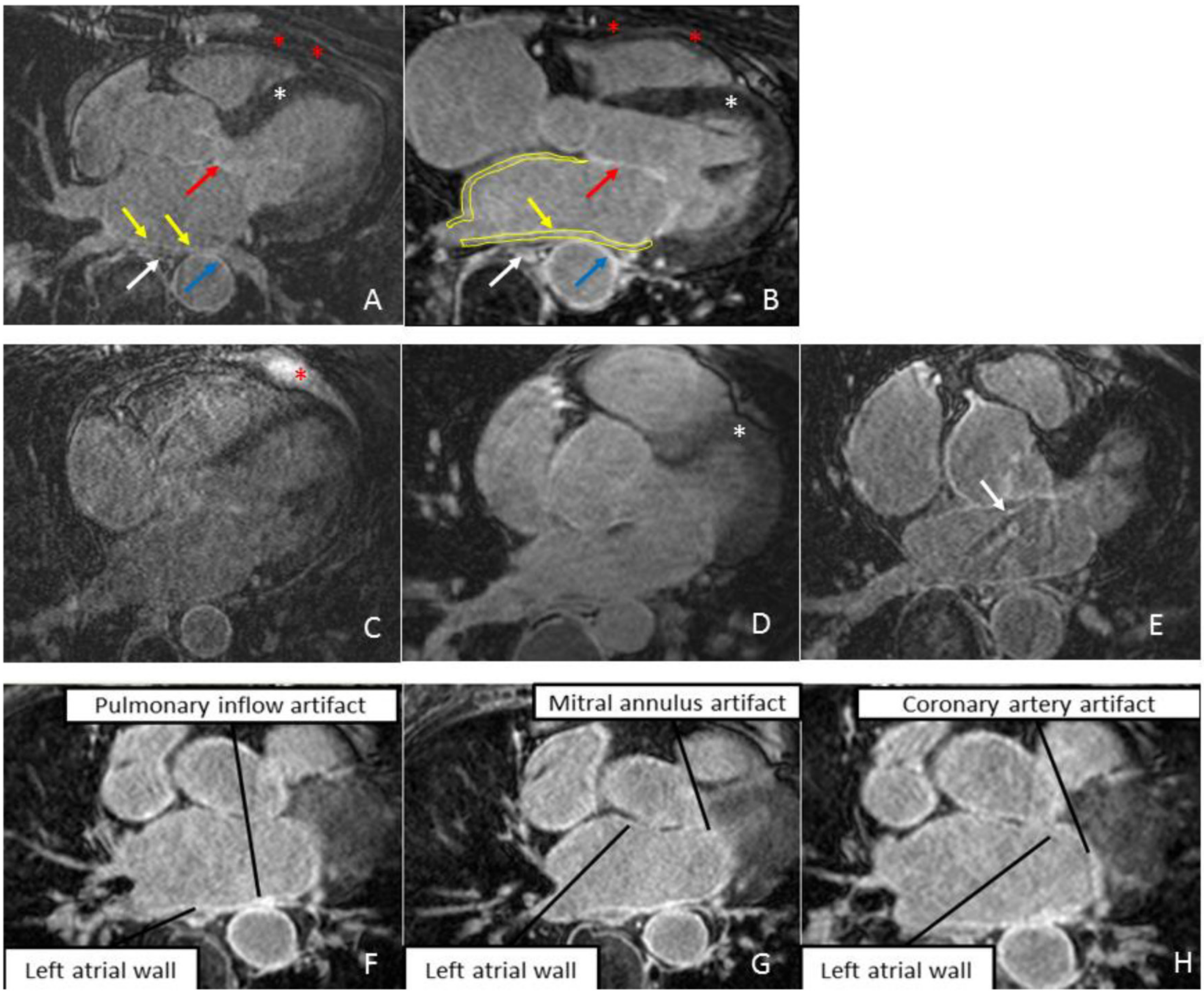


Figure 1: Feasible images of the left atrium (A, B). Left atrial wall (yellow arrows, yellow line); esophagus (white line); late gadolinium enhancement (LGE) in mitral valve (red arrows), in aorta (blue arrows); correct inversion time (white asterisks); correct fat suppression (red asterisks). Common artifacts and structures: image blurring (C, D); unsatisfactory fat suppression (C, red asterisk); navigation artifacts (E, white asterisk), blood flow artifact (F), mitral annulus (G) and coronary artery (H) must be differentiated from left atrial wall.

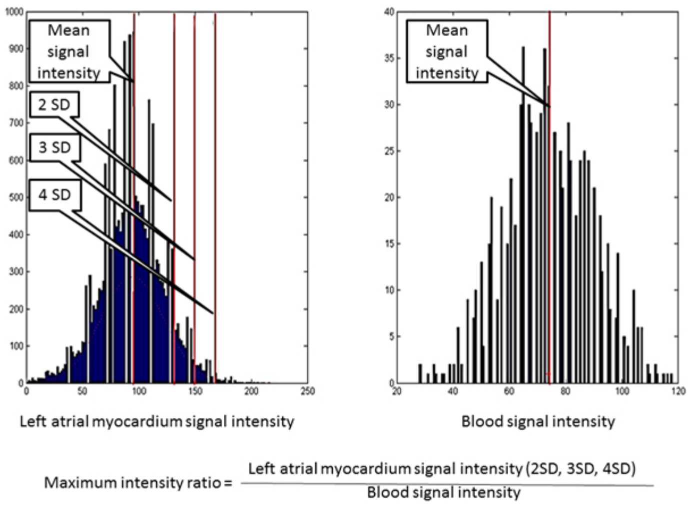


Figure 2: **Quantitative assessment of left atrial and blood signal intensity. Calculation of maximum intensity ratio indicator.**

compared with MIR at 3 SD (AUC 0.824) and 4 SD (0.769). MIR in HV group was considered as ground-truth data for patchy LGE quantification. According to Youden index the threshold value for LA patchy LGE was determined as 1.6 (sensitivity 66%, specificity 91%).

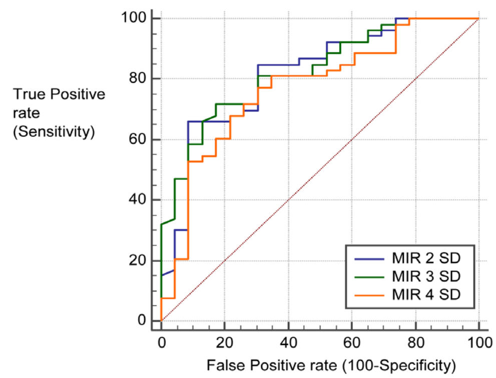
In order to increase the sensitivity of MIR indicator-based threshold ROC-analysis was performed for the subgroup of HV under the age of 40 (n=11) and patients with AF [Figure 4].

According to ROC-analysis the criterion value 1.38 (sensitivity 94%, specificity 98%) corresponding with Youden index was applied as a threshold parameter for LA patchy LGE quantification [Figure 5]. Voxels with IIR exceeding the threshold value were considered as pathologically enhanced, i.e. represented patchy LGE. The extent of LA patchy LGE was expressed as a number of voxels identified as enhanced over the total number of voxels within the endocardial and epicardial boundaries. LA patchy LGE quantification was performed automatically with manually set threshold using LGE Heart Analyzer software package.

Left atrial patchy LGE extent in patients with atrial fibrillation, hypertension and in healthy volunteers

LA patchy LGE was detected in 35.7% of HV (10 cases) [Table 4]. All of these study subjects were over the age of 40. The average extent of LA patchy LGE in this group was 0.78%. The extent of LA patchy LGE in HV correlated with the age (r=0.66) and LA EDV (r=0.4). The highest value of LA patchy LGE among HV (17%) was registered in a 57-year old male with LA EDV 111 ml. No LA patchy enhancement was found in study subjects under the age of 40.

LA patchy LGE was detected in 84.9% of patients with AF (46 cases). The extent of LA patchy LGE in patients with AF was significantly higher than in HV (9.1 [1.72; 18.58] % vs. 0.78 [0.05; 3.5] %, p=0.05, respectively). The highest value of LA patchy LGE (73%) in the AF group was registered in a 64-year old male (LA EDV 75 ml) with frequent paroxysms of AF.



Sample size			81
Positive group			53 (65.4%)
Negative group			28 (34.6%)
Variable	AUC	SE [a]	95% CI [b]
MIR 2 SD	0.847	0.0544	0.711 to 0.896
MIR 3 SD	0.824	0.0490	0.720 to 0.902
MIR 4 SD	0.769	0.0605	0.659 to 0.858

[a] DeLong et al., 1988
[b] Binomial exact

Youden index J for MIR 2 SD curve	0.5734
Associated criterion	>1.612
Sensitivity	66.04
Specificity	91.30

Figure 3: **Receiver Operator Characteristic (ROC) Analysis to differentiate patients with atrial fibrillation from healthy volunteers using maximum intensity ratio indicator. Comparison of differentiation abilities of three ROC-curves of a maximum intensity ratio (MIR) at 2 (blue), 3 (green) and 4 (red) SD performed using area under the curve (AUC) (see table). MIR at 2 SD indicator curve resulted in the highest AUC with 0.847. SD – standard deviation**

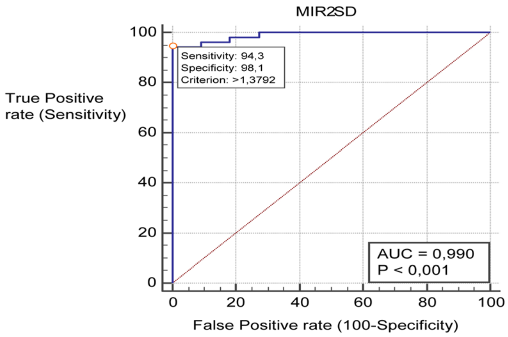
There was no correlation between the type of AF, age, gender, smoking, body mass index and the extent of LA patchy LGE. The extent of patchy LGE in patients with AF correlated with LA EDV (r=0.37) and LA EF (r=-0.4). 25 patients with AF and concomitant hypertension trended toward the higher extent of patchy LGE (9.1 [1.72; 18.58] %) than 28 patients with “lone AF” (4.37 [0.82; 16.03]%).

In the group with hypertension and no history of AF, LA patchy LGE was detected in 72% of patients (18 subjects). The extent of LA patchy LGE in patients with hypertension was intermediate between that of patients from the AF group and HV (3.81 [0.57; 9.51] %). In this group, the highest value of LA patchy LGE (23%) was detected in a 59-year old female (LA EDV 88 ml).

Left atrial patchy LGE location in patients with atrial fibrillation, hypertension, and healthy volunteers

In patients with AF, the predominant location of patchy LGE was in the pulmonary vein region (24 subjects, 52.2%) [Figure 6A, B]. In other cases, patchy LGE was located uniformly in all LA walls [Figure 6 E, F] (15 subjects, 32.6%) or in the LA posterior wall (7 subjects, 11.2%) [Figure 6 C].

In patients with hypertension, patchy LGE was predominately located uniformly in all LA walls (8 subjects, 44.4%) [Figure 6 E, F]. In all other cases patchy LGE was distributed in the pulmonary vein region (5 subjects, 27.7%), in the LA posterior wall (3 subjects,



Sample size	64
Positive group	53 (82.8%)
Negative group	11 (17.2%)
Area under the ROC curve (AUC)	0.990
Standard Error [a]	0.00864
95% Confidence interval [b]	0.925 to 1.000
z statistic	56.674
Significance level P (Area=0.5)	<0.0001

[a] DeLong et al., 1988
[b] Binomial exact

Youden index J	0.9434
Associated criterion	>1.38
Sensitivity	94.34
Specificity	98.10

Figure 4: **Receiver Operator Characteristic (ROC) Analysis to differentiate patients with atrial fibrillation from healthy volunteers at the age under 40 years using maximum intensity ratio indicator (MIR) at 2 SD. MIR at 2 SD indicator curve resulted in AUC 0.990 with the threshold value 1.38 (sensitivity 94%, specificity 98%).**

16.7%), or the in lower part of the LA wall (2 subjects, 11.2%).

In HV mild patchy LGE was located predominately in the lower part of the LA adjacent to the mitral valve (9 subjects, 90%) [Figure 6D] or in the pulmonary vein region (1 subject, 10%).

Discussion

The present study evaluated healthy individuals as a reference cohort for LA patchy LGE quantification and demonstrated the differences in LGE of the LA myocardium between HV, patients with AF, and patients with hypertension and no history of AF.

Since Peters et al. [8] and Oakes et al. [9] independently pioneered successful visualization of the LA myocardium using LGE MRI, various approaches for LA patchy LGE/fibrosis quantification have been proposed and thoroughly reviewed [13,14]. Insufficient data regarding the peculiarities of LA fibrosis in subjects with and without AF limit usefulness of fibrosis quantification and interpretation in routine clinical practice.

Sites of inflammation, interstitial and replacement fibrosis or amyloid deposits typically patchy and non-uniform were elucidated in LA myocardium in association with AF in animal and clinical studies [2-4]. It was hypothesized that these patches can be detected using high resolution LGE MRI. Several studies demonstrated validation of LGE in left ventricle myocardium using myocardial biopsy samples [17]. However, only one study reported validation of LGE in LA myocardium using myocardial biopsy samples in AF [15]. As the present study had no histological validation due to ethical aspects we used term "patchy LGE" instead of "fibrosis".

Table 4: **Mechanical function and quantitative characteristics of late gadolinium enhancement of the left atrium in study groups**

	Atrial fibrillation n=53	AF_{lone} n=28	$AF_{+hypertension}$ n=25	Hypertension n=25	Healthy volunteers n=28
Left atrial end-diastolic volume, ml	79 [65.5; 86.6]*	75 [65.7; 84.3]*	81 [64.7; 87.9]*	71 [54; 88.5]	66.5 [56; 78.5]
Left atrial indexed volume, ml/m²	38.8 [29.5; 43.7]	35.8 [30.5; 44.1]	39.4 [28.4; 42.9]	36.7 [32.4; 44.25]	35.5 [24.6; 38.5]
Left atrial ejection fraction, %	44.5 [34.5, 54.5]*	42 [36.7; 52.2]*	45 [35.6; 50.9]*	54.5 [47.5, 58.5]	56.1 [49; 63.2]
MIR 2 SD	1.69 [1.5; 1.92]*	1.62 [1.3; 1.81]*	2.08 [1.98; 2.27]*	1.54 [1.47; 1.89]*	1.43 [1.24; 1.59]
The extent of LA patchy LGE, %	9.1 [1.72; 18.58]*	4.37 [0.82; 16.30]	10.9 [6.94 19.37]*	3.81 [0.57; 9.51]	0.78 [0.05; 3.5]
Maximal patchy LGE, %	70	36	70	23	17

AF – atrial fibrillation, LA – left atrium, MIR – maximum intensity ratio, LGE – left gadolinium enhancement, * p<0.05 vs healthy volunteers

SI normalization of the image is advantageous for the assessment of LGE in LA using IIR [16]. In the current study, IIR-approach was modified by proposing a fixed indicator MIR. It quantitatively reflects the SI of the most enhanced regions in the LA myocardium. Our results demonstrate that patients with AF and hypertension have significantly higher values of MIR than HV. This observation may reflect the presence of fibrosis or inflammation in the LA myocardium as it was described in histopathological studies [3,6]. Moreover, ROC-analysis has shown that applying MIR indicator at 2 SD allows distinguishing the patients with AF from HV.

In the current study, we evaluated the largest group of HV of different ages (28 persons, 26-59 years of age) so far described in the literature. Our results show that the intensity of LGE in HV (MIR) correlates well with age, and 40 years seems to be the critical age for the development of LA structural changes. These data agree with studies that describe age-related changes of the LA myocardium which may be the result of increase of stiffness of LV in healthy population [18]. LA age-related structural changes in some healthy persons may be an additional risk factor for AF development [1,19].

Our data demonstrate that the subgroup of HV aged under 40 years has low intensity of LGE in the LA myocardium (low values of MIR). This justifies using young HV's MIR as a threshold for LA patchy LGE quantification and expands previously reported data [20]. The threshold value derived from ROC-analysis (1.38) is close to the value reported by Benito et al. (1.2) [20], who also used healthy persons as a reference cohort for LA fibrosis quantification. The minor difference in the threshold values may be due to dissimilarity in techniques of LA wall and blood pool segmentation. In our study, the use of the whole group of HV as a reference cohort gave a higher threshold for fibrosis quantification – 1.6. This data well

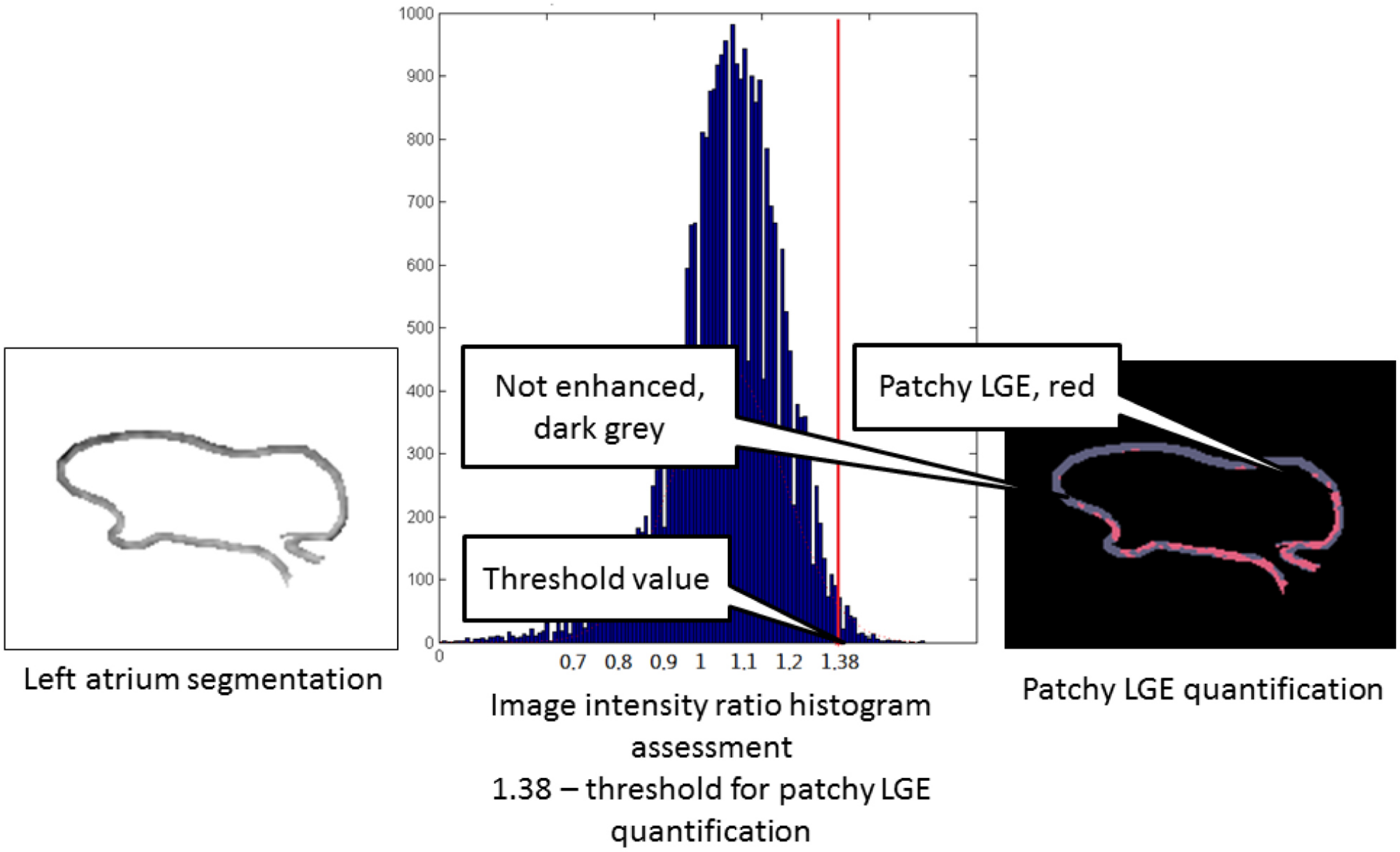


Figure 5: Left atrial patchy late gadolinium enhancement quantification algorithm based on comparison of left atrial voxel image intensity ratio with threshold value obtained from healthy volunteer's data.

agrees with Khurram et al, who offered to use the threshold of 1.6 for denser fibrosis and 0.97 – for less dense fibrosis according to electro-anatomical mapping [16]. Our results suggest that the use of lower threshold (1.38 vs. 1.6) value increases sensitivity of fibrosis quantification.

Patients with AF and especially those with hypertension demonstrated the highest extent of patchy LGE in LA (up to 70%). Patients with "lone AF" had only non-significant trend to lower extent of LA patchy enhancement than patients with AF and hypertension, which is in agreement with the results of Mahnkopf et al. [10]. We demonstrated that the predominant location of patchy LGE was in pulmonary vein and posterior wall regions. This may be explained using data of Hunter et al., who have demonstrated that pulmonary vein ostia regions and LA posterior wall undergo sufficient wall stress associated with AF [21]. Thus, formation of inflammation or fibrosis in these areas might be a result of stretch-induced activation of fibroblasts and myofibroblasts [22]. The extent of LA patchy LGE correlated with LA dilatation and LA EF decrease that is in agreement with the results of Kuppahally et al. [23]. These findings also support the idea that LA dilatation and wall stress are associated with structural changes in myocardium.

In seven patients with "lone AF", LA patchy LGE was not elucidated. These findings may reflect an initial stage of LA damage in association with AF. However, no data regarding the relationship between the minimal LA damage and clinical data were obtained in these persons.

The data regarding the relationship between the extent of LA patchy LGE/fibrosis and the type and persistency of AF are still controversial [9,10,24]. No correlation between the extent of LA patchy LGE and type of AF was found in the current study. This agrees well with the previous reports [10,11]. To reveal the relationship between LA patchy enhancement and AF clinical course it is necessary to set up complex prospective studies, including estimation of individual AF-burden.

It should be mentioned specifically that patients with no history of AF or even healthy persons may also demonstrate LA patchy LGE [25]. We have demonstrated minor LA patchy LGE only in HV aged over 40 years. In general, the mean extent of LA patchy LGE in HV was significantly lower than in patients with AF that is in agreement with the previous reports [26,20]. The extent of LA patchy enhancement

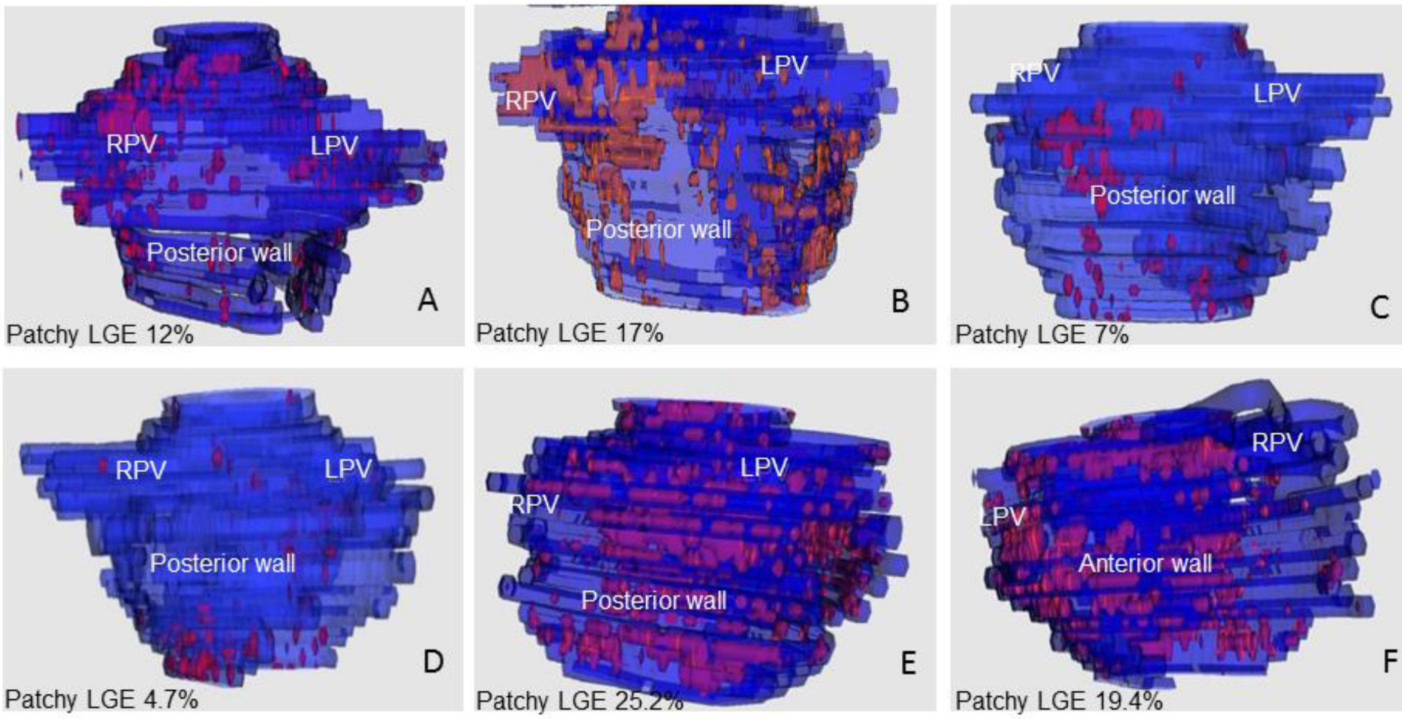


Figure 6: Predominant locations of left atrial patchy late gadolinium enhancement. Blue color marks healthy myocardium, red color marks fibrotic patches. Pulmonary vein ostia region (A, B), seen predominately in patients with AF; posterior wall (C), seen in patients with atrial fibrillation or hypertension; inner part of the posterior wall, in a healthy volunteer (D); uniform distribution (E, F), characteristic for hypertension or atrial fibrillation. LGE – late gadolinium enhancement, RPV – right pulmonary veins ostia region, LPV – left pulmonary veins ostia region. In the left lower corner of each image the extent of patchy late gadolinium enhancement (LGE) is represented.

in HV correlated with age and LA dilatation, and thus may represent age-related changes in LA. The predominant location of patchy LGE in HV adjacent to the mitral valve may reflect age-related changes in this area (calcification of posterior mitral annulus [27]), however, this needs further investigation on a larger group of healthy individuals.

In the current study, the extent of LA patchy LGE in patients with hypertension and no history of AF was intermediate between that of patients with AF and HV. Patients with hypertension demonstrated LA patchy LGE mainly located uniformly in all LA walls unlike the patients with AF. These changes may be a result of both LA wall stress related to elevated blood pressure and renin-angiotensin-aldosterone system activation [28]. Absence of correlation between the extent of patchy LGE in hypertension and clinical data was an unexpected finding of our study. We can only assume that lack of correlation between the extent of patchy LGE and initial grade of hypertension or LA volume may be due to the effective antihypertensive treatment.

In general, these observations support the idea that LA patchy LGE itself is not a specific phenomenon for AF. Evaluation of LA patchy LGE/fibrosis in cardiovascular diseases without the history of AF may reveal the new peculiarities of LA structure in AF.

Conclusion

AF, hypertension or natural aging may be associated with LA structural changes according to high resolution LGE MRI. Quantitative assessment of SI in the LA myocardium using indicator MIR at 2 SD revealed that young HV demonstrate low intensity of LGE in LA myocardium and, thus, are feasible as ground-truth for LA patchy LGE quantification. AF and hypertension seem to be associated with higher extent and different localization of LA patchy LGE than natural aging. The clinical relevance of LA patchy enhancement in persons with and without AF is currently unclear. The mechanisms of patchy structural changes in different locations of LA need further longitudinal studies.

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